Treatment of sleep disturbances in posttraumatic stress disorder: A review

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Abstract—Sleep disturbances are among the most commonly reported posttraumatic stress disorder (PTSD) symptoms. It is essential to conduct a careful assessment of the presenting sleep disturbance to select the optimal available treatment. Cognitive-behavioral therapies (CBTs) are at least as effective as pharmacologic treatment in the short-term and more enduring in their beneficial effects. Cognitive-behavioral treatment for insomnia and imagery rehearsal therapy have been developed to specifically treat insomnia and nightmares and offer promise for more effective relief of these very distressing symptoms. Pharmacotherapy continues to be an important treatment choice for PTSD sleep disturbances as an adjunct to CBT, when CBT is ineffective or not available, or when the patient declines CBT. Great need exists for more investigation into the effectiveness of specific pharmacologic agents for PTSD sleep disturbances and the dissemination of the findings to prescribers. The studies of prazosin and the findings of its effectiveness for PTSD sleep disturbance are examples of studies of pharmacologic agents needed in this area. Despite the progress made in developing more specific treatments for sleep disturbances in PTSD, insomnia and nightmares may not fully resolve.

Key words: antidepressant, antipsychotic, anxiolytic, behavioral, cognitive, desensitization, imagery, insomnia, nightmare, pharmacologic, polysomnography, posttraumatic, prazosin, sleep, stress, trauma, veterans.

INTRODUCTION

Individuals experiencing posttraumatic stress disorder (PTSD) report insomnia (trouble initiating and maintaining sleep) and recurrent distressing dreams among their most common and distressing symptoms. These sleep disturbances have long been thought to play a central role in PTSD, and research has suggested sleep problems may predict development of PTSD after exposure to trauma. Sleep complaints at 1 month, but not at 1 week, post-trauma are a significant predictor of PTSD at 12 months posttrauma (Koren et al. [1]). Insomnia and nightmares

during the first month following a traumatic event predict the development of PTSD, and the absence of these symptoms during this same period of time is a strong predictor of not developing PTSD (Harvey and Bryant [2]). These studies, based upon subjective reports, are supported by polysomnographic evidence that fragmented rapid eye movement (REM) sleep in the first month following a traumatic event is associated with the development of PTSD (Mellman et al. [3]).

"Sleep disruption is reported by 70–87% of people suffering from PTSD with a 48–60% increase in disturbed sleep compared to those who have been traumatized but do not have PTSD" (Maher et al. [4]). Nightmares were reported by 52 percent of veterans with PTSD compared with 5 percent of veterans without PTSD in a nationally representative sample of male Vietnam veterans (Neylan et al. [5]). The presence of nightmares has the strongest correlation with the diagnosis of PTSD, while problems with sleep onset are moderately correlated and difficulties maintaining sleep are weakly correlated with the diagnosis (Neylan et al. [5]). Currently, sleep disturbance is the second most common reason for referrals to mental health services following postdeployment screening of Operation Iraqi Freedom veterans.* Untreated sleep symptoms can persist for years and intensify daytime PTSD symptoms and associated comorbid psychiatric problems (Germain et al. [6]) and, thus, may contribute to the poor clinical outcomes often observed in PTSD. Because sleep has a restorative function (Horne [7]) and affects emotional regulation (Walker [8]), poor sleep may affect the emotional processing of traumatic experiences (Maher et al. [4]). These factors emphasize the need for effective treatment interventions to minimize the impact sleep disturbance has upon people experiencing PTSD.

Studies using objective sleep measures find, compared with nondisabled control subjects, patients with PTSD have (1) greater REM density (frequency of rapid eye movements, characteristic of a dream state) (Kobayashi et al. [9]); (2) more frequent brief awakenings (less than 1 minute) across all stages of sleep, reflecting hyperarousal and possibly nonrestorative sleep (Breslau et al.

[10]); (3) a greater number of shifts from REM to lighter sleep per hour of sleep (Breslau et al. [10]), possibly resulting in nonrestorative sleep; and (4) decreased stage 4 (slow wave) sleep, the most restorative sleep stage (Neylan et al. [11]). A meta-analysis of 20 polysomnographic studies showed PTSD patients had more stage 1 sleep, less slow-wave sleep, and greater REM density than with people without PTSD (Kobayashi et al. [9]). However, polysomnography-based studies yielded inconsistent results with respect to other measures of sleep, such as sleep efficiency (percent of time asleep relative to time in bed), duration of awakenings, body movement during sleep, and time to the first REM episode among individuals with PTSD (Maher et al. [4]). Nonetheless, the extant literature on objectively measured sleep suggests that individuals with PTSD have fragmented and nonrestorative sleep. The findings from objective sleep measures help inform the clinician in selecting treatment modalities that have the capacity to enhance restorative sleep and to normalize the sleep-wake pattern.

The Department of Veterans Affairs (VA) and Department of Defense (DOD) *VA/DOD Clinical Practice Guideline for Management of Post-Traumatic Stress* [12] emphasizes the important role nightmares can play in PTSD-related insomnia. Nightmares classically associated with PTSD are characterized by a repetitive replay of the traumatic event. The more exact the replication, the more likely the nightmare will be repeated (Schreuder et al. [13]). Nightmares that replicate the traumatic event are thought to be a form of uncontrolled re-exposure and thus to contribute to the perpetuation of PTSD. Individuals with PTSD nightmares commonly awaken from the nightmare in an aroused emotional and physiological state. Holocaust survivors with significantly lower rates of dream recall when compared with nondisabled age-matched control subjects were rated as well-adjusted, while survivors with similar rates of dream recall to control subjects were less well-adjusted (Kaminer and Lavie [14]). There is an increased risk of suicide for people experiencing nightmares. A Swedish study of suicide attempters found nightmares were associated with a five-fold increase in risk for high suicidality (Sjöström et al. [15]), and a large epidemiology study from Finland (Tanskanen et al. [16]) revealed a significantly increased risk of suicide for people reporting nightmares compared with those without nightmares. These findings suggest that nightmares play an important role in the perpetuation of PTSD symptoms and that the presence of nightmares can

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be an indicator of more pronounced psychological dysfunction and distress.

The high frequency of sleep disturbances associated with PTSD and their potential role in the development and course of PTSD highlight the importance of improving sleep among individuals diagnosed with PTSD. In this article, we describe some of the primary sleep disturbances associated with PTSD, with a focus on nightmares and insomnia. We then apply a general model of the development and maintenance of insomnia to PTSD-related sleep disturbance and examine evidence for the use of psychotherapy and pharmacotherapy to improve sleep among individuals diagnosed with PTSD, including those with other comorbidities.

METHODS

Primary-source literature and secondary-source reviews were identified using MEDLINE®/PubMed® and Published International Literature on Traumatic Stress (PILOTS) databases. No time constraints were used. The searches were conducted between January 2011 and April 2012. The terms PTSD, stress and stress response, sleep disorder, sleep disturbance, and insomnia were cross-referenced with specific areas of inquiry, i.e., veterans, nightmares, cognitive behavioral therapy, imagery rehearsal, polysomnography, physiology, and drug or drug class. The "Discussion" section is based on the results of the studies reviewed, the VA/DOD Clinical Practice Guideline (CPG) for PTSD, the practice guidelines of the American Academy of Sleep Medicine, and the authors' direct professional experience and scientific investigations. Clinical trial outcomes are described in terms of response rates, statistical significance, and/or effect sizes. This review gives greater weight to controlled studies than to open clinical trials. Recommendations for treatment and conclusions are based on the weight of the evidence available in the scientific literature.

DISCUSSION

Treatment of Sleep Disturbances in Posttraumatic Stress Disorder

The optimal treatment interventions for PTSD relieve symptoms in the re-experiencing, avoidant/numbing, and arousal criteria. However, sleep disturbances often persist despite relief or moderation of other symptoms. As many as one-half of positive responders to PTSD treatment continue to have residual sleep disturbance[*] (Zayfert and DeViva [17]). It is therefore important to thoroughly assess and treat sleep disturbances experienced by patients with PTSD. PTSD is commonly associated with comorbid disorders such as depression; substance abuse including alcohol, nicotine, and stimulants; anxiety; pain syndrome; and traumatic brain injury (TBI). Each of these conditions can contribute to disturbed sleep and must be taken into account when considering treatment choices. Though research indicates that treatment of sleep disturbance in the presence of comorbid conditions can be effective, the contribution of all comorbid diagnoses to sleep disturbance should be factored into the treatment plan of each individual patient.

Sleep Disorders Associated with Posttraumatic Stress Disorder

Research shows that in addition to nightmares and distress about problems initiating and maintaining sleep (insomnia), patients with PTSD are more likely than the general population to have other sleep disorders. Before initiating treatment of insomnia and nightmares, it is important for providers to evaluate the possibility of other sleep disorders and refer patients to sleep specialists when indicated. We review here three sleep disorders that are common among patients with PTSD patients.

Periodic Limb Movement Disorder

Periodic limb movement disorder (PLMD) is defined as sudden repetitive episodes of leg movement occurring on average 5 or more times per hour of sleep. The leg movements are most frequent during stages 1 and 2 of non-REM sleep. This disorder was found to be more common in Vietnam veterans with PTSD than Vietnam veterans without PTSD (Mellman et al. [18]). Other investigators have also found a high incidence of PLMD in Vietnam veterans (Brown and Boudewyns [19]). The primary agents used to treat PLMD, the direct dopamine (D) agonists, have a 90 percent rate of efficacy in randomized controlled trials (RCTs) (Hening et al. [20]).

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However, little is known about the effects of D agonists upon patients with PTSD. Gabapentin has been given a class A recommendation for treating PLMD by the European Federation of Neurological Societies, and gabapentin enacarbil, a pro-drug of gabapentin with increased bioavailabilty, significantly reduced periodic limb movements and wake time (Winkelman et al. [21]). Bupropion has been found to be helpful in a small case series (Nofzinger et al. [22]) and may be considered as an alternative when D agonists or gabapentin are contraindicated or not well tolerated. It is important to note that medications frequently used to treat PTSD, such as selective serotonin reuptake inhibitors (SSRIs), venlafaxine (Yang et al. [23]), and tricyclic antidepressants (TCAs) (Cohrs et al. [24]), may induce or worsen PLMD.

Rapid Eye Movement Sleep Behavior Disorder

The International Classification of Sleep Disorders lists the following minimal criteria for the diagnosis of REM Sleep Behavior Disorder (RBD): the presence of REM sleep without atonia on polysomnography and at least one of the following criteria: (1) sleep-related, injurious, potentially injurious, or disruptive behaviors by history (i.e., dream enactment behavior) and/or (2) abnormal REM sleep behavior documented during polysomnographic montoring. RBD is more common in older adults, with a mean age of onset from 50 to 65 years, and can be associated with and may precede neurodegenerative disorders, such as Parkinson disease, dementia with Lewy bodies, and multiple system atrophy (Boeve et al. [25]). However, in almost 50 percent of RBD cases, no brain lesion is observed (Olson et al. [26]). Individuals with the onset of RBD at age 50 and younger have a significantly higher frequency of psychiatric diagnoses and antidepressant use compared with non-RBD control subjects (Thomas et al. [27]). Antidepressant use may contribute to the development of RBD. Monoamine oxidase inhibitors (MAOIs) and TCAs have been reported to induce RBD (Thomas et al. [27]), and a systematic polysomnographic study found selective serotonergic reuptake antidepressants and venlafaxine to increase electromyogram tonic activity in REM sleep compared with control subjects (Winkelman and James [28]). It has been proposed that individuals with PTSD have a higher prevalence of RBD (Husain et al. [29]) and that this may contribute to the acting out of dreams sometimes observed in this population (Ross et al. [30]). No RCT of drug treatment for RBD has been reported. Clonazepam was found to be effective in one study with 87 percent complete or partial responders (Olson et al. [26]). However, overall limited evidence exists of the efficacy of benzodiazepines for this disorder.[*] Melatonin has "also shown efficacy alone or in combination with clonazepam" (Boeve et al. [31]).

