Drugs & Therapy Perspectives (2023) 39:125–130
https://doi.org/10.1007/s40267-023-00988-0

DISEASE MANAGEMENT

The treatment of post-traumatic nightmares requires more attention

Esther S. Kim[1] · **Connie Kang**[1]

Accepted: 2 March 2023 / Published online: 22 March 2023

Abstract
Nightmares are common and persistent in post-traumatic stress disorder (PTSD). These post-traumatic nightmares (PTNs) are resistant to general PTSD treatment and can last a lifetime even after other symptoms of PTSD resolve. PTNs are associated with significant distress and a decreased quality of life, and also increased risks of self-injury and suicide. PTNs should not be overlooked as a secondary symptom of PTSD; they are one of the most critical symptoms of PTSD to treat. Targeted treatments with the most evidence in the treatment of PTNs include image-rehearsal therapy and prazosin.

Post-traumatic nightmares (PTNs) are common and persistent…

Post-traumatic stress disorder (PTSD) develops in approximately 25–30% of people of any age who experience a stressful event or situation of an exceptionally catastrophic or threatening nature [1]. PTSD can stem from experiencing or witnessing single, multiple or repeated traumatic events such as abuse (including childhood or domestic), accidents of a serious nature, assault (physical or sexual), conflict and war, torture, trauma related to health problems or childbirth experiences (e.g. admission to intensive care, neonatal death), and work-related trauma exposure (including remote exposure) [1].

PTSD can present with a wide range of symptoms [1], including the four symptom clusters [2] of avoidance (of activities, people, places and situations associated with trauma-related stimuli, or of general social contact), emotional numbing, hyperarousal (e.g. anger, hypervigilance, irritability), and re-experiencing or intrusive symptoms (e.g. unwanted thoughts, flashbacks, nightmares) [1–3]. Among these, post-traumatic nightmares (PTNs) have a prevalence as high as 88% [3] and can persist throughout life even if the other symptoms of PTSD resolve [4]. This persistence has led to the conceptualisation of PTNs as an independent sleep disorder [3].

✉ Connie Kang
dtp@adis.com

[1] Springer Nature, Mairangi Bay, Private Bag 65901, Auckland 0754, New Zealand

…and targeted treatment is important

PTNs worsen the prognosis of PTSD, possibly by disrupting the normal processing of traumatic memories during sleep [3]. PTNs can also lead to other sleep disturbances such as insomnia or sleep avoidance that may, in turn, adversely affect daytime PTSD symptoms. PTNs are associated with functional impairment, poor health outcomes, significant distress and a decreased quality of life. In addition, nightmares are an independent risk factor for suicide. Persistent chronic nightmares, in particular, are associated not only with repeated suicide attempts but also with non-suicidal self-injury [3]. Considering this and the resistant nature of PTNs to general PTSD treatment, targeted treatment of PTNs is important [2]. This article summarizes existing and promising treatment options for PTNs, as reviewed by Geldenhuys et al. [3] and Martin et al. [2].

Post-traumatic stress disorder treatments don't always treat PTNs…

PTSD can be treated with psychological therapies, pharmacotherapy, or both [2]. Most guidelines recommend cognitive behavioural therapy (CBT), trauma-focussed CBT, or eye movement desensitisation and reprocessing (EMDR) specifically, as first-line psychological therapy [2]. CBT is a general term that encompasses several different short-term and goal-oriented therapies that involve psychotherapeutic and behavioural techniques striving to modify a person's dysfunctional behaviours, emotions and thoughts [4]. CBT includes cognitive processing therapy, image rehearsal

therapy (IRT) and prolonged exposure therapy [2]. Psychotherapy is recommended over pharmacotherapy for first-line treatment of PTSD in approximately one third of guidelines. SSRIs (e.g. fluoxetine, sertraline, paroxetine) or venlafaxine are first-line pharmacological options [2].

