Treatment of sleep disturbances in post-traumatic stress disorder

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ABSTRACT

Sleep disturbances are very common in patients suffering from post-traumatic stress disorder (PTSD) and can have various negative sequelae, including worsening of perceived levels of stress, depression, and suicidal ideation. Although PTSD treatment can lead to improved sleep in some patients, there are a number of patients whose sleep disturbances do not remit even after treatment and can persist long after the original trauma. There are various non-pharmacological and pharmacological treatment modalities that have been studied. Non-pharmacological therapies include image rehearsal therapy (IRT), cognitive behavioral therapy for insomnia (CBTI), prolonged exposure (PE), and eye-movement desensitization and reprocessing (EMDR). Pharmacological studies include alpha-1-adrenergic receptor antagonists, alpha-adrenergic agonists, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) monoamine oxidase inhibitors (MAOIs), other antidepressants, atypical antipsychotics, benzodiazepines, sedative hypnotics, and antiepileptics. The therapies with the most evidence to support their use are Image Rehearsal Therapy (IRT) and the alpha-1-adrenergic receptor antagonist, prazosin.

KEYWORDS

sleep disturbance, post-traumatic stress disorder (PTSD), nightmare

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a chronic and debilitating condition that affects up to 6.8% of the United States general population.[1-4] This disorder is characterized by specific symptoms that may develop after an individual suffers a traumatic event.[3] The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) groups these symptoms into four clusters: intrusion/re-experiencing, avoidance, negative alterations in cognition and mood, and alterations in arousal or activity (hyperarousal).[5] Depending on the source, sleep disturbances such as nightmares may be considered either an intrusive or hyperarousal symptom. Sleep disturbances are common in patients suffering from PTSD[4-7] and up to 70% of veterans report trauma related sleep disturbances.[3] Sleep disturbances can manifest in a variety of ways. Commonly reported sleep disturbances in patients with PTSD include nightmares, anxiety provoking dreams, frequent awakenings, difficulty falling asleep (sleep latency), difficulty staying asleep (sleep fragmentation), decreased total sleep time, and restless sleep.[3] Although treatments for PTSD can lead to improved sleep in some patients, many times these sleep disturbances require additional modes of therapy for resolution. Unfortunately, there are a limited number of trials to support the use of the treatment options discussed in this article for patients with PTSD-related sleep disturbances. Most of the literature consists of small trials and case studies, and much of the literature is conflicting. Untreated sleep disturbances in PTSD patients can affect all aspects of treatment, and therefore, larger, controlled studies may play an integral role in optimizing PTSD therapy. The sleep deprivation that results from sleep disturbances such as chronic nightmares has been shown to have negative effects on memory, learning, creativity, mood, attention and focus, physical healing, and increases perceived levels of stress.[1] Additionally PTSD related sleep disturbances can persist long after the original trauma.[7] In general, sleep impairment which can lead to nightmare and insomnia is associated with negative psychiatric outcomes such as worsening of depression and suicidal ideation, which can compromise the patient's ability to function in society.[2,8,9] The evidence levels for the therapeutic options evaluated in this review article are discussed in Aurora, et al.[10]

ETIOLOGY/PATHOPHYSIOLOGY

It is believed that one of the causes of sleep disturbances in PTSD involves dysfunctional Rapid Eye Movement (REM) cycles. It is not known if this is the central problem in PTSD or if it is due to an attempt to process distressing material.[7] However, it has been concluded that increased REM density is associated with PTSD.[8] Sleep imaging studies have shown that in PTSD there is hyperactivity in the amygdala and impaired functioning of the medial

frontal cortex. These areas of the brain directly influence the regulation of REM.[9] There is also evidence to support that an increase in noradrenergic activity occurs in patients with PTSD related sleep disturbances. This can leave the patient hyperaroused and sleep deprived.[8] It has been found that patients with PTSD have higher levels of norepinephrine in their cerebrospinal fluid and urine, and that the levels of norepinephrine in the CNS correlate with PTSD severity.[10] There are also behavioral mechanisms that have been suggested. One such mechanism states that insomnia and nightmares are intertwined because nightmares often trigger an inability to initiate or maintain sleep.[11] Another suggestion is that the patient creates certain adaptations to cope with the perceived threat and that these adaptations are incompatible with sleep.[7]