Sleep Disordered Breathing

Obstructive sleep apnea (OSA) is a common form of sleep disordered breathing (SDB), with a prevalence of 3 to 7 percent in men and 2 to 5 percent in women (Lurie [32]). Risks for OSA include obesity, male sex, and older age (Lurie [32]). A VA study of 4,060,504 unique cases identified 118,105 cases of sleep apnea (2.9 percent of the VA sample) (Sharafkhaneh et al. [33]). PTSD was found to be comorbid in 11.9 percent of the sleep apnea patients, while the current prevalence of PTSD in the VA population as a whole is 8.4 percent. However, a large community sample of young adults did not find higher prevalence of SDB in individuals with PTSD compared with control subjects (Breslau et al. [10]). Nonetheless, a conservative approach dictates that SDB be considered during an evaluation of sleep disturbance in PTSD. There is some evidence that successful treatment of SDB can improve PTSD symptoms. A retrospective study of 15 individuals with SDB and PTSD treated with continuous positive airway pressure (CPAP) therapy revealed a 75 percent improvement in nightmares and overall PTSD symptoms (Krakow et al. [34]). A second study found that, although PTSD patients were less likely to adhere to recommendations concerning use of CPAP, patients with PTSD who did adhere to CPAP treatment reported decreased nightmares and improved sleep (El-Solh et al. [35]). A detailed case study of a patient with SDB and PTSD treated with CPAP, with polysomnography to examine sleep architecture, demonstrated normalization of sleep architecture. There was also a dramatic improvement in nightmare frequency and intensity as well as a decreased startle response (Youakim et al. [36]). Our clinical experience suggests that some veterans with OSA do not tolerate CPAP because of association with gas masks and that attention to this issue may enhance adherence.

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If any of the previous sleep disorders have been diagnosed, it is recommended that providers first treat that sleep disorder and determine whether the treatment resolves the disorder and the overall sleep disturbance. If, despite this targeted treatment approach, a PTSD-related sleep disturbance (insomnia and/or nightmares) persists, it is recommended that providers proceed by adding a nonpharmacologic treatment for the specific sleep disturbance. Nonpharmacologic treatment is the first-line choice for PTSD-related sleep disturbance and is less likely to aggravate the identified sleep disorder than a pharmacologic approach. If nonpharmacologic treatment is not effective, pharmacologic treatment can be considered. Because certain pharmacologic agents used for the treatment of PTSD can aggravate PLMD and RBD, they need to be used with caution when these conditions co-occur.

Nonpharmacologic Treatments of Insomnia and Nightmares in Posttraumatic Stress Disorder

Traditionally, insomnia symptoms have been conceptualized as part of the overall syndrome of posttraumatic symptoms, and therefore, providers generally presumed that as posttraumatic symptoms improved so too would sleep. However, research indicates that although trauma-focused therapies improve sleep in some cases, sleep problems often do not remit after otherwise successful treatment of posttraumatic symptoms (Belleville et al. [37], Zayfert and DeViva [17]). The simplest explanation for this is based on a well-accepted model of the development and maintenance of insomnia by Spielman and colleagues (Spielman et al. [38]). The Spielman model hypothesizes that individuals differ in their level of predisposition toward developing insomnia (e.g., overall arousability). Precipitating factors, such as environmental stressors or medical conditions, interact with predisposing factors and produce short-term (acute) sleep disturbance. Over time, an individual's responses to disturbed sleep may serve to maintain it, even after the initial precipitants have been diminished or resolved. Examples of such maladaptive responses, referred to in the Spielman model as perpetuating factors, include spending excessive time in bed awake while "trying to sleep" or engaging in nonsleep activities while in bed. Sleep may be impaired further by the development of conditioned relationships between the bed and responses that are incompatible with sleep, such as wakefulness or elevated anxiety (Perlis et al. [39]).

Trauma is often associated with nightmares and leads to high levels of general arousal and/or excessive vigilance at night, all of which can precipitate sleep problems. Trauma that occurs in the bed, bedroom, or darkness may cause a conditioned fear response in the sleep setting, which is incompatible with sleep (Zayfert and DeViva [17]). For example, the experience of night-time combat during a military deployment or being awoken in the middle of the night during childhood by an abuser may associate the sleep setting with arousal and promote hypervigilance before and during sleep. If individuals with PTSD spend long amounts of time in bed awake, they may re-experience trauma, ruminate, or try to remain vigilant to their environment, all of which are incompatible with sleep and can result in conditioned arousal associated with the sleep environment. Posttraumatic precipitating factors may resolve with successful treatment of PTSD; however, maladaptive sleep-related perpetuating behaviors, such as going to bed very early or napping to "catch up" on lost sleep, may not resolve and may maintain insomnia. It is also possible that standard treatments for PTSD may not sufficiently reduce arousal in the bed or adequately address beliefs about the consequences of poor sleep, and these factors can continue to perpetuate sleep problems. Given the potential effects of perpetuating factors on sleep, it is a realistic possibility that individuals with PTSD who complete and respond well to treatment for PTSD symptoms may still experience poor sleep. Therefore, the next section will examine the effects of trauma-focused and sleep-focused interventions on the sleep of individuals with PTSD.

Trauma-Focused Cognitive-Behavioral Therapy for Posttraumatic Stress Disorder

The VA/DOD CPG [12] and the International Society for Traumatic Stress Studies (Foa et al. [40]) list trauma-focused cognitive-behavioral therapies (CBTs) as first-line options for the treatment of PTSD. The DOD and VA have recently begun national dissemination projects to train large numbers of clinicians in prolonged exposure (PE) therapy and cognitive processing therapy (CPT) for PTSD, and these treatments have become widely available throughout the federal system for Active Duty military and veterans. These treatments contain different combinations of direct engagement with memories of traumatic events (PE through processing after imaginal exposure and CPT through a written account) and challenging of maladaptive beliefs associated with trauma

(PE through postimaginal exposure processing and CPT through systematic identification and restructuring of those beliefs). Both PE and CPT have significant empirical support for use in the treatment of PTSD (Foa et al. [40]).

Most studies of CBT for PTSD report treatment effects on overall PTSD symptom levels. A few studies have reported the effects of trauma-focused CBT on sleep, and the results are varied. These studies generally conclude that, despite an absence of interventions specifically targeting sleep, trauma-focused CBT is generally associated with improvements in sleep. Some studies have found that over half of patients completing trauma-focused CBT also experienced significant improvement in sleep (Cooper and Clum [41], Zayfert and DeViva [17]), though one other study found that only 30 percent of patients no longer reported sleep problems after treatment completion (Belleville et al. [37]). One study comparing the effects of CPT and PE on sleep found that both interventions resulted in significant improvements in sleep, though posttreatment assessment means were above an established cutoff for poor sleep quality in both conditions (Galovski et al. [42]). In a study of female rape victims with PTSD, CBT resulted in remission of PTSD symptoms, which was associated with a reduction of heart rate variability (indicator of sympathetic activity) during REM sleep (Nishith et al. [43]). Zayfert and DeViva [17] found that disturbed sleep and anger problems are the two most frequently reported residual symptoms following successful treatment of PTSD. Zayfert and DeViva also found that trauma-focused CBT was associated with a large decrease in nightmares and that of the patients who reported continued sleep problems after treatment, less than a quarter were still reporting nightmares of sufficient severity to be coded as a clinical symptom.

It is not clear why some patients' sleep problems persist after trauma-focused CBT. As noted previously, it is possible that these patients develop maladaptive patterns of thinking or behavior that interfere with sleep and perpetuate the sleep problems even after such precipitating factors as nightmares and hypervigilance have decreased (Spielman et al. [38], DeViva et al. [44]). Patients may get into a pattern of giving themselves long periods of time in bed, thus increasing the likelihood of lying in bed awake. Patients may also nap in the day to "catch up" and as a consequence decrease their sleep drive, resulting in longer sleep-onset latency at bedtime. In other words, in these cases, insomnia becomes a comorbid disorder that may require specific treatment. A second possibility is that general arousal level does not decrease despite decreases in re-experiencing and avoidance. Zayfert and DeViva [17] found that hyperarousal symptoms were more likely to be present after completion of trauma-focused CBT than avoidance or re-experiencing symptoms. Baseline arousal, and also physiological response to external stimuli, may remain high after other symptoms have decreased or remitted, and that arousal could interfere with sleep.

It is also possible that the specific circumstances of the traumatic event may have caused conditioned arousal to the bed, the bedroom, or darkness, and these conditioned relationships may not have been addressed by trauma-focused treatment. A therapist providing exposure therapy may not inquire about sleep-related avoidance behaviors such as leaving the lights on in the bedroom at night and therefore may miss sleep-related stimuli when constructing an in vivo exposure hierarchy. Similarly, a therapist providing cognitive therapy may not assess beliefs about the safety of the sleep setting. A fourth possibility is that a sustained pattern of waking in an agitated state from nightmares or chronic fear of loss of vigilance results in a fear of sleep itself that increases arousal in the sleep setting and interferes with sleep (Zayfert and DeViva [17]). Fear of the loss of vigilance may also lead to additional safety behaviors that are incompatible with sleep, such as sleeping during daylight hours when others are awake and trying to "stand guard" at night when the rest of the household is sleeping and vulnerable.

Eye Movement Desensitization and Reprocessing

Eye movement desensitization and reprocessing (EMDR) has demonstrated efficacy in the treatment of PTSD based on numerous treatment studies with medium to large effect sizes. The EMDR protocol includes saccadic eye movement tracking across the patient's visual field for a period of 20 s while the patient holds disturbing sensations and negative cognitions. EMDR incorporates validated components of other CBT modalities including exposure, cognitive restructuring, and processing of emotional responses to trauma cues. A review of dismantling studies of EMDR concluded that alternate stimuli can be substituted for the eye movement component with comparable treatment outcomes, and bilateral stimulation does not significantly influence treatment outcome (Spates and Koch [45]). Despite questions related to the role of eye movement, there is evidence

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supporting the efficacy of the EMDR package in the treatment of PTSD, and both the DOD and VA [12] and the International Society for Traumatic Stress Studies (Foa et al. [40]) list EMDR as a first-line option for the treatment of PTSD. There has been little focus on the effect EMDR has on sleep disturbance in PTSD. One study employing polysomnography to examine EMDR's effect on sleep in seven PTSD patients revealed significantly increased sleep efficiency and reduced wake time following sleep onset (Raboni et al. [46]).

Imagery Rehearsal for Nightmares in Posttraumatic Stress Disorder

The high prevalence of nightmares experienced by individuals with PTSD has prompted the application of imagery rehearsal (IR), initially developed to treat chronic nightmares in the general population, to individuals with PTSD (Krakow and Zadra [47]). There are numerous imagery-based protocols for reducing trauma-related nightmares, and these treatments generally include the patient choosing a repetitive distressing nightmare, changing some detail of that nightmare, and rehearsing the new version of the nightmare regularly (Gehrman and Harb [48]). IR can be administered in group or individual format.

IR has proven to be effective for the treatment of chronic nightmares in trauma survivors. Several studies have examined IR provided in a group format. In two separate studies, Krakow and colleagues (Krakow et al. [49–50]) provided three sessions of imagery rehearsal therapy (IRT), a specific IR protocol with the instruction to "change the nightmare in any way you wish" (Krakow et al. [49], p. 594). Both studies reported reduced frequency of nightmares, improved sleep quality, and decreased levels of PTSD symptoms. Forbes et al. provided six 90-minute individual sessions of IR, which was presented to participants as including their making "changes that promote mastery or control" [51] (p. 436) to their nightmares, to a sample of 12 Vietnam veterans with PTSD. This IR intervention resulted in decreases in the frequency of the target nightmare, PTSD symptom severity, and depression. Nappi et al. retrospectively examined records of veterans who completed five sessions of IR in which "therapists guided veterans in writing a highly detailed, vivid, and creative alternative ending [to the target nightmare] that did not elicit negative affect or include distressing content from the target nightmare" [52] (p. 239). The treatment, provided in group

or individual format, was associated with decreases in nightmare frequency and PTSD symptoms, as well as a significant decrease on one measure of insomnia severity. Lu et al. [53] provided group IR based on the Forbes et al. [51] protocol to a sample of 17 male veterans and found no posttreatment effects on nightmares or PTSD symptoms. However, total nights with trauma-related nightmares decreased at 3- and 6-month follow-up points compared with pretreatment, and PTSD symptoms decreased at the 3-month follow-up in the intent-to-treat sample. A large RCT compared IR, based on the treatment protocol used by Forbes et al. [51], to education and relaxation alone in a sample of 124 Vietnam veterans with chronic, severe PTSD. No differences between treatment and control groups were found in the intent-to-treat analysis in nightmare frequency, sleep quality, or PTSD symptoms (Cook et al. [54]).

