SLEEP AND NEUROLOGICAL DISORDERS (JL DEWOLFE, SECTION EDITOR)



Trauma-Associated Sleep Disturbances: a Distinct Sleep Disorder?

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Abstract

Purpose of Review This paper describes a newly proposed sleep disorder, trauma-associated sleep disorder (TSD). Whether or not this represents a truly unique condition is controversial. In this paper, we describe the overlapping features and differences between TSD, post-traumatic stress disorder (PTSD), and rapid eye movement (REM) sleep behavior disorder (RBD). **Recent Findings** While REM sleep without atonia (RWA) and dream enactment are part of the diagnostic criteria for both RBD and TSD, only TSD features nightmares that occur both in non-REM and REM. A key difference between TSD and PTSD is the presence of symptoms during wakefulness in the latter, though the relationship between the two disorders is, as of yet, unclear. It is unknown whether or not a relationship exists between TSD and neurodegeneration; thus, this needs to be explored further. **Summary** Additional research, such as application of TSD diagnostic criteria to more diverse population, would help to determine whether or not TSD is a distinct clinical entity, its relationships to PTSD, as well as the association of this condition with the development of neurodegeneration.

Keywords Sleep disorder \cdot Neurodegeneration \cdot REM sleep without atonia \cdot Post-traumatic stress disorder \cdot Trauma-associated sleep disorder \cdot Nightmare disorder

Introduction

During a critical juncture in Bram Stoker's masterpiece *Dracula*, Professor Van Helsing begins to prepare for the upcoming battle with the infamous vampire. However, he insists that his colleague Mina, one of the novel's more vulnerable characters, stays back by explaining "even if she be not harmed...she may suffer—both in waking, from her nerves, and in sleep, from her dreams" [1]. What Stoker is suggesting with this line, is that even without physical injury, the distress that accompanies a traumatic event can have severe psychological damage on an individual, which can manifest while he or she is asleep.

There is a wide breadth of literature describing various disruptive nocturnal behaviors (DNB) frequently reported

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after experiencing a traumatic event. The most common types of sleep disturbances are insomnia and nightmares [2], but other sleep abnormalities have also been reported such as severely fragmented sleep [3], early morning awakenings [4, 5], autonomic hyperarousal [6], sleep talking, and violently acting out of dreams [6, 7]. These types of parasomnias have been reported in other populations, but there is currently a debate on whether clinicians should adopt a newly proposed parasomnia specific to these trauma-associated sleep disturbances. Mysliwiec and colleagues have made a strong case for the newly defined parasomnia, aptly named traumaassociated sleep disorder (TSD); however, many of these symptoms overlap with other disorders, most notably posttraumatic stress disorder (PTSD) and rapid eye movement (REM) sleep behavior disorder (RBD) [6]. In this article, we review the current understanding, clinical characteristics, and pathophysiology of these disorders.

Differences Between RBD and TSD

Although violent reenactments of dreams while sleeping had been reported centuries ago, it was not formally diagnosed and named until the mid-1980s by Drs. Carlos Scheck and Mark Mahowald who coined the term RBD [8, 9]. In their initial report of four elderly men, they described extreme REM sleep pathologies including "variable loss of chin atonia, extraordinarily increased limb-twitch activity, and increased REM ocular activity and density." These patients also exhibited coordinated limb motions while sleeping, including reaching and searching for nearby objects, punches, and kicks, as well as complex vocalizations. One of their most infamous patients used a nightly ritual in which he "tethered" himself to his bed's headboard using a belt and rope to prevent himself from sporadically jumping out of bed, an improvised remedy he used for over 5 years prior to seeking professional treatment.

Although this clinical history of extreme dream enactment is characteristic of RBD, a patient can still be provisionally diagnosed with the disorder with or without REM without atonia (RWA), based upon clinical judgment and/or response, or lack thereof, to standard treatments for RBD [10, 11]. Selective serotonin re-uptake inhibitors (SSRIs) can contribute to RWA, but this does not preclude diagnosis of either RBD, secondary RBD, or TSD [6, 11].

