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REVIEW ARTICLE

Pharmacological Management of Nightmares Associated with Posttraumatic Stress Disorder

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Abstract

Posttraumatic stress disorder (PTSD) can be a chronic and disabling condition. Post-traumatic nightmares (PTNs) form a core component of PTSD and are highly prevalent in this patient population. Nightmares in PTSD have been associated with significant distress, functional impairment, poor health outcomes, and decreased quality of life. Nightmares in PTSD are also an independent risk factor for suicide. Nightmare cessation can lead to improved quality of life, fewer hospital admissions, lower healthcare costs, and reduced all-cause mortality. Effective treatment of nightmares is critical and often leads to improvement of other PTSD symptomatology. However, approved pharmacological agents for the treatment of PTSD have modest effects on sleep and nightmares, and may cause adverse effects. No pharmacological agent has been approved specifically for the treatment of PTNs, but multiple agents have been studied. This current narrative review aimed to critically appraise proven as well as novel pharmacological agents used in the treatment of PTNs. Evidence of varying quality exists for the use of prazosin, doxazosin, clonidine, tricyclic antidepressants, trazodone, mirtazapine, atypical antipsychotics (especially risperidone, olanzapine and quetiapine), gabapentin, topiramate, and cyproheptadine. Evidence does not support the use of venlafaxine, β-blockers, benzodiazepines, or sedative hypnotics. Novel agents such as ramelteon, cannabinoids, ketamine, psychedelic agents, and trihexyphenidyl have shown promising results. Large randomized controlled trials (RCTs) are needed to evaluate the use of these novel agents. Future research directions are identified to optimize the treatment of nightmares in patients with PTSD.

Key Points

Post-traumatic nightmares (PTNs) are a core component of posttraumatic stress disorder (PTSD) and are highly prevalent, but no pharmacological agent has been specifically approved for PTNs.

Evidence of varying quality exists for prazosin, doxazosin, clonidine, tricyclic antidepressants, trazodone, mirtazapine, fluvoxamine, atypical antipsychotics, gabapentin, topiramate, and cyproheptadine.

Evidence does not support the use of venlafaxine, β-blockers, phenelzine, benzodiazepines, or sedative hypnotics.

Novel agents that are promising but lack more supportive data include ramelteon, cannabinoids (nabilone), ketamine, MDMA, and trihexyphenidyl.

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1 Introduction

Posttraumatic stress disorder (PTSD) can be a debilitating and often chronic disorder that may develop following trauma exposure [1]. Recurrent intrusive memories, nightmares/distressing dreams, hyperarousal, avoidance, and dissociative reactions form part of the symptomatology. For example, patients may exhibit persistent avoidance of people, places, activities, or situations associated with trauma-related stimuli as part of the disorder presentation [2]. Furthermore, negative changes in cognition, depressed mood, irritability, and hyperarousal lead to clinically significant distress and functional impairment [1, 2].

1.1 Sleep Disorders and Posttraumatic Stress Disorder (PTSD)

PTSD-related sleep disorders are a core feature of PTSD [3]. Sleep disorders have a prevalence of 60–90% in individuals with PTSD [4–7]. Variation in reported prevalence may be attributed to different population demographics such as sex, differences in assessment methods, severity of sleep disturbances, and type of trauma exposure [8]. Some of the commonly occurring sleep disorders include insomnia, limb movement disorders (e.g., increase in periodic limb movements), nightmare enactment, and panicked awakenings [9]. The latter have been suggested to be phenomenologically related to sleep terrors [9].

Post-traumatic sleep disturbances can predict PTSD onset and severity [3]. Recent studies suggest that sleep disturbances that precede trauma exposure are a risk factor for PTSD development [8] as well as contribute to the etiology of PTSD rather than only being a secondary symptom [10]. Untreated sleep disturbances can maintain and exacerbate PTSD symptoms [10]. Sleep disturbances are also strongly associated with the experience and perpetration of interpersonal violence [11]. Not only are interpersonal violence victims prone to PTSD and sleep disorders, but PTSD sufferers with sleep disorders are more prone to inflict interpersonal violence [11].

Post-traumatic nightmares (PTNs) are a common phenomenon associated with PTSD, with a reported prevalence as high as 88% [4, 12, 13]. They are considered different from non-trauma based nightmares [14]. Nightmares are a form of dreaming that typically induce fear (less frequently anger or disgust) and will generally wake the dreamer from rapid-eye movement (REM) sleep [15]. Clear recall of the disturbing mentation is usually possible [15]. In addition to the aforementioned characteristics, PTNs consist of re-experiencing prior traumatic experiences, and are typically intrusive, recurrent and emotional [16]. Nightmares constitute one of the DSM-5 criteria for PTSD [2]. PTNs may persist following successful treatment of PTSD [17, 18]. Persistence of nightmares in PTSD had led to the conceptualization of PTNs as an independent sleep disorder [3, 19].

The exact pathophysiology of PTNs remains elusive. It has been suggested that nightmares are a consequence of a more aroused brain during sleep [20]. Several meta-analyses have shown, for example, that patients with PTSD have less slow-wave sleep and lower sleep efficiency [9], and that these disturbances are more severe in patients with PTSD who have PTNs [20]. These patients spend relatively more sleeping time in REM, which is when nightmares occur. This might be related to hyperactivation of the locus coeruleus, the most important norepinephrine nucleus in the brain [9], or decreased parasympathetic tone [21]. Nightmares may occur as a side effect of medications that influence norepinephrine, serotonin, and dopamine, while withdrawal of cholinergic agents or medications that affect gamma-aminobutyric acid (GABA) systems may also induce nightmares [22]. This provides some evidence for the involvement of these neurotransmitters in nightmare production. PTNs worsen the prognosis of PTSD, possibly via the disruption of normal processing of traumatic memories during sleep [20]. PTNs may worsen and be worsened by behavioral changes such as sleep avoidance [14] and by the direct effects on sleep architecture of comorbid substance use [20].

Trauma-related sleep disorders may be comorbid with PTNs. Similarly, PTNs may lead to other sleep disturbances such as sleep avoidance or insomnia [14], and may adversely affect daytime PTSD symptoms [23]. Studies have found that nightmares are an independent risk factor for suicide [24]. Persistent chronic nightmares, in particular, increase suicide risk [24] and are associated with repeated suicide attempts as well as non-suicidal self-injury (NSSI) [25]. This emphasizes the need for early aggressive treatment [25]. PTNs may, furthermore, result in a higher burden of comorbid anxiety disorders and depression, as well as feelings of hopelessness.

