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Management of Post-Traumatic Nightmares: A Review of Pharmacologic and Nonpharmacologic Treatments Since 2010

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Abstract Nightmares are a universal and timeless phenomenon. They occur in most healthy adults as well as a significant portion of clinical populations, especially those exposed to trauma. Considerable advances in the pharmacological and psychological treatment of post-traumatic nightmares have occurred over the last decade with continuing advances in psychological interventions over the last few years. Pharmacologically, the medication prazosin is showing robust clinical effects with minimal side effects. Psychologically, imagery rehearsal therapy commands the greater portion of the nightmare literature due to its established efficacy. These issues are reviewed in the following paper along with recommendations for future studies.

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Introduction

Nightmares are as old as time itself. Jewish mythology recounts the story of Lilith, Adam's wife before Eve, who refused to be subservient to Adam. Upon her exodus from the Garden of Eden, she became a demon that haunted sleeper's dreams [1].

Today, nightmares continue to cause fear, anxiety, and distress. With a lifetime incidence rate likely near 100 %, nightmares are an extremely common occurrence in both clinical and healthy populations [2]. Previous studies have shown that between 8 % and 25 % of adults report at least 1 nightmare per month [3–7], whereas 4 % to 8 % report at least 1 nightmare each week [8]. Increased prevalence of nightmares has also been found in those exposed to a wide range of traumatic experiences [9–11], particularly those suffering from post-traumatic stress disorder (PTSD) subsequent to combat exposure or rape [12–14].

Nightmares are a real health problem and have measurable costs to the individual and society. On an individual level, the sleep deprivation that results from chronic nightmares negatively impacts memory, creativity, learning, attention and focus, mood, physical healing, and increases perceived levels of stress [15–17]. Occupationally, nightmares result in decreased productivity, increased absences, and a decrease in perceived work quality. Related, the annual direct cost of sleep-related problems in this country is $16 billion, with an additional $50-$100 billion in indirect costs associated

with accidents, litigation, property destruction, hospitalization, and death [18].

Although nightmares are the most common re-experiencing symptom of PTSD, reported in 50 %–70 % of those afflicted [19], and the presence of nightmares following a traumatic event predicts delayed onset of PTSD [20], nightmares often occur outside the formal PTSD diagnostic nomenclature. For example, nightmares occur within the context of Acute Stress Disorder (ASD), adjustment disorders, and are expected and normal reactions to acute and chronic combat and operational stress [21]. In addition, nightmares have been associated with myriad medical conditions, medication use, substance abuse, and intermittent periods of elevated stress and anxiety [22]. This point is much more than an academic one. Traditionally, nightmares have not been treated directly, but assumed to improve after successful treatment of the primary condition (eg, PTSD) from which they were hypothesized to originate. As noted elsewhere, likely consequences are that the nightmares are either not treated or treated inadequately leading to continued distress and decrements in social and occupational functioning [23]. Therefore, it is imperative that the clinician be aware of the varied contexts in which nightmares can present clinically. Moreover, the clinician must be well versed in the most current evidence-based interventions available. The latter is the focus of this paper.

In this article, we present the reader with a critical review of the literature on pharmacological and non-pharmacological treatments for nightmares spanning 2010 to present. We chose 2010 as a starting point for 2 reasons. First, sanctioned by the Standards of Practice Committee of the American Academy of Sleep Medicine (AASM), Aurora and colleagues [24••] completed an exhaustive review of pharmacotherapy and behavioral approaches to nightmare treatment. Utilizing Oxford Centre for Evidence-based Medicine Levels of Evidence [25], and a modified version of the RAND/UCLA Appropriateness Method [26] for practice recommendations, a Best Practices Guide was developed and accepted by AASM Board of Directors. Currently, this is the best source for a comprehensive review of pharmacological and psychological treatments for nightmares. Although the article contains a considerable amount of relevant review material, the 2 most notable findings are: (1) prazosin is considered to be a Level A pharmacological intervention and (2) imagery rehearsal therapy is considered to be a Level A behavioral intervention. In this study, interventions with the highest level of supporting data were assigned a Level A rating. Second, a PubMed and PsychLit search revealed no significant reviews on the topic since the Aurora and colleagues paper [24••].