Demographics

There seem to be key demographic differences between patients diagnosed with RBD and those proposed to have TSD.

Although TSD has not yet been extensively studied, in the majority of cases, patients have been young male adults, usually under the age of 40, and typically soldiers exposed to combat [4–7, 12]. RBD on the other hand is much more common in elderly men, usually 50 years or older, and is not associated with combat exposure or traumatic events [13]. Previous studies have shown that RBD can affect younger populations, but this anomaly is now recognized as small subgroup of RBD patients with different associated features and symptoms [14]. More recent data has shown that RBD may be diagnosed more equally between genders and in younger patients [15].

Although both disorders are more common in men, this could be due to diagnostic challenges and/or selection bias. In the original case series, over 85% of both the Schenk and Mahowald patients, and the Mayo Clinic patients, were reported as male [8, 9]. Similarly, most TSD cases are reported in soldiers, a predominantly male population. However, it is entirely possible that RBD and TSD may manifest in women as subclinical, nonviolent behaviors that do not flag the attention of medical providers [16].

Sleep Phenotype

Individuals with TSD are often diagnosed with other sleep disorders, most commonly insomnia and obstructive sleep apnea [6, 17]. It has been theorized that insomnia amplifies and perpetuates trauma-related nightmares in TSD through the decreased inhibition of the amygdala by the medial prefrontal cortex, which results from sleep deprivation [6].

RBD is also often comorbid with other sleep disorders, namely narcolepsy and periodic limb movements [13, 14]. RBD co-occurs more commonly in narcolepsy with cataplexy than narcolepsy without cataplexy [18]. There can be clinical confusion among the disorders; researchers recently described a new variant of periodic limb movement disorder that mimicked RBD and responded well to ropinirole [19]. Patients with RBD may have a milder severity of sleep apnea, possibly owing to increased muscle tone during REM sleep [20].

Nightmares are prevalent in TSD, and less so in RBD. Hefez and colleagues described a Holocaust survivor's recurrent nightmare as "the same anxiety dream, in which he was haunted by his persecutors. This was a repetition of an actual traumatic experience he had at age 6, more than 39 years earlier." This nightmare occurred both in REM and NREM sleep [4]. Dream content is also an important consideration when separating TSD from RBD. The dream content in TSD is often distressing and related to the traumatic event experienced by the individual, while in RBD, there are no specific criteria for dream content. Patients exhibiting both RBD and TSD will describe recurrent dreams, but only in TSD are they based around the reenactment of a traumatic event. Although RBD dreams are sometimes distressful or aversive, they can be mundane or even enjoyable [16, 21].

Waking Phenotype

TSD is not necessarily associated with daytime symptoms, the exception likely being its co-occurrence with daytime symptoms common in PTSD (i.e., hypervigilance, avoidance, re-experiencing the traumatic event) [6, 22, 23, 24••]. However, those with TSD do not necessarily have PTSD, and vice versa. Similarly, the symptoms of RBD are primarily isolated to sleep and not wakefulness. Daytime symptoms that do occur with RBD may be a manifestation of another neurodegenerative process, with which RBD may coincide. Both RBD and TSD may manifest with excessive daytime sleepiness due to sleep fragmentation.

PSG Findings

One of the most important distinguishing characteristics of TSD is that the trauma-related nightmares can occur in both REM and NREM sleep [24••, 25], which is not characteristic in other types of parasomnias. Nightmares that occur in NREM sleep may explain the variable level of recall that has been reported in patients with TSD [25, 26]. Both RBD and TSD are characterized by combative behaviors and complex vocalizations during REM, which can be a source of great distress, if not for the patient, then for his or her bed partner [23, 24••, 25].

PSG studies on individuals exhibiting TSD have demonstrated a hyperarousal of the sympathetic nervous system, including tachycardia, tachypnea, and night sweats [6, 23, 25]. All these symptoms suggest abnormal physiological arousal in the patients. Careful examination of the respiratory data from the PSG must confirm that the heightened arousal is not due to sleep-disordered breathing, which is a frequent comorbidity of TSD [6]. In contrast, there is evidence that there is a blunting or absence of REM-related cardiac and respiratory responses in subjects with idiopathic RBD [27, 28]. RBD can be an early sleep finding in patients with multiple system atrophy, which is characterized by autonomic dysfunction [29].