Recent studies have documented sleep disturbances on polysomnography in trauma-exposed individuals during non-REM sleep, which has led to the proposition of a separate parasomnia called trauma-associated sleep disorder (TSD), originally described in military veterans [26]. It is theorized that TSD results from increased sleep deprivation with consequent decreased inhibition of the amygdala by higher cortical structures [27]. Patients with TSD commonly have comorbid insomnia and obstructive sleep apnea (OSA) [28]. Core features of PTSD, namely dream enactment or REM without atonia (RWA), are, however, absent in PTNs, differentiating the two phenomena. There may also be an absence of daytime symptoms in TSD [26]. These studies suggest that non-REM nightmares that are clinically

relevant can occur with implications for their treatment in TSD. Optimal pharmacological management of TSD is not known [27].

1.2 Treatment Guidelines

Multiple treatment guidelines exist to guide practitioners in the management of patients with PTSD, but only some comment on the management of PTN. Guidelines also differ significantly in the treatments that they recommend for PTNs. Guidelines such as the National Institute for Clinical Excellence (NICE), World Federation of Societies of Biological Psychiatry (WFSBP), American Psychological Association (APA), and International Society for Traumatic Stress Studies (ISTSS) do not address targeted treatment of nightmares, despite the fact that PTNs are often resistant to treatment. The Anxiety Disorders Association of Canada (ADAC) recommends prazosin as first-line treatment of PTN, and others recommend it as third-line management or do not make specific recommendations [29]. Guidelines that do address PTNs often lack detail on the management of PTNs compared to pharmacological recommendations for the management of PTSD [29]. A position paper was released in 2018 by the American Academy of Sleep Medicine (AASM) on the treatment of nightmare disorder in adults, including PTNs [22]. The position paper includes various pharmacological, behavioral and psychological therapies, and provides a good synthesis of treatments that are recommended versus those that are not.

A recent study surveying Australian and New Zealand psychiatrists about their pharmacological management of PTSD and PTNs found that the most frequent used guideline was more than 10 years old, and peer-reviewed journals were the most frequently used source for assisting their practice. Collectively, the psychiatrists had trialed 35 different medications to treat PTNs, emphasizing the lack of guideline recommendations for this disorder [30].

2 Pharmacological Treatment Interventions

Currently, only two slow-acting antidepressants (SAADs), the selective serotonin re-uptake inhibitors (SSRIs) sertraline and paroxetine, have US Food and Drug Administration (FDA) approval for the management of PTSD [1]. These, as well as selective serotonin and noradrenaline reuptake inhibitors (SNRIs), namely venlafaxine, are recommended as first-line treatment for PTSD, and have been confirmed as efficacious in multiple studies [4, 31]. The beneficial effects of these medications on sleep and sleep-related disorders are typically modest, and these agents may even lead to adverse effects [4]. It is known that sleep disturbances may also have an influence on the efficacy of first-line PTSD pharmacological treatments, and consequently constitute a risk factor for poor treatment outcomes [10, 32]. As a result, adjunctive medications are commonly indicated for the management of sleep disorders.

In the sections below we provide a narrative review of the most recent evidence regarding the pharmacological management of PTN, paying attention to efficacy and tolerability. In addition, the mechanism of action of some of these agents are discussed. Relevant publications were identified by searching PubMed and Cochrane databases. All searches included ["PTSD" or "posttraumatic stress disorder"] AND ["nightmares" or "post trauma nightmares" or "PTN"] AND "treatment' with follow-up searches that included specific pharmacological agents. No limit was set on date of publication to include all appropriate publications considering that this is a narrative review. Only articles that were available in English were included. Search matches were not restricted to the type of publication (e.g., review, original research, editorial). All publications that were included were peer reviewed. The literature was accumulated between September and December 2021 and included all published literature up to December 2021.

2.1 Antidepressants

Multiple antidepressant agents from various classes have been extensively researched for their efficacy in the treatment of PTSD. We focus on agents that have been investigated exclusively for their effects on PTSD-related sleep disorders, specifically nightmares.

2.1.1 Selective Serotonin Reuptake Inhibitors (SSRIs)

Sertraline has proven efficacy in the management of PTSD, and is commonly prescribed. A study involving analysis of datasets from two large double-blind placebo-controlled trials ($n = 191$) of sertraline in doses ranging from 50 to 200 mg daily showed significant reductions in symptoms in all three symptom clusters of PTSD, including insomnia and nightmares [33], though the authors also reported insomnia as a common consequence of treatment due to the arousal effects of SSRIs.

Paroxetine may be associated with nightmare induction and is generally not considered a treatment option for PTNs [34].

Fluvoxamine has direct anxiolytic effects and has been reported to produce a significant, yet modest, reduction in all PTSD symptom clusters, including subjective sleep quality and traumatic dreams in two studies [35, 36]. In a prospective cohort study of 24 World War II (WWII) combat veterans who received fluvoxamine as treatment for chronic PTSD, no participant achieved nightmare cessation, but half reported a decrease in nightmares. Several participants ($n =$

10) had to discontinue treatment due to adverse reactions, including gastrointestinal complaints and worsening sleep symptoms [36]. The other open-label prospective study investigating treatment of sleep disturbances in PTSD with fluvoxamine described improvement in all PTSD symptoms, particularly PTN, in a cohort of 21 healthy male Vietnam combat veterans with PTSD, using the Impact of Events Scale-Revised (IES-R) [35]. No significant side effects were reported. Both studies were limited by the lack of a placebo arm and the exclusion of women.

Fluoxetine demonstrated a non-significant improvement in nightmares in civilians with PTSD in a placebo-controlled double-blind RCT ($n = 53$), although the drug resulted in significant improvement in other PTSD symptomatology [37]. Data on adverse events were not reported.

2.1.2 Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

A pooled analysis of two randomized, double-blind, placebo-controlled trials ($n = 687$, placebo, $n = 347$; venlafaxine ER, $n = 340$) that compared venlafaxine ER (dose range 37.5–300 mg/day) with placebo over 12 weeks found no significant differences in improvement in distressing dreams according to the Clinician Administered PTSD scale 17-items (CAPS-17) score [38]. The analysis did, however, show significant improvement in other PTSD symptomatology. The most frequent trauma type in both the placebo (28.8%) and the venlafaxine ER (27.4%) groups was non-sexual assault. Duloxetine (mean daily dose of 81 mg) was studied in a prospective open-label trial of war veterans with PTSD ($n = 20$) where the authors found improvement of all PTSD symptoms, including subjective sleep quality [39]. Side effects commonly reported were constipation, diarrhea, and nausea.