Pharmacological Treatment Interventions

Prazosin

The sympatholytic drug, prazosin, is the first line of medication treatment for post-traumatic nightmares (PTNMs). Its selectivity for alpha 1 receptors of vascular smooth muscle results in dilation of blood vessels and a decrease in blood pressure. Research in the mechanism of action of prazosin suggest that by blocking a portion of the effect of adrenaline in the body it reduces anxiety, improves sleep, and impacts REM to reduce nightmares comorbid with PTSD [27–29]. An additional benefit of prazosin is that it is generally well tolerated and does not produce sedation or medication hangover.

In 2010, Calohan and colleagues published a brief report on the use of prazosin to treat trauma nightmares and severe sleep disturbance in soldiers deployed to Iraq [30]. Thirteen soldiers who reported distressing nightmares with impaired functioning were prescribed prazosin. Data analysis of the Clinical Global Impression of Change scale [31] and selected items from the Clinician Administered PTSD Scale for DSM-IV [32] indicated significant reduction of nightmares and sleep disturbance for these soldiers [30]. Furthermore, the results of the study indicated the soldiers did not report significant adverse reactions to prazosin.

Prazosin is generally well tolerated and, in most cases, does not produce sedation or medication hangover. However, some side effect cautions have been noted in the literature. Along with monitoring for orthostatic hypotension, prazosin, along with other antihypertensives like clonidine, are not considered stand-alone treatments for PTNMs as insomnia and nightmares often return when the medication is stopped [24••, 30, 33, 34].

Risperidone

Atypical antipsychotic agents are indicated for a variety of disorders and symptoms. The current data on the off-label use of risperidone includes the atypical antipsychotic as augmentation therapy or independent pharmacological treatment for PTNMs [35]. Past research has proposed that risperidone reduces PTSD symptoms of anxiety and insomnia due to the combined receptor antagonism of dopamine and serotonin. Similar to antihypertensive agents, risperidone also has alpha-1 and alpha-2 adrenaline receptor affinity further reducing PTSD related symptoms of anxiety, hyperarousal (palpitations, sweating, nausea, and shaking) and nightmares [36–38].

In their case series, Detweiler et al [39] presented 4 case studies of infantry soldiers who were treated for PTNMs with low-dose risperidone. The administration of risperidone at 2 mg in soldiers who were not actively abusing

substances resulted in remission of nightmares the first night of treatment. The 1 veteran who presented with a blood alcohol level greater than 300 mg/mL experienced partial remission of nightmares at 3 mg of risperidone. In addition, risperidone continued to be effective regardless of changes in supplementary medication (antidepressants, anxiolytics, and hypnotics) used to treat comorbid symptoms and disorders associated with PTSD. Similarly, in a letter submitted to the editor, Khachiyants et al [35] presented a case series that found risperidone to be effective for nightmares in a similar veteran population. In both case series significant side effects that included hand tremor, headaches, nausea, and vomiting were reported as well as dose dependent responses to risperidone treatment [35, 39].

Trazodone

The antidepressant and augmenter drug trazodone acts predominately as a 5-HT_{2A} receptor antagonist, which is in part responsible for the drug's antidepressant and antianxiety effects. This antagonism also plays a critical role in sedation leading to improvements in sleep-onset insomnia. Furthermore, it is a potent alpha adrenergic receptor agonist and histaminergic antagonist, which has effects in increasing total sleep time and decreasing amount of REM sleep. However, the drug's histaminergic antagonism is relatively weak and any sleep benefits are likely due to 5-HT_{2A} and alpha adrenergic effects. Its use for PTNMs has been documented in open-label small trials [40].

In a letter to the editor, Tien-Chun and colleagues [41] presented a case report of a 24-year-old Taiwanese man diagnosed with major depression and vivid nightmares who was treated with trazodone. Initially the patient was treated with escitalopram, 10 mg/day for 14 days, resulting in improvement in depressed mood. To treat the unresolved symptom of insomnia and nightmares, 50 mg of trazodone/night was added, resulting in resolution of symptoms. However the patient was unable to tolerate the side effects and trazodone was discontinued. Consequently, the nightmares returned and the insomnia was then treated with 10 mg of zolpidem/night [41]. Lastly, an update on the Psychopharmacology Algorithm project [42] gives emphasis to the use of prazosin and trazodone to begin treatment of PTSD-related fragmented sleep and nightmares. The primary limitation of treatment with trazodone included the inability of the patient to tolerate the side effects of the drug and the return of nightmares when treatment ceased [41].