Nightmares, which are one of the most critical symptoms of PTSD to treat, are often overlooked as a secondary symptom of PTSD [2]. Most guidelines for PTSD do not mention the targeted treatment of nightmares as a symptom of PTSD. Those that do recommend the targeted treatment of nightmares vary in the choice and strength of their recommendations [2]. Effective treatment of nightmares is important and often leads to improvement of other PTSD symptoms [3].

Trauma-focussed CBT additionally includes psychotherapies like EMDR [2]. There is good evidence for IRT and some evidence for sleep-specific CBT in the treatment of nightmares, while the positive efficacy of EMDR in PTNs has not been investigated extensively in randomized controlled trials [3]. In terms of pharmacological therapies, sertraline can lead to significant reductions in nightmares, and fluoxetine is associated with a non-significant improvement in nightmares. Paroxetine is not a treatment option for PTNs because it is associated with nightmare induction, and evidence does not support the use of venlafaxine [3].

Although non-pharmacological therapies are preferred…

Non-pharmacological therapies are currently the preferred treatment for PTNs [3]. The American Academy of Sleep Medicine (AASM) recommends IRT for the treatment of PTN [4], and the American Psychiatric Association suggests it as a treatment option [2, 5]. Behavioural treatment of PTNs is based on the concept that nightmares are acquired/learned behaviours that can be modified with target intervention [6]. In IRT, it is thought that daytime rehearsal of altered dream scripts (i.e. script of recurring nightmare modified with a new scenario and different ending) can alter the conditioned relationship between sleep and nightmares [6]. The AASM also states that the following behavioural and psychological treatment options may be used for the treatment of PTSD-associated nightmares: CBT, CBT for insomnia, exposure, relaxation and rescripting therapy (ERRT; an IRT variant), and EMDR [4].

…patients may want pharmacological agents…

Patients may prefer pharmacological agents over non-pharmacological therapies because they are possibly easier to access than non-pharmacological therapies [3]. Although there is no pharmacological agent that has been specifically approved for the treatment of PTNs, there are established agents that have been used to treat PTNs (Table 1) [3].

The efficacy of prazosin in the treatment of PTSD-associated nightmares has been demonstrated in at least ten studies [4]. However, results from the recent PACT trial (Table 1) has led to the downgrading of the recommendation for use of prazosin to treat nightmare disorder by the AASM. The AASM task force noted that > 75% of patients in either group in that trial were receiving maintenance antidepressant medications, and that a possible interaction between prazosin and antidepressant medications needs to be clarified [4]. Also, whether inconsistencies in findings could be related to the type of trauma population (e.g. civilian vs military [3], with or without psychosocial instability [2]) remains to be determined.

Despite the downgrade because of the contradictory trial, the AASM retains prazosin as an option for treatment and acknowledges that prazosin may remain the first choice for pharmacological therapy because it is apparent to clinicians that many patients have a very good response to prazosin [4]. In addition, subsequent meta-analyses (Table 1) have shown strong evidence for the efficacy of prazosin in reducing PTNs [3]. Although the efficacy of prazosin for the treatment of PTNs has been questioned, it remains the agent with the strongest evidence base for reducing PTNs [3]. The Anxiety Disorders Association of Canada (ADAC) lists prazosin as having level I evidence for reducing trauma nightmares in patients with PTSD [7]. Other guidelines discuss the potential for prazosin use but recommend it as third-line therapy or include no specific recommendation on its use [2].

Although other pharmacological options can be considered for the management of PTNs (Table 1), data supporting their use are low-grade and sparse [3]. Doxazosin may be considered an alternative to prazosin pending further research. Clonidine has some evidence supporting its use, but with caution in patients with cardiac conduction disturbances, ischaemic heart disease and renal impairment. Evidence supporting the use of antidepressant monotherapy (e.g. selective serotonin reuptake inhibitors) is limited. Data for tricyclic antidepressants and mirtazapine (both mostly used as add-on therapy) are from low-evidence studies. Trazodone has some evidence of efficacy but may be poorly tolerated. While single prospective trials support the use of the atypical antipsychotics risperidone, olanzapine and quetiapine as add-on therapy, quetiapine is poorly tolerated. The evidence base for the antihistamine cyproheptadine, which has been investigated as add-on therapy, remains fairly weak. Limited evidence from non-randomized studies support add-on therapy with the anti-seizure medications gabapentin and topiramate. Of note, evidence does not support the use of β-blockers, benzodiazepines (particularly clonazepam), phenelzine, sedative hypnotics or venlafaxine for the treatment of PTNs [3].

