Recent advances in the study of sleep in the anxiety disorders, obsessive-compulsive disorder, and posttraumatic stress disorder
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DISCLOSURES

Funding sources:

Dr. Boland: Office of Academic Affiliations, Advanced Fellowship Program in Mental Illness Research and Treatment, Department of Veterans Affairs.

Dr. Ross: Department of Defense

Conflict of Interest:

Dr. Boland: None

Dr. Ross: None

Synopsis

Sleep disturbance is frequently associated with Generalized Anxiety Disorder, Panic Disorder, Obsessive-Compulsive Disorder, and Posttraumatic Stress Disorder. This article reviews recent advances in understanding the mechanisms of the sleep disturbances in these disorders and discusses the implications for developing improved treatments.

Key Words: sleep, anxiety, generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, circadian rhythms

Key Points

The information provided in this review is designed to help mental health professionals and researchers understand:

- The prevalence of sleep disturbance in anxiety disorders, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD)
- Advances in identifying the mechanisms of sleep disturbance in anxiety disorders, OCD, and PTSD
- The burgeoning research in circadian rhythms in anxiety disorders, OCD, and PTSD and its potential role in treatment advancement
- The importance of dimensional measurement of cognitive processes related to sleep disturbance across diagnostic boundaries
- Recent advances in psychotherapeutic and pharmacologic treatments for sleep disturbance in anxiety disorders, OCD, and PTSD

Abbreviations

CBT	cognitive behavioral therapy
CBT-I	cognitive behavioral therapy for insomnia
CPT	cognitive processing therapy
DSM-IV/5	Diagnostic and Statistical Manual of Mental Disorders, Fourth/Fifth Edition
EERT	exposure, relaxation and rescripting therapy
ERP	exposure and response prevention therapy
fMRI	functional magnetic resonance imaging
GAD	generalized anxiety disorder
IR	imagery rehearsal
MAOI	monoamine oxidase inhibitors
N2	stage 2 sleep
NP	nocturnal panic
OCD	obsessive-compulsive disorder
OSA	obstructive sleep apnea
PD	panic disorder
PE	prolonged exposure
PLM	periodic limb movements
PSG	polysomnography
PTSD	posttraumatic stress disorder
P-wave	pontine wave
RBD	REM behavior disorder
RCT	randomized controlled trial
REMS	rapid eye movement sleep
SNP	single nucleotide polymorphism
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SWS	slow wave sleep
TCA	tricyclic antidepressants

Anxiety disorders are highly comorbid with sleep disorders. In fact, for disorders such as Generalized Anxiety Disorder (GAD), the core diagnostic criteria may include sleep disturbance. High rates of co-occurrence and diagnostic overlap are suggestive of common diatheses among anxiety and sleep disorders. There is a considerable literature documenting sleep disturbances in anxiety disorders (see [1-2] for comprehensive reviews). However, important advances at the interface of sleep and anxiety disorders research have occurred in the past decade, yielding new insights into the etiology and treatment of sleep disturbances in the anxiety disorders. Here, we review and discuss these advances to bring attention to the development of new themes in sleep research in the context of anxiety.

A major advance in psychiatric research is the advent of the Research Domain Criteria [3], which encourage the dimensional examination of behavior to better inform the diagnosis and treatment of mental disorders. In this review, we pay specific attention to ways in which several biological and psychological processes that are not unique to anxiety disorders may be implicated in the relationship between anxiety and sleep disturbance. As an example, we review the burgeoning literature on circadian rhythm disturbances in these disorders and discuss the implications of new findings for the development of novel treatments.

Another significant advance is the re-categorization of mental disorders in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders [4]. Obsessive-Compulsive Disorder (OCD) and Posttraumatic Stress Disorder

(PTSD) are no longer included among the anxiety disorders, but rather are categories of obsessive-compulsive and related disorders and trauma- and stressor-related disorders, respectively. For the purpose of highlighting commonalities in the sleep disturbances of the anxiety disorders as defined by the DSM-IV, including OCD and PTSD, and for maintaining continuity with previous reviews, we include a discussion of the latter two disorders here.

Generalized Anxiety Disorder

GAD, characterized by excessive, persistent, and unrealistic worry, affects approximately 3.1% of adults in the United States [5]. Fifty to seventy percent of patients with GAD report insomnia, which can manifest as initial onset insomnia, sleep continuity disturbance, or early morning awakening. Sleep disturbances in GAD have been shown to persist despite remission of waking anxiety symptoms [6]. This is consistent with a view of insomnia as an independent disorder that can be comorbid with other mental disorders [7].

Sleep Architecture in GAD

Polysomnographic (PSG) studies of GAD have been well reviewed elsewhere [1,2]. These typically demonstrate significantly longer sleep onset latency, decreased sleep time, and reduced N2 sleep in GAD patients compared to healthy individuals. A longer rapid eye movement sleep (REMS) latency recently has been observed in non-medicated, non-depressed children diagnosed with GAD relative to age and gender matched children free of psychiatric or sleep disorders [8]. To date, there are no PSG studies comparing

GAD and insomnia disorder patients, although, given the overlap of symptoms, this may be an important direction for future research.