Current Clinical Trials

According to the US National Institutes of Health, there are currently 40 clinical trials listed for treatment of nightmares [43], the majority of which are focused on behavioral treatments. Pharmacological trials include prazosin, hydrocortisone, gabapentin, paroxetine, tetrahydrocannabinol, eszopiclone, xyrem, and carvedilol.

Non-Pharmacological Treatment Interventions for Post-Traumatic Nightmares

The most well-supported non-pharmacological interventions for post-traumatic nightmares are cognitive-behavioral treatment (CBT) approaches [40]. CBT approaches have proven effective in reducing symptoms of PTSD as well as the frequency and intensity of post-traumatic nightmares [44]. Here we review recent literature documenting treatments for post-traumatic nightmares and related sleep problems.

Imagery Rehearsal Therapy

Imagery rehearsal therapy (IRT) is a time-limited approach to treating post-traumatic nightmares. The theoretical basis for IRT is 2-fold. IRT conceptualizes the chronic occurrence of nightmares as a learned behavior, not merely a manifestation related to stressful life events, and also views the nightmare sufferer as one who has poor mental imagery capability, and does not necessarily have comorbid psychopathology or emotional disturbance [23, 45]. The most well-researched variation of IRT is not a primarily exposure-based intervention [4]. In fact, this model of IRT minimizes exposure to nightmares and traumatic memories in a variety of ways. Initially, participants are informed that they will not be discussing the content of their nightmares or any trauma memories. They are also instructed to pick a less-distressing nightmare for initial rescripting; after that, they are instructed to rehearse the new dream, not the nightmare, which also decreases exposure to nightmare content. A variant of this model relies more on exposure by having participants write out their nightmare. On the whole, IRT combines psychoeducation on sleep, nightmares, and sleep disturbance, the concept of nightmares as a learned behavior, imagery skills and practice, and finally selecting a nightmare, rescripting the nightmare into a revised narrative of the patient's own choosing, and daytime imaginal rehearsal of the rescripted dream [23, 45, 46•, 47].

To examine the effectiveness of IRT in a veteran population, Nappi et al [46•] conducted retrospective chart reviews of 35 veterans who completed a full course of outpatient IRT for chronic, trauma-related nightmares. The authors' findings indicated that those who completed IRT evidenced significant decreases in the frequency and intensity of nightmares, insomnia severity, and subjective daytime PTSD symptoms. A reported 23 % of veterans reported≤1 nightmare per week, which was deemed a complete treatment

response, with 11 % indicating no nightmares in the last week.

In an attempt to isolate the therapeutic factor underlying effective treatment for nightmares, Lancee and colleagues [48] compared IRT, exposure treatment, and diary recording, all delivered via a self-help design, with a waitlist control group. Participants included 399 adults experiencing nightmares who were randomly assigned to a condition. The treatment conditions consisted of 6 weeks of self-help treatment, which was compared with 6 weeks of waiting list. Participants in the treatment groups completed post-treatment assessments 11 weeks after baseline. Results indicated that all 3 treatments significantly reduced nightmare symptoms. IRT and exposure were the most effective treatments for nightmares, though they impacted nightmares in different ways. IRT treatment was associated with a more rapid decrease in nightmare frequency, whereas exposure was more effective in decreasing nightmare distress. IRT and exposure were not significantly different on any variable. Diary recording was found to be effective in decreasing nightmare frequency and distress compared with the waiting list.

Lancee et al [49] conducted another study that compared self-help formats of IRT, IRT with sleep hygiene, and IRT with sleep hygiene plus a lucid dreaming portion to a waitlist control group. Participants included 278 adults reporting nightmares, who were randomized into 1 of the 4 conditions with follow-up assessments conducted at 4, 16, and 42 weeks post treatment. Results indicated that IRT alone was more effective than either of the 2 hybrid treatment conditions or waitlist.

Lancee and colleagues [49] also noted that short-term efficacy of IRT and exposure interventions have been reported in the literature, so the authors set out to examine long-term efficacy of these treatment modalities. Participants included 103 adults in the IRT condition and 95 adults in the exposure condition, both treatments delivered via the Internet in a self-help format. Participants completed baseline assessments, were randomly assigned to a treatment group, engaged in a 6-week self-help intervention, and completed post-treatment follow-up assessments at 4, 16, and 42 weeks post treatment. Results indicated nearly entirely sustained impact of treatment for both IRT and exposure treatment, with no significant differences in outcomes between the 2 groups.

