Pharmacological Treatment of Nightmares and Insomnia in Posttraumatic Stress Disorder: A Review

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Abstract

Symptoms of sleep disturbance, particularly nightmares and insomnia, are a central feature of posttraumatic stress disorder (PTSD). Furthermore, emerging evidence suggests that specific treatment of PTSD-related sleep disturbance improves other symptoms of the disorder, suggesting that such disturbance may, in fact, be fundamental to development and maintenance of the disorder. This mini-review focuses on pharmacological treatment of sleep disturbance in adult PTSD (specifically, studies testing the efficacy of antidepressants, adrenergic inhibiting agents, antipsychotics, and benzodiazepine and non-benzodiazepine hypnotics). We conclude that only prazosin, an adrenergic inhibiting agent, has had its efficacy established by multiple randomized controlled trials. There is also high-level evidence supporting the use of eszopiclone, as well as risperidone and olanzapine as adjunct therapy. Antidepressants such as sertraline, venlafaxine, and mirtrazapine, benzodiazepines such as alprazolam and clonazepam, and non-benzodiazepine hypnotics such as zolpidem appear ineffective in treating PTSD-related sleep disturbance. Most studies that report reduced frequency of nightmares and insomnia also report decreases in overall symptom severity. Such findings suggest that (a) sleep disruption is central to PTSD, and (b) treating sleep disruption may be an effective way to address other symptoms of the disorder, and (c) PTSD symptoms tend to cluster together in predictable ways.

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Sleep disturbance is a central feature of posttraumatic stress disorder (PTSD). Within the four symptom clusters that define its formal diagnostic criteria (re-experiencing, numbness and avoidance, negative alterations in cognitions and mood, and hyperarousal; American Psychological Association, 2013), nightmares feature prominently as a re-experiencing symptom, and difficulties with sleep initiation and maintenance feature prominently as symptoms of hyperarousal.

Sleep disturbance in the aftermath of trauma predicts the development of PTSD (Bryant et al., 2010, Mellman et al., 2007), which suggests that sleep disturbance is more than a secondary symptom of PTSD, and that it may in fact be fundamental to the development and maintenance of the condition (Spoormaker and Montgomery, 2008). Additionally, emerging evidence suggests that specific treatment of PTSD-related sleep disturbance improves other symptoms of the disorder (Casement and Swanson, 2012). From this viewpoint, it is important to understand how to treat sleep disturbance in patients with PTSD, as it seems possible that targeting sleep disturbance specifically, rather than treating PTSD symptomatology generally, may be an effective approach to alleviating at least some of the distress associated with the disorder.

In this brief review, we focus on pharmacological treatment of sleep disturbance in adult PTSD. We describe the nature of sleep disturbance in PTSD and review studies that evaluate, with either primary or secondary sleep-related outcomes, the efficacy of pharmacological treatment for PTSD. We discuss the efficacy of antidepressants, adrenergic inhibiting agents, antipsychotics, and benzodiazepine and non-benzodiazepine hypnotics in improving PTSD-related sleep disturbance. We do not include in the review drugs for which the only evidence regarding efficacy in treating PTSD-related sleep disturbance emerges

from a single open-label study, or from case studies. We conclude by summarizing evidence regarding the question of whether relief of sleep-related symptoms is associated with a reduction in the presence of other symptoms of the disorder.

Sleep Disturbance in PTSD

When compared to healthy controls, PTSD-diagnosed individuals report poor sleep quality. Specifically, they describe poor sleep efficiency, longer sleep latency, disrupted sleep maintenance, an increased number of awakenings, and more frequent occurrence of non-restorative sleep (see, e.g., Herbst et al., 2010).

Studies that feature objective measures of sleep (e.g., polysomnographic [PSG] recordings) do not provide data that are wholly consistent with these self-reports of sleep disturbance in PTSD-diagnosed individuals, however. Specifically, whereas some PSG studies report markedly disturbed sleep in PTSD (Dow et al., 1996; Germain and Nielsen, 2003), others do not (Breslau et al., 2004; Klein et al., 2002). Even within PSG studies which suggest that sleep is disrupted in PTSD, there is disagreement as to whether the amounts of slow-wave sleep (SWS) and rapid eye movement (REM) sleep are increased or decreased (Engdahl et al., 2000; Hefez et al., 1987; Habukawa et al., 2007; Lavie et al., 1979).

