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REVIEW ARTICLES

Acute sleep interventions as an avenue for treatment of trauma-associated disorders

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Scientific evidence that acute, posttrauma sleep disturbances (eg, nightmares and insomnia) can contribute significantly to the pathogenesis of trauma-induced disorders is compelling. Sleep disturbances precipitating from trauma are uniquely predictive of daytime posttrauma symptom occurrence and severity, as well as subsequent onset of mental health disorders, including post–traumatic stress disorder. Conversely, adequate sleep during the acute posttrauma period is associated with reduced likelihood of adverse mental health outcomes. These findings, which are broadly consistent with what is known about the role of sleep in the regulation of emotion, suggest that the acute posttrauma period constitutes a "window of opportunity" during which treatment of sleep disturbances may be especially effective for preventing or mitigating progression of aberrant psychophysiological processes. At this point, the weight of the scientific evidence supporting this possibility warrants initiation of clinical trials to confirm the benefits of targeted prophylactic sleep enhancement, and to establish treatment guidelines as appropriate.

Keywords: post–traumatic stress disorder (PTSD); acute stress disorder (ASD); acute stress reaction (ASR); pharmacological treatment; behavioral treatment; sleep disturbance

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INTRODUCTION

While the factors that precipitate most mental health disorders are often ill-defined, traumatic stress–associated disorders, by definition, stem from exposure to traumatic events. Following trauma, most individuals acutely experience hyperarousal and emotional distress—symptoms that dissipate with time.[1,2] However, for a subset of individuals, initially severe trauma-related symptoms (acute stress reaction, or ASR) may be followed by development of trauma-associated disorders such as acute stress disorder (ASD) and post–traumatic stress disorder (PTSD).[3] Despite knowing the origin of trauma, the pathogenesis from traumatic event to disease state is not well understood. Prior work suggests that individuals with sleep disturbances are at greater risk for developing trauma-related symptoms, and that sleep disturbance is present throughout the development of traumatic stress–related disorders.[4] Accordingly, sleep abnormalities may have predictive value for determining the risk of developing trauma-associated disorders. If so, then it is also possible that treatment of sleep disturbance following trauma exposure may prevent the onset or reduce the severity of trauma-related disorders.

The objectives of this review are to assess the evidence that peri-trauma sleep disruption contributes to the onset of trauma-associated disorders, and to determine the extent to which treatment of sleep disturbances potentially prevents or alleviates traumatic stress–associated symptoms. We review the myriad sleep changes that arise following trauma and persist in ASD and PTSD, as well as those occurring in the absence of a psychiatric diagnosis. Additionally, we examine evidence that disordered sleep is a predisposing factor for maladaptive responses to traumatic stress exposure. Finally, we discuss the possible utility of current and potential treatments for sleep disturbance if administered early following trauma exposure to alleviate psychiatric symptoms. Overall, we review the evidence pertinent to the possibility that early detection and treatment of sleep disturbance following trauma may prevent the development, or reduce the severity, of traumatic stress–related disorders, thereby promoting better long-term mental health outcomes.

TRAUMATIC STRESS AND TRAUMATIC STRESS–RELATED DISORDERS

The defining diagnostic criterion for ASD and PTSD is exposure to a precipitating traumatic event. A trauma is any event that imparts an actual or perceived threat of death, serious injury, or sexual violence.[5] In the immediate aftermath of a traumatic event, some individuals present with an ASR. Symptoms of ASR include emotional distress, hyperarousal, trauma cue or context avoidance, and trouble sleeping.[3,6,7] These symptoms are often short-lived, persisting for no more than 48 hours.[3,8] Although ASR is not formally recognized by the DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders,* fifth edition),[5] it is included in the World

Health Organization's ICD-10 *(International Classification of Diseases, 10th Revision)*.[9] The relatively broad ICD-10 definition of ASR encompasses the DSM-5 definitions of both ASR and ASD, except for the qualifier that if symptoms persist for 3–30 days, ASD can be diagnosed. Individuals with ASD often present with heightened arousal or anxiety, a dissociative or detached state, trauma-related flashbacks, and sleep disruption.[5,8] If posttrauma symptoms persist for longer than 1 month, PTSD can be diagnosed. PTSD symptoms are divided into 4 subclusters (intrusion, avoidance, cognition and mood changes, and alterations in arousal and reactivity), all of which must be present for a diagnosis.[5] Symptoms within each subcluster vary in manifestation, resulting in a wide variety of symptom presentations. Symptoms of PTSD can persist for decades after a traumatic event; chronic PTSD is often a debilitating condition that is treatment-resistant and that rarely remits spontaneously.[10]

Although the trajectory from a traumatic event to ASR, ASD, and PTSD seems linear, this is not always the case. There is conflicting evidence as to whether ASR symptoms are predictive of later ASD and/or PTSD development.[1,11–15] Likewise, it is unclear whether ASD reliably predicts PTSD. A review of 22 studies of ASD found that 50% of patients with ASD later met criteria for PTSD.[16] However, individuals who later develop PTSD are not always diagnosed with ASD following trauma, so although ASR and ASD *may* precede PTSD, they do not always precede development of PTSD. It remains unclear if inconsistent relationships between ASR, ASD, and PTSD reflect diagnostic limitations or actual individual variations in the time course upon which symptoms develop. It is, therefore, perhaps more informative to assess specific symptoms that are predictive of trauma-related disorder development. An emerging body of literature suggests that peri-trauma sleep disturbances are predictive of trauma-related symptoms and the development of PTSD[17] Therefore, understanding how sleep is altered by trauma exposure may help to identify at-risk individuals and possibly inform development of early sleep-enhancing treatment strategies to prophylactically reduce overall trauma-related symptomology and the pathogenesis of PTSD.

SLEEP DISTURBANCE AND THE EMERGENCE OF TRAUMATIC STRESS SYMPTOMS

Disordered sleep is a hallmark symptom of trauma-related disorders and is included in the diagnostic criteria for both ASD and PTSD.[5] However, the pathophysiological processes by which posttrauma sleep disruption reduces adaptive responses to trauma are currently unknown. What is known is that sleep loss or disruption interferes with normal neurological and homeostatic processes and increases neuroinflammation in animals and β-amyloid deposition in humans.[18–20] In fact, chronic sleep disruption has detrimental effects on human health in general,[21] including on neural protective processes that mediate adaptation to physical and psychological stressors.[22] Conversely, improving disrupted sleep can improve physical and mental health.[23] Prior literature supports the role of sleep in reducing symptoms of PTSD and anxiety, possibly via improved regulation of neural pathways that modulate emotion.[24] While this emotional dysregulation may manifest as simple moodiness in day-to-day life, following trauma it can potentially increase the severity of posttrauma symptoms.[24] Additionally, disrupted sleep is intrinsically stressful.[22] Accordingly, it is not surprising that disturbed sleep can synergistically compound other trauma-related effects and exacerbate mental health outcomes.[25]

Due to the unpredictability of traumatic stress exposure, few studies have quantified the acute impact of trauma on human sleep, and no study has utilized polysomnography to measure early posttrauma changes in sleep parameters. Patient self-reports indicate that ∼35% of trauma survivors experience nightmares and ∼58% experience sleep disturbances within 24 hours following a traumatic event, with nocturnal sleep disturbance remaining elevated during the following week.[7,26] There is limited evidence from 2 actigraphy studies that captured objective measures of sleep-wake activity (ie, sleep duration, continuity, and timing) in small populations before and immediately after trauma (eg, missile attacks, earthquake).[27,28] Patients experienced lower than typical sleep efficiency, abnormally extended sleep onset latency, and increased wake after sleep onset. However, these studies did not assess whether trauma imparted any lasting sleep changes or whether—and the extent to which—sleep parameters predicted or reflected posttrauma psychopathology.

Trauma can also produce lingering, deleterious changes to sleep regardless of whether ASD or PTSD is subsequently diagnosed.[29,30] Individuals exposed to missile attacks during the Gulf War reported an increased prevalence of insomnia several months after the war.[31] Persistent insomnia and sleep disturbances have also been reported in survivors of earthquakes and the 9/11 terrorist attacks.[32–34] Early life trauma can result in sleep disturbances years afterward[35,36] and is associated with increased sleep disturbance in adulthood.[30] Similarly, a study of Holocaust survivors with and without traumatic stress diagnoses revealed self-reported sleep disturbances decades later, with the severity of sleep disturbance related to the amount of time imprisoned in concentration camps.[37] It is thought that sleep disturbance initiated by a traumatic experience can be maintained by self-perpetuating factors that accompany insomnia, such as maladaptive thoughts and behavioral patterns surrounding sleep.[38] Overall, the existing literature suggests that long-term trauma-induced sleep disturbance is sometimes, but not always, associated with diagnosable trauma-related mental health problems, irrespective of the trauma type, population, or duration.