Relationship to Neurodegeneration

There is a strong link between RBD and degenerative brain diseases, including Parkinson's disease [30], dementia with Lewy bodies [30, 31], and multiple system atrophy [29]. As of today, there is no clear connection between TSD and these neurodegenerative disorders. However, this could be due to the lack of longitudinal research on this proposed novel parasomnia.

Both RBD and TSD are partially defined by the presence of REM sleep without atonia (RWA), as well as by dream enactment behavior. The significance of RWA in isolation from other findings is not yet understood. RWA without dream enactment could be an early harbinger of neurodegeneration [32•]. Studies are underway in our laboratory to further investigate this question as well as whether there is a link between TSD and neurodegeneration.

Differences Between TSD and PTSD

Trauma-associated sleep disorder may be confused with PTSD due to the close temporal relationship with a traumatic event. In TSD, there is often a triggering event for sleep symptoms, as in PTSD [23, 25]. There is no such inciting event in RBD. Most TSD cases have been reported in veterans, a population in which PTSD is a common comorbidity, with the inciting event usually associated with some form of armed combat [7, 12, 33]. However, other traumatic events can also induce TSD and PTSD as seen in earthquake [34], sea disaster [4], and Holocaust survivors [4].

One of the required criteria for posttraumatic stress disorder (PTSD) is that the traumatic event is persistently re-experienced by the individual [22]. This is most commonly manifested in the form of nightmares. Several studies have shown the high incidence of PTSD patients experiencing nightmares [7, 35–37]. For instance, Neylan and colleagues found that over 52% of Vietnam veterans with PTSD experienced nightmares containing the reenactment of events from their time in the military. In comparison, only 5.7% of veterans without PTSD and 3.4% of civilians reported recurrent nightmares [38].

It is important to note that PTSD nightmares do not include dream enactment or REM without atonia (RWA), a core feature of TSD. Although previous studies have shown that individuals with PTSD may in fact exhibit violent behavior while experiencing a nightmare, such as thrashing and at times even attacking partners, this is not a requirement of the diagnosis and therefore constitutes as a separate sleep disorder [17, 39]. In TSD, dream enactment behavior is one of the primary criteria and a defining symptom of the disorder.

Another important distinction between TSD and PTSD is the lack of daytime symptoms. Individuals reporting TSD do not necessarily have any overt symptoms while awake, as seen in patients with PTSD, including alterations in cognition, mood, and arousal [22]. Although it is likely that TSD is often comorbid with PTSD, there have been reported cases of TSD without PTSD [6].

Treatment

Pharmacologic Therapy

Pharmacological therapy for RBD in the form of clonazepam and high-dose melatonin have been used with reasonable effectiveness [40–46]. While clonazepam treatment produces improvements in disruptive nocturnal behaviors in RBD, it does not restore REM atonia [47]. Interestingly, a small case series reported a reduction in the percentage of tonic REM activity in patients treated with melatonin, but no change in the percentage of phasic REM activity [41].

Pharmacological therapy for TSD is more limited. Prazosin has been a mainstay of treatment for nightmare disorders, including PTSD-associated nightmare disorder [48–50]. In a case series of four young male military veterans, therapy with prazosin improved both disruptive nocturnal behaviors and nightmares [6]. However, a recent large multisite clinical trial in veterans with PTSD and nightmare disorder showed no benefit of sleep symptoms with prazosin [51•]. Clonazepam has also been tried. While clonazepam did improve sleep onset and maintenance insomnia symptoms in a pilot study of patients with combat-related PTSD, it did not improve nightmares associated with combat-related PTSD [52]. Data is limited on the efficacy of other pharmacologic alternatives, such as synthetic cannibinoids [53], antidepressants, and antipsychotics, and anticonvulsants [54–61].