A meta-analysis that attempted to consolidate these discrepant PSG findings (Kobayashi et al., 2007) concluded that PTSD-diagnosed individuals, relative to those without the diagnosis, experience disrupted sleep, characterised by increased stage 1 light sleep, decreased SWS, and increased REM density. Follow-up exploratory analyses suggested that the particular characteristics of sleep disruption in PTSD may vary according to moderating variables such as gender and age.

Pharmacological Treatment of Sleep Disruption in PTSD

The vast majority of studies evaluating the efficacy of pharmacological therapy for PTSD have measured changes in symptom status using standardised self-report and clinician-report instruments that either (a) aggregate scores across different clusters/scales into a single outcome score, or (b) use a single rating scale to assess global functioning. A few studies also report sleep-specific outcomes alongside aggregate or global measures (e.g., Davidson et al., 2001; Stein et al., 2002). Additionally, a small number of studies focuses primarily on changes in sleep-related outcomes and only secondarily on aggregate or global functioning (e.g., Germain et al., 2012; Raskind et al., 2003). Our focus is on the second and third categories of studies. We begin our review by examining the available evidence regarding antidepressants, also summarised in Table 1.

Antidepressants. Traditional approaches to pharmacological treatment of PTSD have involved selective serotonin reuptake inhibitors (SSRIs), which are accepted as first-line treatment for symptoms of the disorder (Baldwin et al., 2014; Berger et al., 2009; Nappi et al., 2012). Reviews of clinical trials suggest that the efficacy of SSRIs for the treatment of PTSD symptomatology, generally, is relatively small when compared to placebo (Berger et al., 2009; Difede et al., 2014).

Regarding SSRI studies that measure sleep quality as an outcome, results are mixed. For example, a double-blind randomised control trial (RCT) of fluoxetine for PTSD reported a small but significant reduction in insomnia symptoms, but not nightmares (Meltzer-Brody et al., 2000). An RCT of sertraline for PTSD showed no improvement in self-reported sleep quality; of note is that a small number of participants taking sertraline rather than placebo reported insomnia as an adverse event (Davidson et al., 2001). This latter finding, although relatively minor in the context of PTSD-related studies, is consistent with data from studies investigating the use of SSRIs in other psychiatric disorders. For instance, a pooled analysis

of three RCTs examining the efficacy of fluoxetine compared to nefazodone for depression showed that the introduction of fluoxetine disrupted sleep continuity (Rush et al., 1998).

Regarding **serotonin-**norepinephrine reuptake inhibitors, only low-level evidence supports their efficacy in PTSD. For instance, two open-label studies of duloxetine showed reductions in the occurrence of sleep disruption and nightmares, as well as improved mood and a decreased number of PTSD symptoms (Villarreal et al., 2010; Walderhaug et al., 2010). The generalisability of these results is limited by the uncontrolled nature of the studies. Furthermore, venlafaxine, specifically, is not recommended for the treatment of nightmares. Although this drug is known to improve PTSD symptoms generally (Jeffreys et al., 2012), a pooled analysis of two RCTs showed no benefit of venlafaxine over placebo for treatment of nightmare frequency and severity (Stein et al., 2009).

Few studies have examined the efficacy of tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) in reducing the occurrence of PTSD-related nightmares and insomnia. Only low-level evidence supports the use of imipramine and phenelzine for this purpose (Boehnlein et al., 1985; Davidson et al., 1987; Kinzie and Leung, 1989; Lerer et al., 1987). Furthermore, the common occurrence of adverse events associated with MAOI use makes that class of drug an unlikely candidate for frequent use (Jeffreys et al., 2012).

