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Treating Nightmares and Insomnia in Posttraumatic Stress Disorder: A Review of Current Evidence

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Abstract

Emerging evidence supports the notion of disrupted sleep as a core component of Posttraumatic Stress Disorder (PTSD). Effective treatments for nighttime PTSD symptoms are critical because sleep disruption may be mechanistically linked to development and maintenance of PTSD and is associated with significant distress, functional impairment, and poor health. This review aimed to describe the state of science with respect to the impact of the latest behavioral and pharmacological interventions on posttraumatic nightmares and insomnia. Published studies that examined evidence for therapeutic effects upon sleep were included. Some behavioral and pharmacological interventions show promise, especially for nightmares, but there is a need for controlled trials that include valid sleep measures and are designed to identify treatment mechanisms. Our ability to treat PTSD-related sleep disturbances may be improved by moving away from considering sleep symptoms in isolation and instead conducting integrative studies that examine sequential or combined behavioral and/or pharmacological treatments targeting both the daytime and nighttime aspects of PTSD.

Keywords

Posttraumatic Stress Disorder; sleep; nightmares; insomnia

1. INTRODUCTION

Nightmares and insomnia are some of the most ubiquitous, distressing, and chronic symptoms of Posttraumatic Stress Disorder (PTSD). Subjective reports of these symptoms are well documented (Spoormaker and Montgomery, 2008) and recent studies substantiate their impact upon objectively assessed sleep quality and continuity(Calhoun et al., 2007; Kobayashi et al., 2007; Westermeyer et al., 2007; Woodward et al., 2000).

Effective treatment of posttraumatic sleep symptoms is important for several reasons. Although temporal relationships between trauma exposure, PTSD, and sleep disruption are

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complex (Babson and Feldner, 2010), emerging evidence lends support to the notion of disrupted sleep as a core component of PTSD (Spoormaker and Montgomery, 2008), linked mechanistically to its development and maintenance(Germain et al., 2008; Ross et al., 1989). Multiple processes may explain the role of disturbed sleep in the developmental pathology of PTSD. Some of these include underlying neurobiological alterations (Germain et al., 2008), compromised generalization of fear extinction secondary to sleep deprivation (Pace-Schott et al., 2009), disruption of sleep-dependent processing of emotional experiences (Walker and van Der Helm, 2009), and repeated resensitization to trauma cues during nightmares (Rothbaum and Mellman, 2001). These plausible mechanistic processes explain the ways in which nightmares and insomnia can interfere with natural recovery from trauma exposure (Babson and Feldner, 2010), contribute to the development of PTSD, and compromise response to evidence-based treatments.

More simply, treating sleep disruption in PTSD is important because nightmares and insomnia are associated with significant distress and daytime impairment(Clum et al., 2001; Kramer et al., 2003; Neylan et al., 1998; Wittmann et al., 2000; Zammit et al., 1999). For example, to the extent trauma-related nightmares or a lack of sleep increase reactivity to emotional cues (Franzen et al., 2009; Yoo et al., 2007), one's ability to function in social and occupational roles may be compromised (Zohar et al., 2005). Furthermore, sleep impairment in general is associated with negative psychiatric outcomes across a range of populations, including increased suicidal ideation(Liu, 2003; Nishith et al., 2001), while sleep fragmentation and deprivation are correlated with neurocognitive deficits (Drummond et al., 2006) and neuroendocrine abnormalities (Knutson and Van Cauter, 2008). Thus, effectively addressing the nighttime PTSD symptom profile may contribute to improved functional outcomes and overall well-being.

Finally, to the extent sleep impairment in PTSD is experienced as distressing, it may serve as a motivation for treatment engagement in a disorder otherwise characterized by avoidance behavior. The absence of relief for that which motivated treatment may promote hopelessness and diminish willingness to participate in future treatment. By contrast, effective treatment of sleep disturbance in this context may lead to subsequent engagement in evidence-based trauma-focused treatments.

In light of the critical need for effective treatments, the primary goal of this paper is to describe the state of science with respect to the impact of the latest behavioral and pharmacological interventions on sleep symptoms in PTSD. Our focus is on the two most common forms of sleep disturbances in PTSD: nightmares and insomnia. It should be noted that the term "nightmare" in this review refers to the PTSD re-experiencing symptom of recurring distressing dreams. Similarly, our use of the term "insomnia" here does not refer to the formal diagnosis of insomnia as specified in the Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR) or the International Classification of Sleep Disorders (ICSD). Rather, we use the term "insomnia" to refer to the hyperarousal-related sleep difficulties experienced in PTSD. While in many cases these would meet criteria for insomnia, many of the studies reviewed focused on enrolling patients with PTSD, without utilizing sleep-specific criteria beyond those required for the diagnosis of PTSD and thus likely include sub-threshold insomnia, as well. We will discuss interventions designed to

treat PTSD more generally, recognizing such reports are often based upon secondary analysis of single-items extracted from PTSD measures, as well as studies with sleep as a primary outcome. This overview of the evidence will identify promising interventions and suggest avenues for future investigation leading to more refined and effective treatments for disrupted sleep in PTSD.

2. EFFECTS OFBEHAVIORAL PTSD TREATMENTS UPON POSTTRAUMATIC NIGHTMARES AND INSOMNIA

Evidence-based, trauma-focused behavioral treatments for PTSD are validated for overall PTSD symptomatology (Foa et al., 2007; Resick and Schnicke, 1993). The extent to which they ameliorate posttraumatic sleep disturbances is less clear because sleep outcomes are rarely examined. The studies reviewed here are the only ones that we know of to report treatment effects upon sleep, though only a small fraction employed current, standardized treatment protocols (e.g., Galovski et al., 2009)and only two reported validated measures of sleep.