The exact mechanism of change in IR is unclear. The most common explanation for its efficacy is that it promotes mastery of the content and images of the nightmare. Though instructions for IR vary widely, the general message that most protocols appear to convey is that patients should select a change to their target nightmare that decreases the negative content or changes the negative ending of the dream (Davis and Wright [55], Gehrman and Harb [48], Nappi et al. [52]), though there are protocols that specifically do not provide guidance on how to change the nightmare (Moore and Krakow [56]). "Mastery of the nightmare" is not a clearly defined construct, but appears to include two components: the recognition of an alternative ending for the nightmare that contains fewer negative connotations about the patient or the world in general, and a decrease in distress related to the nightmare. It should be noted that in one common protocol for exposure therapy for PTSD, one of the stated mechanisms of imaginal exposure (as told to the patient during presentation of treatment rationale) is promoting a sense of self-control and competence in relation to the trauma memory (Foa et al. [57]).

Another explanation for the efficacy of IR is that it facilitates exposure to the nightmare content. Research has indicated that simple *systematic desensitization*, without any change made to content, is helpful in reducing nightmare frequency (Cellucci and Lawrence [58]) and nightmare intensity (Miller and DiPilato [59]). In systematic desensitization protocols, the participant creates a hierarchy of distressing nightmare scenes, is taught relaxation, and then imagines the nightmares in the hierarchy (starting

with the least distressing nightmare), using relaxation whenever anxiety increases. Systematic desensitization has generally been investigated in participants with nightmare disorder but not specifically with PTSD-related nightmares. One study compared desensitization to IR and found no significant differences in effects on nightmare frequency but found that systematic desensitization resulted in a significant decrease in severity of emotions present when waking up from a nightmare while IR did not (Kellner et al. [60]). Though some IR protocols specifically attempt to minimize exposure, Gehrman and Harb [48] have pointed out that rehearsing a changed nightmare script still likely entails some imaginal exposure to the original distressing nightmare content.

It is also possible that IR of trauma-related nightmares facilitates changes in beliefs and meaning associated with the traumatic event. As noted previously, some protocols focus on specific trauma-related themes that are identified in the nightmares or emphasized in trauma-focused treatments (Davis and Wright [55], Swanson et al. [61]). The imagery rescripting and rehearsal procedures used to treat nightmares share some similarities with imagery rescripting and reprocessing treatments for trauma-related intrusive memories, and imagery rescripting and reprocessing is generally viewed as an imagery-based cognitive therapy (Grunert et al. [62], Smucker and Niederee [63]).

The Standards of Practice Committee of the American Academy of Sleep Medicine gave a Level A rating to "imagery rehearsal therapy," which appeared to include protocols by Krakow and colleagues (e.g., Krakow et al. [64]) as well as Forbes et al. [51] for the treatment of nightmare disorder (Aurora et al. [65]), and noted that "IRT appears to be effective in the management of nightmares exhibited in patients with PTSD as well as idiopathic nightmares" (p. 395). In published studies, IR protocols tend to be associated with improvements in nightmare frequency and intensity as well as PTSD symptoms. However, study samples sometimes include participants with nightmares who do not meet diagnostic criteria for PTSD, and most studies include, at best, wait-list control subjects (Nappi et al. [66]). Specific protocols appear to vary widely, and posttreatment scores on measures of PTSD symptoms and sleep problems often remain at clinically significant levels.

Cognitive-Behavioral Therapy for Insomnia

Nonpharmacologic, cognitive-behavioral interventions for the treatment of late-life insomnia have been found to be equal or superior to treatment with hypnotic pharmacologic agents alone or when combined with pharmacologic agents after 8 weeks of treatment and have longer-lasting benefits for up to 24 months following discontinuation of therapy (Morin et al. [67]). Two meta-analytic studies examining the effects of nonpharmacologic treatments on a combined 3,640 subjects with insomnia in the general population demonstrated significant benefit in measures of sleep continuity and subjective quality of sleep in both the short- and long-term (mean follow-up duration 6 months) (Morin et al. [68], Murtagh and Greenwood [69]). In the 2008 practice guideline of the American Academy of Sleep Medicine (Schutte-Rodin et al. [70]), it was recommended that cognitive-behavioral therapy for insomnia (CBTI) be considered effective in the treatment of insomnia, whether that insomnia appears to be "primary" in nature (i.e., unrelated to any other medical or psychiatric condition) or whether it appears to have been initially caused by, or appears to be maintained by, another medical or psychological condition.

CBTI comprises a combination of cognitive and behavioral techniques. *Stimulus control therapy* aims to eliminate conditioned arousal and strengthen the association between bed and sleep. It instructs patients to (1) go to bed only when sleepy, (2) maintain a consistent wake time, (3) get out of bed when unable to sleep, (4) use the bed only for sleep and sex, and (5) avoid napping. *Sleep restriction therapy* aims to consolidate sleep and increase the sleep drive. It instructs patients to decrease and then gradually increase allowed time in bed. *Relaxation training* (progressive muscle relaxation and diaphragmatic breathing exercises) aims to decrease arousal and promote relaxation. *Cognitive restructuring* identifies and modifies negative attitudes and beliefs about sleep and cognitions that interfere with adherence. *Sleep hygiene instructions* aim to eliminate sleep-interfering habits, such as minimizing consumption of substances that interfere with sleep (e.g., caffeine, nicotine, alcohol, and large meals close to or during the sleep period) and ensuring the sleep environment is conducive to sleep (dark, quiet, comfortable, and safe). In addition to the strong evidence in support of the combination of these therapy components, there is significant empirical support for the use of stimulus control and sleep restriction as monotherapies

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(Morin et al. [71]). Evidence for relaxation and sleep hygiene as single components is weak, and the efficacy of cognitive therapy alone has not been tested.

Research of the efficacy of CBTI in PTSD is in its early stages. DeViva et al. [44] found modest positive results providing a version of CBTI adapted to PTSD-related sleep problems to a small clinical sample of patients who had already completed trauma-focused CBT and shown good response. However, patients in this study did not meet diagnostic criteria for PTSD when they received the CBTI, and they already had a history of good response to CBT, thus limiting generalizability to the population of all patients with PTSD.

Combined Imagery Rehearsal and Cognitive-Behavioral Therapy for Insomnia

Several studies have examined IR with some elements of CBTI included in the treatment protocol. In a randomized clinical trial of exposure, relaxation, and rescripting therapy (ERRT), which includes stimulus control, progressive muscle relaxation, and IR encouraging participants "to utilize relevant themes" (p. 127) when changing nightmares, Davis and Wright [55] reported significant improvements in nightmare frequency and severity as well as in PTSD symptom severity in a sample of trauma survivors with nightmares, 66 percent of whom met diagnostic criteria for PTSD. However, Davis and Wright [55] found no improvements in total sleep time or measures of sleep quality. Krakow et al. [50] provided combined IRT and CBTI, including stimulus control, sleep restriction, and sleep hygiene components, to a group of 62 violent crime survivors with PTSD and found improvements in sleep quality and nightmare frequency, along with decreases in PTSD symptoms. Germain et al. [72] provided a single 90-minute session of instructions on IR, stimulus control, and sleep restriction along with a workbook to seven crime victims with PTSD and found that daytime PTSD symptoms, including intrusions and arousal, had significantly improved, but sleep measures had not, 6 weeks later. Swanson et al. [61] provided ten 90-minute groups to a small sample of veterans with PTSD, including five sessions of IR in which patients "rewrote the nightmare to address core themes" (p. 640) identified in other PTSD protocols such as CPT, as well as five sessions of CBTI including sleep restriction, stimulus control, sleep hygiene, cognitive restructuring, and relaxation. They found significant improvements on all measures of sleep

and no changes in posttraumatic symptoms. Ulmer et al. [73] provided combined IR and CBTI in individual format to 22 veterans and found improvements in nightmare frequency, questionnaire and sleep diary measures of sleep quality, and PTSD symptoms. Long et al. [74] found that six sessions of group IR combined with a session of exposure to the original nightmare resulted in improvements from pretreatment to posttreatment in nightmare frequency, sleep quantity, and PTSD symptoms in a sample of 37 veterans with PTSD. The treatment package added a week of exposure to the original unchanged nightmare account (writing the most distressing and/or frequent nightmare and reading it several times until anxiety decreases) and an extra week of rehearsal of the rescripted account, as well as additional unspecified "cognitive-behavior skills for sleep management" (p. 533), to the ERRT protocol of Davis and Wright [55].

Treatment Considerations

Any attempt to treat PTSD-related sleep disturbance needs to be driven by a broad case conceptualization that includes trauma history and PTSD symptoms in addition to sleep symptoms, sleep habits, sleep-related cognitions, nightmares, and other comorbid primary sleep disorders, such as OSA. The clinician should do a preliminary screen for comorbid sleep disorders and refer to a sleep clinic for further assessment and treatment when indicated. The clinician also needs to identify trauma-related factors that may contribute to the patient's presentation, including history of trauma in the sleep context, safety behaviors at night (e.g., perimeter checks, sleeping with a gun near the bed), and fear of losing vigilance (e.g., sleep avoidance).

As noted previously, little research has examined the efficacy of CBTI for PTSD-related sleep difficulties. Case report series and small controlled studies have indicated that CBTI alone, IR alone, and their combination can improve sleep and reduce the severity of PTSD symptoms. Therefore, the use of CBTI should be considered with most patients with PTSD-related insomnia. Adding IR to CBTI should also be considered when the patient experiences both insomnia and nightmares. Clinicians implementing CBTI with PTSD patients need to consider and address some unique aspects of this patient group. This includes addressing high levels of nighttime arousal that are unrelated to worries about sleep, safety-related behaviors and cognitions, maladaptive nighttime

vigilance behavior, and spending time awake during the night trying to figure out the meaning of dreams.

There are two situations in which it is best not to use CBTI and/or IR. The first is with patients who are undergoing or ready to engage in trauma-focused CBT for PTSD (either PE or CPT). This is because trauma-focused CBT is demanding and intensive and adding another therapy that requires behavioral changes may hinder adherence (Manber et al. [75]). Also, research reviewed here indicates that there is a reasonable chance that trauma-focused CBT will improve sleep. In addition, exposure to trauma memories and reprocessing of beliefs and attributions related to trauma are critical components of trauma-focused therapies and similar to the procedures employed in most IR protocols.

Patients who continue to report sleep disturbance after completing CBT for PTSD can then start CBTI. If there are persistent nightmares after trauma-focused CBT, IR may also be added to the treatment plan.

The second situation is the use of CBTI with PTSD-related insomnia with excessive daytime sleepiness, as is the case for PTSD patients with severe comorbid OSA. Sleep restriction therapy, a component of CBTI, is contraindicated when daytime sleepiness is severe because it poses a safety concern.

There is no published research on the best sequencing of IR and CBTI. Until this question is settled, the clinician is advised to weigh each case based on the relative contribution of nightmares to the patient's sleeplessness.

Future Directions

Though early data are promising, there have not been large RCTs to test the efficacy of CBTI for PTSD-related sleep problems (**Table 1**). Nonetheless, given the recommendation of the American Academy of Sleep Medicine supporting the use of CBTI for insomnia comorbid with other problems, the high prevalence of insomnia among veterans (including those with PTSD), the strong evidence for the efficacy of CBTI in primary insomnia, and the emerging evidence about its potential efficacy among PTSD patients, the DOD and VA have recently begun national dissemination projects to train large numbers of clinicians to administer CBTI. The CBTI protocol being disseminated takes into account the possibility that PTSD symptoms such as nocturnal hyperarousal and perceived need for vigilance may complicate standard application of CBTI (DeViva et al. [44]) and necessitate special adaptation of the standard CBTI protocol. The protocol is anchored in case conceptualization (e.g., Persons [76]), taking into account factors that contribute to each patient's unique presentation (Manber et al. [75]). Special considerations for the application of CBTI for patients with PTSD-related sleep problems include, among other things, cognitive therapy techniques such as cost-benefit analysis for addressing fear of going to sleep and presleep perimeter checks, methods for addressing hyperarousal, and interventions to decrease such maladaptive behavior following nightmare arousals as staying awake trying to figure out the meaning of a nightmare (Manber et al. [75]). The CBTI protocol adapted by the VA CBTI rollout did not include training in IR, in part because of limited evidence base for its use for the treatment of nightmares in combat-related PTSD and in part because complete training in CBT for insomnia that is comorbid with medical and psychiatric disorders is intensive and left little time for inclusion of treatment modules for other sleep disorders, including nightmare disorder.

Currently, there are no guidelines regarding the sequencing of CBTI and trauma-focused therapy. For example, it is not known what type or severity of posttraumatic symptoms may interfere with the administration of CBTI or reduce its efficacy. Similarly, it is not clear what types and severity levels of sleep-interfering posttraumatic symptoms require an augmentation of CBTI with specific trauma-focused therapy. It is also not known when combining CBTI and a trauma-focused treatment may be contraindicated, though the task force that developed the VA CBTI dissemination project recommends that for patients undergoing PE therapy, CBTI should be postponed until the end of PE and administered only when residual insomnia is present.