NON-PHARMACOLOGICAL TREATMENTS

There are a number of non-pharmacological approaches to treatment of sleep disturbances in PTSD (Table 1). The treatment with the most evidence is a subtype of Cognitive Behavioral Therapy (CBT) known as Image Rehearsal Therapy (IRT).[12] IRT is often used for chronic nightmares and involves the patient recalling the nightmare, writing it down, and changing part of the nightmare to something more positive.[10] The patient then rehearses the scenario so they are able to displace the original nightmare when it occurs. Studies have shown moderate improvements in REM sleep and REM density, as well as decreased REM sleep latency. These results were paralleled by a decrease in nightmares and sleep complaints with IRT.[9] A series of Randomized Controlled Trials (RCTs) by Krakow et al. were performed to determine if IRT would reduce nightmares, increase sleep quality, and decrease overall distress levels of patients with PTSD compared to a control group. The intervention included three group sessions that focused on treating nightmares. The patients who received IRT were reported to have a significant reduction in the number of nightmares per week, improved sleep, and a decrease in mean PTSD severity scores. The effects were maintained at three and six month follow-up visits. However, only 114 out of 168 participants completed the three and six month follow ups.[7,13] This confers the possibility that patients may find this form of therapy challenging or difficult.[14] However, a meta-analysis of 13 studies using IRT showed that it improved sleep across a diverse range of samples and protocols.[15] A limitation is that only 5 of those 13 studies were RCTs. A limitation in the studies that evaluate the use of IRT in PTSD related sleep disturbances is that some of the study samples include patients with nightmares that do not meet the criteria for PTSD.[16]

CBT based treatments are considered first line by the Veterans Association (VA) and Department of Defense (DoD).[16] Cognitive Behavioral Therapy for Insomnia (CBTI) is another non-pharmacological option for patients with PTSD related sleep disturbances. CBTI uses a combination of cognitive and behavioral techniques including stimulus control therapy, sleep restriction therapy, relaxation training, cognitive restructuring, and sleep hygiene instructions. Although a promising treatment, to date there has been little research evaluating its efficacy in PTSD.[16] Additionally, there is ongoing research assessing if CBTI directly improves PTSD and major depressive disorder (MDD) symptoms.[17] This study is a parallel, single-blind trial. The primary outcome is the intensity and frequency of symptoms as measured by the Clinician Administered PTSD Scale (CAPS). The secondary outcome is severity of insomnia. The study began in January 2013 and is estimated to be completed by June 2015. The control group will receive 12 weeks of Cognitive Processing Therapy (CPT) and focuses on PTSD education, personal impact of trauma, emotions related to thoughts of trauma, and applying healthy thoughts and behaviors. The experimental group will receive 12 weeks of CPT as well as 4 CBTI sessions over 5 weeks.

Self-exposure therapy has also been studied in the treatment of sleep disturbances related to PTSD.[16] This treatment involves graded exposure by making a

Table 1. Non-pharmacologic treatment options

Treatment	Level of Recommendation	Level of Evidence	Number of Studies
IRT	A	1	1
		2	1
		3	1
		4	7
CBTI	No information available	No information available	No information available
Self-exposure therapy	C	2	1
		3	1
EDMR	C	4	2

hierarchical list of anxiety/distressing thoughts or dreams. The patient then mentally rehearses each item at his/her own rate, starting at the least anxiety provoking dream/thought, until the anxiety/distress from that dream/thought subsides.[10,18] In one study, self-exposure therapy was shown to be better than self-relaxation therapy in decreasing the number of nightmares the patient experiences.[10,18] However, nightmare intensity was not greatly reduced after 4 weeks of treatment which may indicate that a longer treatment course is needed or the treatment is not effective. A limitation of this study is there was a high dropout rate (17%).

Lastly, Eye Movement Desensitization and Reprocessing (EDMR) is a viable, non-pharmacological treatment option. EMDR is a first-line treatment per the International Society for Traumatic Stress Studies for PTSD; however, there have been few studies exploring its use in sleep disturbances in PTSD.[16] EMDR is a multifaceted treatment, integrating elements from many therapeutic modalities. The goal of EMDR is to reprocess distressing memories by recalling distressing thoughts and images along with saccadic eye movement tracking across the visual field for 20 seconds. This therapy stimulates neural mechanisms similar to REM sleep; using voluntary eye movements when experiencing distressing thoughts and images helps to reduce the anxiety associated with them.

It appears that an important element of successful non-pharmacologic treatment of nightmares is writing down the nightmare and rehearsing it while awake.[7] Germain, et al have suggested that it is the increased mastery over negative dream elements that is the core of the therapeutic process.[14] If the patient is experiencing both nightmares and insomnia, using both CBTI and IRT may be helpful.[16]

PHARMACOLOGICAL TREATMENTS

Although non-pharmacological treatments are considered first line therapy by the VA/DoD for PTSD related insomnia and nightmares, pharmacological treatments also have an important role in therapy.[16] Pharmacological modalities may be warranted when patients are treatment refractory or when patients are not adherent with non-pharmacological measures. A summary of pharmacological treatments can be found in Table 2.