Non-pharmacologic Interventions

In RBD, PTSD, and likely TSD, it important to evaluate and treat any other concomitant sleep disorders, such as obstructive sleep apnea and insomnia. It is also critical to optimize sleep hygiene, which includes keeping a regular lights off/lights on schedule, as well as to ensure adequate sleep opportunity. There are several non-pharmacologic options for treatment PTSD-associated nightmare disorder, including image rehearsal therapy (IRT); exposure, relaxation, and re-scripting therapy (ERRT); lucid dreaming therapy; systematic desensitization and exposure therapy [36, 54, 58, 62]. IRT and ERRT have been studied extensively and are well-established, but data supporting the use of the other aforementioned therapies are limited [62–64]. Cognitive behavioral therapy for insomnia has been shown to improve sleep in patients with PTSD-associated nightmare disorder, but effects on nightmare frequency and severity have been variable [65–67]. However, no non-pharmacological interventions have been specifically studied in TSD or RBD.

Conclusions

While trauma-associated sleep disorder is characterized by a unique set of features, there is a great deal of overlap of these features with those of other disorders, such as REM sleep behavior disorder and posttraumatic stress disorder. Dream enactment behavior and REM without atonia are part of the diagnoses of both RBD and TSD. The relationship between TSD and PTSD remains unclear, but both can be associated with nightmares. Larger scale, longitudinal studies are needed to evaluate the full spectrum of TSD and whether this is a distinct sleep disorder with long-term neurological consequences, like RBD.

At the Portland VA, we have established a large data repository of over 600 veterans with polysomnography along with questionnaires on PTSD, traumatic brain injury, medications, and dream enactment behavior. Polysomnography data will be reviewed to identify REM without atonia, disruptive nocturnal behaviors captured on video, and tachycardia on EKG. Veterans will be followed prospectively for evidence of neurodegenerative disease. Future directions should expand to civilian populations, as well as in women, adolescents, and children—such work would provide support of TSD as a distinct, generalizable clinical sleep disorder.

Take-Home Points

- Trauma-associated sleep disorder (TSD) has been recently proposed to be a unique sleep disorder based upon initial studies in military veteran populations by Mysliwiec and colleagues.
- While there is some overlap between TSD and REM sleep behavior disorder, there are a few key differences, such as the presence of a triggering traumatic event and nightmares.
- While there is some overlap between TSD and posttraumatic stress disorder, there are a few key differences, such as lack of daytime symptoms.

 Much research remains to be done on TSD for it to be validated as a unique clinical entity, such as application of diagnostic criteria to more diverse populations, treatment of the disorder, and its possible relationship to neurodegeneration.

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Compliance with Ethical Standards

Conflict of Interest Tara D. Rachakonda, Nadir M. Balba, and Miranda M. Lim have no financial or other conflicts of interest to disclose.

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References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- •• Of major importance
- 1. Stoker B. Drácula 1897. Bram Stoker; 2014.
- Lavie P. Sleep disturbances in the wake of traumatic events. N Engl J Med. 2001;345(25):1825–32.
- Insana SP, Kolko DJ, Germain A. Early-life trauma is associated with rapid eye movement sleep fragmentation among military veterans. Biol Psychol. 2012;89(3):570–9.
- 4. Hefez A, Metz L, Lavie P. Long-term effects of extreme situational stress on sleep and dreaming. Am J Psychiatry. 1987;
- Mellman TA, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. Am J Psychiatry. 1995;152(1):110–5.
- Mysliwiec V, O'Reilly B, Polchinski J, Kwon HP, Germain A, Roth BJ. Trauma associated sleep disorder: a proposed parasomnia encompassing disruptive nocturnal behaviors, nightmares, and REM without atonia in trauma survivors. J Clin Sleep Med: JCSM: Off Publ Am Acad Sleep Med. 2014;10(10): 1143–8.
- Van der Kolk B, Blitz R, Burr W, Sherry S, Hartmann E. Nightmares and trauma: a comparison of nightmares after combat with lifelong nightmares in veterans. Am J Psychiatry. 1984;
- Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep. 1986;9(2):293–308.