Pharmacologic Treatments of Insomnia and Nightmares in Posttraumatic Stress Disorder

The VA/DOD CPG [12] recommends nonpharmacologic treatments as the first-line treatments for insomnia and nightmares in PTSD. However, patients are not always accepting of nonpharmacologic treatments or may not experience sufficient symptom relief with treatments like CBTI and IR. In these circumstances, pharmacologic treatment has an important role in the treatment plan. While not all patients accept medication treatment for PTSD, it is the most common form of treatment for PTSD in the VA healthcare system. A review in 2004 of 274,297 VA patients with PTSD revealed 80 percent of this population was receiving a psychotropic agent

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Table 1.
Summary of studies of imagery rehearsal and cognitive-behavioral therapy for insomnia and nightmares in trauma survivors and individuals with posttraumatic stress disorder (PTSD).

Authors	Treatment Sample/Control	Treatment	Sleep Results	Nightmare Results	PTSD Symptom Results
Cook et al., 2010 [54]	124 VN veterans w/PTSD/ "sleep and NM management" control intervention	Same model as Forbes et al. [51]	No significant change	No significant change	No significant change
Davis & Wright, 2007 [55]	17 trauma survivors w/NMs, most diagnosed w/PTSD, delayed treatment control	Three 120 min groups; ERRT; participants "encouraged to utilize relevant themes" to change nightmares; SH/SC/PMR	Improvement on questionnaire subscale, restfulness after waking	Decreased NM frequency, intensity	Decrease in symptom severity, rate of diagnosis
Forbes et al., 2001 [51]	12 VN veterans w/PTSD, no control	Six 90 min groups; group discussed potential NM changes; goal was "alterations that promote mastery or control"	Not measured	Decreased target NM frequency, intensity; no change in other NMs	Decrease in symptom severity
Germain et al., 2007 [72]	7 adult crime victims w/PTSD, no control	One 90 min session; "participants were instructed to change NM they had had in any way they wanted"; SC/SR w/ workbook	No significant change	No significant change	Decrease in daytime intrusions & arousal
Krakow et al., 2000 [49]	169 women w/ PTSD from sexual assault, wait list control	Two 180 min group sessions, 1 60 min group session; "change NM any way you wish"	Improvement on questionnaire	Decreased NM frequency, nights w/NMs	Decrease in symptom severity
Krakow et al., 2001 [50]	60 females "predominantly consisting of sexual assault survivors w/PTSD," treatment as usual control	Same as Krakow et al. [49]	Improvement on questionnaire	Decreased NM frequency, nights w/NMs	Decrease in symptom severity
Krakow et al., 2001 [64]	62 assault or crime victims w/PTSD, no control	Three 180 min group sessions, 1 60 min group session; instructions to change NM "any way you wish"; SH/SC/SR	Improvement on two questionnaires	Decreased NM frequency, nights w/NMs	Decrease in symptom severity
Long et al., 2011 [74]	37 male veterans in PTSD program, no control	Six 90 min sessions, "cognitive-behavioral skills for sleep management," exposure to original NM; imagery rescripting based on ERRT of Davis & Wright [55]	Increased total sleep time	Decreased NM frequency	Decrease in symptom severity
Lu et al., 2009 [53]	15 veterans w/PTSD and trauma-related NMs at least weekly, no control	Same model as Forbes et al. [51]	No significant change	Decreased NM frequency, nights with NMs	Decrease in symptom severity
Nappi et al., 2010 [52]	35 veterans experiencing significant distress from recurrent NMs, most diagnosed w/PTSD, no control	Four or five 60 min individual or 120 min group sessions; instructions to change NM "any way you wish" but "identify and elaborate on an alternative, neutral, and/or pleasant ending…that [would] not elicit negative affect or include distressing content"	Improvement in one questionnaire, no change on another	Decreased NM frequency, intensity	Decrease in symptom severity
Swanson et al., 2009 [61]	8 veterans w/ PTSD & poor sleep, no control	Ten 90 min groups; 5 sessions CBTI, 5 sessions IR that "rewrote the nightmare to address core themes"	Large effect sizes on self-monitoring & questionnaire measures	Large effect sizes on NM frequency, distress	No significant change
Ulmer et al., 2011 [73]	22 veterans w/ PTSD diagnosis, positive screen for sleep disorder, endorsement of NMs; "usual care" control	Six 60 min individual sessions, 3 session of IR instructing participants to "change NM in any way they liked"; 3 sessions of SC/SR/SH/CR	Significant improvements on self-monitoring & questionnaire measures	Decreased NM frequency	Decrease in symptom severity

CBTI = cognitive-behavioral therapy for insomnia; CR = cognitive restructuring; ERRT = exposure, relaxation, and rescripting therapy; IR = imagery rehearsal; NM = nightmare; SC = stimulus control; SH = sleep hygiene; SR = sleep restriction; PMR = progressive muscle relaxation; VN = Vietnam; w/ = with.

(Mohamed and Rosenheck [77]). The distribution of classes of medication prescribed was antidepressants 89 percent; anxiolytics/sedative hypnotics 64 percent; and antipsychotics 34 percent. It is suggested this substantial use of medication is "due to the targeting of specific symptoms of PTSD and comorbid disorders rather than being based on diagnosis." Despite the extensive use of medications to treat PTSD sleep-related symptoms, there are limited controlled studies to inform clinicians on how to best prescribe medication for insomnia and nightmares. It is also important to note that successful treatment of comorbid medical conditions that contribute to sleep disturbance like PLMD, RBD, OSA, chronic pain, gastresophageal reflux disease, and benign prostatic hypertrophy (BPH) can obviate the need for psychotropic medications, including sedative hypnotics. Over the past 20 years, there has been a growing body of research examining medication efficacy for the full spectrum of PTSD signs and symptoms. This review will focus on the effect pharmacologic treatment has on the sleep component of the symptom presentation.

Antidepressant Agents

Selective serotonin reuptake inhibitors. The SSRIs are the most commonly prescribed medication for the treatment of PTSD. Large RCTs conducted with sertraline (Brady et al. [78], Davidson et al. [79]) and paroxetine (Marshall et al. [80]) resulted in U.S. Food and Drug Administration approval for their use with PTSD. The effect size for overall symptom relief is modest, $d = 0.3–0.4$. The VA/DOD CPG [12] recommends sertraline and paroxetine as first-line treatments for PTSD. The effect SSRIs have upon sleep quality and nightmares is inconsistent. Overall sleep quality is reported to be improved with SSRIs, but it is important to note that individuals taking SSRIs also report insomnia as a side effect. SSRIs can increase arousals from sleep, decrease total sleep time, and suppress REM sleep (Singareddy and Balon [81]). SSRIs frequently require augmentation with another medication to help unresponsive sleep disturbances or to counteract the effect SSRIs may have in contributing to the sleep disturbance. There have been few studies with SSRIs in which measuring the effect upon sleep quality has been the primary objective. One study with fluvoxamine that had a small sample size focused on its effects on sleep in patients with PTSD (Neylan et al. [82]). Fluvoxamine improved all domains of sleep quality with a large effect on combat-related dreams. How-

ever, fluvoxamine is seldom used in PTSD treatment because of its side-effect profile relative to its efficacy.

Serotonin antagonist/reuptake inhibitors. The drugs in this class are serotonin (5-HT)-potentiating non-SSRIs. They have been shown to improve sleep disturbance in PTSD in small uncontrolled clinical trials. Nefazodone prescribed at doses of 500–600 mg per day to 10 Vietnam combat veterans with PTSD had a strong effect on nightmares ($d = 1.43$) and total sleep time ($d = 1.95$) (Neylan et al. [83]). Increased sleep maintenance and increased slow-wave sleep were also demonstrated by polysomnography in the same study. It is important to note that nefazodone has a black box warning because of the rare but potentially serious adverse effect of hepatotoxicity. Trazodone is one of the most commonly prescribed medications for the treatment of PTSD sleep disturbances. It is thought to be helpful for insomnia secondary to SSRIs because its mechanism of action counters the $5\text{-}HT_2$ agonist effects of SSRIs. It is generally well tolerated at low doses (50–200 mg/night). A survey of 74 veterans with PTSD found trazodone's effect on insomnia and nightmares to be extremely helpful for sleep disruption in 88 percent and for nightmares in 72 percent of the population (Warner et al. [84]). Despite the extensive use of trazodone, there have been no RCTs to demonstrate its efficacy for insomnia related to PTSD, and research in primary insomnia (Roth et al. [85]) raises concern about impairments of short-term memory, verbal learning, and motor skills. Cyproheptadine has antihistamine as well as $5\text{-}HT_2$ antagonist actions. Initial open clinical trials reported benefit for PTSD-related sleep disturbance. But a well-controlled trial found cyproheptadine was not effective for PTSD sleep disturbance and may have exacerbated sleep problems (Jacobs-Rebhun et al. [86]).

Antidepressants with mixed receptor mechanism of action. Mirtazapine has $5\text{-}HT_2$ and $5\text{-}HT_3$ antagonist, α_1-antagonist, and antihistamine mechanisms of action. This mechanism of action profile offers promise that mirtazapine can enhance sleep quality. Mirtazapine was reported to reduce the frequency and intensity of nightmares in 75 percent of a series of more than 300 refugees who experienced "catastrophic stress levels" (Lewis [87]). The one controlled clinical trial of mirtazapine treatment for PTSD reported improved PTSD symptoms and associated anxiety but did not specifically measure the effects upon the sleep of the 29 subjects in the study (Davidson et al. [88]). Mirtazapine carries a significant

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risk for weight gain, which in addition to other health risks can also increase the risk for new onset and exacerbation of sleep apnea (Serretti and Mandelli [89]). Venlafaxine enhances 5-HT, norepinephrine, and D activity. Venlafaxine is recommended by the VA/DOD CPG [12] as a first-line treatment for PTSD. Venlafaxine's effectiveness for the treatment of PTSD was demonstrated in a large ($N = 329$) multinational RCT (Davidson et al. [90]). Sleep quality measures were not reported in this study. There were significant improvements in the PTSD re-experiencing and avoidance/numbing clusters but not for hyperarousal. This would suggest venlafaxine may have been helpful for nightmares but not for improving sleep onset or maintenance. However, the Standards of Practice Committee of the American Academy of Sleep Medicine does not recommend venlafaxine for the treatment of nightmares in adults (Aurora et al. [65]) based on the findings in a pooled analysis of the Clinician-Administered PTSD Scale (CAPS) on 687 patients with PTSD treated with venlafaxine (Stein et al. [91]). There was no significant difference between venlafaxine and placebo in effect on distressing dreams and difficulty in falling and staying asleep.

Tricyclic antidepressants. Imipramine, amitriptyline, and desipramine have mixed norepinephrine and 5-HT enhancement as their mechanism of action. All have been tested for efficacy in PTSD in older, small, randomized trials (Frank et al. [92], Davidson et al. [93], Reist et al. [94]). There was modest re-experiencing and hyperarousal symptom improvement from imipramine ($d = 0.25$), moderate improvement for amitriptyline ($d = 0.64$), and no benefit from desipramine ($d = 0.05$). Amitriptyline and imipramine may be prescribed at low doses for sleep disturbance in PTSD, but the evidence for their efficacy is sparse and their potential toxicity, including increased risk for cardiac conduction disturbances and anticholinergic activity that can worsen symptoms of BPH by causing frequent awakening due to nocturia, makes them limited in their utility.

Monoamine oxidase inhibitors. Phenelzine is the MAOI most studied and used for the treatment of PTSD. In a comparative review, MAOIs were found to be more effective than TCAs for the treatment of PTSD (Southwick et al. [95]). Phenelzine was used to treat Israeli combat veterans with PTSD. Improvement in sleep disturbance was the only symptom with a clinically impressive change (Lerer et al. [96]). The MAOIs are limited in their utility because of the dietary and drug restrictions needed to avoid the associated risk for hypertensive crisis.

Anxiolytic and Sedative Hypnotic Agents

Hypnotic drugs are recommended as a second-line approach to the management of insomnia in PTSD by the VA/DOD CPG [12].