The pharmacological agent with the most evidence to support its use in the treatment of sleep disturbances in PTSD is prazosin. It is currently recommended by the Standards of Practice Committee of the American Academy of Sleep Medicine for use in treating PTSD-associated nightmares.[10] Prazosin is the only alpha-1-adrenergic receptor antagonist that crosses the blood brain barrier (BBB) and is classified as an antihypertensive. The fact that it crosses the BBB is why it has been found effective in treating nightmares. The noradrenergic blocking capabilities of prazosin may help to normalize REM disruption.[9] In a placebo controlled study, prazosin was associated with increased sleep time and increased REM sleep time without affecting sleep-onset latency. The average therapeutic dose was 3 mg, however effective doses ranged between 1 and 10 mg. The length of treatment ranged between 3 and 9 weeks and was reported to be well tolerated.[10,19,20,21] There is a recent study that supports the use of higher doses of prazosin. In a randomized, placebo controlled study, veterans of conflict in Iraq and Afghanistan were given a maximum of 5 mg midmorning and 20 mg at bedtime for men, and a maximum of 2 mg midmorning and 10 mg at bedtime for women.[22] Primary endpoints included the nightmare component of the CAPS scale, the Pittsburgh Sleep Quality Index, and the change item anchored to functioning on the Clinical Global Impressions Scale. Prazosin was found to be superior to placebo for all three primary outcome measures. A possible limitation to this study is that high dose prazosin was compared to placebo and not to traditional dosing of prazosin. In the afore mentioned study, there were two patients who required hospitalization due to serious adverse events. One patient was hospitalized for suicidal ideation, and the other subject was hospitalized for a suicide attempt.

Another class of drugs that have been investigated are alpha adrenergic agonists, such as guanfacine and clonidine. These medications block the outflow of sympathetic nervous system signals throughout the brain. The Standards of Practice Committee of the American Academy of Sleep Medicine state that clonidine may be considered for treatment of PTSD-associated nightmares.[10] Two case series report efficacy of 0.2 to 0.6 mg of clonidine in divided doses to reduce PTSD related nightmares.[10,23,24]

Selective Serotonin Reuptake Inhibitors (SSRIs) are considered first line treatments for PTSD and used to treat all four symptom clusters affiliated with PTSD.[25-27] However, there is conflicting evidence regarding these agents for treating sleep disturbances. SSRIs that have been studied in treating sleep disturbances in patients with PTSD include fluoxetine, sertraline, and paroxetine.[28] Fluoxetine has inconsistent evidence regarding its usage. Some studies have shown that fluoxetine can lead to

Table 2. Pharmacologic treatment options

Treatment	Level of Recommendation	Level of Evidence	Number of Studies
Alpha-1-Adrenergic Receptor Antagonists			
Prazosin	A	1	3
		4	4
Alpha Adrenergic Agonists			
Clonidine	C	4	2
Guanfacine	No information available	No information available	No information available
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Fluoxetine	No information available	No information available	No information available
Paroxetine	No information available	No information available	No information available
Selective Norepinephrine Reuptake Inhibitors (SNRIs)			
Duloxetine	No information available	No information available	No information available
Venlafaxine	B (negative results)	1	1
Tricyclic Antidepressants (TCAs)			
Amitriptyline	C	4	1
Imipramine	C	4	1
Monoamine Oxidase Inhibitors (MAOIs)			
Phenelzine	C	4	2
Misc. Antidepressants			
Mirtazapine	No information available	No information available	No information available
Fluvoxamine	C	4	2
Nefazodone	C	4	3
Trazodone	C	4	1
Atypical Antipsychotics			
Aripiprazole	C	4	1
Olanzapine	C	4	1
Risperidone	C	4	2
Benzodiazepines			
Clonazepam	No recommendation; Sparse data	2	1
Temazepam	No information available	No information available	No information available
Sedative Hypnotics			
Eszopiclone	No information available	No information available	No information available
Zolpidem	No information available	No information available	No information available
Antiepileptics			
Gabapentin	C	4	1
Topiramate	C	4	1

significant improvements in total sleep time, sleep onset latency, and wake after sleep onset;[26,8] while other studies have found that fluoxetine decreases total sleep time, is associated with shallower levels of sleep, and increases the amount of daytime sleepiness.[8,27] In a RCT of sertraline, there was no reported improvement in sleep quality and insomnia was frequently reported.[28] Placebo controlled trials have shown paroxetine to be efficacious in reducing PTSD related sleep disturbances.[28,29]