The presence of chronic, trauma-related sleep disturbances in participants who do not meet criteria for a mental health disorder diagnosis has led to the proposal of a new parasomnia: trauma-associated sleep disorder (TSD).[39] TSD is a putative parasomnia characterized by nightmares, disruptive nocturnal behavior (eg, thrashing or tossing), dream-enactment behavior, REM sleep without atonia, and enhanced sympathetic activity during sleep.[40,41] Some of the symptoms of TSD are similar to those exhibited by patients with nightmare disorder and rapid eye movement (REM) sleep behavior disorder (RBD), but unlike these other disorders, TSD is characterized by dream-enactment behaviors and complex vocalizations during nightmares that are precipitated by a specific, identifiable traumatic event. Further work is warranted to better understand and

validate TSD as a formal diagnosis, but the data cited in support of this putative diagnosis nevertheless serves as additional evidence that long-term sleep disturbance can result from exposure to traumatic events.

Although sleep disturbance is among the diagnostic criteria for ASD, few studies have examined how self-reported sleep is changed in ASD, and no studies have yet documented ASR- or ASD-associated changes with objectively measured sleep parameters (eg, polysomnographically). In 1 of the few studies in which ASD and sleep were both assessed, 91% of ASD patients reported difficulty sleeping and 73% reported nightmares.[42] However, in this and other studies based on data collected from case reports of individuals admitted to hospitals following bodily injury, it is unclear whether, or the extent to which, the reported sleep disturbances were due to ASD or due to physical pain following traumatic injury.[43–45] Despite a dearth of objective data on sleep and ASD, the previously described research suggesting that sleep loss exacerbates the stress response makes plausible the hypothesis that ASR and ASD constitute an early window during which sleep-promoting intervention might help prevent the development, or mitigate the long-term effects, of PTSD.

The long-term impact of trauma on sleep is evident from numerous studies documenting sleep disturbances in PTSD. While there is consensus that PTSD impacts sleep, there is less agreement regarding which sleep parameters are affected.[46–48] Commonly self-reported sleep disturbances in PTSD patients include interrupted sleep, insomnia, and a general feeling that sleep is nonrestorative.[49–52] Objective studies of PTSD's impact on sleep vary by study, but some general themes are evident in the scientific literature: REM sleep is dysregulated in PTSD, with both increased and decreased amounts of REM having been reported.[53–62] The dysregulation of REM sleep may be linked to the increased prevalence of trauma-related nightmares that are one of the hallmark symptoms of PTSD.[51,52,63–65] Individuals with PTSD also tend to spend more time in, or exhibit more transitions to, light (stage N1) non-REM sleep at the expense of deep (stage N3) non-REM sleep.[62,63,66–69] Total sleep time and sleep efficiency are decreased in PTSD patients—potentially due to an increased rate of arousals from sleep.[53,54,56,59,63,66–68,70–75] Additionally, PTSD has a high comorbidity with obstructive sleep apnea (OSA).[76] OSA can worsen existing trauma-related sleep disruptions and contribute to neuroendocrine and metabolic dysregulation commonly present in PTSD.[76] As with other PTSD symptoms, the sleep-related symptoms of PTSD also vary by sex. Women with PTSD display an increased percentage of REM sleep as well as reduced total sleep time compared to women without PTSD.[61,62] Men with PTSD display an increased percentage of N2 sleep and a reduced percentage of N3 sleep compared to healthy men. Compared to men with PTSD, women with PTSD have increased total sleep time but also increased wake after sleep onset. These sex-specific differences may partially explain the differential rates of PTSD in men (4%–5%) vs women (9%–14%) reported in the National Comorbidity Survey in 1990–1992.[77] Overall, the breadth of literature regarding sleep disturbance characteristics in PTSD patients may inform the development of putative targets for intervention, whether at early or later time points following traumatic stress. For example, if a novel pharmacotherapy is observed to normalize REM sleep, based on the existing literature of sleep and PTSD, it might be hypothesized that this compound could then be used in a targeted way to improve both sleep and other trauma-related symptoms.

In addition to being a symptom of trauma exposure, sleep disturbances may increase the vulnerability to PTSD and/or be a marker of subthreshold PTSD. Overall, several studies have provided evidence that poor sleep in proximity to trauma may contribute to the pathogenesis of PTSD.[4,73,78,79] Patients who reported sleep issues before experiencing a hurricane or bodily injury were at increased risk of developing PTSD, panic disorder, and other psychiatric symptoms.[73,80] Similarly, studies of veterans have shown that sleep complaints prior to a combat deployment are associated with onset and severity of PTSD and depression symptoms during postdeployment, and these associations remain even when controlling for predeployment psychiatric symptoms.[78,81,82] Sleep disturbances precipitating from a traumatic event also increase the risk of developing symptoms of PTSD. Studies of combat veterans have shown that postdeployment sleep disturbances are associated with symptoms of PTSD, depression, and substance abuse 3–12 months following deployment.[83–85] Likewise, survivors of automobile accidents and political violence have demonstrated sleep disturbance in the aftermath of trauma that was associated with the development of PTSD symptoms up to a year later.[86,87] Interestingly, while early sleep issues are predictive of later PTSD symptom severity, early PTSD symptoms are not associated with the later development of sleep disturbances—suggesting that sleep complaints following trauma may be an early marker for subsequent PTSD diagnosis.[87] Although these studies provide a cohesive narrative regarding the impact of sleep disturbances on PTSD onset, their interpretation is limited by the use of self-reported sleep measures. Of course, the unpredictable occurrence of trauma limits the feasibility of recording objective measures of sleep prior to traumatic events. More feasible would be the collection of self-reported sleep measures combined with the objective sleep data from wearable devices across multiple time points in populations at high risk for exposure to trauma. Together, self-reported and objective data might be used in future studies to further elucidate the relationship between sleep disturbance and the pathogenesis of trauma-related disorders.

Despite limitations, the current literature suggests that: a) sleep disturbance arising from trauma is commonly present throughout the development of trauma-related disorders, and likely contributes to both the onset and maintenance of these disorders[17]; b) adequate sleep reduces the risk of developing PTSD and other mental health disorders[23,88]; and c) sleep disturbance (as might be measured using a variety of metrics such as those provided by commercial fitness trackers) occurring in close temporal proximity to a traumatic event is maladaptive and associated with poor mental health outcomes. Accordingly, it is reasonable to hypothesize that treatments which improve sleep continuity and quality, or that normalize sleep may be beneficial at all time points, regardless of the duration of the trauma-associated disorder. More work is needed to understand how specific changes in sleep exacerbate traumatic stress symptoms, particularly those changes acutely following a traumatic

event, and to determine whether, and the extent to which, sleep phenotype is predictive of susceptibility to posttrauma psychopathology. Such knowledge would assist in the development of interventions that are tailored for individual sleep phenotypes.

SHOULD INDIVIDUALS SLEEP IMMEDIATELY FOLLOWING TRAUMATIC STRESS?

Although the scientific literature generally suggests that sleep promotes psychological resilience, there is also some evidence that sleep deprivation immediately following trauma may be adaptive and constitute a useful strategy for mitigating subsequent mental health problems. The use of sleep deprivation posttrauma has not yet been tested and validated as a treatment method at this time, as a number of clinical studies would be needed to test the effectiveness of this approach. Based mainly on findings from a broad scientific literature demonstrating that sleep facilitates the consolidation of memories,[89,90] it has been hypothesized that posttrauma sleep loss should interfere with consolidation of the contextual fear and emotionally charged memories,[91,92] thereby reducing their negative effects. This hypothesis has received some support. Two studies utilizing films to induce analog trauma found that sleep deprivation after viewing the films reduced generalized fear responses, intrusive memories, and scores on the Impact of Event Scale.[93,94] Similar beneficial effects of sleep deprivation have been demonstrated in human and rodent studies, producing evidence that weakening the memory of the traumatic event reduces the subsequent impact on markers of stress.