Benzodiazepines. Benzodiazepines (BZs) bind to BZ binding sites within the γ-aminobutyric acid (GABA)-A (GABA$_A$) receptor resulting in GABA central nervous system inhibitory activity. Although widely prescribed for the treatment of PTSD, especially for PTSD sleep disturbance, BZs have not been found to be helpful in preventing the development of PTSD or improving intrusion, avoidance, and numbing symptoms. There have been remarkably few studies examining the efficacy of BZs for PTSD sleep disturbances. This is especially true for long-term efficacy. One small study examined the short-term effects of clonazepam on PTSD-related sleep disturbances and found no improvement (Cates et al. [97]). The VA/DOD CPG [12] does not recommended BZs for long-term (>1 month) or short-term use for the treatment of PTSD because of lack of demonstrated efficacy, the substantial prevalence of alcohol and substance abuse in veterans with PTSD, and the risk for developing habituation and dependence. A meta-analysis of sedative hypnotic treatment for insomnia in a general population of individuals (2,417) over the age of 60 concluded that in using BZs the benefits were marginal and outweighed by the risks, which included cognitive and psychomotor impairment, daytime fatigue, falls, and motor vehicle accidents (Glass et al. [98]).

Benzodiazepine receptor agonists. This class of drugs selectively binds to the BZ omega-1 site within the GABA$_A$ receptor to produce sedation but with minimal anticonvulsant and muscle relaxant action compared to the BZs. These drugs are considered to be preferable to the BZs by the VA/DOD CPG [12] as a second-line treatment for PTSD-related insomnia because of their shorter half-life, slower development of tolerance, lower risk for withdrawal reactions, and lower risk for dependence. The fact that hypnotic agents with a short half-life confer an increased risk for acute confusional states needs to be taken into consideration in treatment choice and management during treatment. An RCT of 788 individuals with primary insomnia treated nightly with eszopiclone, a member of this class, demonstrated sustained efficacy in a number of measures of sleep continuity, with no evidence of tolerance, withdrawal symptoms, or rebound insomnia upon completion of the study (Krystal et al. [99]). However, studies of the efficacy of this class of drugs for

treating PTSD sleep disorder are limited. A case series of veterans with PTSD treated with zolpidem reported improvement in insomnia and nightmares that was sustained for more than 1 year in some cases (Dieperink and Drogemuller [100]). Controlled studies are needed to objectively demonstrate the utility of this class of drugs for PTSD sleep disturbance.

Antipsychotic Agents

The atypical antipsychotic agents are becoming more frequently used as an adjunctive treatment, especially for insomnia, in PTSD patients not responding to first-line antidepressant treatment. The VA/DOD CPG [12] does not recommend the use of atypical antipsychotics for sleep disturbance in PTSD because of the potential for adverse events relative to the benefits for this indication. The atypical antipsychotics can be considered in cases of associated psychosis, agitation, and severe unremitting PTSD symptoms.

Olanzapine. Olanzapine has $5\text{-}HT_2$ and D_2 antagonism as its mechanisms of action. Olanzapine had a strong effect size ($d = 1.07$) in reducing overall PTSD symptoms and significantly improved sleep ($p = 0.01$) in a double-blind RCT of adjunctive treatment to SSRI nonresponders in a veteran population (Stein et al. [101]). Olanzapine should be used with caution because of its risk for producing weight gain and inducing new-onset diabetes mellitus.

Quetiapine. Quetiapine has $5\text{-}HT_2$, D_2, and α_1-andrenergic antagonism with antihistamine properties as its mechanisms of action. This profile results in a sedating drug that is being used frequently at low doses (25–100 mg) for this purpose in the VA healthcare system. In a VA study of the off-label use of all antipsychotic medication prescriptions written during 2007, 10.6 percent of veterans with PTSD were given at least one prescription of quetiapine during the course of the year (Leslie et al. [102]). A retrospective chart review of 125 veterans treated with adjunctive quetiapine at low doses (155 ± 130 mg) found there was much or very much improved sleep in 62 percent and decreased nightmares in 25 percent with "minimal" side effects in this series (Sokolski et al. [103]). However, other studies point out that quetiapine's potential for adverse effects, even at low doses, especially a significant increase in weight gain (Williams et al. [104]) and body mass index (Cates et al. [105]), limit its usefulness for treating sleep disturbances.

Risperidone. Risperidone has $5\text{-}HT_2$, D_2, and α_1-andrenergic antagonism as its mechanisms of action. Reports of risperidone's utility as an adjunctive PTSD treatment for nonresponders to other pharmacologic agents date back to 1998. In a 2008 study, 25 civilians with PTSD who did not fully respond to a course of treatment with sertraline were placed in an RCT with risperidone (Rothbaum et al. [106]). The risperidone group had significantly more improvement in sleep ($p = 0.03$) than the control group. The VA has subsequently completed a 6-month multisite RCT of risperidone augmentation in a SRRI treatment-resistant population of 247 veterans with combat-related PTSD (Krystal et al. [107]). The main outcome measures were the CAPS, Montgomery-Asberg Depression Rating Scale, Hamilton Anxiety Scale, Clinical Global Impression scale, and 36-Item Short Form Health Survey for Veterans. The Pittsburg Sleep Quality Index (PSQI) was also used as a measure. At the conclusion of treatment, when compared with placebo, risperidone did not reduce overall PTSD, depression, or anxiety symptoms and was associated with more frequent side effects in this population of veterans. The pretreatment PSQI scores were high (a mean of 13.6 for the placebo group and 13.9 for the risperidone group). The results from a secondary analysis determining the effect of treatment on the PSQI score have not yet been published.

Adrenergic Inhibiting Agents

Guanfacine. α_2-adrenergic receptor agonists such as guanfacine act at noradrenergic autoreceptors to inhibit the firing of noradrenergic neurons, effectively inhibiting the release of brain norepinephrine. Based on some promising open trials in treating PTSD patients with clonidine, another agent in this class, a small RCT with guanfacine was conducted to confirm the clonidine findings (Neylan et al. [108]). Guanfacine has the advantage of being longer acting than clonidine and thus is better tolerated. The study found no differences between guanfacine and placebo in all measures of PTSD symptoms, including sleep disturbance. This class of adrenergic inhibiting agents is now seldom used to treat PTSD sleep disturbances and is not recommended in the VA/DOD CPG [12].

Prazosin. In contrast to guanfacine, prazosin specifically has an α_1-receptor antagonist mechanism of action. Prazosin was initially noted in 2003 to be helpful for PTSD sleep disturbance, including nightmares, in a small controlled study of combat veterans (Raskind et al.

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[109]). Subsequent larger studies with a more specific focus on PTSD sleep disturbance, especially nightmares, have confirmed the earlier findings with large effect sizes for improvement in sleep quality ($d = 1.0$) and distressing dreams ($d = 0.94$) (Raskind et al. [110]). Examination of nightmare content found a shift from threatening content of actual past combat events to more "normal" dream content. The mechanism by which prazosin relieves nightmares is unknown. Dr. Raskind proposes a model explaining prazosin's effectiveness: (1) PTSD nightmares occur during light sleep and disrupted REM sleep, (2) light sleep is increased by stimulation of central nervous system α_1-receptors, and (3) prazosin's inhibitory effect on α_1-receptors decreases light sleep and normalizes REM sleep. Prazosin was tested in a population of civilians with PTSD in a RCT that also included nonpolysomnographic measurement of REM activity in the patient's home (Taylor et al. [111]). The significant improvement in sleep quality and reduction in frequency and quality of nightmares noted in the studies of combat-related PTSD were repeated in this civilian population. Also notable was an associated increase in mean REM duration and total REM sleep time. PTSD is commonly associated with TBI. The VA Cleveland Polytrauma Center conducted a carefully designed observational study with a group of 74 Operation Iraqi Freedom/Operation Enduring Freedom veterans exposed to an explosion in combat, with mild TBI characterized by residual headaches and cognitive deficits (Ruff et al. [112]). Of the group, 71 were comorbid for PTSD. Only 5 of the group reported restful sleep. Prazosin, tapered up to a treatment dose of 7 mg at bedtime, and sleep hygiene counseling were given over a 9-week period to determine whether this approach would improve sleep, headaches, and cognitive function. All members of the group completed sleep hygiene counseling, and 62 remained on prazosin for the full 9-week period. Those veterans who remained on prazosin had more restful sleep, decreased intensity and frequency of headaches, and improvement in cognition. Six months following the start of treatment, 64 veterans in the group were taking prazosin. The improvements observed at 9 weeks were maintained at 6 months. Prazosin was well tolerated. The investigators hypothesize that improvement in sleep was a significant factor in the improvement of TBI-related headache and cognition. A controlled study is needed to verify these promising findings in this challenging to treat population. Prazosin, while generally well tolerated, can cause dizzi-

ness, fainting, drowsiness, decreased energy, and headache. The mean dose in treatment studies was approximately 10 mg daily. It is best to start with a low dose (1 mg) and slowly increase the dose as tolerated until symptom relief occurs. Based on the studies conducted up to this time, prazosin is recommended by the Standards of Practice Committee of the American Academy of Sleep Medicine as the first-line pharmacologic treatment of PTSD-associated nightmares (Aurora et al. [65]). The VA/DOD CPG [12] recommends prazosin as an adjunctive treatment for cases in which severe nightmares remain unresponsive to first-line treatment (i.e., SSRIs). More investigation using objective measures is needed to understand the effect prazosin has on sleep architecture and how this correlates with the reported improvement in sleep quality and nightmare reduction. A proposal for such a study in a VA population of combat veterans with PTSD using home polysomnography and actigraphy (measurement of sleep-wake time through body movement) is currently under review.

Treatment Considerations

Pharmacologic treatment should be guided by the principal of using the least complex approach to achieve the broadest relief of signs and symptoms. The SSRIs (sertraline and paroxetine) and the selective norepinephrine reuptake inhibitor, venlafaxine, are recommended as a first-line pharmacologic treatment for PTSD by the VA/DOD CPG [12] based on large RCTs. Many patients experience a global improvement in PTSD symptoms, including sleep disturbance. Only in cases in which these first-line medications are not well tolerated or do not significantly relieve PTSD symptoms, including sleep disturbances, should other medications be considered. There is evidence that mirtazapine and nefazodone are helpful for PTSD-related sleep disturbances and can be considered as single-agent alternatives to the SSRIs or venlafaxine. However, mirtazapine can cause significant weight gain that may cause or exacerbate sleep apnea, and nefazodone needs to be used with caution because of the rare but serious risk of liver damage. Trazodone is infrequently used as a single agent to relieve global PTSD symptoms because of the sedation and postural hypotension it produces at full antidepressant doses. The TCAs and MAOIs are seldom used as single-agent alternatives for the treatment of PTSD because of their side-effect profiles. In circumstances in which sleep disturbance continues despite otherwise successful CBT or

antidepressant treatment, adjunctive medications should be considered. There is evidence from clinical observation and polysomnography that trazodone at low doses (up to 200 mg at bedtime) is helpful in improving sleep quality. It can be prescribed long-term without the risk of developing tolerance to its effects. Prazosin is an α-1 inhibiting agent, has the strongest evidence of any medication for the relief of nightmares, and is recommended by the VA/DOD CPG [12] as an adjunctive agent for this purpose. Prazosin can also be used alone to treat nightmares and insomnia. Other adrenergic inhibiting agents, such as guanfacine, have not proven to be helpful for this indication. The antipsychotic quetiapine is commonly used to treat sleep disturbance, but it and other antipsychotic agents are not recommended by the VA/DOD CPG [12] because of their poor risk to benefit ratio for this indication. Finally, BZs are not recommended for the short- or long-term treatment of sleep disturbance in PTSD by the VA/DOD CPG [12] because of a lack of proven efficacy and the risks for habituation and dependence. The BZ receptor agonists such as zolpidem and eszopiclone are a safer alternative to the BZs with regard to habituation and dependence. At this time, given the limited evidence for their efficacy in PTSD-related sleep disturbance, it is prudent to prescribe them for short-term use (days to weeks) on a schedule of 3–5 days a week (**Table 2**).

CONCLUSIONS

Nightmares and insomnia are common, persistent, and significant problems in individuals with PTSD. Commonly occurring comorbid conditions such as depression, substance abuse, anxiety, TBI, other sleep disorders, and chronic pain can further contribute to sleep disturbance. A comprehensive assessment of the contributing factors to the sleep disturbance is needed so that the clinician can optimize treatment and decide when referral for additional consultation and treatment may be indicated. In order to arrive at an accurate diagnosis and optimize treatment, the assessment should also include a detailed review of the nature of the presenting sleep problem, including sleep habits, associated daytime symptoms, and thought patterns that may contribute to the problem or to adherence with treatment recommendations.