2.1.3 Tricyclic Antidepressants (TCAs)

TCAs primarily act as serotonin-noradrenaline reuptake inhibitors. They may, in addition, have high-affinity antagonistic effects at 5-HT2, 5-HT6, 5-HT7, alpha1-adrenergic, and N-methyl-D-aspartate (NMDA) receptors, with some of these mechanisms enhancing their therapeutic effects and others leading to unwanted side effects [22]. They are mostly REM suppressors and improve REM latency [22]. A small case series of 12 Cambodian concentration camp survivors with PTSD showed significant improvement in nightmare frequency and intensity and cessation of intrusive symptoms, including nightmares, in four of the ten cases reviewed after treatment over a 1-year follow-up period [40]. Treatment varied across participants and included unique combinations of TCAs (including imipramine 75–150 mg/day, doxepin 50–150 mg/day, and amitriptyline 100 mg/day).

2.1.4 Mono-Amine Oxidase Inhibitors (MAOIs)

Inconsistent evidence exists for the use of phenelzine. A case series of war veterans with treatment-resistant PTSD ($n = 5$) showed cessation of nightmares at a dose ranging between 45 and 75 mg/day within 1 month in all participants, with benefits persisting in 60% of the study population after treatment discontinuation, with no significant reported side effects [41]. An open-label prospective study evaluating phenelzine as treatment for PTSD in 25 Israeli combat veterans for at least 4 weeks, however, did not find statistically significant outcomes, with poor efficacy on PTSD and Hamilton Anxiety scales, and a high drop-out rate due to adverse reactions (dizziness, drowsiness, and malaise) [42]. Sleep disturbances (insomnia and nightmares) were the only symptoms that showed substantial positive change. Ultimately, treatment for all patients was stopped, as response was short-lived, very mild, or plateaued. Non-reversible MAOIs are a less appealing choice of treatment due to dietary restrictions that need to be made, as well as a high incidence of drug-drug interactions and the potential of a hypertensive crisis if taken with sympathomimetic medications or high tyramine-containing foods [14, 22]. These drugs do not appear to be an ideal choice for the treatment of PTN.

2.1.5 Serotonin Antagonist and Reuptake Inhibitors (SARIs)

Trazodone is a triazolopyridine derivative and is frequently used as treatment for insomnia and nightmares due to its sedative effects [22]. A retrospective cohort study examining the usefulness of trazodone in treating insomnia and nightmares in a group of 74 war veterans found that it significantly decreased nightmare frequency and improved sleep quality in 72% of participants when administered at a dose ranging between 50 and 200 mg nightly [43]. Side effects were common (60% of patients reported adverse reactions), particularly daytime sedation, dizziness, and headaches, resulting in drop-outs, as well as more serious effects, such as priapism (12%), worsening of nightmares, and severe agitation. Trazodone may be of particular benefit in patients with comorbid alcohol use disorder and OSA, where the use of benzodiazepines is contraindicated or should be avoided [4]. A randomized cross-over study suggested trazodone may be effective in increasing the respiratory arousal threshold in patients with OSA [44]. Controlled trials would be beneficial in drawing definite conclusions regarding efficacy.

Nefazodone was studied in multiple open-label trials, and showed some efficacy in nightmare reduction in PTSD in civilian and war veterans, with one study reporting a 30% reduction in nightmares at dosages titrated up to 600 mg/day [45, 46]. Six open-label trials were pooled in the aforementioned analysis ($n = 105$) [45]. A documented risk of

hepatic failure makes it an unfavorable option for treatment, although this adverse event is rare [47]. Side effects such as bitter taste, increased appetite, drowsiness, headaches, dry mouth, dizziness, and hypersomnia have been reported.

2.1.6 Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs)

SSRIs when augmented with the NaSSA, mirtazapine (dosage not reported) have anecdotally been reported to reduce the frequency and intensity of nightmares in war veterans with PTSD, with up to 75% improvement reported in more than 300 observed cases [48]. Mianserin (dosage range 10–30 mg/night), another agent in this class, resulted in significant improvement in nightmares when combined with sertraline in an RCT ($n = 85$), although the trial design did not permit differentiating agent-specific beneficial effects [49] It has been hypothesized that the benefits of adding mianserin may be due to inhibition of histamine H1 receptors by this agent [10]

2.2 Adrenergic Agents

Prazosin is an α1-adrenergic receptor antagonist, typically used in the treatment of hypertension and benign prostatic hypertrophy (BPH), that has been studied for nearly 20 years following observation in a Vietnam veterans support group of a reduction in PTSD symptoms [50]. Multiple studies of varying levels of evidence exist demonstrating prazosin's efficacy [51–55]. Prazosin blocks sympathetic activity throughout the brain [56]. α1-Adrenergic activity is associated with fear, startle, and sleep responses, suggesting that an α1-antagonist may be effective in treating some PTSD symptoms, particularly hyperarousal and nightmares [57]. In addition, post-synaptic α1-adrenergic receptor attenuation, which prazosin induces, has been shown to disrupt the reconsolidation of fear memories [58]. Noradrenaline levels are increased in the cerebrospinal fluid (CSF) as well as in the urine of patients with PTSD compared to patients without, and levels in the CSF may correlate with symptom severity [56]. A 2018 RCT ($n = 304$) by Raskind et al. in a military population with chronic PTSD and nightmares, compared prazosin (maximum dose 20 mg/day in males; 12 mg/day in females) to placebo and found no difference between the groups at 10 weeks in terms of reduction in PTNs, as measured by the CAPS item B2 or any other measure [59]

Nonetheless, a recent pooled systematic review and meta-analysis ($n = 589$), which included eight placebo-controlled trials in adults with PTSD, including the Raskind et al. study, showed a statistically significant improvement in PTNs, but not in sleep quality, with prazosin. Dosage ranged between 3.1 and 16 mg/day and the range of treatment duration was 3–26 weeks [60]. Another recent systematic review and meta-analysis including four RCTs and two crossover studies (including Raskind et al.) ($n = 429$) reported a significant reduction in nightmares and improved sleep quality, as well as overall benefits on various PTSD symptoms [50]. Participants in the majority of studies were mainly male and US Veteran or active-duty military personnel. The results were generally consistent regardless of gender, age, dosage, or duration of treatment [60]. In view of the Raskind et al. study, the American Academy of Sleep Medicine (AASM) recently downgraded its recommendation for prazosin in PTNs, but retains it as an option for treatment. It should be noted, however, that the AASM guidelines were published before the two meta-analyses [50, 60], which, in our opinion, offer strong evidence for the efficacy of prazosin in reducing PTNs. Commonly reported side effects of prazosin include hypotension, dizziness, headaches, and syncope. Although not well studied in youth populations, prazosin was also found safe and effective in nightmare reduction in pediatric patients and adolescents with PTSD [22]

Terazosin, another alpha 1-adrenergic antagonist, has limited support in small case studies (one case study and one case series of four patients) in adults with PTSD, but has been proposed as an alternative to prazosin, especially after prazosin failure, at a dosage range of 2–6 mg/day [61, 62]. Doxazosin, in a similar class but with a longer half-life and fewer side effects [63], produced nightmare resolution in a small case series of three patients with PTNs and comorbid major depressive disorder (MDD). Dosages ranged between 2 and 4 mg per night [64]. A retrospective chart review of 51 patients with PTSD found full cessation of nightmares in 25% of adults with PTNs after 12 weeks of treatment [63]. Once-daily dosing is possible due to a longer half-life and this may lead to improved adherence and fewer side effects, making it a possible alternative to prazosin [65].