Table 1 Examples of established agents and evidence for the treatment of post-traumatic nightmares in adults, as reviewed by Geldenhuys et al. [3]

Treatment	Study design	Efficacy and safety
Prazosin	RCT in military veterans with chronic PTSD and frequent nightmares ($n = 304$) [PACT trial] [8]	Prazosin (max 12 mg/day in females and 20 mg/day in males) did not lead to a significant difference in reduction in post-traumatic nightmares, as measured by the CAPS-5 item B2 ("recurrent distressing dreams") or any other measure, compared with PL at 10 weeks
		AEs include dizziness and light-headedness
	Systematic review and meta-analyses of RCTs in PTSD, including the PACT trial [8] ($n = 589$ [9], $n = 429$ [10])	Prazosin 3.1–16 mg/day for 3–26 wks significantly improved nightmare symptoms, but not overall PTSD symptoms or sleep quality, compared with PL [9]
		Significantly improved nightmares, overall PTSD and sleep quality [10]
Doxazosin	Retrospective chart review of pts with PTSD ($n = 51$) [11]	Nightmares fully ceased in 25% of adults following 12 wks of treatment
Clonidine	Retrospective chart review of 478 medication trials in 327 combat veterans with PTSD [12]	Partial response in 63% of pts receiving clonidine 0.1–2 mg
Sertraline	Mixed models analysis of two large PL-controlled trials ($n = 191$) [13]	Significantly ↓ symptoms in all three PTSD symptom clusters, including nightmares and insomnia
		Insomnia is a common consequence of the arousal effects of SSRIs
Fluvoxamine	Prospective cohort study of combat veterans with chronic PTSD ($n = 24$) [14]	Half of the participants reported a ↓ in nightmares
		Gastrointestinal complaints and worsening sleep symptoms were among the AEs leading to treatment discontinuation in several participants
Tricyclic antidepressants	Case series of concentration camp survivors with PTSD ($n = 12$) [15]	Treatment including unique combinations (e.g. amitriptyline, doxepin, imipramine) led to significant improvements in nightmare frequency and intensity as well as the cessation of intrusive symptoms, including nightmares, in some pts
Trazodone	Retrospective cohort study in war veterans ($n = 74$) [16]	Trazodone 50–200 mg nightly significantly ↓ the frequency of nightmares and improved sleep quality in 72% of participants
		AEs were common and included dizziness, daytime sedation, headaches, priapism, worsening nightmares and severe agitation
Mirtazapine	Anecdotal evidence in veterans with PTSD and sleep disturbances [17]	Reported to ↓ the frequency and intensity of nightmares; more than 300 observed cases had up to 75% improvement
Risperidone	RCT in pts with PTSD ($n = 267$) [18]	Small but significant improvements in sleep quality, nightmare severity and quality of life
		AEs can include drowsiness, headache, nausea and vomiting, and weight gain [19]
Olanzapine	RCT in pts with SSRI-resistant PTSD ($n = 19$) [20]	Olanzapine added on to existing therapy significantly ↓ sleep symptoms, including insomnia and nightmares, and improved subjective sleep quality
		Weight gain with metabolic complications is a common AE [3]
Quetiapine	Retrospective chart review in veterans with PTSD ($n = 237$) [21]	Although quetiapine produced a similar reduction in night-time symptoms compared with prazosin, quetiapine recipients (35%) were more likely than prazosin recipients (18%) to discontinue treatment because of AEs [21]
	Open-label trial (6 wks) in combat veterans with PTSD ($n = 20$) [22]	Adjunctive therapy with quetiapine 25–300 mg daily was associated with modest yet significant improvements in subject sleep quality, duration, latency and disturbances (including terror episodes)
		AEs include sedation (37%), weight gain, hyperglycaemia and hyperlipidaemia
Cyproheptadine	Case series [23]	Inconsistent results, with some showing efficacy in decreasing nightmares
Gabapentin	Retrospective review ($n = 30$) [24]	Gabapentin ↓ nightmares and led to a moderate improvement in sleep duration
Topiramate	Double-blind, PL-controlled trial in civilians with PTSD ($n = 38$) [25]	Topiramate 25–400 mg/day led to non-significant overall improvement on the CAPS-5 but a significant improvement in the re-experiencing scale (includes nightmares)
		AEs include glaucoma, headache, loss of appetite, memory concerns, pain, suicidal ideation and urticaria [26]