CBT for PTSD does not always successfully relieve insomnia or nightmares. CBTs designed to specifically treat insomnia and nightmares, such as CBTI and IRT, offer promise for a more robust improvement in PTSD sleep disturbances. CBT has been demonstrated to be at least as or more effective and with more sustained benefit than medication treatment for sleep disturbance and is considered the first-line treatment for PTSD-related sleep disturbances by the VA/DOD CPG [12]. The VA rollout of CBTI is focused on training mental health providers in the VA to provide CBTI and therefore will make CBTI more accessible to veterans. By providing an individual with skills to master symptoms that have been very distressing, CBTI can also help address demoralization that is commonly experienced by traumatized individuals. Anecdotal reports suggest that successful treatment of insomnia with CBTI may help prepare veterans to engage in trauma-focused therapy, though this possibility has not been tested.

Despite the fact that nonpharmacologic treatments are considered the first-line treatments for PTSD-related sleep disturbances, medication treatments have an important place in the management of insomnia and nightmares in PTSD. Medication can be used as the sole treatment or as an adjunct to CBTI or IRT. There is a need for RCTs comparing the relative efficacy of pharmacotherapy combined with CBTI and/or IRT as well as RCTs to compare the relative sequencing of pharmacological and nonpharmacological treatments for improving sleep in patients with PTSD. Medication treatment studies designed to assess the overall response of PTSD symptoms infrequently assess the effects of treatment on insomnia and nightmares. Antidepressant agents are recommended as the initial choice for treating the full range of PTSD symptoms. The anxiolytic and sedative hypnotic agents would appear to be a logical choice for treating sleep disturbances that do not respond to antidepressant treatment. However, the BZs, while commonly prescribed for PTSD sleep disturbance, are judged not to have long-term benefit and carry the risk for potential harm from habituation and dependence. Antipsychotic agents such as quetiapine are also commonly prescribed for treating sleep disturbances, but their adverse effects significantly reduce their utility, and they are not recommended by the VA/DOD CPG [12] for this indication. Prazosin is one of the few medications in this review that has been studied specifically to determine its effect on PTSD-related sleep disturbances. The VA/DOD CPG [12] recommends prazosin as an adjunctive treatment for PTSD nightmares unresponsive to CBT and/or antidepressant treatment.

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Table 2.
Summary of pharmacologic treatment for insomnia and nightmares in trauma survivors and individuals with posttraumatic stress disorder (PTSD).

Pharmacologic Agent	Study Design	Sleep Results	NM Results	PTSD Results	Treatment Considerations
SSRIs	Multiple large RCTs w/sertraline, paroxetine, & fluoxetine. Small open trial w/fluvoxamine.	Overall improvement in sleep quality but w/significant individual variation.	Limited data from large RCTs. Fluvoxamine helped relieve combat-related dreams.	Significant overall Sx improvement w/modest effect size in large RCTs.	VA/DOD CPG recommends SSRIs as 1st line Tx for overall PTSD, including sleep disturbance.
Venlafaxine	Large RCT (Davidson et al.).	Not reported in Davidson et al. No difference compared w/placebo in large pooled analysis study.	Not reported in Davidson et al. No difference compared w/ placebo in large pooled analysis study.	Significant improvement in re-experiencing, avoidance/numbing but not hyperarousal Sxs.	VA/DOD CPG recommends venlafaxine as 1st line Tx for overall PTSD. Not recommended by the AASM for Tx of NMs.
Mirtazapine	Small controlled trial (Davidson et al.). Large case series.	Not reported in Davidson et al. Not reported in case series.	Not reported in Davidson et al. Reduced frequency & intensity of NMs in case series.	More effective than placebo on some measures of PTSD.	May be helpful for PTSD-related sleep disturbance, but does carry significant risk for weight gain.
Nefazodone	Small uncontrolled clinical trials. One trial included polysomnography.	Improved sleep maintenance, total sleep time, & SWS.	Reduced frequency of NMs.	Improved overall PTSD Sxs.	May be helpful for PTSD-related sleep disturbance. Carries rare but serious risk for hepatotoxicity & is not recommended by AASM for Tx of NMs.
Trazodone	Small RCT w/ polysomnography (Roth et al.). VA survey of effects upon insomnia.	Decreased midsleep awakenings, increased sleep maintenance & SWS. Improved sleep disruption for 88% of pts.	Effect on NMs not reported in RCT. Helpful for NMs in 72% of pts.	Limited data on its effectiveness for overall PTSD Sxs.	Use is primarily limited to Tx of sleep disturbance because of side effects at higher doses. Listed in VA/DOD CPG as one of hypnotic agents to consider for PTSD-related sleep disturbance.
TCAs	Three small RCTs.	Little information about benefit for sleep.	Little information about benefit for NMs.	Amitriptyline & imipramine helped re-experiencing & arousal but not avoidant/numbing symptoms. Desipramine no better than placebo.	Not mentioned by VA/DOD CPG as option for Tx of sleep disturbance. Carry risk for cardiac conduction problems & anticholinergic side effects.
MAOIs	Phenelzine is most studied MAOI. Small RCT & open trials.	Phenelzine improved sleep in open trial.	Little information about benefit for NMs.	MAOIs more effective than TCAs for PTSD in comparative review.	Usefulness is limited by side effects & need for dietary restrictions to avoid hypertensive crisis.

Table 2. (cont)

Summary of pharmacologic treatment for insomnia and nightmares in trauma survivors and individuals with posttraumatic stress disorder (PTSD).

Pharmacologic Agent	Study Design	Sleep Results	NM Results	PTSD Results	Treatment Considerations
Prazosin (α_1- adrenergic receptor antagonist)	RCTs in veteran (Raskind et al.) & civilian populations (Taylor et al.).	Significant improvement in sleep quality. Large effect size ($d = 1.0$). Significant increase in total sleep time.	Significant reduction in frequency and intensity of NMs. Large effect size ($d = 0.94$). Significant reduction in frequency of NMs.	Efficacy for overall PTSD Sxs has not been established.	Recommended by VA/DOD CPG as adjunctive agent for Tx of NMs. Recommended by AASM as 1st line Tx of PTSD-associated NMs.
Guanfacine (α_2-adrenergic receptor agonist)	Small RCT in veterans w/PTSD (Neylan et al.).	No difference in sleep quality compared w/placebo.	Effect on NMs not measured.	No more effective than placebo for overall PTSD Sxs.	Not effective for treatment of PTSD, including sleep disturbance.
BZs	Placebo-controlled cross-over trial w/6 combat veterans (Cates et al.).	Ineffective in improving sleep quality.	Ineffective in relieving NMs.	No benefit for re-experiencing & avoidance/numbing Sxs.	Not recommended by VA/DOD CPG due to concerns about significant risk for dependence.
BZ Receptor Agonists	Large 6 mo RCT w/eszopiclone for primary insomnia (Krystal et al.). Case series of 3 combat veterans w/PTSD.	Significant improvement in sleep onset, awakenings, total sleep time, & quality of sleep. Improved insomnia.	NMs were not studied. Improved NMs.	No reports on effectiveness of these agents for overall PTSD Sxs.	VA/DOD CPG suggests using this class of drug as hypnotic agent rather than BZs due to their shorter half-life and lower risk for dependence.
Antipsychotic Agents	Multiple RCTs as adjunctive agents PTSD Tx. Risperidone largest RCT (Krystal et al.). Chart review for adjunctive use of quetiapine.	Olanzapine improved sleep. Risperidone study did not report sleep results. Quetiapine improved sleep.	NMs were not studied in olanzapine trial. Quetiapine reduced NM frequency by 25%.	Olanzapine improved overall PTSD Sxs. Risperidone did not reduce overall PTSD, depression, or anxiety Sxs.	VA/DOD CPG recommends that all antipsychotics are to be avoided for Tx of sleep disturbance due to their poor risk to benefit ratio for this indication.

AASM = American Academy of Sleep Medicine, BZ = benzodiazepine, CPG = clinical practice guideline, DOD = Department of Defense, MAOI = monoamine oxidase inhibitor, NM = nightmare, pts = patients, RCT = randomized controlled trial, SSRI = selective serotonin reuptake inhibitor, Sx = symptom, SWS = slow-wave sleep, TCA = tricyclic antidepressant, Tx = treatment, VA = Department of Veterans Affairs.

Sleep disturbance in PTSD has been an ongoing challenge for clinicians treating traumatized individuals. Progress has been made in identifying treatments that provide relief from the suffering associated with insomnia and nightmares. CBT and some pharmacologic treatments offer relief. However, even when using best practices, insomnia and nightmares may not fully resolve in all patients, suggesting the need to develop treatments that are even more specific to the unique features of PTSD sleep disturbances.

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REFERENCES

1. Koren D, Arnon I, Lavie P, Klein E. Sleep complaints as early predictors of posttraumatic stress disorder: a 1-year prospective study of injured survivors of motor vehicle accidents. Am J Psychiatry. 2002;159(5):855–57. [PMID:11986142] http://dx.doi.org/10.1176/appi.ajp.159.5.855

2. Harvey AG, Bryant RA. The relationship between acute stress disorder and posttraumatic stress disorder: a prospective evaluation of motor vehicle accident survivors. J Consult Clin Psychol. 1998;66(3):507–12. [PMID:9642889] http://dx.doi.org/10.1037/0022-006X.66.3.507

3. Mellman TA, Pigeon WR, Nowell PD, Nolan B. Relationships between REM sleep findings and PTSD symptoms during the early aftermath of trauma. J Trauma Stress. 2007;20(5):893–901. [PMID:17955526] http://dx.doi.org/10.1002/jts.20246

4. Maher MJ, Rego SA, Asnis GM. Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact and approaches to management. CNS Drugs. 2006;20(7):567–90. [PMID:16800716] http://dx.doi.org/10.2165/00023210-200620070-00003

5. Neylan TC, Marmar CR, Metzler TJ, Weiss DS, Zatzick DF, Delucchi KL, Wu RM, Schoenfeld FB. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatry. 1998;155(7):929–33. [PMID:9659859]

6. Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. Sleep Med Rev. 2008;12(3):185–95. [PMID:17997114] http://dx.doi.org/10.1016/j.smrv.2007.09.003

7. Horne JA. Human sleep, sleep loss and behaviour. Implications for the prefrontal cortex and psychiatric disorder. Br J Psychiatry. 1993;162:413–19. [PMID:8453439] http://dx.doi.org/10.1192/bjp.162.3.413

8. Walker MP. The role of sleep in cognition and emotion. Ann N Y Acad Sci. 2009;1156:168–97. [PMID:19338508] http://dx.doi.org/10.1111/j.1749-6632.2009.04416.x

9. Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. Psychophysiology. 2007;44(4):660–69. [PMID:17521374] http://dx.doi.org/10.1111/j.1469-8986.2007.537.x

10. Breslau N, Roth T, Burduvali E, Kapke A, Schultz L, Roehrs T. Sleep in lifetime posttraumatic stress disorder: a community-based polysomnographic study. Arch Gen Psychiatry. 2004;61(5):508–16. [PMID:15123496] http://dx.doi.org/10.1001/archpsyc.61.5.508

11. Neylan TC, Lenoci M, Maglione ML, Rosenlicht NZ, Metzler TJ, Otte C, Schoenfeld FB, Yehuda R, Marmar CR. Delta sleep response to metyrapone in post-traumatic stress disorder. Neuropsychopharmacology. 2003;28(9): 1666–76. [PMID:12799616] http://dx.doi.org/10.1038/sj.npp.1300215

12. Management of Post-Traumatic Stress Working Group [Internet]. VA/DOD clinical practice guidelines for management of post-traumatic stress. Washington (DC): Department of Veterans Affairs, Department of Defense; 2010. Available from: http://www.healthquality.va.gov/ptsd/ptsd_full.pdf

13. Schreuder BJ, van Egmond M, Kleijn WC, Visser AT. Daily reports of posttraumatic nightmares and anxiety dreams in Dutch war victims. J Anxiety Disord. 1998; 12(6):511–24. [PMID:9879032] http://dx.doi.org/10.1016/S0887-6185(98)00032-2

14. Kaminer H, Lavie P. Sleep and dreaming in Holocaust survivors. Dramatic decrease in dream recall in well-adjusted survivors. J Nerv Ment Dis. 1991;179(11):664–69. [PMID:1940889] http://dx.doi.org/10.1097/00005053-199111000-00003

15. Sjöström N, Hetta J, Waern M. Persistent nightmares are associated with repeat suicide attempt: a prospective study. Psychiatry Res. 2009;170(2–3):208–11. [PMID:19900715] http://dx.doi.org/10.1016/j.psychres.2008.09.006

16. Tanskanen A, Tuomilehto J, Viinamäki H, Vartiainen E, Lehtonen J, Puska P. Nightmares as predictors of suicide. Sleep. 2001;24(7):844–47. [PMID:11683487]

17. Zayfert C, DeViva JC. Residual insomnia following cognitive behavioral therapy for PTSD. J Trauma Stress. 2004;17(1):69–73. [PMID:15027796] http://dx.doi.org/10.1023/B:JOTS.0000014679.31799.e7

18. Mellman TA, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. Am J Psychiatry. 1995;152(1):110–15. [PMID:7802100]

19. Brown TM, Boudewyns PA. Periodic limb movements of sleep in combat veterans with posttraumatic stress disorder. J Trauma Stress. 1996;9(1):129–36. [PMID:8750456] http://dx.doi.org/10.1002/jts.2490090111

20. Hening WA, Allen RP, Earley CJ, Picchietti DL, Silber MH; Restless Legs Syndrome Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep. 2004;27(3):560–83. [PMID:15164915]

21. Winkelman JW, Bogan RK, Schmidt MH, Hudson JD, DeRossett SE, Hill-Zabala CE. Randomized polysomnography study of gabapentin enacarbil in subjects with restless legs syndrome. Mov Disord. 2011;26(11):2065–72.