A retrospective review of data from 27 patients no longer meeting criteria for PTSD following trauma-focused cognitive behavioral therapy (Zayfert and DeViva, 2004) is often cited to substantiate the refractory nature of sleep difficulties following PTSD treatment. In this study, sleep disturbances were assessed using single-items (difficulty sleeping and distressing dreams) from the Clinician Administered PTSD Scale (CAPS). Approximately half of the sample endorsed difficulty sleeping following treatment, the majority of which reported clinically significant insomnia. Only one PTSD symptom (anger) was reported with greater frequency than insomnia following treatment. At post-treatment, nightmares were among the least frequently endorsed symptom indicating a significant decrease in this sleep disturbance even among those participants that continued to endorse insomnia. Findings from this study are limited because validated sleep measures were not used. Nevertheless, this is the only study to examine relative frequency of symptoms post-treatment.

Cooper and Clum (1989) examined effectiveness of imaginal exposure (“flooding”) therapy as an adjunct to treatment as usual for PTSD among Veterans (N =14). This study used a new and admittedly unvalidated subscale of sleep disturbance. The treatment group demonstrated significant improvements in difficulty sleeping and hours of sleep per week relative to the control group. Nevertheless, the treatment group, per self-report, was only sleeping a mean of 6.1 and 5.7 hours per week at post-treatment and follow-up, respectively. Of note, all participants in the treatment group reported elimination of or greater than 50% reduction in nightmares, a significant decrease relative to the control group. By contrast, in a slightly larger study (N = 24; (Keane et al., 1989) of the same therapy, there was no detected treatment effect for sleep disturbance (assessed by one item on a PTSD symptom checklist). Re-experiencing symptoms significantly improved; however, effects upon nightmares specifically were not reported. Two waitlist control studies examined effects of distinct treatments (both of which included exposure-based components) upon sleep difficulties (Gersons et al., 2000; Lange et al., 2003) and findings were similarly discrepant (see Spoormaker& Montgomery, 2008).

The effects of Eye Movement Desensitization and Reprocessing (EMDR) therapy (Shapiro, 2001) upon sleep outcomes were reported in two studies. While validity of the theoretical underpinning of EMDR has been questioned (McNally, 1999), some theorize (Stickgold, 2002) this standardized behavioral treatment reduces PTSD to the extent it induces a neurobiological state similar to REM sleep, a period during which emotional-memory processing is theorized to occur (Walker and van Der Helm, 2009). Based upon this rationale, Raboni et al. examined effects of EMDR upon sleep quality using polysomnography(Raboni et al., 2006). This is the only study of behavioral PTSD treatment to include an objective measure of sleep as a primary outcome. Participants (N = 7) demonstrated significant decreases from pre-treatment to one-week post-treatment on PSG sleep onset latency and wake after sleep onset. Unfortunately, as highlighted by Spoormaker and Montgomery (2008), findings may be largely attributed to habituation because PSG results from the first night were used as a baseline (there is a well known disruption in sleep during the first night in a lab known as “the first night effect”). Subjective sleep measures that may have corroborated objective findings were not included and nightmares were not assessed. The second study of EMDR (Vaughan et al., 1994) demonstrated significant decreases on a 1-item assessment of nightmares relative to control groups, although effects on sleep quality or quantity were not reported.

In the largest study to date (N = 108) to examine effects of evidence-based behavioral treatment for PTSD upon a validated sleep measure, significant improvements on all scales of the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) were reported 2-weeks and 9-months following treatment with either Cognitive Processing Therapy (CPT) or Prolonged Exposure (PE) (Galovski et al., 2009). Nevertheless, PSQI scores remained in the clinically significant range for all participants, despite both treatments reducing overall PTSD symptoms and related mental health problems. Effects upon nightmares were not reported. Findings from this study are noteworthy because it is the only study to report changes in sleep in response to the most current and validated behavioral treatment protocols for PTSD.

Taken together, findings are inconsistent with regard to effectiveness of empirically supported behavioral PTSD treatments for reducing insomnia. When detected, improvements in difficulty sleeping appear small relative to improvements in other PTSD symptoms (Spoormaker and Montgomery, 2008) and nonclinical levels of sleep quality or quantity are not achieved. Although rarely reported, effects of these treatments upon nightmares appear promising for treatment responders. It should be noted that only one of the reviewed studies used a validated subjective measure of sleep quality (Galovski et al., 2009) and only one employed an objective measure (Raboni et al., 2006). These measurement issues compromise the validity of conclusions regarding the extent to which posttraumatic sleep disturbances remit following standard evidence-based PTSD treatments and constitute an important direction for future research.

3. BEHAVIORAL TREATMENTS FOR POSTTRAUMATIC NIGHTAMRES

Some authors havesuggested nightmares become a distinct and co-occurring syndrome during the course of PTSD (Spoormaker et al., 2006). At first glance, data such as that

reported by Forbes et al. (2001) suggest this may be the case. In this study, 77% of Veterans who completed a 3-month intensive inpatient program for PTSD reported persisting trauma-related nightmares for which they sought further treatment (Forbes et al., 2001). However, the mean total CAPS score of this sample was 85.3 indicating endorsement of several PTSD symptoms. In fact, there is no evidence, to date, suggesting nightmares are uniquely refractory to treatment. By contrast, as reviewed above, some evidence suggests nightmares are significantly reduced for those patients that respond to evidence-based behavioral PTSD treatments in general (Cooper and Clum, 1989; Vaughan et al., 1994; Zayfert and DeViva, 2004).

Nevertheless, nightmares are one of the most frequently reported and distressing PTSD symptoms (Nappi et al., 2010a) and, thus, may be a motivator for treatment engagement. Moreover, some evidence suggests nightmares reported immediately after a traumatic event correlate with development of PTSD (Mellman et al., 2001). Thus, treatment focused upon this symptom, or on sleep in general, holds potential to promote further engagement in treatment and may diminish the likelihood one will develop PTSD.