Regarding **receptor-acting antidepressants**, a number of open-label studies of nefazodone report (a) reductions in the prevalence of subjectively reported nightmares, (b) decreased overall sleep disruption (e.g., prolonged sleep latency and increased awakenings), and (c) improved PSG sleep parameters such as total sleep time and percentage of time spent in SWS (see e.g., Davidson et al., 1998; Gillin et al., 2001; Neylan et al., 2003; for review of other open-label studies, see Van Liempt et al., 2006). There is very little high-level evidence, however, to support the use of this medication for reduction of PTSD-related nightmares and insomnia. One small RCT (N = 26) comparing nefazodone to sertraline found

that both medications improved self-reported sleep quality (McRae et al., 2004). In that study, more participants taking nefazodone than sertraline reported insomnia as an adverse event, although nefazodone did decrease the occurrence of nightmares more than sertraline did. Recommendations based on that study must be made with the following caveats in mind: (a) the sample size was small, (b) there was no placebo control, and (c) nefazodone must be prescribed with caution and its use monitored consistently because in rare cases it causes hepatotoxicity (Rosack, 2002).

Another **receptor-acting antidepressant**, trazodone, is often prescribed for PTSD-related sleep disturbance (Maher et al., 2006). However, only low-level evidence (viz., survey, open-label, and clinical observation studies) supports the efficacy of this medication in reducing nightmares and insomnia (Ashford and Miller, 1996; Hertzberg et al., 1996; Warner et al., 2001).

Regarding mirtrazapine, **another receptor-acting antidepressant**, an early report based on clinical observation (Lewis, 2002) suggested **it** may be effective in treating PTSD-related sleep disruption. However, a recent RCT that evaluated mirtazapine as an adjunct therapy to sertraline in PTSD-diagnosed individuals showed that the combined pharmacotherapeutic intervention offered no advantage over sertraline alone in reducing self-reported sleep disruption (Schneier et al., 2015).

Adrenergic inhibiting agents. Among this class of drugs, prazosin, a lipophilic drug originally developed to treat hypertension, has garnered the most empirical support for treatment of PTSD-related sleep disturbance (Green, 2014). Prazosin crosses the blood-brain barrier easily, and, **blocks** activity at α_1 receptor sites. This action ameliorates the increase in noradrenergic activity that PTSD-diagnosed individuals experience frequently, and especially at night (Berger et al., 2009).

Six independent double-blind (RCTs) have evaluated whether prazosin, as adjunct to participants' currently prescribed medication regimen, is effective at reducing the occurrence of PTSD-related nightmares. Five of those studies (Ahmadpanah et al., 2014; Raskind et al., 2003, 2007, 2013; Taylor et al., 2008) reported that participants taking prazosin, rather than placebo in addition to their currently prescribed regimen, had decreased nightmare frequency and intensity, as well as a reduction in other PTSD symptoms. The sixth (Germain et al., 2012) did not report such improvements, but did show that PTSD-diagnosed individuals taking the combination pharmacotherapy had, relative to placebo, reduced insomnia severity and improved daytime PTSD symptoms. In all of these studies, blood pressure and adverse events for participants taking prazosin were comparable to those taking placebo, indicating that the medication was well tolerated.

Numerous other studies provide lower-level evidence that corroborates the findings presented by those six RCTs (see, e.g., Calohan et al., 2010; Thompson et al., 2008; for a review, see Berardis et al., 2015). For instance, a chart review examining the efficacy of prazosin and quetiapine in reducing night-time symptoms of PTSD showed that both drugs improved such night-time symptoms over a 6-month period. However, prazosin was more likely to be used 3-6 years later, was associated with fewer adverse effects, and was more likely to be discontinued due to the resolution of symptoms (Byers et al., 2010).

There is no high-level evidence for the efficacy of other adrenergic inhibiting agents in treating PTSD-related nightmares and insomnia. However, clonidine has been the subject of small-sample open-label trials and case studies (Kinzie and Leung, 1989; Kinzie et al., 1994). These studies report reductions in subjective sleep complaints and in nightmares.

Antipsychotics. Olanzapine, risperidone, and quetiapine have been used to treat symptoms of PTSD (Berger et al., 2009). These **antipsychotic** drugs antagonise dopamine and serotonin receptors, and have affinity for α_1 **and histamine H1** receptor sites. There is

some high-level support for this class of drugs as adjunctive therapy to other treatment, but not as monotherapy. For example, an RCT examining the efficacy of olanzapine as an adjunct to SSRI treatment for PTSD found that, relative to placebo, it reduced sleep disturbance as well as other symptoms (Stein et al., 2002). Data from an open- label study support those findings (Jakovljevic et al., 2003). In contrast, Butterfield and colleagues (2001) showed that olanzapine as monotherapy, in comparison with placebo, was ineffective for treating PTSD-related sleep disturbance.