[PMID:21611981]
http://dx.doi.org/10.1002/mds.23771

22. Nofzinger EA, Fasiczka A, Berman S, Thase ME. Bupropion SR reduces periodic limb movements associated with arousals from sleep in depressed patients with periodic limb movement disorder. J Clin Psychiatry. 2000; 61(11):858–62. [PMID:11105739]
http://dx.doi.org/10.4088/JCP.v61n1108

23. Yang C, White DP, Winkelman JW. Antidepressants and periodic leg movements of sleep. Biol Psychiatry. 2005; 58(6):510–14. [PMID:16005440]
http://dx.doi.org/10.1016/j.biopsych.2005.04.022

24. Cohrs S, Rodenbeck A, Hornyak M, Kunz D. [Restless legs syndrome, periodic limb movements, and psychopharmacology]. Nervenarzt. 2008;79(11):1263–64, 1266–72.
[PMID:18958441]
http://dx.doi.org/10.1007/s00115-008-2575-2

25. Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, Benarroch EE, Ahlskog JE, Smith GE, Caselli RC, Tippman-Peikert M, Olson EJ, Lin SC, Young T, Wszolek Z, Schenck CH, Mahowald MW, Castillo PR, Del Tredici K, Braak H. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain. 2007;130(Pt 11):2770–88.
[PMID:17412731]
http://dx.doi.org/10.1093/brain/awm056

26. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain. 2000;123(Pt 2):331–39.
[PMID:10648440]
http://dx.doi.org/10.1093/brain/123.2.331

27. Thomas A, Bonanni L, Onofrj M. Symptomatic REM sleep behavior disorder. Neurol Sci. 2007;28:21–36.
http://dx.doi.org/10.1007/s10072-007-0735-y

28. Winkelman JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia. Sleep. 2004; 27(2):317–21. [PMID:15124729]

29. Husain AM, Miller PP, Carwile ST. Rem sleep behavior disorder: potential relationship to post-traumatic stress disorder. J Clin Neurophysiol. 2001;18(2):148–57.
[PMID:11435805]
http://dx.doi.org/10.1097/00004691-200103000-00005

30. Ross RJ, Ball WA, Sullivan KA, Caroff SN. Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry. 1989;146(6):697–707. [PMID:2658624]

31. Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med. 2003;4(4):281–84.
[PMID:14592300]
http://dx.doi.org/10.1016/S1389-9457(03)00072-8

32. Lurie A. Obstructive sleep apnea in adults: epidemiology, clinical presentation, and treatment options. Adv Cardiol. 2011;46:1–42. [PMID:22005188]
http://dx.doi.org/10.1159/000327660

33. Sharafkhaneh A, Giray N, Richardson P, Young T, Hirshkowitz M. Association of psychiatric disorders and sleep apnea in a large cohort. Sleep. 2005;28(11):1405–11.
[PMID:16335330]

34. Krakow B, Lowry C, Germain A, Gaddy L, Hollifield M, Koss M, Tandberg D, Johnston L, Melendrez D. A retrospective study on improvements in nightmares and post-traumatic stress disorder following treatment for co-morbid sleep-disordered breathing. J Psychosom Res. 2000; 49(5):291–98. [PMID:11164053]
http://dx.doi.org/10.1016/S0022-3999(00)00147-1

35. El-Solh AA, Ayyar L, Akinnusi M, Relia S, Akinnusi O. Positive airway pressure adherence in veterans with post-traumatic stress disorder. Sleep. 2010;33(11):1495–1500.
[PMID:21102991]

36. Youakim JM, Doghramji K, Schutte SL. Posttraumatic stress disorder and obstructive sleep apnea syndrome. Psychosomatics. 1998;39(2):168–71. [PMID:9584544]
http://dx.doi.org/10.1016/S0033-3182(98)71365-9

37. Belleville G, Guay S, Marchand A. Persistence of sleep disturbances following cognitive-behavior therapy for post-traumatic stress disorder. J Psychosom Res. 2011;70(4): 318–27. [PMID:21414451]
http://dx.doi.org/10.1016/j.jpsychores.2010.09.022

38. Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. Psychiatr Clin North Am. 1987;10(4):541–53. [PMID:3332317]

39. Perlis ML, Jungquist C, Smith MT, Posner D. Cognitive Behavioral Treatment of Insomnia: A session-by-session guide. New York (NY): Springer; 2005.

40. Foa EB, Keane TM, Friedman MJ, Cohen JA, editors. Effective treatments for PTSD: Practice guidelines from the International Society for Traumatic Stress Studies, 2nd edition. New York (NY): Guilford Press; 2009.

41. Cooper NA, Clum GA. Imaginal flooding as a supplementary treatment for PTSD in combat veterans—a controlled study. Behav Ther. 1989;20(3):381–91.
http://dx.doi.org/10.1016/S0005-7894(89)80057-7

42. Galovski TE, Monson C, Bruce SE, Resick PA. Does cognitive-behavioral therapy for PTSD improve perceived health and sleep impairment? J Trauma Stress. 2009; 22(3):197–204. [PMID:19466746]
http://dx.doi.org/10.1002/jts.20418

43. Nishith P, Duntley SP, Domitrovich PP, Uhles ML, Cook BJ, Stein PK. Effect of cognitive behavioral therapy on heart rate variability during REM sleep in female rape victims with PTSD. J Trauma Stress. 2003;16(3):247–50.
[PMID:12816336]
http://dx.doi.org/10.1023/A:1023791906879

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SCHOENFELD et al. Review of treatment of PTSD sleep disturbances

44. DeViva JC, Zayfert C, Pigeon WR, Mellman TA. Treatment of residual insomnia after CBT for PTSD: case studies. J Trauma Stress. 2005;18(2):155–59. [PMID:16281208] http://dx.doi.org/10.1002/jts.20015

45. Spates CR, Koch E. From eye movement desensitization and reprocessing to exposure therapy: a review of the evidence for shared mechanisms. Jpn J Behav Anal. 2003; 18(2):62–75.

46. Raboni MR, Tufik S, Suchecki D. Treatment of PTSD by eye movement desensitization reprocessing (EMDR) improves sleep quality, quality of life, and perception of stress. Ann N Y Acad Sci. 2006;1071:508–13. [PMID:16891609] http://dx.doi.org/10.1196/annals.1364.054

47. Krakow B, Zadra A. Clinical management of chronic nightmares: imagery rehearsal therapy. Behav Sleep Med. 2006;4(1):45–70. [PMID:16390284] http://dx.doi.org/10.1207/s15402010bsm0401_4

48. Gehrman PR, Harb GC. Treatment of nightmares in the context of posttraumatic stress disorder. J Clin Psychol. 2010;66(11):1185–94. [PMID:20865767] http://dx.doi.org/10.1002/jclp.20730

49. Krakow B, Hollifield M, Schrader R, Koss M, Tandberg D, Lauriello J, McBride L, Warner TD, Cheng D, Edmond T, Kellner R. A controlled study of imagery rehearsal for chronic nightmares in sexual assault survivors with PTSD: a preliminary report. J Trauma Stress. 2000;13(4): 589–609. [PMID:11109233] http://dx.doi.org/10.1023/A:1007854015481

50. Krakow B, Hollifield M, Johnston L, Koss M, Schrader R, Warner TD, Tandberg D, Lauriello J, McBride L, Cutchen L, Cheng D, Emmons S, Germain A, Melendrez D, Sandoval D, Prince H. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. JAMA. 2001;286(5):537–45. [PMID:11476655] http://dx.doi.org/10.1001/jama.286.5.537

51. Forbes D, Phelps A, McHugh T. Treatment of combat-related nightmares using imagery rehearsal: a pilot study. J Trauma Stress. 2001;14(2):433–42. [PMID:11469167] http://dx.doi.org/10.1023/A:1011133422340

52. Nappi CM, Drummond SP, Thorp SR, McQuaid JR. Effectiveness of imagery rehearsal therapy for the treatment of combat-related nightmares in veterans. Behav Ther. 2010;41(2):237–44. [PMID:20412888] http://dx.doi.org/10.1016/j.beth.2009.03.003

53. Lu M, Wagner A, Van Male L, Whitehead A, Boehnlein J. Imagery rehearsal therapy for posttraumatic nightmares in U.S. veterans. J Trauma Stress. 2009;22(3):236–39. [PMID:19444882] http://dx.doi.org/10.1002/jts.20407

54. Cook JM, Harb GC, Gehrman PR, Cary MS, Gamble GM, Forbes D, Ross RJ. Imagery rehearsal for posttraumatic nightmares: a randomized controlled trial. J Trauma Stress. 2010;23(5):553–63. [PMID:20839311] http://dx.doi.org/10.1002/jts.20569

55. Davis JL, Wright DC. Randomized clinical trial for treatment of chronic nightmares in trauma-exposed adults. J Trauma Stress. 2007;20(2):123–33. [PMID:17427914] http://dx.doi.org/10.1002/jts.20199

56. Moore BA, Krakow B. Imagery Rehearsal Therapy: An emerging treatment for posttraumatic nightmares in veterans. Psychol Trauma. 2010;2(3):232–38. http://dx.doi.org/10.1037/a0019895

57. Foa EB, Hembree EA, Rothbaum BO. Prolonged exposure therapy for PTSD: Emotional processing of traumatic experiences (therapist guide). New York (NY): Oxford University Press; 2007.

58. Cellucci AJ, Lawrence P. The efficacy of systematic desensitization in reducing nightmares. J Behav Ther Exp Psychiary. 1978;9:109–14. http://dx.doi.org/10.1016/0005-7916(78)90054-X

59. Miller WR, DiPilato M. Treatment of nightmares via relaxation and desensitization: a controlled evaluation. J Consult Clin Psychol. 1983;51(6):870–77. [PMID:6140275] http://dx.doi.org/10.1037/0022-006X.51.6.870

60. Kellner R, Neidhardt J, Krakow B, Pathak D. Changes in chronic nightmares after one session of desensitization or rehearsal instructions. Am J Psychiatry. 1992;149(5):659–63. [PMID:1349459]

61. Swanson LM, Favorite TK, Horin E, Arnedt JT. A combined group treatment for nightmares and insomnia in combat veterans: a pilot study. J Trauma Stress. 2009; 22(6):639–42. [PMID:19908322]

62. Grunert BK, Weis JM, Smucker MR, Christianson HF. Imagery rescripting and reprocessing therapy after failed prolonged exposure for post-traumatic stress disorder following industrial injury. J Behav Ther Exp Psychiatry. 2007;38(4):317–28. [PMID:18037391] http://dx.doi.org/10.1016/j.jbtep.2007.10.005

63. Smucker MR, Niederee JL. Treating incest-related PTSD and pathogenic schemas through imaginal exposure and rescripting. Cogn Behav Pract. 1995;2:63–93. http://dx.doi.org/10.1016/S1077-7229(05)80005-7

64. Krakow B, Johnston L, Melendrez D, Hollifield M, Warner TD, Chavez-Kennedy D, Herlan MJ. An open-label trial of evidence-based cognitive behavior therapy for nightmares and insomnia in crime victims with PTSD. Am J Psychiatry. 2001;158(12):2043–47. [PMID:11729023] http://dx.doi.org/10.1176/appi.ajp.158.12.2043

65. Aurora RN, Zak RS, Auerbach SH, Casey KR, Chowdhuri S, Karippot A, Maganti RK, Ramar K, Kristo DA, Bista SR, Lamm CI, Morgenthaler TI; Standards of Practice Committee; American Academy of Sleep Medicine. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 2010;6(4):389–401. [PMID:20726290]

66. Nappi CM, Drummond SP, Hall JM. Treating nightmares and insomnia in posttraumatic stress disorder: a review of current evidence. Neuropharmacology. 2012;62(2):576–85. [PMID:21396945] http://dx.doi.org/10.1016/j.neuropharm.2011.02.029

67. Morin CM, Colecchi C, Stone J, Sood R, Brink D. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. JAMA. 1999;281(11):991–99. [PMID:10086433] http://dx.doi.org/10.1001/jama.281.11.991

68. Morin CM, Culbert JP, Schwartz SM. Non-pharmacological interventions for insomnia: a meta-analysis of treatment efficacy. Am J Psychiatry. 1994;51:1172–80.