3.1. Imagery Rehearsal Therapy (IRT) for Posttraumatic Nightmares

IRT is a short-term treatment that integrates psychoeducation on nightmares, instruction on and experiential exercises of imagery, and a cognitive restructuring imagery technique. Although a standardized treatment protocol has not been used across studies, IRT typically excludes formal exposure to nightmare content beyond completion of a one-time written description of the nightmare. Rather, patients are instructed to “rescript” the content of a nightmare such that it no longer culminates in a distressing ending and, then, imaginally rehearse the “rescript” during daily visualization sessions (Krakow and Zadra, 2006).

Findings from case studies, uncontrolled effectiveness studies, and waitlist control trials suggest IRT contributes to clinically significant reductions in nightmare frequency and psychiatric distress, including daytime PTSD symptoms, among trauma-exposed patients. These studies have been critically reviewed elsewhere (Lancee et al., 2008; Spoormaker and Montgomery, 2008; Wittmann et al., 2000).

More recently, IRT was tested in two small, uncontrolled effectiveness studies among Veterans with PTSD(Lu et al., 2009; Nappi et al., 2010b). In both, results mirrored those from earlier IRT trials. Participants reported decreased nightmare frequency and related distress, although in the study by Lu et al. (2009), effects were not detected until 3-months post-treatment. The extent to which concurrent or post-IRT treatments impacted results was not controlled in either study, limiting conclusions regarding whether or not IRT accounted for pre-post changes.

To date, only onerandomized clinical trial (RCT) that included an active, placebo therapy control group has been reported (Cook et al., 2010). In this study, neither IRT nor the active control group demonstrated meaningful improvements over time or differed on primary outcome measures. Cook et al. (2010) suggest several reasons why this study may not be the hypothetical nail in the coffin for IRT, including characteristics of the sample (male Vietnam Veterans with chronic, severe PTSD), group delivery of the treatment, and potential of IRT

as an adjunctive treatment for those who have already participated in and responded to trauma-focused therapy.

Further complicating our understanding of how rescripting works is the lack of reported data regarding an association between treatment adherence and clinical outcomes. Only one study has reported adherence (i.e., whether or not participants rehearsed imagery at home; Lu et al., 2009). More than half (53%; N=8) of participants in this study reported they never rehearsed imagery outside of session. There was not enough power to justify examination of whether or not those who rehearsed differed from those who did not (Lu, personal communication, 2010). Investigation of whether or not repeated imagery rehearsal is a necessary component of IRT and, if so, determination of a sufficient dose of imagery (or the extent to which such visualization can even be sustained) should be tested in future trials. In addition, treatment adherence findings reported by Lu et al. (2010) raiseconcerns related to the acceptability of IRT among patients with PTSD, or at least subgroups of PTSD patients (e.g., combat Veterans). While treatment completion rates in Krakow et al. (2001) and Cook et al. (2010) were 75% and 83%, respectively, adherence with the rehearsal instructions were not reported. Thus, treatment acceptability of IRT needs to be systematically studied.

In sum, IRT has not been shown as more efficacious than nonspecific therapy effects, although only one study has directly tested this. Demonstrating superiority to a nonspecific placebo is important to establishing efficacy of a treatment in general (Borkovec, 1993; Schnurr, 2007)and with IRT may be more critical given findings indicative of the equivalent potency (relative to imagery rehearsal and with respect to reducing nightmare frequency)of merely recording one’s nightmares (e.g.,(Neidhardt et al., 1992). There are several possible explanations for the current findings, some of which are speculative. Potentially, the therapeutic dosage is too low (< 6 sessions) or diluted, or treatment effects are delayed (Lu et al., 2009). Theoretically, IRT protocols that explicitly exclude discussions of or exposure to nightmare content may unintentionally contribute to perpetuation of avoidance in PTSD, which is perhaps why some investigators suggest IRT be used after successful trauma-focused treatment (Cook et al., 2010; Lu et al., 2009). Indeed, the notion of purposely excluding discussions of mental content that elicits distress is contradictory to current cognitive behavior theory that drives efficacious PTSD treatment (Foa et al., 2007). Alternatively, the failure to demonstrate superiority of IRT over common therapy factors may be attributed to methodological issues and the limited number of studies published to date. Most notable are the lack of a standardized treatment protocol, the significant variations in sample characteristics, and large dropout rates (Spoormaker et al., 2006) across studies. Finally, while potential mechanisms of action have been proposed for IRT (Krakow et al., 2000), their veracity is yet to be tested with the exception of one study (Germain et al., 2004) that unfortunately did not report whether an association between the proposed mechanism and outcomes was detected. All of these areas represent potential future directions for this line of work and several ongoing studies of IRT (NCT01009112, NCT00734799, NCT00691626, NCT00291031, NCT00393874) may address some of these questions.

3.2. Exposure Therapy for Posttraumatic Nightmares

Efficacy of imaginal exposure to posttraumatic memories for PTSD is well-established (Foa et al., 2003), and exposure has been examined for nightmares, albeit with inconsistent methodology, within three contexts: 1) in isolation; 2) within systematic desensitization; and 3) combined with both relaxation and rescripting. As with many of the interventions discussed thus far, imaginal exposure appears to hold some promise as a treatment for nightmares, but more work is needed.