Clonidine is an agonist on the alpha-2-adrenergic auto receptor, has anti-sympathetic effects throughout the CNS [56], and is used as an antihypertensive and a therapeutic agent in opioid withdrawal. Alpha-2-adrenergic activation with subsequent noradrenergic outflow down-regulation may be beneficial in PTNs by dose-dependent changes in REM sleep [22]. There is limited evidence of its efficacy in treating PTN. Although a retrospective chart review of 478 medication trials in 327 combat veterans with PTSD found a partial response in 63% of patients on clonidine doses ranging from 0.1 to 2 mg, none achieved resolution of symptoms [66]. In the same study, just over half of patients on prazosin had no response to treatment. The limited data indicate that clonidine may have a future role as a therapeutic agent, but more supportive data are needed [66]. It may be considered as an alternative treatment for distressing nightmares, but caution needs to be exercised in patients with ischemic heart

disease, cardiac conduction disturbances, and renal impairment [67].

2.3 Atypical Antipsychotics

There are limited but promising data on the use of atypical antipsychotics in the management of PTNs [14]. These agents may be effective as adjunctive therapy in treating SSRI-resistant insomnia and nightmares in patients with PTSD [68]. The use of these agents as monotherapy is not advised. They may be of particular benefit in patients with comorbid psychotic symptoms, flashbacks, and bipolar disorder [69].

Risperidone is a serotonin-dopamine antagonist (particularly at 5-HT2A, 5-HT7, and D2 receptors), with significant antagonism of α1- and α2-noradrenergic receptors, which possibly mediates its efficacy. A retrospective chart review in adults with PTSD found full cessation of nightmares in 43% of patients with PTNs, and a change in nightmare patterns in 85% of patients, including a reduction in frequency and intensity of nightmares [70]. Effective doses ranged from 0.5 to 4 mg/day [69]. Another chart review found a 77% partial or full cessation of nightmares at doses ranging from 1 mg/day to 6 mg/day [66]. A pilot open-label flexible-dose trial ($n = 17$) in combat veterans with PTSD found significant improvement in subjective sleep quality, with reduction in trauma-related dreams, nightmares and less frequent awakenings [71]. For most of these patients, risperidone was an add-on medication and doses ranged from 1 mg to 3 mg. A placebo-controlled RCT ($n = 267$) evaluating risperidone as adjunctive treatment to antidepressants and other medications for PTSD, found small but statistically significant reductions in parameters used to assess efficacy, including improvement in sleep quality, less severe nightmares, and overall improvement in quality of life [72]. Adverse effects were only reported in one study, and included tremors, headache, nausea and vomiting, drowsiness, and weight gain, and were reported to cease after discontinuation of risperidone [70]. Existing evidence supports risperidone augmentation for PTNs, but future studies, particularly controlled clinical trials, are required.

Olanzapine, a 5-HT2C and dopamine D2 antagonist, increases slow-wave sleep and suppresses REM sleep [22]. In a small case series ($n = 5$) of patients with treatment-resistant PTSD and PTNs, olanzapine augmentation of SSRIs showed rapid improvement of insomnia and nightmares in all patients without any adverse events reported [73]. These findings were supported by a retrospective chart review in combat veterans, where full remission of nightmares was attained with olanzapine at doses of 2.5–10 mg [66]. A double-blind placebo-controlled study ($n = 19$) focusing on SSRI-resistant patients with PTSD, found a significantly greater reduction than placebo on sleep symptoms, including nightmares and insomnia, and improved subjective sleep quality with olanzapine augmentation to existing therapy [74]. Another double-blind placebo-controlled study, however, found no significant difference between olanzapine as monotherapy and placebo on sleep disturbances, but this study was limited by the sample size ($n = 15$), short study period (10 weeks), and the fact that olanzapine was used as primary stand-alone therapy, and not as an augmenting agent [75]. A common side effect of olanzapine is weight gain, with metabolic complications.

Quetiapine was studied in a 6-week open-label trial ($n = 20$) as adjunctive therapy to current medication in combat veterans with PTSD and sleep disturbances, and demonstrated significant yet modest improvements in subjective sleep quality, latency, duration, and disturbances, including terror episodes at dosages of 25–300 mg daily [76]. Caution is advised in interpreting these data due to the small sample size and short duration of study (6 weeks). A historical prospective cohort study was conducted by retrospective chart review to identify veterans with PTSD ($n = 237$) who were prescribed quetiapine or prazosin. Quetiapine (dosage range 25–600 mg/day) produced a similar reduction in night-time symptoms to prazosin, but participants were more likely to discontinue quetiapine due to adverse effects compared to prazosin (35% vs. 18%) [77]. Common reported side effects were sedation (37%), hyperglycemia, weight gain, and hyperlipidemia [76]. Larger RCTs, preferably double blinded, are needed to define the potential benefit of this drug in treating PTN.

Aripiprazole, a dopamine (D2-receptor) partial agonist, showed significant reductions in sleep disturbances and nightmares in four out of five war veterans with PTSD in a case series where it was used for 4 weeks as augmentation to sertraline and/or cognitive behavior therapy [78]. Final doses ranged from 15 to 30 mg/day. One patient experienced paradoxical excitement as an adverse event, which led to discontinuation. However, in a retrospective chart review of four patients on aripiprazole, three failed to improve in terms of PTNs [66]. There is currently only low-grade evidence for the efficacy of aripiprazole for PTSD and for PTNs specifically.

2.4 β-Blockers

Propranolol, a non-selective β-adrenergic blocker, has been investigated as a possible treatment and preventive agent for PTSD [79], but this agent as well as other β-blockers are often associated with paradoxical sleep disturbances, including nightmares and insomnia [80]. It has been proposed that propranolol has potential utility as an add-on to prazosin, to dampen the emotional content of traumatic memories (intrusive daytime symptoms and heightened physiological reactivity to trauma flashbacks). The optimal dose of

propranolol as add-on has not been determined [81]. While the combination of propranolol and prazosin may target different noradrenergic mechanisms, no formal studies exist to support this, with much of the evidence deriving from animal studies [81].