However, such studies may not be adequately representative of real-world traumatic experiences. The contextual fear associated with a real-world trauma in which there is a perceived threat to life likely produces a much more salient fear association than that produced by laboratory contextual fear tasks, which are limited to using stimuli that are no more than mildly aversive. Similarly, it is difficult to draw direct comparisons between laboratory tasks evaluating emotional memory formation and traumatic memory formation. Emotional memory-based laboratory tasks commonly require participants to identify and recall information about contrasting neutral and negatively charged stimuli. While these tasks are useful for evaluating the formation of memories with an emotional valence, the extent to which findings from these studies are generalizable to real-world traumatic experiences—which almost by definition involve exposure to actual danger and/or significant injury and pain—is likely limited. Also, laboratory studies invariably utilize healthy participants who are not in a state of posttrauma hyperarousal. Following actual trauma, heightened sympathetic activity, particularly noradrenergic activity, may promote hyperconsolidation of highly salient traumatic experiences[95]—making subsequent sleep-dependent memory consolidation processes less critical for establishing the traumatic memory in the short term, and contributing to the persistence of these memories even years after the trauma occurred. Because it is not clear that memory consolidation processes for real-world trauma are qualitatively comparable to memories produced by exposure to relatively mild stressors in laboratory settings, and because ethical considerations preclude exposing study participants to truly traumatic events (eg, exposing participants to actual physical danger), generalization from such studies is problematic, and the potential real-world utility of posttrauma sleep deprivation as a therapeutic intervention remains uncertain.

Even more problematic for the hypothesis that sleep deprivation may be beneficial is the finding from prior studies that sleep deprivation following fear learning and analog trauma fails to improve psychological outcomes. Sleep deprivation after viewing a trauma film increased or had no effect on the number of intrusive memories.[96,97] Prior research has also shown that while positive or neutral memories are susceptible to sleep deprivation, negative memories are relatively resistant.[98] Additionally, sleep deprivation following cued fear learning impairs the ability to recall extinction of the fear memory, a deficit that is similar to what is thought to occur in PTSD,[99] and probably contributes to the persistence of this disorder. Conversely, some studies in both rodents and humans have shown that adequate sleep following trauma exposure promotes better outcomes.[88,97] For example, optogenetically enhancing sleep in rats following a model of fear trauma (exposure followed by extinction) improves recall of extinction to fear.[100] In humans, sleep after viewing a traumatic film reduces the subsequent number of intrusive memories and level of distress.[97] In fact, studies have shown that improving sleep reduces mental health symptoms across a variety of conditions (particularly in those with comorbid sleep disruption).[23] It is, therefore, reasonable to hypothesize that sleep enhancement immediately following traumatic stress exposure reduces, rather than exacerbates, negative mental health outcomes.

Several prior studies have indeed found that adequate sleep following trauma exposure is associated with better mental health outcomes,[88,97] whereas sleep disturbance correlates positively with overall symptom severity in trauma-related disorders. Patients with ASD or PTSD often present with sleep-related complaints, although these complaints are not always recognized as being trauma-related—especially when nightmares are not a primary complaint. A number of studies have found that the severity of PTSD symptoms varies as a function of the severity of sleep disturbance,[101] and treatment of sleep disturbance often improves other PTSD symptoms.[102,103] Therefore, addressing sleep disturbances, especially during the early posttrauma phase, may reduce trauma-related symptoms and prevent or mitigate PTSD pathogenesis. Despite the evidence-based logic behind this approach, few studies have evaluated treatments for acute sleep disturbances following trauma exposure.

INTERVENTIONS TO TREAT SLEEP DISTRBANCE AND TRAUMATIC STRESS–RELATED SYMPTOMS

Current guidelines for treatment of some aspects of sleep disturbance in PTSD exist, but they do not specifically address adverse sleep changes early after trauma.[104–106] For posttrauma symptoms persisting beyond 2 days, existing guidelines recommend a brief 4- to 5-session trauma-focused cognitive behavioral therapy with additional tailored management of other acute symptoms (eg, pain, rage, hyperarousal, anger, etc).[107] Several guidelines also recommend the use of psychological

first aid in the early aftermath of trauma.[107,108] Though psychological debriefing has been utilized in the immediate aftermath of trauma, existing treatment guidelines do not recommend its use due to mixed evidence supporting its efficacy.[108,109] Tailored treatments for acute sleep disturbances, including relaxation techniques and sleep hygiene education, are also recommended with the caveat that there is little evidence for their effectiveness in the acute phase.[108] In the clinical setting, sleep-related treatments for PTSD may be administered by primary care providers, behavioral health providers, or sleep medicine physicians. The approaches taken by these professionals vary according to their training. Generally, providers make efforts to normalize sleep. Clinicians, regardless of specialty, are familiar with sleep hygiene practices, which include obtaining 7–8 hours of sleep, setting structured wake and sleep times, making the bedroom environment optimal for sleep, and avoiding activities or substances that may impact sleep. However, sleep hygiene changes as a stand-alone treatment for insomnia and sleep disturbances has not been shown to be effective.[110] Patients who have experienced trauma may need a multidisciplinary approach to improve outcomes.

Therapies used to treat sleep in PTSD are largely unevaluated in addressing sleep disturbances arising early after trauma. We assess current nonpharmacologic and pharmacologic treatment recommendations for PTSD and gauge their potential applicability for sleep-specific symptoms in the acute period (immediately to 30 days) following trauma (see **Table 1**). Ideally, any of the discussed treatments could be initiated in the days following trauma in individuals demonstrating sleep disturbance to both regulate sleep and support recovery from the traumatic exposure. As there is very little existing evidence collected during the acute period after trauma exposure, evidence from clinical trials would be needed to support early use of both behavioral and pharmacologic treatments.

Behavioral and nonpharmacologic therapies

Cognitive behavioral therapy for insomnia (CBTi) is a first-line recommended treatment for insomnia because, compared to pharmacotherapy alone, it actually produces superior, long-term improvements in sleep.[104,111] A meta-analysis of randomized controlled trials of CBTi for sleep disturbances in PTSD revealed that these improvements include shorter sleep onset latency, reduced wake after sleep onset, and improved sleep efficiency, concomitant with reductions in in daytime PTSD symptom severity.[112] Thus, although pharmacotherapy is superior for providing relief from insomnia acutely, CBTi provides more sustained relief.[113,114] The downsides to CBTi are: a) that it requires more effort by the patient, and b) it can take several weeks for benefits to manifest.[115] While this is less of a concern in treating PTSD, the increased length of treatment limits the usefulness of CBTi for treatment of acute sleep disturbances resulting from trauma.

Nevertheless, there may be a role for short courses of CBTi (2–12 weeks), possibly as adjunctive therapies, for the treatment of acute, posttrauma sleep disturbance,[112] since they have also been found to be effective at reducing insomnia in PTSD patients and have relatively low attrition rates.[112] Stimulus control and sleep restriction, 2 components of CBTi, have been identified as evidence-based, stand-alone treatments for insomnia and may require less time to implement, although they may not have the durability of CBTi in the long-term outcomes.[116–118] Brief behavioral therapy for insomnia (BBTi) is a manualized 4-session treatment module that focuses on stimulus control and sleep restriction. It was designed for medical providers who did not have the time to implement CBTi and is associated with improvement of sleep efficiency both at early and late follow-up.[119] Limited research exists for the use of BBTi in the setting of acute trauma or PTSD.[120]

It should be noted that if a patient is undergoing exposure-related treatments for PTSD, hyperarousal and nightmares may initially, albeit temporarily, be exacerbated by these treatments.[106] For patients with nightmare-related issues, providers will often prescribe a form of cognitive behavioral therapy called imagery rehearsal therapy (IRT), which focuses on imagery rescripting and imaginal exposure.[121] Other techniques include systematic desensitization and progressive muscle relaxation to assist patients with sleep initiation, especially in patients with prominent hypervigilance symptoms. These nonpharmacologic techniques are generally paired with pharmacotherapy addressing hypervigilance and sleep complaints, such as prazosin or clonidine.[106] One study identified a reduction in nightmares at 6 months follow-up after 3 sessions of IRT (two 3-hour sessions 1 week apart with a 1-hour follow-up 3 weeks later), whereas other studies demonstrated sustained benefit after a single IRT session.[122,123] Therefore, is it possible that IRT can be implemented early after trauma exposure with long-term effects on sleep outcomes.

Prolonged exposure (PE) therapy is a cognitive therapy designed to treat symptoms of PTSD. PE effectively reduces daytime symptoms of PTSD and is a recommended first-line treatment for PTSD.[124] Immediate treatment with PE within 12 hours of trauma exposure reduces the severity of posttrauma symptoms at 4 weeks and 12 weeks.[125] Similarly, early treatment of ASD patients with PE reduces the likelihood of later developing PTSD.[126] However, the effects of PE on trauma-related sleep disturbances are mixed. One study found that PE improves self-reported sleep quality in PTSD with sustained improvements for at least 1 year,[127] while another found that PE does not improve sleep in PTSD.[128] Further, preexisting sleep disturbances decrease the efficacy of PE to improve symptoms of PTSD.[129,130] While PE is effective when initiated acutely following trauma to prevent PTSD, it does not have rapid effects, and additional studies are necessary to determine whether PE is effective for treating acute trauma-related sleep disturbance.