3.2.1. Exposure in Isolation—The only study to examine imaginal exposure of nightmare content in isolation compared this technique to a relaxation group and waitlist control (Burgess et al., 1998). Both imaginal exposure and relaxation were delivered via self-instruction guidelines mailed to participants. The sample was comprised of community members meeting minimal criteria for frequency and chronicity of nightmare. There was no assessment for PTSD, the discontinuation rate was high (61% in the exposure group), and there was no report of adherence to self-guided instructions. The exposure group reported significantly fewer nightmares and increased overall well-being relative to relaxation and waitlist control, but this difference may have been biased by only those experiencing a benefit staying in the study. There were no group differences on nightmare intensity.

3.2.2. Exposure within Systematic Desensitization—In three small RCTs (Celluci and Lawrence, 1978; Kellner et al., 1992; Miller and DiPilato, 1983), imaginal exposure of nightmare content was implemented in the form of systematic desensitization (SD), the pairing of imagery of nightmare content with an incompatible response. In sum, findings from these studies, reviewed in detail elsewhere (Davis, 2008; Lancee et al., 2008), suggest exposure in the context of SD may reduce nightmares and increase confidence in management of nightmare-related affective response. However, characteristics of the samples in each study (undergraduate students or community members with no confirmation of PTSD diagnosis) limit generalization of findings to PTSD patients. Furthermore, there was some evidence that the act of daytime imagery rehearsal contributes to decreases in nightmares regardless of whether content of the imagery focused upon the nightmare.

3.2.3. Exposure, Rescripting and Relaxation Therapy (ERRT)—ERRT is a multicomponent, 3-session group treatment protocol for posttraumatic nightmares that includes nightmare tracking, psychoeducation about sleep and nightmares, sleep hygiene, exposure to a nightmare, nightmare rescripting (as in IRT), and relaxation techniques. The exposure component is not conducted imaginally. Rather, it involves writing one's nightmare in detail, reading the nightmare script aloud, and identifying trauma themes in the nightmare in a group therapy session. ERRT is based upon a comprehensive model of posttraumatic nightmares that implicates predisposing (e.g., arousability), precipitating (e.g., traumatic event), and perpetuating (e.g., physiological dysfunction, cognitive distortions and misconceptions, avoidance behaviors) factors in the maintenance of posttraumatic nightmares (Davis, 2008).

To date, one case series (Davis and Wright, 2005), two RCTs (Davis and Wright, 2007; Rhudy et al., 2010), and one effectiveness study (Swanson et al., 2009) of ERRT have been

published. In one of the controlled trials, 43 participants were randomly assigned to ERRT or a waitlist control group. Two-thirds of the mostly female sample met criteria for PTSD. Intent-to-treat analyses revealed significantly greater decreases in frequency and severity of nightmares, sleep problems, PTSD symptoms, and depression in the ERRT group relative to waitlist immediately following treatment. Assessment of all treated participants at 6-month follow-up demonstrated a 32% decrease in the number of participants diagnosed with PTSD, although participation in alternative treatments was not assessed or controlled. The same research group recently conducted a second randomized, waitlist-controlled trial of ERRT (Rhudy et al., 2010) and demonstrated significantly reduced subjective and physiological (facial EMG, skin conductance, and heart rate) reactivity to nightmare content in the ERRT group relative to the waitlist group up to 6-months post-treatment. Effect sizes were large. Findings are compelling because they implicate extinction of nightmare related distress as a plausible treatment mechanism. The next step would be to demonstrate an association between changes in reactivity and treatment outcomes and such work is reportedly in process (Rhudy et al., 2010).

An uncontrolled effectiveness study (N = 10) of ERRT in combination with Cognitive Behavioral Therapy for Insomnia (CBT-I; see section 4.) among Veterans demonstrated significant improvements in sleep quality and reduction in nightmare frequency and distress following a 10-week treatment protocol. Notably, on daily yes/no assessments of adherence to rescripting and relaxation homework, Veterans reported rates of 74% and 86%, although whether adherence was associated with outcome was not determined. The uncontrolled nature of the study and combined treatment protocol make it difficult to determine if effects can be attributed uniquely to ERRT.

Unfortunately, as with IRT, the extent to which effects of ERRT exceed nonspecific therapy effects remains unknown. Also parallel with IRT, feasible theoretically-based change mechanisms have been proposed for ERRT (Davis, 2008), but they are yet to be tested in a manner that would identify which component(s) of this protocol affects change. This remains an important next step for research on ERRT and the design of the most recent ERRT trial (Rhudy et al., 2010) suggests this type of mechanistic investigation is forthcoming.

Overall, evidence from studies that include an exposure component suggests treatments that include this technique, a relaxation component, or both may contribute to reductions in nightmares. Conclusions are limited, though, as many of the studies did not confirm PTSD diagnoses and reported relatively small effects. Critically, to date, no test of a standardized exposure therapy technique for nightmares has been conducted. This is notable because the limited degree of exposure implemented in the trials reviewed here may be insufficient to allow for the emotional processing necessary to sustainably correct the fear structure (Foa and Kozak, 1986). Potentially, nightmare content is not sufficient or stable enough to be amenable to repeated and prolonged exposure. On the other hand, it may be the case that only a minimal dose of exposure (e.g., writing and reading the nightmare one time) is needed to extinguish nightmare-related distress. The study by Rhudy et al. (2010) supports this possibility. Clearly, this is an area worth examining systematicallyamong samples of patients with confirmed PTSD diagnosis. Studies of ERRT and an exposure-based therapy

for nightmares are currently being conducted (NCT01220401, NCT00513045). A PTSD diagnosis is not reported as an inclusion criterion in either trial, although participants in NCT01220401 are required to have experienced a PTSD Criterion A event (Balliett, personal communication, 2011).