Cook and colleagues [50] conducted a randomized controlled trial to test the effectiveness of group IRT against a CBT-based "sleep and nightmare management" group among 124 Vietnam War veterans experiencing recurrent nightmares secondary to chronic, severe combat-related PTSD. Results indicated improvement in overall sleep quality and a reduction in PTSD symptoms for both groups; however, neither treatment group evidenced changes in nightmare frequency. No significant differences were found between groups. Of note, Cook et al's (2010) version of IRT places a greater emphasis on exposure to nightmare content, with patients transcribing their nightmare and reading it aloud to the group, which is contrasted with Krakow and Zadra's [45] sleep-oriented approach, which minimizes exposure to nightmare content.

Ulmer and colleagues [51] observed that for many patients with PTSD who undergo treatment, lingering nightmares and other sleep difficulties often persist. The authors hypothesized that a hybrid sleep intervention for PTSD (SIP) and other PTSD-related sleep difficulties including nightmares may be more effective than using either IRT or CBT in isolation. They proposed and studied a hybrid intervention consisting of IRT and CBT for insomnia. Study participants were 22 veterans who experienced nightmares, PTSD, and insomnia and were randomly assigned to the SIP treatment group or treatment as usual. Four participants dropped out of the SIP treatment group. Data from participants who completed the study revealed a significant decrease in nightmare frequency for the SIP treatment group compared with treatment as usual. Due to improvements in sleep quality and insomnia severity and reduced nightmare frequency and global PTSD symptoms, the authors suggest that the SIP treatment may be an effective intervention for PTSD-related sleep disturbance and nightmares.

Exposure, Relaxation, and Rescripting Therapy (ERRT)

ERRT is a short-term treatment technique that emphasizes exposure to nightmare content. ERRT consists of relaxation training, psychoeducation about trauma, PTSD, nightmares, and sleep hygiene, coaching to modify sleep habits, nightmare exposure, and nightmare rescripting focused on trauma-related themes [52].

Davis and colleagues [52] examined the effects of ERRT on 54 participants, with 75.9 % of participants reporting that their nightmares began post trauma, and 24.1 % reporting lifelong idiopathic nightmares. Participants were randomly assigned to a treatment group or a waitlist control group, and assessments were completed at 1 week and 6 months post treatment. Results indicated that ERRT was effective in treating both post trauma nightmares and lifelong idiopathic nightmares in terms of changes in sleep quality, nightmare frequency and severity, as well as symptoms of PTSD, and depression. These results held true in spite of different levels of psychopathology among the groups. The authors posit that based on these results, ERRT is an effective treatment for nightmares regardless of degree of psychopathology or the type of nightmare.

In an investigation of objective markers of nightmare-related physiological response following ERRT, Rhudy and colleagues [53] compared physiological responses of

participants who had undergone ERRT with those who had not received nightmare treatment. The authors' rationale for assessing physiological responses is that nightmare-related fear may advance and sustain nightmare chronicity. Forty participants were randomized to either the ERRT or waitlist control group. Physiological assessments (facial EMG, heart rate, skin conductance) were taken at a pretreatment baseline, and 1 week, 3 months, and 6 months after treatment. Study results indicated that EERT reduced subjective reactions and physiological arousal to nightmare imagery, with these improvements generally retained at the 6-month follow-up.

Davis and colleagues [52] conducted a randomized clinical trial to assess for the effectiveness of ERRT for the treatment of post-traumatic nightmares. Participants included 47 individuals who were randomly assigned to the treatment group or a waitlist control group. Results indicated improvement in the treatment group vs the control group within 1 week post treatment. Additionally, significant improvements in nightmare frequency and severity, sleep quality and quantity, PTSD symptoms, and other mental health symptoms were seen in the treatment group when assessed 6 months post treatment.

Wanner and colleagues [54] noted the importance of pursuing specialized nightmare treatments for veterans, as most nightmare treatments are studied with civilian participants. The authors reported on 2 case studies of Vietnam veterans who were treated for post-traumatic nightmares using a variation of ERRT, as the original version of ERRT has been effective in treating post-traumatic nightmares in civilians. Both patients evidenced clinically-significant PTSD and depressive symptom reduction as well as moderate improvement in sleep quality from pre- to post-treatment.