Cognitive processing therapy (CPT) is a cognitive intervention that assists trauma survivors in addressing and contextualizing the highly negative affect surrounding a traumatic event, thereby allowing them to process the event in an adaptive manner. CPT is effective at treating symptoms of PTSD and trauma exposure; however, studies assessing the efficacy of CPT to address PTSD-related sleep disturbances have produced mixed results.[131–134] Limited evidence suggests that augmenting CPT with a sleep-directed therapy improves sleep disturbances and overall PTSD symptoms, but sleep improvements are not

Table 1—Current nonpharmacologic and pharmacologic treatment recommendations for post–traumatic stress disorder (PTSD).

Modality	Therapeutic Agent	Indications	Benefits	Contraindications/Risks	Pitfalls	Sleep Effects	Clinical Trials
Medications	Selective serotonin reuptake inhibitors (sertraline, paroxetine)	PTSD	Improvement in daytime PTSD symptoms	1) Black box warning for suicidal thoughts and behaviors in patients younger than 24 years old 2) Risk for gastrointestinal bleeding with chronic NSAID use 3) Mania in patients with comorbid bipolar disorder 4) Adverse effects to fetus possible in pregnant patients 5) Risk for serotonin syndrome	1) Takes 4–6 weeks to reach full therapeutic effect 2) May induce restless legs syndrome, periodic limb movements, and bruxism, which can disrupt sleep 3) May induce REM sleep without atonia/ REM behavior disorder	1) Suppressed REM sleep 2) Increased REM latency	
Medications	Serotonin norepinephrine reuptake inhibitors (venlafaxine)	PTSD	Improvement in daytime PTSD symptoms	1) Black box warning for suicidal thoughts and behaviors in patients younger than 24 years old 2) Risk for gastrointestinal bleeding with chronic NSAID use 3) Mania in patients with comorbid bipolar disorder 4) Adverse effects to fetus possible in pregnant patients 5) Risk for serotonin syndrome	1) Takes 4–6 weeks to reach full therapeutic effect 2) May induce restless legs syndrome, periodic limb movements, and bruxism, which can disrupt sleep 3) May induce REM sleep without atonia/ REM behavior disorder	1) Suppressed REM sleep 2) Increased REM latency 3) Sleep disruption due to noradrenergic effect	
Medications	Serotonin antagonist and reuptake inhibitors (trazodone, nefazodone)	1) Depression 2) Off-label use for insomnia	1) Antidepressant effect at high doses 2) Improved sleep continuity at low and high doses 3) May decrease nightmares	1) Hepatotoxicity (nefazodone) 2) Caution in patients at high risk for falls (may cause dizziness, hypotension, or syncope)	Mixed results on objective measures of sleep disturbance in PTSD	1) Improves sleep quality 2) Decreases latency 3) Increases stage 3 sleep	NCT03668041
Medications	Atypical antipsychotics (quetiapine, olanzapine, risperidone)	Off-label use for PTSD associated nightmares and sleep disturbances	1) Reduction in PTSD sleep disturbances correlated with improvements in overall PTSD symptoms 2) Rapidly effective–within 1–4 days of administration, nightmares and sleep disturbances improved	1) QTc prolongation (quetiapine) 2) Hyperprolactinemia (risperidone) 3) Pancreatitis (olanzapine) 4) Orthostatic hypotension 5) Black box warning for suicidal thoughts and behaviors in patients younger than 24 years old	1) May cause daytime sedation 2) Long-term use associated with metabolic dysregulation 3) Long-term use associated with extrapyramidal symptoms	1) Decreased nightmares 2) Decreased sleep latency	

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Table 1—Current nonpharmacologic and pharmacologic treatment recommendations for post–traumatic stress disorder (PTSD). (*Continued*)

Modality	Therapeutic Agent	Indications	Benefits	Contraindications/Risks	Pitfalls	Sleep Effects	Clinical Trials
				6) Adverse effects to fetus possible in pregnant patients 7) Risk for myocardial infarction			
Medications	α-1 Adrenergic receptor antagonist (prazosin)	Off-label use for nocturnal symptoms of PTSD (ie, nightmares and hyperarousal)	1) Improves sleep disturbances in PTSD patients with elevated nocturnal central sympathetic activity 2) Not sedating	Orthostatic hypotension	1) Might not be effective for PTSD patients without elevated central sympathetic activity 2) Slow titration required in some patients who develop orthostatic hypotension (ie, 1 mg every 4–7 days) 3) Mixed evidence for PTSD-related nightmares	May improve sleep quality in patients with elevated sympathetic activity	NCT03997864
Medications	α-2 Adrenergic receptor agonist (clonidine)	Off-label use for nocturnal symptoms of PTSD	Decreases nightmare frequency and improves PTSD-related sleep disturbances in patients who do not response to prazosin	Orthostatic hypotension	Suppresses REM sleep	1) Decreases nightmare frequency 2) Improves sleep quality 3) Decreases sleep latency 4) Suppresses REM sleep	NCT04877093
Medications	Benzodiazepine γ-aminobutyric-A receptor agonists	1) Anxiety 2) Sleep onset insomnia (triazolam and temazepam) 3) Sleep maintenance insomnia (temazepam)	Improves anxiety and insomnia associated with PTSD	1) Abuse, misuse and addiction 2) Dependence and withdrawal 3) Anterograde amnesia 4) Adverse effects to fetus during pregnancy	1) Paradoxical reactions (behavioral disinhibition and aggressive behavior) 2) Unclear impact on memory consolidation and cognitive functions	1) Decreased sleep latency 2) Improved sleep continuity 3) Decreased stage 3 sleep and REM sleep 4) Increased stage 2 sleep and sleep spindles	
Medications	Non-benzodiazepine Z-drug γ-aminobutyric-A receptor agonists (zolpidem, zopiclone, and eszopiclone)	Sleep onset or sleep maintenance insomnia	Improved sleep with less risk of abuse and dependence than benzodiazepines	1) Prolonged use at high doses in PTSD is associated with increase of PTSD and poorer health outcomes 2) Contraindicated in patients with a history of parasomnias 3) Caution in patients taking other CNS depressant medications and in the	Mixed evidence to support use in trauma-exposed populations	1) Decreased sleep latency 2) Improved sleep quality 3) Improved total sleep time 4) Decreased wake after sleep onset	

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Table 1—Current nonpharmacologic and pharmacologic treatment recommendations for post–traumatic stress disorder (PTSD). (*Continued*)

Modality	Therapeutic Agent	Indications	Benefits	Contraindications/Risks	Pitfalls	Sleep Effects	Clinical Trials
				setting of substance dependence (Schedule IV controlled substance) 4) May cause delirium, changes in thinking or behavior, aggression, disinhibition, agitation, anxiety, and worsening of worsening of depression 5) May induce complex sleep behaviors			
Medications	Dual orexin receptor antagonists (suvorexant, lemborexant)	Sleep maintenance insomnia	Improved sleep with less risk of abuse and dependence than benzodiazepines. Do not suppress REM sleep.	1) Contraindicated in narcolepsy patients 2) Caution prescribing for depressed patients and in the setting of substance dependence (Schedule IV controlled substance)	No evidence in trauma-exposed populations	1) Improved total sleep time 2) Decreased wake after sleep onset	NCT02704754, NCT03642028, NCT02849548
Medications	Synthetic cannabinoid (nabilone)	Experimental use for PTSD and insomnia	1) Improved overall symptom severity of PTSD and reduces the frequency of trauma-related nightmares and increases sleep length 2) May assist with pain-related sleep disturbances; dual action in PTSD patients with chronic pain 3) Rapidly effective 4) Effects sustained to 9 weeks	1) May impair physical or mental abilities, especially when performing tasks which require mental alertness 2) Use with caution in patients with depression, mania, or psychosis; may unmask an underlying mental health condition 3) Risk for dependency	1) Limited evidence in trauma-exposed populations 2) Action on sleep-wake circuit is not well understood	May promote sleep by activation of cannabinoid type 1 receptors	
Medications	NMDA (*N*-methyl-D-aspartic acid) receptor antagonist (ketamine)	1) Off-label use for severe, treatment-resistant depression 2) Experimental use for PTSD and PTSD-related sleep disturbances	1) Rapidly effective 2) Potential dual effect in patients with history of depression and trauma exposure	1) Contraindicated in patients with significant cardiac history 2) Risk for dependence 3) Caution in patients on medications that contribute to respiratory depression 4) Risk for prolonged emergence from anesthesia, including vivid hallucinations and delirium	Mixed evidence for use in trauma-exposed populations	Beneficial effect on mood may be linked to its ability to alter sleep-wake behavior and the amplitude of circadian systems—potentially by modulating expression of circadian rhythm genes[254,257]	NCT04032301, NCT04889664, NCT04771767
Medication-assisted therapy	β-Adrenergic receptor antagonist (propranolol)	Experimental use for acute posttrauma treatment to	May prevent development of PTSD posttrauma due to administration before or after	1) Hypotension 2) May cause nightmares	Mixed evidence for use in trauma-exposed populations		NCT03752918