4. BEHAVIORAL TREATMENTS FOR POSTTRAUMATIC INSOMNIA

Cognitive Behavioral Therapy for Insomnia (CBT-I) is the most well validated treatment for primary insomnia (Smith et al., 2002), and there are many studies to suggest CBT-I is efficacious for insomnia related to psychiatric conditions (Smith et al., 2005). Despite its wide dissemination and the prominence of sleep disturbance in PTSD, we are aware of only four published studies examining this treatment in a PTSD sample (DeViva et al., 2005; Germain et al., 2007; Krakow et al., 2001; Swanson et al., 2009). Across these studies, participants reported significant decreases in nightmares and improvements in sleep quality on daily diaries and validated self-report sleep assessments, with moderate to large effect sizes. In three of these studies, significant improvements were also detected on measures of daytime PTSD and other psychiatric symptoms (Germain et al., 2007; Krakow et al., 2001b; Swanson et al., 2009). Of note, three of these studies combined the critical components of CBT-I with a nightmare-focused treatment (ERRT in Swanson et al., 2009; IRT in Germaine et al., 2007 and Krakow et al., 2001), diminishing the extent to which sleep quality improvements can be attributed to CBT-I, while demonstrating the potential effectiveness of a treatment protocol that simultaneously addresses both PTSD sleep disturbances.

Taken together, findings from these trials provide initial support for the use of CBT-I to address sleep disturbances in PTSD patients, but should be considered in light of the fact a standardized protocol was not used across studies and treatment modalities and duration varied. Nevertheless, the principal components of CBT-I (sleep restriction, stimulus control, sleep hygiene) were included in each study.

Interestingly, there is yet to be a RCT of CBT-I among PTSD patients that has controlled for nonspecific therapy effects and time and none of the studies reviewed here tracked or controlled for participation in alternative treatments. Given the prominence of sleep disturbance in PTSD, conducting a well-controlled trial of CBT-I in PTSD patients is an important next step in establishing its efficacy for this special population. Several trials are ongoing (NCT00881647, NCT01009112, NCT01176123, NCT00734799, NCT00691626).

5. PHARMACOLOGICAL TREATMENT FOR POSTTRAUMATIC NIGHTMARES AND INSOMNIA

Comprehensive reviews of the pharmacological treatment of PTSD-related nightmares and insomnia were published in 2006 (Maher et al., 2006; van Liempt et al., 2006a; van Liempt et al., 2006b), concluding generally that evidence-based guidelines for specifically treating PTSD-related nightmares and insomnia could not be established due to a lack of RCTs and methodological limitations in existing studies. The need for more methodologically rigorous controlled trials was recently echoed by a best practice guide for the treatment of nightmares (idiopathic and posttraumatic) published by the American Academy of Sleep Medicine

(AASM;(Aurora et al., 2010). In addition, these reviews emphasized the minimal response of sleep disturbance in PTSD to SSRIs and the lack of support for benzodiazepines, tricyclic antidepressants, and monoamine oxidase inhibitors as safe, tolerable treatments for PTSD-related nightmares and insomnia. Broader reviews of pharmacotherapy for PTSD in general support such conclusions (Berger et al., 2009; Ravindran and Stein, 2010).

Here, we review studies of pharmacological treatment interventions for posttraumatic nightmares and insomnia published since the aforementioned sleep-focused reviews. We included only studies reporting sleep quality and/or nightmare outcomes. Case studies were excluded given a potential publication bias for positive findings for these studies (Berger et al., 2009).

5.1. Antidepressants

5.1.1. Selective Serotonin Reuptake Inhibitors (SSRIs)—Maher et al. (2006) and van Liempt et al. (2006b) provided a detailed review of the evidence for sertraline, fluoxetine, fluvoxamine, and paroxetine for posttraumatic sleep disturbances available prior to 2006. Briefly, evidence suggested small effects for this class of drugs. These and other reviews have also pointed out that SSRIs can disrupt sleep: reducing REM sleep, increasing REM latency and worsening sleep continuity (Wilson and Argyropoulos, 2005). Since then, no published studies have examined efficacy of these SSRIs for PTSD-related sleep and nightmares. There are, however, at least two ongoing RCTs of paroxetine among PTSD patients that include sleep outcomes (NCT00215163 and NCT00202449).

5.1.2. Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)—Until recently, efficacy of dual reuptake inhibitors of serotonin and norepinephrine (SNRIs) specifically for posttraumatic nightmares and insomnia had not been studied. However, a study of duloxetine for PTSD in a sample of “treatment refractory” Veterans with comorbid PTSD and major depression was recently published (Walderhaug et al., 2010). In this 8-week, open-label trial, significant improvements in PTSD and mood symptoms were detected and significant reductions in nightmares were specifically noted. Given the uncontrolled nature of the study and lack of a validated sleep assessment, these findings should be considered preliminary. There are two ongoing trials of duloxetine for PTSD (NCT00583193, NCT00763178); however, examination of effects upon sleep is not a primary aim in either investigation. Another widely used SNRI, venlafaxine, was demonstrated effective for treatment of PTSD in general (Davidson et al., 2006), but does not appear effective for reducing associated sleep symptoms. In fact, the AASM’s best practice guide indicates venlafaxine is not suggested for posttraumatic nightmares (Aurora et al., 2010). In a symptom-specific pooled analysis of two venlafaxine RCTs (N = 687), there were no significant differences between drug and placebo on the distressing dreams and difficulty sleeping CAPS items at any time point (Stein et al., 2009).