- Schenck CH, Bundlie SR, Patterson AL, Mahowald MW. Rapid eye movement sleep behavior disorder: a treatable parasomnia affecting older adults. JAMA. 1987;257(13):1786–9.
- Iranzo A, Santamaria J, Tolosa E. The clinical and pathophysiological relevance of REM sleep behavior disorder in neurodegenerative diseases. Sleep Med Rev. 2009;13(6):385–401.
- REM sleep behavior disorder. 2014. In: Sateia M, editor. International Classification of Sleep Disorders. 3rd edition. Darien (IL): American Academy of Sleep Medicine. p. 246–243.
- 12. Schlosberg A, Benjamin M. Sleep patterns in three acute combat fatigue cases. J Clin Psychiatr. 1978.
- Fantini ML, Michaud M, Gosselin N, Lavigne G, Montplaisir J. Periodic leg movements in REM sleep behavior disorder and related autonomic and EEG activation. Neurology. 2002;59(12): 1889–94.
- Schenck CH. REM sleep behavior disorder. In: Sleep Medicine. Berlin: Springer; 2015. p. 391–405.
- Ju Y-E, Larson-Prior L, Duntley S. Changing demographics in REM sleep behavior disorder: possible effect of autoimmunity and antidepressants. Sleep Med. 2011;12(3):278–83.
- Oudiette D, De Cock VC, Lavault S, Leu S, Vidailhet M, Arnulf I. Nonviolent elaborate behaviors may also occur in REM sleep behavior disorder. Neurology. 2009;72(6):551–7.
- Wallace D, Shafazand S, Ramos A, et al. Insomnia characteristics and clinical correlates in Operation Enduring Freedom/Operation Iraqi Freedom veterans with post-traumatic stress disorder and mild traumatic brain injury: an exploratory study. Sleep Med. 2011;12(9):850–9.
- Nightingale S, Orgill JC, Ebrahim IO, de Lacy SF, Agrawal S, Williams AJ. The association between narcolepsy and REM sleep behavior disorder (RBD). Ju Y-ES. Rapid eye movement sleep behavior disorder in adults younger than 50 years of age. Sleep Med 2013;14(8):768–774.
- Gaig C, Iranzo A, Pujol M, Perez H, Santamaria J. Periodic limb movements during sleep mimicking REM sleep behavior disorder: a new form of periodic limb movement disorder. Sleep. 2017;40(3): 1–6.
- Bugalho P, Mendonça M, Barbosa R, Salavisa M. The influence of sleep disordered breathing in REM sleep behavior disorder. Sleep Med. 2017;37:210–5.
- Siclari F, Wienecke M, Poryazova R, Bassetti CL, Baumann CR. Laughing as a manifestation of rapid eye movement sleep behavior disorder. Parkinsonism Relat DIsord. 2011;17(5):382–6.
- Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.
- Mysliwiec V, Brock MS, Thomas AL, Creamer JL. The extreme nocturnal manifestation of trauma: trauma associated sleep disorder. In: Sleep and combat-related post traumatic stress disorder. Berlin: Springer; 2018. p. 215–25.
- 24.•• Mysliwiec V, Brocks MS, Creamer JL, O'Reilly BM, Germain A, Roth BJ. Trauma associated sleep disorder: a parasomnia induced by trauma. Sleep Med Rev. 2018;37:94–104. This is an article that proposes trauma-associated sleep disorder as a distinct clinical entity from REM sleep behavior disorder
- Kramer M, Kinney L, Scharf M. Sleep in delayed stress victims. Sleep Res. 1982;11:113.
- 26. Cicogna P, Natale V, Occhionero M, Bosinelli M. Slow wave and REM sleep mentation. Sleep Res Online. 2000;3(2):67–72.
- Ferini-Strambi L, Oldani A, Zucconi M, Smirne S. Cardiac autonomic activity during wakefulness and sleep in REM sleep behavior disorder. Sleep. 1996;19(5):367–9.
- Lanfranchi LA, Fradette L, Gagnon JF, Colombo R, Montplaisir J. Cardiac autonomic regulation during sleep in idiopathic REM sleep behavior disorder. Sleep. 2007;30(8): 1019–25.