2.5 Benzodiazepines and Non-Benzodiazepine Hypnotics

Benzodiazepines bind to binding sites within the GABA-A receptors resulting in potentiation of their inhibitory effects [82]. Although commonly used agents, they are considered controversial, and few studies have been conducted to examine their efficacy. Caution is always advised with the use of this group of agents, due to the risk of dependency (particularly in patients with a history of substance abuse, which is common in patients with PTSD), withdrawal symptoms after prolonged use, and cognitive suppression [68]. They may also worsen OSA, which is a common comorbid condition in PTSD [68]. A small single-blind, placebo-controlled clinical trial evaluated the use of clonazepam (dosage range 1–2 mg at night) to improve sleep disturbances, particularly PTNs, in combat veterans with PTSD. Clonazepam proved to be largely ineffective in improving any measured sleep parameter and nightmare frequency, although the study was limited by the sample size ($n = 6$) [83]. Another double-blind, crossover trial ($n = 10$) showed that alprazolam may improve insomnia but did not improve nightmares [84]. The dosage of alprazolam was not reported.

A single small double-blind, cross-over trial ($n = 40$) compared triazolam (0.5 mg/night) and nitrazepam (5 mg/night), both benzodiazepine hypnotics, to assess their effects on disturbed sleep [85]. It was not clear whether the study population suffered from nightmare disorder or PTSD. Both drugs produced a decrease in reported unpleasant dreams, but both were only studied for one night each [85]. Minimal side effects were observed. These agents may be considered as add-on therapy to treat nightmares according to the AASM position paper [22], although supportive data are minimal [56]. In sum, benzodiazepines as treatment for PTNs are largely unsupported by the existing evidence-base.

Zolpidem, a non-benzodiazepine imidazopyridine hypnotic, showed benefit in treating insomnia in war veterans with PTSD at a dosage of 10 mg per night, with alleviation of nightmares in most patients who were treated at an outpatient clinic in an anecdotal report [86]. In contrast to typical benzodiazepines, zolpidem is safer and tends to induce tolerance and withdrawal effects much less often than its benzodiazepine counterparts [87]. Available evidence is, however, minimal and does not support routine use. A more recent RCT ($n = 32$) examining the efficacy of zolpidem (dosage 10 mg per night) over 2 weeks as adjunctive therapy to SSRIs found that when compared to hypnotherapy (twice a week for 2 weeks), it did not decrease sleep disturbance or other PTSD-related symptoms, with results favoring the use of hypnotherapy [88].

2.6 Antiseizure Drugs

Gabapentin, a calcium channel blocker, is typically used for seizures, neuropathic pain, and restless legs syndrome [14]. It has been used as adjunctive treatment in PTSD due to its sedating properties and short half-life [89]. Although commonly used off label in treating anxiety disorders, gabapentin appears ineffective as monotherapy in patients with PTSD. In a retrospective review ($n = 30$) [89], gabapentin demonstrated moderate improvement in sleep duration and a decrease in nightmares [89]. The authors showed that 77% of patients had marked or moderate improvement in insomnia, based on the Clinical Global Impression Scale, at average doses of 1344 ± 701 mg at different time points at follow-up, and some participants showed a decrease in frequency and/or intensity of nightmares [89]. However, a recent systematic review evaluating gabapentin's use in psychiatric disorders concluded that evidence remains limited for its use in PTNs [90]. Sedation and mild dizziness are commonly reported side effects [56].

Topiramate, a sodium channel blocker, has been used for a wide variety of conditions, including epilepsy, prophylaxis of migraines, and weight control [14]. The drug also has other effects that are theoretically beneficial for nightmare reduction, including GABA-A receptor agonism, anti-glutaminergic effects, and modulation of carbonic anhydrase isoenzymes [22]. A data review of 35 patients and a prospective open-label study ($n = 33$) showed promising results in reducing PTNs in civilians with PTSD when administered at a dose range of 12.5–500 mg daily for 1–119 weeks [91, 92]. Some patients, however, discontinued treatment due to side effects, including urticaria, glaucoma, loss of appetite, headache, pain, suicidal ideation, and memory concerns [56]. Another open-label pilot study ($n = 29$) in a combat-related PTSD group focused on topiramate as add-on therapy to other agents in managing PTSD (target dose 200 mg/day), and showed a 40% reduction in the prevalence of nightmares as well as in the frequency of nightmares per week [93]. A small double-blind, placebo-controlled trial ($n = 38$) in a civilian population with PTSD showed non-significant overall improvement based on the CAPS at a dose range of topiramate of 25–400 mg/day. However, improvement on the re-experiencing scale, which includes nightmares, was statistically significant [94]. Topiramate may be beneficial as add-on therapy; however, findings from these small studies need to be confirmed in controlled clinical trials.

2.7 Histamine Receptor Antagonists

Cyproheptadine is an antihistamine that causes REM suppression due to both serotonin 5-HT1A auto-receptor antagonism, resulting in increased serotonin outflow, as well as potent anticholinergic effects [95]. The findings of several small case series have been inconsistent, with some showing efficacy in reducing nightmares [96]. The largest study, an open-label augmentation trial in adults at a Veterans Administration Treatment Center with PTSD ($n = 36$ who were started on cyproheptadine, and 16 of the whole were included in the efficacy analysis), showed no significant improvement in any outcomes related to nightmares at dosages ranging from 4 to 8 mg/day [97]. The AASM still recommends it as a possible adjunctive treatment for nightmares [22]. We are not aware of any recent studies investigating the effects of cyproheptadine on PTNs, and RCTs are needed.

A placebo-controlled RCT comparing prazosin and hydroxyzine (maximum dose 100 mg) over 8 weeks in patients with PTSD (n = 100) showed that both agents led to PTSD-related nightmare improvement compared to controls, although prazosin was superior [98]. We found only one study where hydroxyzine was studied in a PTSD sample. Diphenhydramine has no supportive data for PTNs in PTSD that we are aware of.

2.8 Buspirone

Buspirone is a 5-HT1A receptor agonist approved by the FDA for use in the treatment of generalized anxiety disorder [68]. A case series of three patients [98] and an open trial ($n = 8$) [99] found improvement in some PTSD symptoms including insomnia and flashbacks on buspirone at a dosage range of 35–60 mg/day (case series) within 5–29 days and 5–30 mg/day (open trial) over 4 weeks, but no significant effects on nightmares were reported [99, 100]. These studies are dated and RCTs are needed to confirm these effects, and explore the potential of buspirone for alleviating nightmares.

2.9 Melatonin Agonists

Melatonin receptor agonists, such as ramelteon, are approved for the use of insomnia in the general population [4]. These agents theoretically have potential to be used in PTSD-related sleeping disorders but according to the authors have not yet been evaluated for this indication or for PTN. A pre-clinical study conducted in mice found improvement in all PTSD-like behaviors after chronic administration of ramelteon [101]. This makes ramelteon an attractive candidate for human studies.