5.1.3. Other Antidepressants—There are no newer studies, of which we are aware, testing the effects of other antidepressants on sleep disturbance in PTSD since the 2006 reviews. Those reviews covered the literature on nefazodone and trazodone, both 5-HT_2 receptor antagonists with α_1-adrenoceptor blocking properties. Evidence generally did not

support the efficacy of either medication for sleep problems in PTSD with the exception of one study demonstrating large and significant reductions in both subjective and objective sleep difficulties for nefazodone(Neylan et al., 2003). In addition, the AASM's best practice guide characterized the evidence for trazodone as "low grade and sparse" (Aurora et al., 2010) and specifically recommend against nefazodone for the treatment of nightmares. Despite these facts, trazodone continues to be prescribed frequently for PTSD-related sleep difficulties, especially in the Veterans Affairs Healthcare System (Rosen et al., 2004; Warner et al., 2001). Maher et al. (2006) and van Liempt et al. (2006b) also reported preliminary support for mirtazapine, an antidepressant with α_2-adrenoreceptor antagonist, strong antihistaminergic, and $5HT_2$ receptor antagonist properties. There is an ongoing trial of mirtazapine as an adjunct to SSRI treatment that utilizes validated sleep measures (NCT01178671).

5.2. Antipsychotics

Atypical antipsychotics– with antidopaminergic activity, antihistaminic effects, 5-$HT_{2A/C}$ receptor antagonism and affinity for α-adrenergic receptors – have been investigated primarily as adjunctive treatments for PTSD. Previously (Maher et al., 2006; van Liempt et al., 2006), preliminary support for olanzapine, quetiapine, levomepromazine, and risperidonewas demonstrated in small open-label studies and case reports, andone study of olanzapine utilizing a placebo-controlled trial, examining sleep. Since 2006, of the atypical antipsychotics, only findings related to risperidone's efficacy for posttraumatic nightmares and insomnia have been reported (David et al., 2006; Rothbaum et al., 2008). The primary aim of the first open-label study (N=17; David et al., 2006) was to determine effects of add-on risperidone upon sleep symptoms using valid retrospective sleep measures and prospective daily sleep diaries. Following 6-weeks of treatment, participants reported significantly improved PSQI global sleep quality scores (although scores remained in the clinically significant range) and significant decreases in number of awakenings and nightmares, per diary report. There was no control group and no control for concurrent psychosocial interventions. The second study was an RCT of risperidone versus placebo as an adjunct to SSRI treatment for overall PTSD symptoms (Rothbaum et al., 2008). Although sleep outcomes were not primary, significant decreases on the sleep item of the Davidson Trauma Scale in the risperidone group relative to placebo was reported. Findings are limited by the use of a single-item assessment of sleep. Nevertheless, the data from both studies together suggest an RCT of adjunctive risperidone that uses comprehensive and valid assessments of nighttime PTSD symptoms is warranted.

5.3. Anticonvulsants

Limited evidence was available to support the use of anticonvulsants for PTSD-related sleep disturbances at the time of the van Liempt et al. (2006b) and Maher et al. (2006) reviews, with the exception of small open label trials of gabapentin and topiramate. Only two studies to report effects of anticonvulsants on sleep outcomes in a PTSD sample have appeared since then. The first was an open label trial of eight weeks of topiramate as an adjunct medication in 43 male Veterans with PTSD (Alderman et al., 2009). There was no significant pre-post difference on a measure of sleepiness, but the proportion of patients reporting nightmares and sleep-related anxiety significantly decreased. Methodological

issues limit study conclusions. Results were reported for only 29 treatment completers and dichotomous, single-item assessments of nightmares and sleep-related anxiety were extracted from an unvalidated measure of sleep quality. A trial of add-on topiramate that is both placebo-controlled and employs validated sleep and nightmare assessments is yet to be conducted and a recent clinical practice review described the evidence for topiramate for posttraumatic nightmares as low grade and sparse(Aurora et al., 2010). The second study was a mixed open-label and double-blind, placebo-controlled trial of tiagabine (a selective GABA reuptake inhibitor) in 29 PTSD patients (Connor et al., 2006). Following 12 weeks of open-label administration, participants reported significant decreases on the PSQI, although scores remained in the clinically significant range. Responders (N = 18) were crossed over to 12 weeks of tiagabine or placebo and at study end and sleep improvements were maintained, but there were no significant differences between drug and placebo on the PSQI. There are no ongoing RCTs of tiagabine for PTSD or related nightmares and insomnia. Several studies of topiramate for PTSD were recently completed (NCT00203463, NCT00208130, NCT00204386) or ongoing (NCT01087736, NCT00725920, NCT00571246). However, that we know of, none of these include sleep quality or nightmares as primary or even secondary outcomes. Other anticonvulsants (e.g., lamotrigine) have shown some efficacy for PTSD symptoms in general (Hertzberg et al., 1999), but they have not been studied for their effects upon posttraumatic sleep disruption. While the current evidence for the impact of anticonvulsants on PTSD-related nightmares and insomnia is weak, it is suggestive enough that future trials of these medications would benefit from the addition of validated sleep measures.

5.4. Adrenergic-Inhibiting Agents

Increased central noradrenergic activity is implicated in the pathophysiology of PTSD and linked specifically to intrusive and hyperarousal symptoms, such as nightmares and difficulty sleeping(Boehnlein and Kinzie, 2007; Southwick et al., 1997; Strawn and Geracioti, 2008). This mechanism highlights the potential for pharmacological agents that diminish the hyperactivity of centrally-acting norepinephrine to augment therapeutic response and specifically target nighttime symptoms, without sedating side effects and risk of addiction. In this class of drugs, prazosin has been studied most extensively and is emerging as the most empirically supported noradrenergic antagonist for treatment of posttraumatic sleep disturbances. Although few in number, studies of other anti-adrenergic agents, including propranolol, guanfacine, and clonidine, provide, at best, minimal support for the efficacy of these agents in the reduction of trauma-related nightmares and insomnia and are reviewed in detail elsewhere (Berger et al., 2009; Maher et al., 2006; Ravindran and Stein, 2010; van Liempt et al., 2006b).