AE(s) adverse event(s), *CAPS-5* Clinician-Administered PTSD Scale for DSM-5, *PL* placebo, *pts* patients, *PTSD* post-traumatic stress disorder, *RCT(s)* randomized controlled trial(s), *SSRI(s)* selective serotonin release inhibitor(s), *wks* weeks, ↓ decrease(d)

Table 2 Examples of agents with potential but requiring further investigation for the treatment of post-traumatic nightmares in adults, as reviewed by Geldenhuys et al. [3]

Treatment	Study design	Efficacy and safety
Melatonin agonists		
Ramelteon	Pre-clinical study in mice with PTSD-like behaviours [27]	Chronic administration of ramelteon improved all PTSD-like behaviours [27]
Synthetic cannabinoids		
Nabilone	Open-label study in pts with treatment-resistant nightmares in PTSD ($n = 47$) [28]	Nabilone 0.2–4.0 mg nightly as an adjunct to standard treatment led to a total cessation or lessening severity of nightmares in 72% of pts
	RCT of crossover design in male military personnel with PTSD and treatment-resistant trauma-related nightmares ($n = 10$) [29]	Treatment with nabilone 0.5–3.0 mg for 7 weeks led to a significant ($p = 0.03$) ↓ in nightmares (measured by the CAPS-5 Recurring and Distressing Dream scores) compared with placebo
		Most common AEs include dry mouth, headaches, and rarely nausea and vomiting [3]
N-methyl-D-aspartic acid receptor antagonists		
Ketamine	Proof-of-concept, randomized, double-blind, crossover trial in adults with a diagnosis of chronic PTSD related to a range of trauma exposures ($n = 41$) [30]	A single IV infusion of ketamine at a sub-anaesthetic dose of 0.5 mg/kg significantly ($p = 0.02$) and rapidly ↓ PTSD symptom severity (measured using IES-R) 24 h after infusion compared with an IV infusion of midazolam 0.045 mg/kg, without clinically significant persistent dissociative symptoms
	RCT in pts aged 18–70 years with chronic PTSD related to a range of trauma exposures ($n = 30$) [31]	Repeated IV infusions of ketamine 0.5 mg/kg (approximately three times a week for two weeks) led to significant improvements in PTSD symptoms (total CAPS-5 scores) from baseline to week 2 ($p = 0.004$) compared with midazolam, with significantly ($p = 0.03$) more ketamine recipients achieving a ≥ 30% reduction in scores from baseline compared with midazolam recipients (67% vs 20%)
		Ketamine infusions generally well tolerated, with only transient haemodynamic and psychoactive AEs
Psychedelic agents		
MDMA	Phase 3 RCT in pts with chronic and severe PTSD ($n = 90$) [32]	Three doses of MDMA administered in conjunction with manualized therapy over 18 weeks resulted in a significant ($p < 0.0001$) improvement in PTSD symptoms (measured by CAPS-5) from baseline compared with placebo, without AEs of abuse, suicidality or QT prolongation [32]
Anticholinergics		
Trihexyphenidyl	Mixed open-label ($n = 22$) and single-blind ($n = 12$) study series in pts with treatment-refractory PTSD-related nightmares and flashbacks (results presented in aggregate) [33]	Trihexyphenidyl 2 mg two or three times a day led to a notable effect on nightmare reduction (on the CAPS-5) within 2 weeks of treatment, with 88% of patients reporting improvement to mild or no nightmares [33]