- Plazzi G, Corsini R, Provini F, Pierangeli G, Martinelli P, Montagna P, et al. REM sleep behavior disorders in multiple system atrophy. Neurology. 1997;48(4):1094–7.
- Marion M-H, Qurashi M, Marshall G, Foster O. Is REM sleep behaviour disorder (RBD) a risk factor of dementia in idiopathic Parkinson's disease? J Neurol. 2008;255(2):192–6.
- Gagnon J-F, Postuma RB, Mazza S, Doyon J, Montplaisir J. Rapideye-movement sleep behaviour disorder and neurodegenerative diseases. Lancet Neurol. 2006;5(5):424–32.
- 32.• Stefani A, Gabelia D, Högl B, Mitterling T, Mahlknecht P, Stockner H, et al. Long-term follow-up investigation of isolated rapid eye movement sleep without atonia without rapid eye movement sleep behavior disorder: a pilot study. J Clin Sleep Med. 2014;11(11): 1273–9. This pilot study showed that isolated REM sleep without atonia may be an early biomarker of synuclein-mediated neurodegeneration.
- Mysliwiec V, McGraw L, Pierce R, Smith P, Trapp B, Roth BJ. Sleep disorders and associated medical comorbidities in active duty military personnel. Sleep. 2013;36(2):167–74.
- Mellman TA, Hipolito MMS. Sleep disturbances in the aftermath of trauma and posttraumatic stress disorder. CNS spectrums. 2006;11(8):611–5.
- Daly CM, Doyle ME, Radkind M, Raskind E, Daniels C. Clinical case series: the use of prazosin for combat-related recurrent nightmares among Operation Iraqi Freedom combat veterans. Mil Med. 2005;170(6):513–5.
- Long ME, Hammons ME, Davis JL, Frueh BC, Khan MM, Elhai JD, et al. Imagery rescripting and exposure group treatment of posttraumatic nightmares in veterans with PTSD. J Anxiety Disord. 2011;25(4):531–5.
- Pigeon WR, Campbell CE, Possemato K, Ouimette P. Longitudinal relationships of insomnia, nightmares, and PTSD severity in recent combat veterans. J Psychosom Res. 2013;75(6):546–50.
- Neylan TC, Marmar CR, Metzler TJ, Weiss DS, Zatzick DF, Delucchi KL, et al. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatr. 1998;155(7):929–33.
- Husain AM, Miller PP, Carwile ST. REM sleep behavior disorder: potential relationship to post-traumatic stress disorder. J Clin Neurophysiol. 2001;18(2):148–57.
- Schenck CH, Bundlie SR, Patterson AL, Mahowald MW. Rapid eye movement sleep behavior disorder: a treatable parasomnia affecting older adults. JAMA. 1987;257(13):1786–9.
- Takeuchi N, Uchimura N, Hashizume Y, Mukai M, Etoh Y, Yamamoto K, et al. Melatonin therapy for REM sleep behavior disorder. Psychiatry Clin Neurosci. 2001;55(3):267–9.
- 42. Schenck CH, Mahowald MW. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. Sleep. 2002;25(2):120–38.
- Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demongraphic, clinical and laboratory findings in 93 cases. Brain. 2000;123(pt 2):331–9.
- Schenck CH, Hurwitz TD, Mahowald MW. Symposium: normal and abnormal REM sleep regulation: REM sleep behaviour disorder: an update on a series of 96 patients and review of the world literature. J Sleep Res. 1993;2(4):224–31.
- Kunz D, Bes F. Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. Mov Disord. 1999;14(3):507–11.
- Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med. 2003;4(4):281–4.