5.4.1. Prazosin—Two recent reviews (Berger et al., 2009; Miller, 2008) indicate prazosin, an α_1-adrenergic receptor inhibiting agent, is a promising pharmacologic treatment for posttraumatic nightmares and related sleep disturbance. Taken together, conclusions in these extensive reviews were made on the basis of four open label trials (Daly et al., 2005; Peskind et al., 2003; Raskind et al., 2000; Taylor and Raskind, 2002), one retrospective chart review (Raskind et al., 2002), and three RCTs (Raskind et al., 2007; Raskind et al., 2003; Taylor et al., 2008) that examined prazosin for nighttime PTSD symptoms. In the RCTs, prazosin was

superior to placebo on subjective measures of nightmares and sleep difficulties and objective sleep measures, though all three trials were conducted by the same research group.

Findings from four studies published since these reviews further substantiate efficacy of prazosin for reduction of posttraumatic nightmares and related sleep disturbances and support its effectiveness in special populations. The first was a retrospective chart review of 23 refugees diagnosed with chronic PTSD and treated with prazosin (as an adjunct to current psychotropic regiment) at a stable dose for eight weeks (Boynton et al., 2009). Results indicated significant decreases on the CAPS distressing dreams item and improvements in overall PTSD severity. Change on the distressing dreams item was associated with duration of prazosin treatment and dosage achieved. Although uncontrolled, this study demonstrated effectiveness of prazosin for trauma-related distressing dreams among severely traumatized patients.

In another uncontrolled, yet novel observational study (Ruff et al., 2009), effects of prazosin in combination with sleep hygiene counseling upon sleep and TBI-related outcomes were examined among Veterans with mild traumatic brain injury (TBI). Following nine weeks of treatment and at six-month follow-up, sleep and cognitive functioning improved and headache pain and frequency decreased. Although the extent to which effects can be attributed to prazosin (versus the behavioral sleep intervention, time and other confounding variables) are not clear, findings suggest effects of prazosin upon sleep may, in part, promote recovery among Veterans with TBI. Given the impact of TBI on sleep (Orff et al., 2009)and the comorbidity of TBI and PTSD in the cohort of military personnel that have served in Iraq and Afghanistan (e.g.,(Hoge et al., 2008), further research into the efficacy and benefits of treating sleep disruption in TBI patients is warranted.

Prazosin is typically studied in terms of its effects upon posttraumatic nightmares, however, many patients with PTSD describe distressed awakenings that are not necessarily associated with nightmare content. Thompson et al. (2008) distinguished between nightmares and nonnightmare distressed awakenings and examined effects of prazosin upon both of these outcomes, as well as sleep difficulty in general (Thompson et al., 2008). Significant decreases were detected on all outcomes in this open label trial of Veterans (N = 22).

Only one study to date has compared prazosin to another psychotropic intervention, the atypical antipsychotic, quetiapine. Byers et al. (2010) conducted a retrospective chart review of Veterans prescribed prazosin (N = 62) or quetiapine (N = 175) for nighttime PTSD symptoms, in addition to ongoing psychotropic regiment (Byers et al., 2010). Groups demonstrated similar improvements at six months. Nevertheless, Veterans prescribed prazosin were less likely to discontinue the drug and thus demonstrated greater improvements at the final time point. The prazosin group also reported fewer adverse effects. Although conclusions are limited due to the uncontrolled nature of the study, findings highlight the potential specific link between heightened adrenergic activity and sleep disturbance in PTSD given equal effectiveness of prazosin (which inhibits solely α_1-adrenergic receptors) and quetiapine (with dopamine receptor antagonism, histamine H_1 receptor antagonism, $5HT_{2a/c}$ receptor antagonism, and anticholinergic effects in addition to α_1- and α_2-adrenergic receptor antagonism).

Additional randomized, placebo-controlled trials of prazosin have not been published since those reviewed by Berger et al. (2009). Based upon the current evidence, prazosin is the only pharmacological intervention receiving a grade of “recommended”by the AASM’s best practice guide (see Aurora et al., 2010)for the treatment of PTSD-related nightmares. Several studies are underway that will potentially address important unanswered questions regarding efficacy of prazosin versus placebo and SSRIs and prazosin as an adjunct to SSRIs and behavioral treatments (NCT00393874, NCT00202449, NCT00532493, NCT00990106, NCT00183430).

5.4.2. Doxazosin—A small, open-label pilot trial of doxazosin, a selective postsynaptic α_1-adrenergic antagonist, was recently published (De Jong et al., 2010). Though doxazosin does not cross the blood-brain barrier as readily, its mechanism of action is similar to prazosin. Doxazosinis available as an extended release form that allows for faster achievement of therapeutic dosing and fewer titration steps than required by prazosin. Participants in the pilot trial demonstrated significant decreases on the CAPS difficulty sleeping and distressing dreams items after 8 weeks of doxazosin. Lack of a control group and valid sleep assessment limit conclusions.

5.5. Sedative hypnotics

Though benzodiazepines and sedative hypnotics are commonly used in patients with PTSD (Harpaz-Rotem et al., 2008; Mohamed and Rosenheck, 2008), few studies have examined the efficacy of benzodiazepines for treatment of sleep disturbance in PTSD. Those that have found limited to no use for this class of medications(Cates et al., 2004; Mellman et al., 2002).