69. Murtagh DR, Greenwood KM. Identifying effective psychological treatments for insomnia: a meta-analysis. J Consult Clin Psychol. 1995;63(1):79–89. [PMID:7896994] http://dx.doi.org/10.1037/0022-006X.63.1.79

70. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med. 2008; 4(5):487–504. [PMID:18853708]

71. Morin CM, Hauri PJ, Espie CA, Spielman AJ, Buysse DJ, Bootzin RR. Nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine review. Sleep. 1999;22(8):1134–56. [PMID:10617176]

72. Germain A, Shear MK, Hall M, Buysse DJ. Effects of a brief behavioral treatment for PTSD-related sleep disturbances: a pilot study. Behav Res Ther. 2007;45(3):627–32. [PMID:16777060] http://dx.doi.org/10.1016/j.brat.2006.04.009

73. Ulmer CS, Edinger JD, Calhoun PS. A multi-component cognitive-behavioral intervention for sleep disturbance in veterans with PTSD: a pilot study. J Clin Sleep Med. 2011;7(1):57–68. [PMID:21344046]

74. Long ME, Hammons ME, Davis JL, Frueh BC, Khan MM, Elhai JD, Teng EJ. Imagery rescripting and exposure group treatment of posttraumatic nightmares in Veterans with PTSD. J Anxiety Disord. 2011;25(4):531–35. [PMID:21354767] http://dx.doi.org/10.1016/j.janxdis.2010.12.007

75. Manber R, Carney C, Edinger J, Epstein D, Friedman L, Haynes PL, Karlin BE, Pigeon W, Siebern AT, Trockel M. Dissemination of CBTI to the non-sleep specialist: proto-col development and training issues. J Clin Sleep Med. 2012;8(2):209–18. [PMID:22505869]

76. Persons JB. Empiricism, mechanism, and the practice of cognitive-behavioral therapy. Behav Ther. 2005;36:107–18. http://dx.doi.org/10.1016/S0005-7894(05)80059-0

77. Mohamed S, Rosenheck RA. Pharmacotherapy of PTSD in the U.S. Department of Veterans Affairs: diagnostic- and symptom-guided drug selection. J Clin Psychiatry. 2008;69(6):959–65. [PMID:18588361] http://dx.doi.org/10.4088/JCP.v69n0611

78. Brady K, Pearlstein T, Asnis GM, Baker D, Rothbaum B, Sikes CR, Farfel GM. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. JAMA. 2000;283(14):1837–44. [PMID:10770145] http://dx.doi.org/10.1001/jama.283.14.1837

79. Davidson JR, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. Arch Gen Psychiatry. 2001;58(5):485–92. [PMID:11343529] http://dx.doi.org/10.1001/archpsyc.58.5.485

80. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. Am J Psychiatry. 2001;158(12):1982–88. [PMID:11729013] http://dx.doi.org/10.1176/appi.ajp.158.12.1982

81. Singareddy RK, Balon R. Sleep in posttraumatic stress disorder. Ann Clin Psychiatry. 2002;14(3):183–90. [PMID:12585568] http://dx.doi.org/10.3109/10401230209147455

82. Neylan TC, Metzler TJ, Schoenfeld FB, Weiss DS, Lenoci M, Best SR, Lipsey TL, Marmar CR. Fluvoxamine and sleep disturbances in posttraumatic stress disorder. J Trauma Stress. 2001;14(3):461–67. [PMID:11534878] http://dx.doi.org/10.1023/A:1011100420978

83. Neylan TC, Lenoci M, Maglione ML, Rosenlicht NZ, Leykin Y, Metzler TJ, Schoenfeld FB, Marmar CR. The effect of nefazodone on subjective and objective sleep quality in posttraumatic stress disorder. J Clin Psychiatry. 2003;64(4):445–50. [PMID:12716248] http://dx.doi.org/10.4088/JCP.v64n0415

84. Warner MD, Dorn MR, Peabody CA. Survey on the usefulness of trazodone in patients with PTSD with insomnia or nightmares. Pharmacopsychiatry. 2001;34(4):128–31. [PMID:11518472] http://dx.doi.org/10.1055/s-2001-15871

85. Roth AJ, McCall WV, Liguori A. Cognitive, psychomotor and polysomnographic effects of trazodone in primary insomniacs. J Sleep Res. 2011;20(4):552–58. [PMID:21623982] http://dx.doi.org/10.1111/j.1365-2869.2011.00928.x

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86. Jacobs-Rebhun S, Schnurr PP, Friedman MJ, Peck R, Brophy M, Fuller D. Posttraumatic stress disorder and sleep difficulty. Am J Psychiatry. 2000;157(9):1525–26. [PMID:10964881] http://dx.doi.org/10.1176/appi.ajp.157.9.1525

87. Lewis JD. Mirtazapine for PTSD nightmares. Am J Psychiatry. 2002;159(11):1948–49. [PMID:12411239] http://dx.doi.org/10.1176/appi.ajp.159.11.1948-a

88. Davidson JR, Weisler RH, Butterfield MI, Casat CD, Connor KM, Barnett S, van Meter S. Mirtazapine vs. placebo in posttraumatic stress disorder: a pilot trial. Biol Psychiatry. 2003;53(2):188–91. [PMID:12547477] http://dx.doi.org/10.1016/S0006-3223(02)01411-7

89. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry. 2010;71(10):1259–72. [PMID:21062615] http://dx.doi.org/10.4088/JCP.09r05346blu

90. Davidson J, Baldwin D, Stein DJ, Kuper E, Benattia I, Ahmed S, Pedersen R, Musgnung J. Treatment of post-traumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. Arch Gen Psychiatry. 2006;63(10):1158–65. [PMID:17015818] http://dx.doi.org/10.1001/archpsyc.63.10.1158

91. Stein DJ, Pedersen R, Rothbaum BO, Baldwin DS, Ahmed S, Musgnung J, Davidson J. Onset of activity and time to response on individual CAPS-SX17 items in patients treated for post-traumatic stress disorder with venlafaxine ER: a pooled analysis. Int J Neuropsychopharmacol. 2009;12(1):23–31. [PMID:18544181] http://dx.doi.org/10.1017/S1461145708008961

92. Frank JB, Kosten TR, Giller EL Jr, Dan E. A randomized clinical trial of phenelzine and imipramine for posttraumatic stress disorder. Am J Psychiatry. 1988;145(10): 1289–91. [PMID:3048121]

93. Davidson JR, Kudler HS, Smith R, Mahorney SL, Lipper S, Hammett E, Saunders WB, Cavenar JO Jr. Treatment of posttraumatic stress disorder with amitriptyline and placebo. Arch Gen Psychiatry. 1990;47(3):259–66. [PMID:2407208] http://dx.doi.org/10.1001/archpsyc.1990.01810150059010

94. Reist C, Kauffmann CD, Haier RJ, Sangdahl C, DeMet EM, Chicz-DeMet A, Nelson JN. A controlled trial of desipramine in 18 men with posttraumatic stress disorder. Am J Psychiatry. 1989;146(4):513–16. [PMID:2648867]

95. Southwick SM, Giller YR, et al. Use of tricyclics and monoamine oxidase inhibitors in the treatment of post-traumatic stress disorder: a quantitative review. In: Murburg MM, editor. Catecholamine function in post-traumatic stress disorder: Emerging concepts. Arlington (VA): American Psychiatric Press; 1994.

96. Lerer B, Bleich A, Kotler M, Garb R, Hertzberg M, Levin B. Posttraumatic stress disorder in Israeli combat veterans. Effect of phenelzine treatment. Arch Gen Psychiatry. 1987;44(11):976–81. [PMID:3314769] http://dx.doi.org/10.1001/archpsyc.1987.01800230056010

97. Cates ME, Bishop MH, Davis LL, Lowe JS, Woolley TW. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. Ann Pharmacother. 2004;38(9):1395–99. [PMID:15252193] http://dx.doi.org/10.1345/aph.1E043

98. Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ. 2005; 331(7526):1169–75. [PMID:16284208] http://dx.doi.org/10.1136/bmj.38623.768588.47

99. Krystal AD, Walsh JK, Laska E, Caron J, Amato DA, Wessel TC, Roth T. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. Sleep. 2003;26(7):793–99. [PMID:14655910]

100. Dieperink ME, Drogemuller L. Zolpidem for insomnia related to PTSD. Psychiatr Serv. 1999;50(3):421. [PMID:10096658]

101. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiatry. 2002;159(10): 1777–79. [PMID:12359687] http://dx.doi.org/10.1176/appi.ajp.159.10.1777

102. Leslie DL, Mohamed S, Rosenheck RA. Off-label use of antipsychotic medications in the Department of Veterans Affairs health care system. Psychiatr Serv. 2009;60(9): 1175–81. [PMID:19723731] http://dx.doi.org/10.1176/appi.ps.60.9.1175

103. Sokolski KN, Denson TF, Lee RT, Reist C. Quetiapine for treatment of refractory symptoms of combat-related posttraumatic stress disorder. Mil Med. 2003;168(6):486–89. [PMID:12834142]

104. Williams SG, Alinejad NA, Williams JA, Cruess DF. Statistically significant increase in weight caused by low-dose quetiapine. Pharmacotherapy. 2010;30(10):1011–15. [PMID:20874038] http://dx.doi.org/10.1592/phco.30.10.1011

105. Cates ME, Jackson CW, Feldman JM, Stimmel AE, Woolley TW. Metabolic consequences of using low-dose quetiapine for insomnia in psychiatric patients. Community Ment Health J. 2009;45(4):251–54. [PMID:19472052] http://dx.doi.org/10.1007/s10597-009-9200-0

106. Rothbaum BO, Killeen TK, Davidson JR, Brady KT, Connor KM, Heekin MH. Placebo-controlled trial of risperidone augmentation for selective serotonin reuptake inhibitor-resistant civilian posttraumatic stress disorder.

J Clin Psychiatry. 2008;69(4):520–25. [PMID:18278987]
http://dx.doi.org/10.4088/JCP.v69n0402

107. Krystal JH, Rosenheck RA, Cramer JA, Vessicchio JC, Jones KM, Vertrees JE, Horney RA, Huang GD, Stock C; Veterans Affairs Cooperative Study No. 504 Group. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. JAMA. 2011;306(5):493–502. [PMID:21813427]
http://dx.doi.org/10.1001/jama.2011.1080

108. Neylan TC, Lenoci M, Samuelson KW, Metzler TJ, Henn-Haase C, Hierholzer RW, Lindley SE, Otte C, Schoenfeld FB, Yesavage JA, Marmar CR. No improvement of post-traumatic stress disorder symptoms with guanfacine treatment. Am J Psychiatry. 2006;163(12):2186–88. [PMID:17151174]
http://dx.doi.org/10.1176/appi.ajp.163.12.2186

109. Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, Dobie DJ, Hoff D, Rein RJ, Straits-Tröster K, Thomas RG, McFall MM. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry. 2003;160(2):371–73. [PMID:12562588]
http://dx.doi.org/10.1176/appi.ajp.160.2.371

110. Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Shofer J, O'Connell J, Taylor F, Gross C, Rohde K, McFall ME. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry. 2007;61(8):928–34 [PMID:17069768]
http://dx.doi.org/10.1016/j.biopsych.2006.06.032

111. Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, Peskind ER, Raskind MA. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry. 2008;63(6):629–32. [PMID:17868655]
http://dx.doi.org/10.1016/j.biopsych.2007.07.001

112. Ruff RL, Ruff SS, Wang XF. Improving sleep: initial headache treatment in OIF/OEF veterans with blast-induced mild traumatic brain injury. J Rehabil Res Dev. 2009;46(9):1071–84. [PMID:20437313]
http://dx.doi.org/10.1682/JRRD.2009.05.0062