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Table 1—Current nonpharmacologic and pharmacologic treatment recommendations for post–traumatic stress disorder (PTSD). (*Continued*)

Modality	Therapeutic Agent	Indications	Benefits	Contraindications/Risks	Pitfalls	Sleep Effects	Clinical Trials
		prevent development of PTSD	memory reactivation sessions in the context of exposure-based therapy			1) Suppressed REM sleep at higher doses 2) Decreases melatonin secretion which can precipitate sleep disruptions and contribute to circadian rhythm abnormalities	
Medication-assisted therapy	3,4 Methylenedioxy-methamphetamine (MDMA)–assisted psychotherapy	Experimental use for PTSD that targets memory consolidation and fear response which has been associated with improved self-reported sleep	1) MDMA enhances the positive effects of therapy by increasing the ability of the patient to tolerate negative emotions associated with recalling traumatic events 2) Decreases patient drop-out and improves treatment success	1) Contraindicated in patients with significant cardiac history 2) Risk for dependence 3) Reports of suicidal ideation while taking MDMA 4) Risk for anxiety, agitation, hyperactivity, delirium 5) Risk for serotonin syndrome 6) Risk for hepatotoxicity 7) Risk for hyperthermia	May increase bruxism, anxiety, and jitteriness, which could potentially cause sleep disturbance	Improved self-reported sleep	
Therapy	Cognitive Behavioral Therapy for insomnia	Sleep onset or sleep maintenance insomnia	Long-term sleep improvements compared to pharmacotherapy alone and improvement of overall PTSD severity	Contraindicated in patients with bipolar disorder, epilepsy, and those at high risk for falls.	1) May require longer treatment course to be effective (> 12 weeks) 2) Not a good treatment for patients who do not follow up regularly or have trouble implementing treatment recommendations	Improved sleep onset latency, WASO, and sleep efficiency	
Therapy	Brief behavioral therapy for insomnia (BBTi)	Sleep onset or sleep maintenance insomnia	1) Manualized therapy designed for medical providers who did not have the time to implement CBTi and is associated with improvement of sleep efficiency both at early and late follow-up	Contraindicated in patients with bipolar disorder, epilepsy, and those at high risk for falls.	No evidence for trauma-exposed populations	1) Improved sleep onset latency 2) Decreased wake after sleep onset 3) Improved sleep efficiency	

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Table 1—Current nonpharmacologic and pharmacologic treatment recommendations for post–traumatic stress disorder (PTSD). (*Continued*)

Modality	Therapeutic Agent	Indications	Benefits	Contraindications/Risks	Pitfalls	Sleep Effects	Clinical Trials
			2) Rapidly effective–4-session treatment module that focuses on stimulus control and sleep restriction				
Therapy	Imagery rehearsal therapy (IRT)	PTSD-related nightmares	1) Improvement of nightmares and nighttime hyperarousal through imagery rescripting and imaginal exposure, systematic desensitization, and progressive muscle 2) Rapidly effective–within 1–4 sessions	Contraindicated in patients with cognitive deficits, severe mental illness, and high levels of anxiety, stress, or avoidance	Limited evidence for use in acute stress disorder	Decreased nightmares and hyperarousal leading to improved sleep outcomes	
Therapy	Prolonged exposure (PE) therapy	PTSD and ASD	1) Cognitive therapy for PTSD that when implemented early for the treatment of ASD patients reduced the likelihood of later developing PTSD 2) Rapidly effective–treatment within 12 hours of trauma exposure reduces symptom severity at 4 weeks and 12 weeks after trauma	Contraindicated if imminent threat of suicidal or homicidal behavior, recent (past 3 months) serious self-injurious behavior, and current psychosis	1) Mixed evidence for use for trauma-related sleep disturbances 2) Preexisting sleep disturbances decrease the efficacy of PE to improve symptoms of PTSD	Effects on objective measure of sleep are unknown.	
Therapy	Cognitive processing therapy (CPT)	PTSD	Cognitive intervention which assists trauma survivors to contextualize and process the highly negative affect surrounding a traumatic event in an adaptive manner	Contraindicated in psychotic patients, in the presence of substance dependence, if severe dissociative reactions or panic attacks, if imminent risk of self-harm, and if the patient is in abusive relationship	1) Mixed evidence for use for trauma-related sleep disturbances 2) Hyperarousal may precede improvement in certain PTSD symptom domains which may worsen sleep 3) Requires multiple sessions	Effects on objective measure of sleep are unknown.	
Therapy	Eye movement desensitization and reprocessing (EMDR)	PTSD	Exposure-based psychotherapy that involves the recollection of traumatic events while focusing on external stimuli	1) Contraindicated in psychotic patients 2) Avoid use in patients with ocular disorders,	1) Limited evidence supporting use for trauma-related sleep disturbances	Effects on objective measure of sleep are unknown.	

(continued on following page)

Table 1—Current nonpharmacologic and pharmacologic treatment recommendations for post–traumatic stress disorder (PTSD). (*Continued*)

Modality	Therapeutic Agent	Indications	Benefits	Contraindications/Risks	Pitfalls	Sleep Effects	Clinical Trials
			(lateral eye movements) in order to decouple the emotional saliency from the recall of traumatic events	particularly those with impaired eye movements 3) Caution in patients with severe dissociative reactions, bipolar disorder, substance abuse, chronic pain or unstable medical disorders, and history of abuse	2) Requires multiple sessions		
Therapy	Accelerated resolution therapy (ART)	PTSD	1) Adapted, condensed form of EMDR for PTSD with large effect sizes for the mean reduction in PCL-5 scores 2) Rapidly effective–1 to 5 treatment sessions	1) Contraindicated in psychotic patients 2) Avoid use in patients with ocular disorders, particularly those with impaired eye movements 3) Caution in patients with severe dissociative reactions, bipolar disorder, substance abuse, chronic pain or unstable medical disorders, and history of abuse	Limited evidence supporting use for trauma-related sleep disturbances	Effects on objective measure of sleep are unknown.	
Technologies	Transcranial magnetic stimulation (TMS)	PTSD	Utilizes electromagnetic currents on the skull to improve daytime PTSD symptom severity	1) Increased risks for seizures 2) Contraindicated for implanted metallic hardware, cochlear implants, and electrical devices 3) Caution with unstable general medical disorders	No evidence for acute stress disorder	May improve sleep quality through promoting slow wave sleep and REM sleep and inhibiting a hyperarousal state in the cerebral cortex	

attributed to CPT.[135,136] Additionally, during the treatment course with CPT, hyperarousal may precede improvement in certain PTSD symptom domains.[132] Hyperarousal may impair the individual's ability to fall or stay asleep, which may initiate or perpetuate current sleep problems. Therefore, CPT is highly manualized and is more widely available clinically, but current studies do not support its use in addressing trauma-related sleep disturbance. Additional evidence is needed to make definitive statements regarding the use of CPT for both acute trauma and sleep disturbance.

Eye movement desensitization and reprocessing (EMDR) is an exposure-based psychotherapy that involves the recollection of traumatic events while focusing on external stimuli. During EMDR, the patient is directed through a series of lateral eye movements that allow the patient to decouple the emotional saliency from the recall of traumatic events. It is hypothesized that the eye movements associated with EMDR mimic the eye movements in REM sleep, allowing for the adaptive processing of traumatic memories.[137,138] However, 1 randomized clinical trial demonstrated that the PTSD symptoms reduction was a result of an external focus of attention, regardless of whether eye movements were implemented or eyes were fixed on a nonmoving hand.[139] EMDR has been shown to be equivalent to, if not superior to, cognitive behavioral therapy for the treatment of PTSD.[140] EMDR takes about the same number of sessions as PE for combat-associated trauma. It is therefore not a rapid treatment, but it could be administered acutely following a traumatic event. Accelerated resolution therapy (ART) is an adapted form of EMDR for PTSD that typically requires 1–5 one-hour sessions over 3 weeks, and it has been shown to be effective with large effect sizes as measured on the PTSD Checklist for DSM-5.[141,142] Some preliminary evidence suggests that administration of one 45- to 60-minute session within 96 hours of a traumatic event results in a significant reduction of symptoms in patients with ASRs.[143] More research to investigate the efficacy of ART as a treatment for acute traumatic stress symptoms and sleep disturbance is warranted.