Agomelatine is a melatonin receptor agonist (MT1 and MT2) and a 5-HT2C receptor antagonist approved for use in MDD. Its effects on melatonin receptors enables resynchronization of irregular circadian rhythms with beneficial effects on sleep architectures [102]. A case report of a patient with PTSD reported improvement in all PTSD symptoms including nightmares after 5 weeks of treatment, at a maximum dose of 50 mg/day [102].

2.10 *N*-Methyl-D-Aspartate (NMDA) Receptor Antagonists

Ketamine is a non-competitive antagonist of the glutamate *N*-methyl-D-aspartate (NMDA) receptor [103]. It is typically used as a dissociative anesthetic agent, but interest in its psychiatric use has grown with the finding that it has rapid-acting antidepressant effects [104]. It is postulated that the chronic stress experienced in PTSD may impair synaptic connectivity, which is mostly mediated by glutamate [105]. Ketamine may exert its effect by facilitating fear extinction and blocking memory reconsolidation, thus improving the ability to process traumatic memories [106]. A randomized, double-blind, crossover trial ($n = 41$) showed significant PTSD symptom reduction in all three symptom clusters after a single infusion of ketamine, with rapid, yet temporary, symptom reduction [107]. A follow-up RCT ($n = 30$) showed significant efficacy with repeated ketamine infusions over 2 weeks, with 67% of patients showing improvement in overall PTSD-symptoms on the CAPS-5, and clear superiority over placebo (midazolam) [108]. Although none of these studies were specifically focused on nightmares in PTSD, ketamine clearly has tremendous potential in PTSD management [103], and future studies of ketamine, possibly in combination with psychotherapy, are encouraged with follow-up of outcomes, particularly those related to PTNs, over a longer timeline.

Memantine is a non-competitive glutamate NMDA receptor antagonist with additional antagonist effects at serotonin 5-HT3, nicotinic α7 and α4-β2 receptors, typically used in treatment of dementia [109]. A small open-label 12-week trial of memantine (maximum dose 20 mg/day) in four patients with PTSD showed promising results, especially in decreasing hyperarousal symptoms and insomnia [110]. Strong evidence for efficacy in reducing PTNs is lacking.

2.11 Synthetic Cannabinoids and Cannabis

Nabilone is a synthetic cannabinoid-1 (CB1) receptor agonist and an analgesic and anti-emetic [22]. PTSD is characterized by amygdala hyper-reactivity, which plays a vital role in hyperarousal and other symptoms. CB1-receptors are highly expressed in the amygdala [111] and modulate emotional memory, fear, and anxiety [112], which supports the potential benefit of cannabinoids in PTSD management. Nabilone at a dosage range of 0.2–4 mg nightly

was assessed as adjunctive therapy to standard treatment in a pilot open-label clinical trial in patients with treatment-resistant nightmares in PTSD ($n = 47$) [113]. These patients showed significant improvements, with a 72% reduction in nightmares, and even complete resolution of nightmares in some [112]. This led to further studies, with a small ($n = 10$) placebo-controlled RCT providing evidence for its beneficial effects as add-on therapy [114]. Nabilone was reasonably tolerated, with the most common side effects being dry mouth, headaches, and, rarely, nausea and vomiting. Two recent systematic reviews of preclinical and clinical studies support the potential use of nabilone in the treatment of PTNs, but acknowledged notable limitations of existing studies, mostly related to small sample sizes and low-quality study designs [115, 116]. Further well-designed trials with larger and more diverse clinical populations and over longer time periods are recommended. Cannabinoids are also being studied for a variety of other sleep disorders. There remain concerns around the safety and long-term effects of medicinal cannabinoids [115, 116].

Cannabis sativa, the cannabinoid-containing plant species, contains more than 100 cannabinoids, of which tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most studied [117]. Due to the wide variety of cannabis strains, the cannabinoid content of these strains also varies [116]. An open-label pilot study of THC (5 mg/day), as add-on to prior initiated psychotropics in ten patients with PTSD, found a statistically significant improvement in sleep quality, nightmare frequency, and hyperarousal symptoms, with minimal side effects reported (dry mouth, headache, and dizziness) and no dropouts [118]. Results must, however, be interpreted with caution due to the small sample size, other concomitant medication (80% were on benzodiazepines), and the lack of a control group. Further well-designed and adequately powered studies are required.

CBD is a non-psychotomimetic cannabinoid. A retrospective case series of adults with PTSD ($n = 11$) examining CBD use at a dosage 2–100 mg/day over 8 weeks reported a 28% symptom reduction, particularly for nightmares, using the PTSD Checklist for DSM-5 (PCL-5) [119]. This study was limited by a small sample size and possible selection bias (e.g., disproportionate demographic representation) (Table 1).

It is important to note that the use of cannabinoids, namely THC, may pose a risk of the development of psychotic disorders in susceptible individuals [120]. This highlights the need for appropriate screening of participants included in clinical trials and close monitoring. Cannabinoids represent an important area of investigation in PTSD, and more specifically for PTNs in PTSD, and larger placebo controlled RCTs are indicated.

2.12 Psychedelic Agents

Psychedelic drugs (also known as hallucinogens and entactogens) refer to compounds with the potential to induce a wide range of psychological, cognitive, emotional, and physical effects [121]. A recent review concluded that psychedelic-assisted psychotherapy might serve in some cases to enhance efficacy in terms of overall symptom reduction in patients with PTSD [106]. Proposed mechanisms include decreased triggering of patient fear responses and improvement of detachment through enhanced empathy and openness to new perspectives [106].

Psilocybin, a mushroom-based psychotropic agent, has effects attributed to 5-HT2A agonist actions with resultant potent modulation of prefrontal cortex network activity [106]. This receptor activity has been found to be elevated in individuals coping with stress, thus down-regulation of prefrontal 5-HT2A receptors may be a putative therapeutic target [121]. Psilocybin may serve as a catalyst for psychotherapy and may reduce amygdala reactivity during emotional processing [106]. It may also reduce avoidance, increase emotional capacity, and induce emotional breakthrough experiences, largely by facilitating fear extinction and promoting neural plasticity [122], leading to an increased ability to process traumatic memories [106]. Specific research related to treatment of PTSD and PTNs is lacking. Tentative clinical evidence that psilocybin may be beneficial is promising, though rigorous studies are required. Unpredictability of response, which may be dose-dependent, and heightened arousal and sensitivity induced by psilocybin are challenges that need to be addressed [106].