Despite widespread commercial use, there is sparse empirical data to support the use of nonbenzodiazepine hypnotics to manage posttraumatic insomnia and nightmares. In previous reviews (Maher et al., 2006; van Liempt et al., 2006), evidence for these agents was limited to one zolpidem case series (Dieperink and Drogemuller, 1999) and only two studies have appeared since then. The first, a RCT comparing 14 days of zolpidem to four sessions of hypnotherapy over the same time period among PTSD patients receiving SSRIs and supportive psychotherapy, failed to support the use of zolpidem in this population (Abramowitz et al., 2008). Conclusions are limited because there was no placebo control for drug or therapy. Nevertheless, findings with regard to hypnotherapy were promising. Patients in this group reported improved sleep quality on daily diaries, as well as decreased PTSD symptoms, relative to those in the zolpidem group. A study of sleep-directed hypnosis as an adjunct to CPT is currently underway (NCT00725192). In the second study, Alderman and Gilbert (2009) sought to characterize response to zoplicone in Australian Vietnam Veterans with PTSD (Alderman and Gilbert, 2009). Participants entered the study with poor quality sleep and no pre-post differences were detected after six months of open-label zoplicone, which was used nightly by the majority of participants. Together, findings do not support the use of nonbenzodiazepine hypnotics to treat sleep disruption in PTSD, though controlled investigation of these agents has not been pursued.

6. CONCLUSIONS

It is clear that sleep disruption, specifically nightmares and insomnia, are ubiquitous in PTSD. Furthermore, they are among the most distressing symptoms for many patients and they contribute to daytime impairment, as well as potentially exacerbate other symptoms of PTSD. Despite this, there have been relatively few studies to directly examine the impact of a given intervention on sleep problems in PTSD, and even fewer that have utilized validated measures of sleep. Thus, currently, our treatment arsenal is quite limited when it comes to managing sleep disturbance in PTSD. Perhaps one of the strongest conclusions of this review is the idea that we need both more intervention studies designed specifically to address sleep problems in PTSD, and studies of treatments focused on daytime PTSD symptoms should include valid measures of sleep to better assess how well such interventions address the nighttime symptoms.

6.1. Behavioral Interventions

With respect to the behavioral treatments reviewed, there remain more questions than answers. For example, some evidence suggests nightmares may subside following evidence-based treatments for PTSD, but thus far most studies have not done an adequate job of systematically assessing nightmares. Stronger evidence is clearly needed before making a definitive conclusion. While several nightmare-specific interventions have been developed and tested, the field needs better controlled studies of these treatments to determine if they work relative to placebo and, if so, in which types of patients (e.g., subthreshold PTSD, sexual trauma, combat trauma, etc.). It will also be extremely important to identify the processes by which the treatments achieve their effects. To date, minimalresearch has addressed mechanisms of action and work is needed to do this in an effort to better understand nightmares in the overall context of PTSD and how to best treat them. Emerging theory on posttraumatic nightmares may facilitate this work (Levin and Nielsen, 2007). In contrast to nightmares, insomnia appears to continue after evidence-based treatments for PTSD, and this would be consistent with the four-factor model of insomnia (Perlis et al., 2005), especially the conditioned arousal component. Again, though, the majority of studies have not systematically examined insomnia with validated measures of sleep. CBT-I appears to be a promising intervention in PTSD, based on the available studies, and more work in this area will be valuable. Specifically, future studies should consider how we might need to tailor CBT-I for this population, given the physiological and psychological changes associated with PTSD that may be unique relative to other populations in whom CBT-I has been validated. Finally, the fact that HPA axis function is altered in PTSD patients raises the possibility that related sleep disruption (Otte et al., 2007) could be long-lasting. If this is true, then an entirely new approach to treating sleep difficulties in this population may be necessary. For example, behavioral treatments that focus upon management or acceptance of nightmares and sleep loss, as opposed to elimination or reduction of these symptoms, may be more appropriate.

6.2. Pharmacological Interventions

In 2006, critical reviews of the literature on pharmacological management of sleep problems in PTSD called for randomized, placebo-controlled trials using sleep outcomes to determine

more definitively, if agents that appear promising in open-label trials are: a) effective relative to placebo; and b) show effects on validated measures (objective and subjective) of sleep (Maher et al., 2006; van Liempt et al., 2006). Since then, very few studies have actually done that. The exception would be prazosin, which has been or is currently being tested against placebo with validated sleep measuresand has been shown to be efficacious. Moreover, if and when sleep improvements over baseline have been detected in published studies, patients often still score in the clinically significant range for sleep difficulties (e.g., David et al., 2006) or rebound upon discontinuation (e.g., Raskind et al., 2003). Overall, the current review argues currently employed medications have clinically significant limitations, from an effectiveness perspective, for behavioral sleep difficulties in PTSD. This provides, in turn, further impetus to conduct the randomized controlled trials called for in earlier reviews and to test combined pharmacological and behavioral interventions, as suggested elsewhere(Aurora et al., 2010).

7. FUTURE DIRECTIONS

Two major initiatives are needed to address the issues raised in this review regarding the incomplete state of knowledge on how to best treat nightmares and insomnia in PTSD. First, all studies of PTSD intervention, regardless of the primary outcomes, should strongly consider including validated measures of sleep as secondary outcome measures. Additionally, not a single study found for this review addressed 24-hour circadian rhythms in PTSD patients. Thus, it is completely unknown if circadian disruption in this population, if present, corrects with treatment.

Second, intervention research in this arena may benefit by moving away from considering sleep symptoms in isolation and instead addressing them more holistically within the framework of PTSD. This can be accomplished by conducting more integrative studies that examine sequential or combined treatments targeting both daytime and nighttime symptoms and functioning. Such studies may focus on behavioral interventions, pharmacological interventions or both. At least two such studies are underway (e.g., NCT00725192, NCT01009112).

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Research Highlights

- Sleep difficulties, especially insomnia and nightmares, are ubiquitous in PTSD.
- Behavioral interventions for PTSD may reduce nightmares but likely not insomnia.
- Behavioral treatment of0nightmares is promising and requires much stronger evidence.
- CBT for Insomnia warrants randomized clinical trials and potential modifications specific to PTSD.
- No drug other than prazosin is supported for treating sleep symptoms in PTSD.