There are a variety of stimulation technologies that have been assessed for their potential utility to treat PTSD, including deep-brain stimulation, vagus nerve stimulation, transcranial direct current stimulation, and transcranial magnetic stimulation (TMS).[144] Notably, TMS has shown potential efficacy for PTSD symptomology, and there is mechanistic evidence to suggest it may regulate sleep disturbance. TMS utilizes electromagnetic currents that are placed on the skull and reach the neurons of the cortex, causing depolarization and forcing an action potential.[145] TMS has the potential to modulate aberrant maladaptive circuits and is US Food and Drug Administration (FDA)-approved for other neuropsychiatric conditions, including major depressive disorder and obsessive compulsive disorder.[146] Preliminary studies, have demonstrated reduced Pittsburgh Quality Index scores in patients with insomnia.[147] It is hypothesized that repetitive TMS may improve sleep quality through promoting slow wave sleep and REM sleep, inhibiting a hyperarousal state in the cerebral cortex, altering sleep-related hormones and metabolic activity, and increasing hippocampal neurogenesis.[147–150] In the treatment of PTSD patients, medium effect sizes have been observed, particularly when high frequency stimulation was applied over the right dorsolateral prefrontal cortex.[151–155] No studies have assessed the efficacy of TMS in an acute trauma setting, but the potential benefits, in terms of promoting sleep and reducing trauma-related symptoms, are considerable.

Overall, few studies have assessed the efficacy of behavioral and nonpharmacologic therapies to treat sleep disturbances acutely posttrauma. While prior studies support the use of CPT, PE, and EMDR to address daytime symptoms of PTSD, the existing evidence does not support their use to address acute sleep disturbances. CBTi is the only behavioral therapy discussed that is specifically designed to treat sleep disturbances. Notably, sleep restriction is a component of CBTi, and its use posttrauma should be carefully considered, as the current literature does not support the use of sleep restriction acutely posttrauma to prevent the consolidation of a traumatic experience. However, once sleep disturbances have set in posttrauma, a targeted sleep restriction under the guidance of a clinician to consolidate nocturnal sleep periods for CBTi would likely prove beneficial. Another consideration of behavioral and nonpharmacological treatments is time. The time course required to produce therapeutic benefits would likely exceed the "acute phase" posttrauma. The combination of pharmacologic therapy to address acute symptoms alongside a nonpharmacologic or behavioral therapy to provide more sustained relief would likely be advantageous. Providing other posttrauma symptoms do not limit which therapies can be applied (eg, exposure therapies should not be initiated in ASD patients expressing severe dissociation or avoidance), initiating these therapies as soon as possible is recommended to target sleep disturbance associated with acute trauma exposure.

Pharmacologic therapies

Several pharmacological guidelines have been established to treat sleep-related symptoms of PTSD, while limited pharmacologic guidelines exist for ASD and for very early acute symptoms (within the first 72 hours).[104,106,107] It is likely that most pharmacotherapies recommended for PTSD will be ineffective at treating symptoms of acute trauma, especially trauma-related sleep disturbances, as several treatments recommended for PTSD have the potential to cause sleep disturbance or require a time course too long to be effective. Conversely, several treatments are not recommended for use in PTSD although they are effective at treating acute trauma-related sleep disturbances. We examine current treatment guidelines for PTSD to gauge their effectiveness for addressing trauma-related sleep disturbances (see **Table 1**).

Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants used to treat of a variety of mental health conditions. The SSRIs sertraline and paroxetine are first-line, FDA-approved treatments for daytime PTSD symptoms.[156–159] However, SSRIs generally suppress REM sleep and increase REM latency.[160] SSRIs also impact NREM sleep by increasing light stage sleep, nighttime arousals, and wake after sleep onset. Additionally, adverse effects of SSRIs may further exacerbate insomnia, including restless legs syndrome, periodic nocturnal limb movements, REM sleep without atonia (RSWA), and, less commonly, RBD.[161–163] RSWA is defined as increased tonic or phasic motor tone identified on electromyography channels during REM sleep, whereas RBD is

characterized by both RSWA and dream-enacting behavior. Studies have reported as high as a 10-fold risk of RSWA with antidepressant use, and there is increased likelihood as high as 1.9 times the odds of developing RBD.[163,164] The mechanism behind the SSRI induction of RSWA and RBD appears to be linked to the complex double-switch model of REM-on and REM-off neurons on the brainstem.[165] Some have suggested that SSRIs may just unmask an underlying condition rather than cause RBD because withdrawal of the medication does not always result in resolution of the symptoms.[166,167] As previously discussed, PTSD has been associated with what has been proposed to be a new parasomnia called TSD that resembles RBD (except that onset of TSD is clearly precipitated by a traumatic event), and it is unknown whether SSRIs unmask or contribute to the development of this sleep disturbance.

Additionally, several case reports have linked SSRI use to restless legs syndrome, which may be misattributed as anxiety or hyperarousal prior to sleep and thus prolong sleep latency.[168,169] However, evidence to support the connection has been mixed.[163,170–172] Previous studies have identified that SSRIs induce or worsen periodic limb movements during sleep, which in some patients can increase arousals and contribute to poor sleep quality.[173–175] Although SSRIs may take 4–6 weeks to reach full therapeutic effect for PTSD-related symptoms, the effects on REM sleep are most significant early in treatment and diminish over time.[176] Therefore, if given for acute trauma victims, SSRIs may impact sleep even before patients experience other trauma-related symptom relief. However, it should be noted that most studies that examine the influence of SSRIs on sleep occur in the context of depressed patients. Depression decreases REM latency and increases REM density during the first sleep cycles, so it is hypothesized that improvement of depression may also be related to REM sleep deprivation.[177] REM sleep appears to be dysregulated in PTSD, and evidence suggests that multiple sleep phenotypes occur, with some patients having increased REM sleep and others having decreased REM sleep. It may be that SSRIs impact sleep differently in the setting of acute trauma due to individual variability. However, as SSRIs acutely disrupt sleep and require weeks to reach full therapeutic potency, it is unlikely that they would provide benefit for treating acute sleep disturbance.

Serotonin and norepinephrine reuptake inhibitors (SNRIs) are another class of antidepressants used to treat PTSD.[178] The SNRI venlafaxine is used to treat daytime symptoms of PTSD, and like SSRIs, venlafaxine can exacerbate insomnia, increase REM latency, and suppress REM sleep.[179] Additionally, SNRIs have been associated with the same sleep disturbances as SSRIs, including restless legs syndrome, periodic limb movements, RSWA, and RBD.[163,164,175] In the case of RSWA and RBD, norepinephrine suppresses REM sleep by activating the REM-OFF cells in the locus coeruleus, while at the same time, norepinephrine is required for the activation of REM sleep. This REM sleep deprivation state impacts brain excitability, which is believed to lead to motor activation in the context of REM sleep initiation. Moreover, venlafaxine is ineffective at treating nightmares in PTSD and, like SSRIs, requires several weeks to reach full therapeutic effect.[178] Although useful for treating daytime symptoms of PTSD, caution should be used in prescribing both SSRIs and SNRIs in acutely traumatized individuals prior to a PTSD diagnosis. Additional research would be needed to evaluate if normalization of REM could be achieved with SNRI use in acutely traumatized individuals demonstrating increased levels of REM sleep.

Serotonin antagonists and reuptake inhibitors (SARIs) are used to treat depression and anxiety but are more commonly prescribed off-label as a treatment for insomnia due to their sedative effects via antagonism of histamine receptors.[180] SARIs are weak inhibitors of serotonin reuptake but are also strong antagonists of postsynaptic 5-hydroxytryptamine subfamily 2 (5-HT_2) receptors which promotes sleep continuity.[181,182] Studies of the SARIs trazodone and nefazodone in PTSD patients show improved sleep and reduced frequency of nightmares.[183–190] However, the effect of nefazodone on objective measures of sleep disturbances in PTSD have been mixed,[186,188] which contributes to why trazodone is commonly used to treat sleep disturbances in PTSD.[191] While both SARIs are rapidly effective, nefazodone has a risk of hepatotoxicity, and long-term off-label use should be avoided.[192] In comparison, trazodone is safer for longer duration of use and helps maintain sleep by decreasing arousals.[193] However, in some individuals, trazodone may precipitate increased anxiety symptoms and trazodone's active metabolite, *meta*-chlorophenylpiperazine (*m*-CPP), may cause panic symptoms in a minority of patients with existing mental health conditions.[194] Trazodone should be considered as a potential treatment for acute trauma-related sleep disturbances, due to its widely accepted safety and ability to improve sleep continuity. A clinical trial comparing trazodone to other sleep aids in treating sleep disturbances in currently underway (Identifier: NCT03668041), but studies evaluating the utility of trazadone for improving sleep disturbance in acutely traumatized individuals are also necessary.