AEs adverse events, *CAPS-5* Clinician-Administered PTSD Scale for DSM-5, *IESR* Impact of Event Scale-Revised, *IV* intravenous, *MDMA* 3,4-methylenedioxymethamphetamine, *pts* patients, *PTSD* post-traumatic stress disorder, *RCT* randomized controlled trial, ↓ decreased

…and the decision regarding treatment should be shared

Upon determination to treat the nightmares, the decision regarding optimal therapeutic intervention (behavioural or pharmacological) should be shared between the patient and clinical provider [6]. The severity of the nightmares, accessibility of the treatment modality (e.g. some may not be readily available in rural areas), cost of treatment, duration of treatment and patient preference should all be taken into consideration [2, 6].

Additional agents require further investigation

Pharmacological agents that are promising but lack more supportive data are presented in Table 2. The use of ramelteon, cannabinoids, ketamine, 3,4-methylenedioxymethamphetamine and trihexyphenidyl are not yet advised in routine management [3]. Although data are sparse for these agents and their use is controversial, they should not be overlooked. Further evaluation is needed to determine the efficacy of these agents in the treatment of a range of PTSD symptoms, including PTNs [3].

Take home messages

- PTNs are one of the most critical symptoms of PTSD requiring treatment
- Targeted treatment of PTNs is important because they are resistant to general PTSD treatment
- Recommend non-pharmacological therapies first, IRT in particular
- Consider prazosin if pharmacological therapy is warranted
- Additional treatments are available, though of low-grade or limited data, and novel agents are being explored

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and conflict of interest E. S. Kim, a contracted employee of Adis International Ltd/Springer Nature, and C. Kang, a salaried employee of Adis International Ltd/Springer Nature, declare no relevant conflicts of interest. All authors contributed to the review and are responsible for the article content.

Ethics approval, Consent to participate, Consent for publication, Availability of data and material, Code availability Not applicable.