Furthermore, individuals who participated in a RCT of risperidone adjunctive to sertraline for refractory PTSD showed reduced symptoms of insomnia relative to those receiving placebo. There were, however, no between-group differences with regard to other symptoms of the disorder (Rothbaum et al., 2008). Lower-level evidence corroborates these findings (David et al., 2006).

Regarding the efficacy of quetiapine for PTSD-related sleep disruption, one open-label study and one chart review described, respectively, improvements in self-reported sleep quality and decreased sleep disturbance and nightmares (Byers et al., 2010; Robert et al., 2005). Both studies included participants who were taking other psychotropic medications.

Benzodiazepines and non-benzodiazepine hypnotics. Benzodiazepines are commonly prescribed for PTSD-related insomnia (Nappi et al., 2012). Available evidence does not support their use, however. Two small-sample RCTs examining the efficacy of alprazolam and clonazepam in reducing symptoms of PTSD, including insomnia and nightmares, found that these medications had no advantage over placebo (Braun et al., 1990, Cates et al., 2004). Furthermore, some studies suggest that benzodiazepines might interfere with the extinction of fear conditioning, and may therefore impede recovery after trauma exposure (van Minnen et al., 2002). This class of drugs is also associated with the risk of

dependence, especially in individuals with a history of substance abuse, and with severe withdrawal symptoms after prolonged use in some patients (Maher et al., 2006).

Although non-benzodiazepine hypnotics have a better side effect profile than traditional benzodiazepines, and do not disrupt sleep architecture (Nutt and Stahl, 2010), the available evidence does not support their use for treatment of PTSD-related nightmares and insomnia. For example, an RCT examining the efficacy of zolpidem as adjunctive therapy to an SSRI found that, compared to hypnotherapy, the drug did not decrease sleep disturbance or other PTSD-related symptoms (Abramowitz et al., 2008).

In contrast to these negative findings, participants in a recent placebo-controlled cross-over RCT of eszopiclone reported a reduction in PTSD-related symptoms (e.g., improved overall sleep quality and reduced sleep latency; Pollack et al., 2011). This study was somewhat limited by its small sample size ($N = 24$) and its short duration (3 weeks in each condition).

Summary and Conclusions Regarding the Relevance of Sleep-Focused PTSD Treatment

Although numerous studies have tested the efficacy of a range of antidepressants, adrenergic inhibiting agents, antipsychotics, and benzodiazepine and non-benzodiazepine hypnotics in treating PTSD-related sleep disturbance, only prazosin has had its efficacy established in more than one RCT. There is also, however, high-level evidence supporting the use of eszopiclone, as well as risperidone and olanzapine as adjunct therapy, in treating PTSD-related insomnia and nightmares. Evidence is less strong for fluoxetine and nefazodone.

The available evidence suggests that antidepressants such as sertraline, venlafaxine and mirtrazapine, benzodiazepines such as alprazolam and clonazepam, and non-

benzodiazepine hypnotics such as zolpidem are not effective in treating PTSD-related sleep disturbance.

Most studies that report reduced frequency of PTSD-related nightmares and insomnia also report improved global functioning and decreases in overall symptom severity (see, e.g., Raskind et al., 2013; Stein et al., 2002; but see Rothbaum et al., 2008). Although these studies cannot demonstrate a causal relationship between improved sleep and improved overall functioning, their results support the hypothesis that sleep disruption is not merely a secondary symptom of PTSD, but is central to the disorder.

Understanding sleep disruption as a central component of PTSD has important implications. It allows one to integrate two separate, but substantial and growing, strands of literature: first, studies showing that healthy sleep is critical for intact memory functioning, emotion regulation, and fear extinction (Walker, 2009), and, second, studies showing that declarative memory impairment, emotion dysregulation, and problems with fear extinction are commonly reported in PTSD (Brewin et al., 2007; Litz et al., 2000; Rauch et al., 2006). This integration suggests that sleep disruption in PTSD might contribute to manifestation of other symptoms. Hence, treating sleep disruption may not only provide a novel and effective way to address other symptoms of the disorder, but may also support the argument that PTSD symptoms do not exist in isolation but rather tend to cluster together in predictable ways.

Conflicts of Interest

The authors declare no conflict of interest.

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