- Ferri R, Marelli S, Ferini-Strambi L, Oldani A, Colli F, Schenck CH, et al. An observational clinical and video-polysomnographic study of the effects of clonazepam in REM sleep behavior disorder. Sleep Med. 2013;14(1):24–9.
- Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, et al. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry. 2009;63(6):629–32.
- 49. Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, et al. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soliders returned from Iraq and Afghanistan. Am J Psychiatry. 2013;170(9):1003–10.
- Raskin MA, Thompson C, Petrie EC, Dobie DJ, Rein RJ, Hoff DJ, et al. Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. J Clin Psychiatry. 2002;63(7):565–8.
- 51.• Raskind MA, Peskind ER, Chow B, Harris C, Davis-Karim A, Holmes HA, et al. Trial of prazosin for post-traumatic stress disorder in military veterans. N Engl J Med. 2018;378(6):507–17. This is the latest randomized control clinical trial of prazosin therapy in military veterans; interestingly, it failed to demonstrate efficacy of prazosin therapy in alleviating distressing dreams
- Cates ME, Bishop MH, Davis LL, Lowe JS, Woolley TW. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. Ann Pharmacother. 2004;38(9):1395–9.
- 53. Cameron C, Watson D, Robinson J. Use of a synthetic cannabinoid in a correctional population for post-traumatic stress disorderrelated insomnia and nightmares, chronic pain, harm reduction and other indications: a retrospective evaluation. J Clin Psychpharmacol. 2014;34(5):559–64.
- Maher MJ, Rego SA, Asnis GM. Sleep disturbances in patients with post-traumatic stress disorder. CNS Drugs. 2006;20(7):567–90.
- Walderhaug E, Kasserman S, Aikins D, Vojvoda D, Nishimura C, Neumesiter A. Effects of duloxetine in treatment-refractory men with posttraumatic stress disorder. Pharmacopsychiatry. 2010;43(2):45–9.
- Neylan TC, Metzler TJ, Schoenfeld FB, Weiss DS, Lenoci M, Best SR, et al. Fluvoxamine and sleep disturbances in posttraumatic stress disorder. J Trauma Stress. 2001;14(3):461–7.

- van Liempt S, Vermetten E, Geuze E, Westenberg HGM. Pharmacotherapy for disordered sleep in post-traumatic stress disorder: a systematic review. Int Clin Psychopharmacol. 2006;21(4): 193–202.
- Nappi CM, Drummond SPA, Hall JMH. Treating nightmares and insomnia in post-traumatic stress disorder: a review of current evidence. Neuropharmacology. 2012;62(2):576–85.
- Detweiler MB, Kachiyants N, Detweiler JG, Ali R, Kim KY. Risperidone for post-traumatic combat nightmares: a report of four cases. Consult Pharm. 2011 Dec;26(12):920–8.
- David D, De Faria L, Mellman TA. Adjunctive risperidone treatment and sleep symptoms in combat veterans with chronic PTSD. Depress Anxiety. 2006;23(8):489–91.
- Alderman CP, McCarthy LC, Condon JT, Marwood AC, Fuller JR. Topiramate in combat-related posttraumatic stress disorder. Ann Pharmacother. 2009;43(4):635–41.
- Nadorff MR, Lambdin KK, Germain A. Pharmacolocial and nonpharmacological treatments for nightmare disorder. Int Rev Psychiatr. 2014;26(2):225–36.
- Aurora RN, Zak RS, Auerbach SH, Casey KR, Chowdhuri S, Karippot A, et al. Standards of practice committee; American Academy of Sleep Medicine. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 2010;6(4):389–401.
- Spoormaker VI, van den Bout J. Lucid dreaming treatment for nightmares: a pilot study. Psychother Psychosom. 2006;75(6): 389–94.
- Talbot LS, Maguen S, Metzler TJ, Schmitz M, McCaslin SE, Richards A, et al. Cognitive behavioral therapy for insomnia in posttraumatic stress disorder: a randomized controlled trial. Sleep. 2014;37(2):327–41.
- Marolies SO, Rybarczyk B, Vrana SR, Leszczyszyn DJ, Lynch J. Efficacy of a cognitive-behavioral treatment for insomnia and nightmares in Afghanistan and Iraq veterans with PTSD. J Clin Psychol. 2013;69(10):1026–42.
- 67. Krakow B, Johnston L, Melendrez D, Hollifield M, Warner TD, Chavez-Kennedy D, et al. An open-label trial of evidence-based cognitive behavior therapy for nightmares and insomnia in crime victims with PTSD. Am J Psychiatry. 2001;158(12):2043–7.