Atypical antipsychotics are FDA-approved to manage symptoms of schizophrenia but are also used off-label to treat symptoms of ASD and treatment-resistant PTSD.[195] Antipsychotics as a drug class are heterogeneous, with some agents being more activating and others possessing more sedating effects.[196] With respect to sleep, atypical antipsychotics like quetiapine, olanzapine, and risperidone generally cause mild sedation, which aids in normalizing sleep in trauma-related disorders. Studies of the atypical antipsychotics risperidone, quetiapine, and olanzapine in patients with PTSD have found decreased nightmares and sleep disturbances, typically within 1–4 days of initial administration.[195,197–204] Reductions in sleep disturbances are correlated with improvements in overall PTSD symptoms, suggesting that improved sleep from atypical antipsychotics can benefit daytime PTSD symptoms. Atypical antipsychotics are acutely effective and are, therefore, used following trauma exposure and in ASD.[205] Studies of risperidone in acutely traumatized patients have found decreased hyperarousal with fewer sleep disturbances and nightmares within 48 hours of administration.[44,45] While atypical antipsychotics are effective acutely, chronic use can cause significant metabolic dysregulation and increase the risk of myocardial infarction.[206,207] Thus, they may be helpful for managing sleep disruptions and traumatic stress–related symptoms acutely posttrauma but may not be suitable for managing persistent sleep disturbances or PTSD symptoms over long time periods.

The α-1 adrenergic receptor antagonist prazosin is an antihypertensive drug that has been lauded as an off-label treatment

for nocturnal symptoms of PTSD. Prazosin is nonsedating and does not improve sleep disturbances in healthy individuals or daytime symptoms in those with PTSD.[208] However, in PTSD, where nocturnal central sympathetic activity is elevated,[209] prazosin improves sleep disturbances.[210–212] Early small-scale studies found that prazosin is particularly effective at alleviating PTSD-related nightmares regardless of age or trauma type.[213–220] However, a recent large-scale phase 3 study found that prazosin was ineffective for treating nightmares and sleep disturbances in PTSD.[208] As a result, prazosin has been downgraded from a first-line treatment for trauma-related nightmares.[104] Prazosin has been effective at relieving sleep disturbances in putative trauma-associated sleep disorder patients, suggesting that it may have wide applicability for treating trauma-related sleep issues.[40] While prazosin has a rapid onset, is generally well tolerated, and is safe to use in conjunction with other therapies, it requires titration up to a tolerable level (often greater than 10 mg/day) to target nightmare symptoms due to the fact that postural hypotension has been associated with rapid titration of this medication.[210] Studies typically utilize a flexible titration schedule, and in clinical practice, it can take weeks to reach a therapeutic effect. A slow titration may limit the utility of prazosin in some patients with acute trauma exposure. Clinical trials are currently underway (Identifier: NCT03997864), but more research is needed to understand prazosin's potential efficacy for relieving sleep disturbances acutely after trauma. Given its well established safety profile, prazosin may be a reasonable treatment option for early treatment of sleep disturbances following trauma.

The α-2 adrenergic receptor agonist clonidine is used to treat hypertension but has also been used to treat sleep and behavioral disruptions in attention-deficit hyperactivity disorder due to its mild sedative effects.[221] Clonidine improves overall PTSD symptoms but has primarily been used to address nightmares and sleep disruptions in PTSD in patients who do not respond to prazosin.[222,223] In PTSD, clonidine decreases nightmare frequency and improves sleep quality and sleep latency.[222,224–226] However, clonidine suppresses REM sleep in healthy individuals and in individuals with PTSD,[227] which could exacerbate existing REM changes resulting from trauma. A clinical trial is currently underway (Identifier: NCT04877093) to assess the use of low dose clonidine in assessing daytime and night symptoms of PTSD, but further research is necessary to evaluate the use of clonidine to improve sleep disturbance acutely following trauma.

The β-adrenergic receptor antagonist propranolol has also been proposed as an acute posttrauma treatment to prevent the development of PTSD.[228] However, studies have failed to replicate initial findings suggesting propranolol administered acutely posttrauma prevents the development of PTSD symptoms.[229–231] Propranolol has a beneficial effect when administered before or after memory reactivation sessions, which suggests that more research should examine the timing of propranolol administration in the memory reconsolidation process.[232,233] These results may indicate that propranolol has some utility when used in combination with PE or other exposure-based therapy methods. When considering effects on sleep, propranolol has little therapeutic benefit for sleep disturbances and can worsen symptoms of insomnia in patients with existing sleep issues.[234] Adverse effects of propranolol can include vivid dreams and nightmares,[235] and at higher dosages propranolol can suppress REM sleep.[236] Moreover, β-blockers like propranolol decrease the secretion of melatonin, which can precipitate sleep disruptions and contribute to circadian rhythm abnormalities.[237,238] Although propranolol may provide relief for daytime trauma-related anxiety, there is not currently sufficient evidence to suggest its use to treat sleep disturbance acutely following trauma.

Benzodiazepines are γ-aminobutyric acid (GABA)-A receptor agonists widely used to treat symptoms of anxiety and insomnia as they tend to decrease sleep latency and improve sleep continuity. Despite seeming well suited to address hyperarousal and sleep disturbances following trauma, benzodiazepines are not recommended for use in individuals with PTSD due to their abuse potential and tendency to worsen aggression, depression, and psychotherapy outcomes.[239] Additionally, benzodiazepines are ineffective at alleviating trauma-related sleep disturbances and general symptoms of PTSD. Furthermore, there is some evidence to suggest that benzodiazepines worsen PTSD symptoms and when used acutely following trauma may increase the risk of PTSD developing.[239,240] Benzodiazepines generally increase NREM stage 2 sleep and spindle activity while suppressing slow-wave sleep (stage 3) and REM sleep.[241] As slow wave sleep and REM sleep are important for memory consolidation and other cognitive functions,[89] it is unclear how these sleep changes may uniquely impact victims of acute trauma, especially in conjunction with other therapies that seek to process recent memories. Due to lack of efficacy, increased risk, and high potential for abuse, benzodiazepines are not recommended for sleep disturbances in acutely traumatized individuals.

The nonbenzodiazepine Z-drugs (zolpidem, zopiclone, and eszopiclone) are positive allosteric modulators of the GABA-A receptor and are used primarily to treat insomnia by decreasing sleep latency and improving sleep quality without significant changes to sleep architecture.[242] Although the Z-drugs have fewer adverse side effects and reduced risk of abuse compared to benzodiazepines, few studies have demonstrated that they mitigate sleep issues in PTSD. Prolonged use of zolpidem, especially at high doses, is also associated with increased incidence of PTSD and poorer health outcomes in military service members[243]—although prolonged use of sleep aids in general suggests there may be chronic underlying sleep issues, making it difficult to parse the reason for this effect. Studies of eszopiclone in treating sleep disturbances in PTSD have had mixed results.[242,244] Overall, it is unclear whether Z-drugs have potential for alleviating acute trauma-related sleep disturbances, but the limited, available research does not support use following acute traumatic stress. More research should be undertaken to understand the utility and longer-term outcomes of using Z-drugs to treat sleep disturbances associated with trauma.

Hypothalamic orexins are responsible for modulating fear learning, arousal, and sleep-waking behavior.[245] Dual orexin receptor antagonists (DORAs) have been touted as a superior treatment for insomnia as they do not suppress REM sleep like benzodiazepines and Z-drugs.[246] The DORA suvorexant is efficacious in treating insomnia and does not produce as severe adverse side effects or risk of abuse as benzodiazepines.[246]

No evidence exists evaluating the effectiveness of suvorexant to treat sleep disturbances in PTSD or acutely following trauma, although multiple clinical trials are underway (Identifier: NCT02704754, NCT03642028, NCT02849548). However, there is evidence from animal models to suggest that orexin receptor antagonists alleviate traumatic stress–related effects as well as support extinction of fear memory.[247,248] Reports of suvorexant inducing nightmares (likely due to its potentiating effect on REM sleep) may limit its utility in treating sleep disturbances following trauma and raises concerns for those with RBD.[246,249] Alternatively, as REM sleep is commonly dysregulated in PTSD, suvorexant may be able to support increases in REM in populations that experience suppressed REM resulting from trauma. Due to the current lack of results evaluating suvorexant for use in trauma-related disorders, further studies of suvorexant in acutely traumatized individuals and those with PTSD are needed to assess its therapeutic potential, though the ongoing clinical trials may provide additional insight regarding suvorexant utility.