The Serotonin and Norepinephrine Reuptake Inhibitor (SNRI), venlafaxine, is not recommended by the Standards of Practice Committee of the American Academy of Sleep Medicine guidelines.[10] A study of venlafaxine ER (37.5 – 300 mg/d) in the treatment of 340 subjects with PTSD related sleep disturbances showed no significant differences between venlafaxine ER and placebo on the Clinician Administered PTSD Scale Symptoms, item 17 (CAPS-SX_{17}) 'Distressing Dreams'. No adverse effects were reported in the study, and there was no long-term follow up.[10,30]

Duloxetine, a SNRI, was recently studied in a sample of treatment refractory patients. Significant reductions in nightmares were reported; however, the study was uncontrolled and did not use a validated sleep assessment.[31,2] Tricyclic antidepressants, specifically amitriptyline and imipramine, have been shown to increase the length of the sleep cycle and decrease the number of awakenings when acutely administered in older, small RCTs.[8,16] However, most TCAs also decrease the amount of REM sleep, which is associated with sleep

fragmentation.[25] Their utility is limited due to potential severe adverse effects, including cardiac conductivity abnormalities and anticholinergic activity.[16] TCAs are considered third line therapy by the VA/DoD and are usually considered when other options have failed.[25,32]

The monoamine oxidase inhibitor (MAOI), phenelzine, has been reported to decrease insomnia and reduce nightmares. One small study (n=5) reported complete elimination of nightmares in three patients after one month and remained nightmare-free for up to 18 months after the trial. Effective doses ranged between 30 and 90 mg.[10,33] Another study (n=21) found that treatment resulted in minimal and short lived effects.[10,34] The adverse effects of this medication class limit its usefulness in treatment. Additionally, many patients with PTSD have comorbid substance abuse issues, so these patients would be less likely to be adherent to the strict dietary restrictions that accompany the administration of this class of medication. As with TCAs, MAOIs are also considered third line therapy by VA/DoD and are utilized when other treatment options have failed.[2,32]

Other antidepressants that have been investigated include mirtazapine, trazodone, nefazodone, and fluvoxamine. In a study of 60 hospitalized veterans, trazodone was found to decrease the frequency of nightmares in patients with sleep disturbances with PTSD but also had significant adverse effects such as orthostatic hypotension, daytime sleepiness, headache, dizziness, and priapism. Dosages ranged from 25 to 600 mg, with a mean of 212 mg.[10,35] Trazodone is a 5-HT_2 receptor antagonist with alpha-1-adrenoreceptor blocking actions. Although evidence is 'low grade and sparse' according to the Standards of Practice Committee of the American Academy of Sleep Medicine, trazodone is commonly used in PTSD-related sleep disturbances.[36] Nefazodone is not recommended as first line therapy by the Standards of Practice Committee of the American Academy of Sleep Medicine due to increased risk of hepatotoxicity.[2] There are two case series that report moderate-to-high efficacy of using up to 300 mg of fluvoxamine.[2,8,37,38] The greatest efficacy was seen in trauma related dreams and sleep maintenance.[25,38] However, fluvoxamine was poorly tolerated due to gastrointestinal symptoms. In one study, only 11 of the 24 original subjects completed the trial.[25,37]

Atypical antipsychotics such as olanzapine, risperidone, and aripiprazole have small case series studies that evaluate their efficacy in treating sleep disturbances in PTSD. It is thought that atypical antipsychotics may reduce PTSD related anxiety and insomnia because of the dual antagonism of serotonin and dopamine.[1] A small, uncontrolled case study reported rapid improvement in symptoms after the addition of 10-20 mg of olanzapine to the patient's treatment regimen. However, there was no quantification of medication effect and no long term follow up. There were no adverse effects seen.[10,39] Two case series reported moderate to high efficacy of risperidone in treating PTSD related nightmares. Dosages ranged from 0.5 mg to 3 mg/day in these studies. Adverse effects were not noted in either study, and there was no long term follow up.[10,40,41] A case series evaluated the effect of 15-30 mg of aripiprazole at bedtime with CBT or aripiprazole with sertraline in patients with combat PTSD. There was significant improvement in both arms of the study, but not total resolution of sleep disturbances such as nightmares in this population.[10,42] The lack of empiric evidence for each of these studies greatly limits the generalizability of these results.