3,4-Methylenedioxymethamphetamine (MDMA), commonly known as ecstasy, recently received FDA approval for further study in the treatment of PTSD, with ongoing multicenter studies [106]. MDMA has a wide variety of CNS effects, including release of serotonin, dopamine, noradrenaline, oxytocin, prolactin, vasopressin, and cortisol [106]. MDMA may reduce the fear response, facilitate fear extinction, improve traumatic memory processing, and act as a catalyst for psychotherapy. Neurobiologically, MDMA attenuates activity of the amygdala while activating the frontal cortex [123]. This activity is often impaired in patients with PTSD [124]. MDMA may, therefore, enhance psychotherapeutic interventions, particularly imaginal exposure, cognitive restructuring, corrective attachment, and fear extinction, especially when administered in a controlled environment [106]. A pooled analysis from six RCTs showed a significant reduction in PTSD symptom scores, including intrusive events, when compared to control groups [125]. A phase III randomized double-blind placebo-controlled trial ($n = 90$) found overall improvement in CAPS-5 scores, without any adverse effects of abuse potential,

Table 1 Summary of evidence of pharmacological agents for post-traumatic nightmares (PTNs)

	Positive (favors intervention)	Negative (does not favor intervention)	Ambivalent (no clear conclusions can be drawn)
Systematic review or meta-analysis	Prazosin [59, 60]	Venlafaxine [37]	Gabapentin [89]—evidence too limited to give opinion MDMA [89]—no specific evidence for PTNs
Evidence based clinical guidelines	Adjunctive cyproheptadine [22]		
RCTs (including single-blind and non-placebo-controlled trials)	Sertraline ($n=191$) [32] Fluoxetine ($n=53$) [36] Adjunctive mianserin ($n=85$) [48] Adjunctive risperidone ($n=267$) [71] Adjunctive olanzapine ($n=19$) [73] Hydroxyzine ($n=100$) [97] Trihexyphenidyl ($n=34$) [126]	Olanzapine monotherapy [74] Alprazolam [83] Zolpidem [87]	Topiramate [93]—no specific evidence for PTNs Ketamine [106, 107]—no specific evidence for PTNs Nitrazepam/triazolam [84]—diagnosis of included patients not clear; very short follow up (1 night) Clonazepam ($n=6$) [82]
Open label non-randomized trials, case-control and cohort studies	Fluvoxamine [34, 35] Trazodone [42] Nefazodone [44, 45] Risperidone [70] Quetiapine [75, 76] Gabapentin [88] Topiramate [90, 91] Adjunctive topiramate [92] Cyproheptadine [96] Buspirone [99] Nabilone [112] THC [117]	Phenelzine [41] Aripiprazole [65]	Duloxetine [38]—no data on PTNs specifically Memantine [109]—no data on PTNs specifically
Retrospective chart reviews	Clonidine [65] Risperidone [65, 69] Olanzapine [65, 72]		
Systematic review of descriptive/qualitative data		Paroxetine [33]	
Single descriptive/qualitative studies	Tricyclic antidepressants [39] Phenelzine [40] Mirtazapine [47] Terazosin [50, 61] Doxazosin [62] Aripiprazole [77] Zolpidem [85] Buspirone [98] Agomelatine [101] CBD [118] Cortisol [129]		
Expert opinion	Adjunctive propranolol [80] Mirtazapine [47]		
Preclinical data only	Ramelteon [100]		
No known studies for PTNs or other sleep disturbances in PTSD	Psilocybin		

CBD cannabidiol, *MDMA* 3,4-methylenedioxymethamphetamine, *RCT* randomized controlled trial, *THC* tetrahydrocannabinol

suicidality, or QT-prolongation reported [126]. Although MDMA improved intrusive symptoms, data are lacking regarding nightmare reduction specifically.

2.13 Anticholinergics

Trihexyphenidyl is a central anticholinergic drug with a high blood-brain barrier (BBB) penetration, with effects on the limbic and reticular activating system (RAS) by blocking

acetylcholine [127]. Trihexyphenidyl is typically used to manage disorders like parkinsonism and dystonia, and to alleviate cholinergic side effects of other medications. A recent mixed single-blind ($n = 12$) and open-label ($n = 22$) study of 34 patients with treatment-refractory PTSD-related nightmares and flashbacks, who had received between 2 and 15 years of psychiatric treatment without therapeutic benefits, found a notable effect on nightmare reduction within 2 weeks of treatment, which was statistically significant [127]. The authors reported a rapid result within less than 24 h and 71–88% efficacy in the treatment of nightmares as well as intrusive flashbacks, with most patients reporting nightmares as mild or not present after treatment [127]. These benefits may be explained by the hypothesis that PTSD symptoms are induced by an increase in acetylcholine release, as demonstrated in a case study of PTSD-like symptoms induced by acetylcholinesterase inhibitors [128]. Conversely, anticholinergic effects on brain structures involved in memory formation might explain the reduction in flashbacks [127]. A study in a mouse model also found trihexyphenidyl to have potential prophylactic use in emergent PTSD symptoms and aversive fear memory formation [129]. Cognitive adverse effects of anticholinergic agents may be a potential concern. RCTs are needed since provisional results show a significant and rapid impact on PTNs (Table 2).

2.14 Corticosteroids

A small case series ($n = 3$) found that low-dose cortisol led to a reduction in the frequency of intrusive memories and nightmares [130]. Preliminary evidence suggests that hydrocortisone may have beneficial effects in reducing PTSD risk and development [131], but to our knowledge there are no data related to the treatment of nightmares. Since PTSD prevention may effectively lead to nightmare prevention and reduction, this line of investigation is of importance.

3 Summary of Pharmacological Treatment Interventions

Prazosin is recommended for the treatment of PTSD-associated nightmares, with good evidence supporting its efficacy.

There are other options that may be considered in the management of PTNs in PTSD, but data are low-grade and sparse. There is limited evidence supporting the use of antidepressant monotherapy (SSRIs and SNRIs), specifically for managing nightmares, and some trials showed adverse impacts on other sleep parameters. Evidence exists for the use of the TCAs and mirtazapine, but these agents are mostly used as add-on therapy, and they were low-evidence studies. Trazodone has some evidence of efficacy but was poorly tolerated in one retrospective cohort.

Amongst the antipsychotics, there is evidence from single prospective trials to support the use of risperidone, olanzapine, and quetiapine as add-on therapy. Quetiapine compared favorably to prazosin in a study but was poorly tolerated. Based on trial data, olanzapine is not supported as monotherapy.

Doxazosin may be considered as an alternative to prazosin in future, depending on the outcome of further research, due to its simpler dosing regimen. Clonidine also has some evidence to support its use. There is limited evidence from non-randomized studies to support the use of the antiseizure medications topiramate and gabapentin as add-on therapy. The antihistamine cyproheptadine has also been investigated as add-on therapy, but the evidence base remains fairly weak.

Venlafaxine, phenelzine, benzodiazepines (particularly clonazepam), and sedative hypnotics are not supported by the evidence.