Nabilone is a synthetic cannabinoid used to treat chemotherapy-induced nausea and chronic pain.[250] Nabilone also improves pain-related sleep disturbances in patients with chronic pain.[251] In PTSD, nabilone overall symptom severity and reduces the frequency of trauma-related nightmares and increases sleep length.[252] These improvements occur rapidly and are sustained out to 9 weeks with no withdrawal symptoms reported.[253] Nabilone's ability to improve sleep in chronic pain patients may be particularly beneficial for addressing sleep disturbances posttrauma as pain can occur from trauma-related injury. Increased pain is also predictive of PTSD diagnosis; therefore, nabilone may have a dual benefit in preventing later diagnosis.[254] Moreover, nabilone's effectiveness at reducing nightmare frequency makes it a potential alternative for patients who cannot take prazosin. Cannabinoids generally promote sleep by activation of cannabinoid type 1 receptors, although their action on the sleep-wake circuit is not well understood.[255] As such, future research should evaluate nabilone and other cannabinoids for their ability to regulate sleep disturbance acutely following trauma, especially in cases of injury where pain may disrupt normal sleep.

Ketamine is an NMDA (*N*-methyl-D-aspartic acid) receptor antagonist is an FDA-approved therapy for treatment-resistant depression and anesthesia[256,257] and has also been used to treat sleep disturbances in individuals with PTSD.[258,259] Recent research suggests that ketamine's beneficial effect on mood may be linked to its ability to alter sleep-wake behavior and the amplitude of circadian systems—potentially by modulating expression of circadian rhythm genes.[257,260] While rapidly effective, the administration of ketamine following acute trauma exposure has yielded mixed results. Two studies found that ketamine administration acutely following trauma increased symptoms of ASD and likelihood of developing PTSD,[261,262] 2 studies found no change in outcomes, and 1 study found a decreased incidence of PTSD.[263–266] Multiple clinical trials are underway, which will assist in elucidating the impact of ketamine on PTSD symptoms (Identifiers: NCT04032301, NCT04889664, NCT04771767). Given these conflicting findings, additional research is necessary to gauge the therapeutic potential of ketamine before it can be considered a viable treatment for sleep disturbance acutely following trauma.

3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy is an experimental treatment that targets memory consolidation and fear response in chronic PTSD patients.[267] As part of this treatment strategy, therapists ask patients to recall specific traumatic memories after taking MDMA, a triple monoamine reuptake inhibitor that promotes release of multiple neurotransmitters, including dopamine, serotonin, and norepinephrine as well as oxytocin, cortisol, prolactin, and vasopressin.[268] It is believed that MDMA enhances the positive effects of therapy by increasing the ability of the patient to tolerate negative emotions associated with recalling traumatic events, which decreases patients dropping out and improves treatment success.[267] Preliminary studies support its use in PTSD patients, including clinically significant reductions in Clinician-Administered PTSD Scale scores and improved self-reported sleep.[268,269] However, in some patients, it may increase bruxism, anxiety, and jitteriness, which could potentially contribute to further sleep disturbance.[269,270] Additionally, MDMA is a known drug of abuse and a few incidences of increased suicidal ideation have been observed as part of these clinical trials[267]; therefore, caution should be taken in administering it outside of a strongly controlled psychotherapeutic environment. Multiple clinical trials are ongoing to investigate the use of MDMA in PTSD treatment, with a more limited number assessing its efficacy in treating PTSD-related sleep disturbances (Identifier: NCT03752918). Additional evidence is needed to understand if this treatment would be effective acutely following trauma for both sleep disturbance and other trauma-related symptoms, though MDMA would likely not be a first-line treatment for acute disturbance.

Overall, there is a paucity of research on early treatment for both sleep disturbance and trauma-related symptoms following an acute traumatic stress event. Based on mechanistic understanding of pharmacologics and results from clinical trials for PTSD or trauma-related sleep disturbance, caution should be taken with SSRIs and SNRIs in the setting of acute trauma as they can cause sleep disturbance early before reaching full therapeutic effect. On the other hand, there is some evidence that SSRIs and SNRIs drugs could be used in a targeted fashion by clinicians to decrease REM sleep, which could be undertaken in select individuals if specific sleep characteristics were identified early by clinicians. The evidence for use of adrenergic pharmacotherapies is mixed; therefore, additional inquiry is needed to understand their potential utility for sleep disturbance acutely following trauma. Generally, the existing, albeit limited, evidence for GABAergic modulators suggests minimal utility for trauma-related sleep disturbance. However, there is some early evidence supporting the use of SARIs, atypical antipsychotics, dual orexin receptor antagonists, and cannabinoids to quickly restore trauma-disturbed sleep. Clinical trials for early implementation of pharmacologic treatment of trauma-related sleep disturbance are warranted and based on what is known about the trajectory of sleep and trauma following a traumatic stress event. Such pharmacologics have potential to prevent long-term trauma-related symptoms.

DISCUSSION AND FUTURE DIRECTIONS

Currently, little is known about how sleep is altered acutely following real-life trauma. Only 2 actigraphy studies have quantified objective changes to sleep parameters within 48 hours of trauma,[27,28] and no studies have characterized objective sleep parameters in ASD. This constitutes a critical knowledge gap. Sleep studies in ASD sufferers may be especially informative, since they could potentially reveal whether, and the extent to which, sleep disturbance predicts the likelihood that initial trauma-related symptoms will persist and become chronic. This is a reasonable hypothesis because it is known that sleep facilitates emotional and declarative memory consolidation, and REM sleep is thought to aid in the proper contextualization of traumatic experiences.[24] Thus, the characterization of early posttrauma sleep disturbances may be critical for understanding the initial formation of trauma-related symptoms as well as the pathogenesis of chronic trauma-related disorders.

Prior studies provide compelling evidence that peri-trauma sleep disturbance increases the risk of developing PTSD. However, the pathophysiological processes by which sleep disturbance contributes to the development of PTSD are unclear. Do posttrauma sleep disturbances independently contribute to PTSD development, or do they reflect trauma-induced changes in neural circuitry that increase susceptibility to PTSD? How and why does sleep disturbance prior to trauma increase vulnerability to PTSD in otherwise neuro-typical and psychologically healthy individuals? Would improving the sleep of poor sleepers increase their resilience to trauma? Further studies examining the effects of sleep and sleep loss in preclinical models of trauma exposure will likely aid in elucidating the mechanisms by which sleep mediates risk of developing trauma-related disorders.

Several nonpharmacologic and pharmacologic interventions have been evaluated as treatments for sleep disturbance in PTSD, but few studies have tested the same drugs acutely posttrauma or in ASD. Of those few studies that have evaluated the utility of various interventions for improving sleep in ASD, small sample sizes and/or lack of proper controls limit interpretations relevant to clinical practice. Clearly, well powered and well controlled studies are necessary to accurately gauge each intervention's effectiveness for improving sleep and reducing traumatic stress symptoms. Furthermore, it is suggested that new therapies be developed that are specifically designed to treat trauma-related disorders—a process that will be made easier via an improved understanding of the pathophysiology of trauma-induced symptoms and disorders. Mechanistic preclinical studies investigating trauma-induced neurological changes and their time course could identify novel targets for pharmacological interventions. In fact, it is possible that multiple treatments will need to be developed since the trauma-related pathophysiology may evolve and cascade over time—eg, as exposure to trauma persists and different adaptive mechanisms are serially recruited and exhausted.

Although more work is needed to definitively establish whether, and the extent to which, a reciprocal cause-effect relationship between sleep disturbance and stress-related pathologies exists, the current evidence suggesting the likelihood of such a relationship is substantial and, in our opinion, compelling. At the very least, better sleep—both before and after traumatic events—is associated with better outcomes. Accordingly, it is suggested that the time has come to aggressively study the potential utility of improving sleep characteristics that are disordered during the acute posttrauma phase, with an ultimate aim of developing evidence-based sleep-enhancing treatment guidelines for ASR/ASD and potential prevention of PTSD.

ABBREVIATIONS

ASD, acute stress disorder
ASR, acute stress reaction
CBTi, cognitive behavioral therapy for insomnia
CPT, cognitive processing therapy
EMDR, eye movement desensitization and reprocessing
FDA, US Food and Drug Administration
GABA, γ-aminobutyric acid
IRT, imagery rehearsal therapy
MDMA, 3,4 methylenedioxymethamphetamine
PE, prolonged exposure
PTSD, post–traumatic stress disorder
RBD, REM sleep behavior disorder
REM, rapid eye movement
RSWA, REM sleep without atonia
SARI, serotonin antagonist and reuptake inhibitor
SNRI, serotonin and norepinephrine reuptake inhibitor
SSRI, selective serotonin reuptake inhibitor
TMS, transcranial magnetic stimulation
TSD, trauma-associated sleep disorder

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