References

1. National Institute for Health and Care Excellence. Post-traumatic stress disorder. 2018. http://www.nice.org.uk/guidance/ng116. Accessed 2 Mar 2023.
2. Martin A, Naunton M, Kosari S, et al. Treatment guidelines for PTSD: a systematic review. J Clin Med. 2021;10(18):4175.
3. Geldenhuys C, van den Heuvel LL, Steyn P, et al. Pharmacological management of nightmares associated with posttraumatic stress disorder. CNS Drugs. 2022;36(7):721–37.
4. Morgenthaler TI, Auerbach S, Casey KR, et al. Position paper for the treatment of nightmare disorder in adults: an American Academy of Sleep Medicine Position Paper. J Clin Sleep Med. 2018;14(6):1041–55.
5. Ursano RJ, Bell C, Eth S, et al. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. Am J Psychiatry. 2004;161(Suppl 11):3–31.
6. El-Solh A. Management of nightmares in patients with post-traumatic stress disorders: current perspectives. Nat Sci Sleep. 2018;10:409–20.
7. Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14(Suppl 1):S1.
8. Raskind MA, Peskind ER, Chow B, et al. Trial of prazosin for post-traumatic stress disorder in military veterans. N Engl J Med. 2018;378(6):507–17.
9. Zhang Y, Ren R, Sanford LD, et al. The effects of prazosin on sleep disturbances in post-traumatic stress disorder: a systematic review and meta-analysis. Sleep Med. 2020;67:225–31.
10. Reist C, Streja E, Tang CC, et al. Prazosin for treatment of post-traumatic stress disorder: a systematic review and meta-analysis. CNS Spectr. 2021;26(4):338–44.
11. Roepke S, Danker-Hopfe H, Repantis D, et al. Doxazosin, an α-1-adrenergic-receptor antagonist, for nightmares in patients with posttraumatic stress disorder and/or borderline personality disorder: a chart review. Pharmacopsychiatry. 2017;50(1):26–31.
12. Detweiler M, Pagadala B, Candelario J, et al. Treatment of post-traumatic stress disorder nightmares at a Veterans Affairs medical center. J Clin Med. 2016;5(12):117.
13. Davidson JRT, Landerman LR, Farfel MG, et al. Characterizing the effects of sertraline in post-traumatic stress disorder. Psychol Med. 2002;32(4):661–70.
14. Boer M, Op den Velde W, Falger PJ, et al. Fluvoxamine treatment for chronic PTSD: a pilot study. Psychother Psychosom. 1992;57(4):158–63.
15. Boehnlein JK, Kinzie JD, Ben R, et al. One-year follow-up study of posttraumatic stress disorder among survivors of Cambodian concentration camps. Am J Psychiatry. 1985;142:956–9.
16. Warner MD, Dorn MR, Peabody CA. Survey on the usefulness of trazodone in patients with PTSD with insomnia or nightmares. Pharmacopsychiatry. 2001;34:128–31.
17. Lewis JD. Mirtazapine for PTSD nightmares. Am J Psychiatry. 2002;159(11):1948–9.
18. Krystal JH, Pietrzak RH, Rosenheck RA, et al. Sleep disturbance in chronic military-related PTSD: clinical impact and response to adjunctive risperidone in the Veterans Affairs cooperative study #504. J Clin Psychiatry. 2016;77(4):483–91.
19. Khachiyants N, Ali R, Kovesdy CP, et al. Effectiveness of risperidone for the treatment of nightmares in veterans with posttraumatic stress disorder. J Clin Psychopharmacol. 2010;30(6):735–7.
20. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiatry. 2002;159(10):1777–9.
21. Byers MG, Allison KM, Wendel CS, et al. Prazosin versus quetiapine for nighttime posttraumatic stress disorder symptoms in veterans. J Clin Psychopharmacol. 2010;30(3):225–9.
22. Robert S, Hamner MB, Kose S, et al. Quetiapine improves sleep disturbances in combat veterans with PTSD. J Clin Psychopharmacol. 2005;25(4):387–8.
23. Singareddy R, Baron R. Sleep in posttraumatic stress disorder. Ann Clin Psychiatry. 2002;14(3):183–90.
24. Hamner MB, Brodrick PS, Labbate LA. Gabapentin in PTSD: a retrospective, clinical series of adjunctive therapy. Ann Clin Psychiatry. 2001;13(3):141–6.
25. Tucker P, Trautman RP, Wyatt DB, et al. Efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder. J Clin Psychiatry. 2007;68(2):201–6.
26. Aurora RN, Zak RS, Auerbach SH, et al. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 2010;6(4):389–401.
27. Fukunaga K, Yabuki Y, Takahata I, et al. Neurological mechanism and therapeutic strategy for posttraumatic stress disorders. Nihon Yakurigaku Zasshi. 2018;152(4):194–201.
28. Fraser GA. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). CNS Neurosci Therap. 2009;15(1):84–8.
29. Jetly R, Heber A, Fraser G, et al. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: a preliminary randomized, double-blind, placebo-controlled cross-over design study. Psychoneuroendocrinology. 2015;51:585–8.
30. Feder A, Parides MK, Murrough JW, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder. JAMA Psychiat. 2014;71(6):681–8.

31. Feder A, Costi S, Rutter SB, et al. A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. Am J Psych. 2021;178(2):193–202.
32. Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med. 2021;27(6):1025–33.
33. Sogo K, Sogo M, Okawa Y. Centrally acting anticholinergic drug trihexyphenidyl is highly effective in reducing nightmares associated with post-traumatic stress disorder. Brain Behav. 2021;11(6): e02147.