Table 2 Pharmacological management (by drug class and agent) of post-traumatic nightmares (PTNs) in adults

Drug class	Agent
Established agents	
Adrenergic agents	Prazosin, doxazosin, terazosin, clonidine
Antidepressants	Fluvoxamine, tricyclics, trazodone, mirtazapine
Atypical antipsychotics	Risperidone, olanzapine, quetiapine
Antihistamines	Cyproheptadine
Antiseizure drugs	Gabapentin, topiramate
Novel agents (needing further investigation)	
Melatonin agonists	Ramelteon
Synthetic cannabinoids	Nabilone
NMDA receptor antagonists	Ketamine
Psychedelic agents	MDMA
Anticholinergics	Trihexyphenidyl

MDMA 3,4-methylenedioxymethamphetamine, *NMDA* N-methyl-D-aspartate

The use of ramelteon, ketamine, cannabinoids, MDMA, corticosteroids, and trihexyphenidyl is not yet advised in routine management, but some of these agents seem to be promising, and further evaluation of these novel agents as therapeutic agents for PTSD and PTNs are needed.

4 Psychological and Other Interventions

Although this review focuses on the pharmacological management of PTNs, it must be noted that significant improvements have been observed, not only in sleep quality but also sleep onset, latency, efficiency, and other sleep disturbances, with psychological and behavior therapy.

Sleep-specific cognitive behavior therapy (CBT) has shown significant improvements, as supported by a meta-analysis of 11 RCTs [13, 17]. However, even after successful CBT for PTSD, nightmares may recur or persist [17]. There is also good evidence for the effectiveness of image-rehearsal therapy (IRT) [22]. A meta-analysis looking of IRT for PTNs showed a large reduction in nightmare frequency from the initial assessment, with effects sustained up to 6–12 months [3]. IRT is the only treatment that the AASM currently recommends for PTNs [22]

The benefits of combining CBT for insomnia (CBTI) with other CBT modalities have also been emphasized by other authors [132]. An RCT investigating CBTI combined with IRT ($n = 40$) reported subjective and objective PTSD-night-time symptom improvement [133]. Despite treatment success, 60% of this treatment group still reported residual nightmares occurring at least once a week immediately post-therapy cessation, signifying a lack of sustained effect [133]. Another RCT in sexual assault victims with PTSD ($n = 42$) found improved night-time symptoms with combined CBT and IRT, compared to CBT alone [134]. Various other CBT modalities have also been extensively reviewed, including cognitive processing therapy, with promising results [3, 135]. A recent case study reported that Eye Movement Desensitization and Reprocessing (EMDR) led to a rapid resolution of PTNs in a 31-year-old female [136]. These findings concur with a positive non-randomized controlled trial in a military population conducted more than 25 years ago [137]. However, the efficacy of this treatment option has not been extensively investigated in RCTs. El-Solh provides a good perspective on behavioral and psychological therapies for further reading [95].

In managing nightmares in PTSD, it is also important to pay particular attention to patients' cultural belief systems and values (e.g., nightmares and dreams may be perceived as a form of communication from ancestors or gods in some African cultures, to provide guidance or instructions in distressing times), as these may impact on treatment success, as clinically determined [138].

5 Discussion

At the time of writing this review, there were no recommended first-line pharmacological interventions for PTNs. Prazosin is still considered first-line treatment, despite a recent study showing non-significant results in alleviating distressing dreams and sleep quality in a military population [59]. Meta-analyses, which included that study, however, still found significant results [50, 60]. It remains to be determined whether inconsistencies in findings may be related to the type of trauma population (i.e., military vs. civilian).

Many of the other agents reviewed here are promising. These agents offer great potential in further enhancing treatment efficacy. While data are sparse and their use controversial, cannabinoids, ketamine, psychedelic agents, and anticholinergics are novel agents that represent intriguing options for future management and should not be overlooked, especially for the management of a range of PTSD symptoms. For all of these agents, the benefits need to be weighed against the risks, for example the risks of developing psychotic disorders in susceptible individuals administered a formulation containing THC [116].

The importance of adequately managing PTNs is underlined by most studies, which report a decrease in overall PTSD symptom severity, improvement in global functioning, and overall improvement in health and quality of life consequent to reduction in frequency of PTNs [139]. This supports the notion that sleep disruption is not merely a secondary symptom of PTSD, but a core component of the disorder. Furthermore, better sleep can influence fear learning, decrease emotional reactivity, increase emotional coping and emotional processing, and increase cognitive abilities, including concentration, in turn enhancing the response to psychological interventions, such as IRT [4].

When making treatment decisions, clinicians should always consider the level of evidence relating to efficacy, potential side effects, medication interactions, and psychiatric and non-psychiatric comorbidity. Polypharmacy should preferably be avoided by utilizing a single agent that can positively impact on several symptom domains [14]. Combining pharmacological and psychotherapeutic treatments may be beneficial for some patients but has not yet been well studied in RCTs.

MDD is often a comorbid disorder in patients with PTSD and PTNs, which should be considered when interpreting the influence of pharmacological agents on symptoms and the ratings of nightmares in these patients. There is limited research examining the role of treating PTSD-related sleep problems in patients with comorbid anxiety,

depression, chronic pain syndrome, and other disorders, each of which may has its own influence on sleep. Comorbid OSA and insomnia may occur with PTNs influencing the choice of therapy (see [4]).

6 Conclusion and Future Directions

Nightmares are a common and debilitating phenomenon in patients with PTSD, therefore clinicians should always ask about and monitor PTNs and other symptoms of sleep disruption in this population group. Since nightmares are an independent risk factor for suicide, an early approach to treatment may be advisable. Although there is limited prospective evidence that this approach yields better outcomes, the current evidence base of association with chronicity does support such an approach. More focus should be placed on the prevention of PTNs following significant trauma exposure.

Currently nonpharmacological therapies (especially IRT [3]) are the preferred treatment for PTNs [22]. Pharmacological agents are, however, often more available, may be easier to access, and may be the patient's preferred form of treatment. Although the efficacy of prazosin has been questioned, it is arguably the preferred pharmacological option. Prazosin remains the agent with the strongest evidence base for reducing PTNs, with several controlled trials and two positive meta-analyses. Findings from trials of novel agents may alter our therapeutic approach in the future.

In addition to the line of research proposed, the importance of assessing how sleep problems/nightmares interfere with otherwise effective treatments in RCTs cannot be overemphasized [68]. Investigation of whether early aggressive management of PTNs leads to better outcomes compared to treatment as usual is another prudent avenue of investigation. Consistency in nightmare metrics in RCTs would improve the ability to compare results across trials and provide a more universal and comparable standard. This requires validated and standardized tools to assess the presence and severity of PTNs and aid comparison of results across trials.

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