Benzodiazepines, although often prescribed for sleep disturbances, are not recommended to be used in the treatment of PTSD patients with sleep disturbances because the potential risks of these agents outweigh the benefits.[16] A single-blind, placebo controlled, crossover trial found that clonazepam was ineffective for treatment of PTSD related sleep disturbances. Although 1-2 mg improved sleep initiation and maintenance, differences were not statistically significant, and there was no improvement in nightmare intensity.[10,43] Temazepam was tested in a placebo controlled trial and was shown to improve subjective measures of sleep but the effects were not maintained after treatment.[36,21] In addition, benzodiazepines may worsen sleep apnea, which is often a comorbid condition in patients with PTSD.[25]

The sedative hypnotics zolpidem and eszopiclone have also been evaluated for efficacy in treating PTSD related sleep disturbances. These medications are less likely than benzodiazepines to exacerbate sleep apnea[25] and have a lower risk for tolerance, dependence, and withdrawal.[16] They are preferred over benzodiazepines and are considered second-line therapy for PTSD-related insomnia by the VA/DoD.[16] Zolpidem has been found to decrease insomnia and may also help to alleviate nightmares.[16,44,45] A RCT of 788 patients treated with eszopiclone for primary insomnia reported increased sleep continuity with no indication of tolerance, withdrawal symptoms, or rebound insomnia. However, there is limited evidence regarding the efficacy of this medication in PTSD related insomnia.[16,46]

Antiepileptics such as topiramate and gabapentin have also been studied. There was a case series that studied

the efficacy of topiramate in sleep disturbances in PTSD. Dosage began at 12.5 to 25 mg and was increased at 25 to 50 mg intervals until a therapeutic response was achieved or the drug could no longer be tolerated.[2,10,47] The study reported that 79% of patients had a reduction in nightmares and full suppression of nightmares in 50% of patients when using topiramate. Follow-up ranged between 1 and 119 weeks, and 9 patients discontinued treatment due to adverse effects. Adverse effects that were reported were urticaria, loss of appetite, acute narrow angle glaucoma, severe headaches, overstimulation/panic, emergent suicidal ideation, and memory concerns.[10,47] More controlled studies using topiramate may be useful as the reduction in nightmares appears to be substantial in this case series. A retrospective study using 300-3600 mg of gabapentin as adjunctive therapy for PTSD related sleep disturbances showed a medium to high effect in improvement of insomnia and reduction of nightmares over a follow up period of 1 to 36 months. The mean dosage for patients with marked clinical improvement was 1344 ± 701 mg. Common adverse effects associated with gabapentin include sedation and mild dizziness.[10,48]

CONCLUSION

Although there are a number of treatment modalities available for treating PTSD related sleep disturbances, empiric evidence supporting these treatments is lacking.

CBT based non-pharmacologic therapies are currently considered first line for treating PTSD-related sleep disturbances. The treatment modality with the most evidence to support its use is IRT. IRT is highly effective in reducing the intensity of chronic nightmares and negative emotions that are related to nightmares. An additional benefit of IRT is that if improved sleep may lead to an improvement in patients' mood and reduction in daytime symptoms of PTSD. Veterans and sexual assault victims were shown to benefit from IRT and thus may be considered ideal candidates for this treatment.

Pharmacologic therapies are currently considered second-line as an adjunct to non-pharmacological therapies in patients who have not responded to non-pharmacologic measures alone. Prazosin, an alpha-adrenergic receptor antagonist, has the most evidence supporting its use in PTSD- related sleep disturbances. The doses that were used in most of the studies ranged between 1 and 10 mg/day, however there is a recent study that has used doses up to 25 mg/day. While studies have reported that prazosin is well tolerated, it is not a benign medication. Adverse effects that may limit its use include orthostatic hypotension, dizziness, syncope, pedal edema, tachycardia, angina and priapism. Certain patient populations including patients with unstable angina, heart failure, arrhythmias or orthostatic hypotension may need more vigilant monitoring.

Although all of the other pharmacologic agents may not have a lot of support, the Standards of Practice Committee do provide recommendations for a number of these agents.The other medication classes that have been studied include adrenergic agonists, SSRIs, SNRIs, TCAs, MAOIs, atypical antipsychotics, benzodiazepines, sedative hypnotics, and anticonvulsants. Much of the literature surrounding these medications is conflicting and most of the studies were uncontrolled, lacked appropriate follow-up, or did not use validated assessment tools. In conclusion, sleep disturbances associated with post-traumatic stress disorder may be treated utilizing various non-pharmacologic and pharmacologic methods. In the future, a focus on quality studies is necessary for a successful approach to evidence-based medicine and improvement in patient care.

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