Long and colleagues [55] sought to investigate the mechanism of change underlying effective post-traumatic nightmare treatment with ERRT. The authors conducted a secondary data analysis of a parent study which included 40 participants who were randomly assigned to either treatment for post-traumatic nightmares with ERRT or a waitlist control group. Results indicated that treatment with ERRT evidenced a significant decrease in post-traumatic cognitions, which was observed through 6 month follow-up. The observed change in cognitions was significantly associated with a decrease in PTSD symptoms, which lends evidence to the hypothesis that improvement in trauma-related cognitions may be possible as a result of imagery rescripting.

Long and colleagues [56] further examined the effectiveness of "imagery rescripting and exposure therapy" (IRET), a multicomponent variation of ERRT, which has been modified to treat PTSD and chronic post-traumatic nightmares in veterans. The rationale for creating this multicomponent treatment is that most of the research up to this point has been conducted primarily with a civilian population. Participants included 37 veterans experiencing PTSD and associated nightmares who participated in 6 IRET multicomponent group sessions. Treatment data was obtained through a retrospective chart review. Findings comparing pre- and post-treatment measures suggested that participants in the IRET group evidenced significant reductions in PTSD severity and nightmare frequency, as well as enhanced sleep quantity. The authors equated the level of symptom reduction and effect sizes to those seen in a randomized controlled trial treating civilians with PTSD and trauma-related nightmares. The authors propose that IRET is an effective treatment for PTSD and post-traumatic nightmares in veterans.

Lucid Dreaming Therapy (LDT)

LDT is a method in which the dreamers become aware that they are dreaming and thus may exert some control over the dream and influence their dream through imagery [57].

Been and Garg [58] described a case of a high-risk male patient who initially presented to the emergency department after making 4 suicide attempts in the past week and a history of 3 previous inpatient psychiatric hospitalizations. The patient had been previously diagnosed with PTSD, depression, and alcohol dependence, was drinking 16 standard drinks a day at the time of admission, and reported sleeping about 2 hours a night on account of experiencing severe nightmares. The patient was hospitalized and a trial of LDT was initiated. After several days of engaging in LDT, the patient's sleep quality and quantity markedly improved, with the patient reporting 6 hours of uninterrupted sleep per night; the patient voluntarily discharged himself 16 days after admission.

Combined Treatment

To add greater breath to treatment possibilities, recent studies have also examined the combination of drug and cognitive-behavioral treatments. Gehrman and Harb present a case illustration of successful treatment of a patient diagnosed with chronic, severe PTSD and comorbid depression who was successfully treated with a combination of prazosin, Imagery Rehearsal Therapy, and scheduled awakenings [59]. The nightmares were the focus of treatment after prolonged exposure therapy course did not resolve her PTSD symptoms and associated nightmares.

Between October 2006 and March 2012, Germain and colleagues conducted one of the first randomized controlled trials to examine chronic sleep disturbances in military veterans against several treatment modalities [34]. They randomized study participants into a behavioral sleep

intervention condition or a medication intervention, which was then randomized again into Prazosin or placebo. Study results indicated significant reduction in insomnia severity and daytime PTSD symptoms in the behavioral sleep intervention condition and in the medication intervention (prazosin) groups. 61.9 % of participants in the intervention groups reported sleep improvement compared with 25 % of participants in the control/placebo group [34].

Conclusion

Since 2010, there have been modest advances in the understanding of effective pharmacological and psychological treatments for post-traumatic nightmares. The vast majority of research during this period has been on behavioral and cognitive interventions, with relatively little novel information regarding pharmacotherapy.

Although advances in treatment are greatly needed, studies exploring the mechanisms of actions for both medication and psychological interventions are needed in order for this area to advance. For example, it is unknown if medications such as prazosin or risperidone provide therapeutic benefits due to challenging abnormal receptors and chemicals or tamping down emotional reactions, which lead to a decrease in the nightmares' intensity and frequency. A similar argument can be made for psychological interventions. It is unknown if behavioral and cognitive methods promote adaptive neurochemical and structural changes or if clinical gains are a result of the benefits of improved sleep or traditional principles of exposure therapy.

Future studies should parse out the various components related to positive clinical effects in both pharmacological and psychological treatments for post-traumatic nightmares. Specifically, for medication interventions, imaging studies will help determine the exact nature of the effects. For psychological interventions, head-to-head studies comparing exposure vs non-exposure will be of great benefit. Further, dismantling studies exploring the explained clinical variance in the different components of treatment (eg, psychoeducation, therapeutic alliance, imagery rehearsal) will provide greater insight into the effective as well as inert aspects of the various approaches.

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