Dimensions of Psychological Contributions to Sleep Disturbance in GAD

The cardinal feature of GAD is excessive cognitive activity, predominantly future- oriented worry and the tendency to think repetitively about causes, contexts, and consequences of negative experiences, referred to as rumination [9]. These forms of cognition also have been shown to be relevant to the sleep disturbances in other disorders, including depression, and to sleep difficulties among individuals without mental health diagnoses. An examination of these processes as they pertain to sleep disturbance broadly may aid in the development of more targeted interventions for the sleep disturbance in GAD. For example, in a sample of individuals without a GAD diagnosis, those who were characterized as “worriers” evidenced increased sleep disturbance compared to non-worriers [10]. Similarly, “worry about the future” was a significant contributor to sleep disturbance among college students who were not diagnosed with GAD [11]. Rumination also has been associated with sleep disturbance. A longitudinal study of a non-clinical sample found that rumination at baseline predicted a reduction in sleep quality at follow-up, and rumination, specifically, was associated with poorer sleep quality among individuals who expressed high levels of worry [12]. Future research on the sleep disturbance in GAD may benefit from a focus on the distinct effects of rumination and worry.

There is some evidence that emotional dysregulation, also referred to as mood lability or difficulty modulating emotional responses, may play an important

role in the relationship between sleep disturbance and anxiety in GAD. One study demonstrated that, relative to normal controls, individuals with GAD experienced greater sleep discontinuity, daytime sleepiness, difficulty waking in the morning, daytime dysfunction, and nightmare frequency; and that poor emotion regulation fully mediated the relationship between GAD diagnosis and the majority of these parameters, most notably daytime dysfunction [13].

Circadian Rhythms in GAD

Circadian rhythm abnormalities have long been identified as key mechanisms in mood disorders, with important treatment implications [14]. Similarly, examination of the role of circadian rhythms in GAD may provide new avenues for treating the sleep disturbance in GAD. Sipilä and colleagues [15] examined 12 circadian clock-related genes in individuals with anxiety disorders compared to healthy controls and found evidence of an association of two single nucleotide polymorphisms (SNP) with GAD specifically; two additional SNPs were associated with a group of anxiety disorders that included GAD. This finding suggests that there is a genetic predisposition to GAD that implicates circadian processes. Consistent with this view, GAD has also been associated with a diminished circadian rhythm of blood pressure among patients with hypertension [16]. The hypothesis that individuals with GAD have a genetic predisposition to circadian rhythm abnormalities and may be more susceptible to sleep disturbance, including the development of comorbid insomnia disorder, warrants empirical validation. Future research on the role of circadian rhythm disruption in GAD may be important to advancing treatment for disturbed sleep in GAD.

Treatment of GAD Sleep Disturbances: Psychotherapy

There is some evidence that the treatment of GAD can ameliorate insomnia in affected individuals. Individual and group cognitive behavioral therapy (CBT) for GAD, not specifically targeting sleep disturbance, have been shown to significantly reduce insomnia symptoms [17, 18].

To the best of our knowledge, CBT for Insomnia (CBT-I) has not been studied in patients with GAD, although some studies of the efficacy of CBT-I have included in their samples a small proportion of participants with concomitant psychiatric diagnoses including GAD [19]. It has been suggested that sleep restriction, a core component of CBT-I, would be poorly tolerated by highly anxious patients as it might increase anxiety about not getting enough sleep, which could further reduce sleep time [20]. Similarly, although some stimulus control strategies promoted by CBT-I may be beneficial for patients with GAD (e.g., scheduling a worry time, getting out of bed when unable to control anxious thoughts), others may lead to worry about adhering to a strict sleep/wake schedule [20]. Future research could identify predictors of positive response to CBT-I among individuals with GAD. Additionally, the development of a treatment protocol that incorporates elements of CBT-I into the concurrent treatment of anxiety symptoms could be highly beneficial in GAD with a significant insomnia component.

Treatment of GAD Sleep Disturbances: Pharmacotherapy

Several medications have been shown to be effective in treating the sleep disturbance characteristic of GAD. The addition of eszopiclone, a non-

benzodiazepine drug that acts as an agonist at the benzodiazepine receptor, to the selective serotonin reuptake inhibitor (SSRI) escitalopram significantly improved sleep and daytime function, and decreased anxiety, in a placebo-controlled study in GAD patients [21]. Treatment with pregabalin, approved as an anticonvulsant and for neuropathic pain, was well tolerated and associated with significant reductions in insomnia and daytime anxiety among individuals with GAD [22]. The melatonin receptor agonist ramelteon was associated with reduced sleep onset latency and increased sleep time, as well as improvement in other, non-sleep-related GAD symptoms, in a community sample of adults with GAD [23]. Agomelatine, a melatonin agonist and serotonergic antagonist, was effective in reducing insomnia and daytime symptoms in individuals with GAD [24]. Given the importance of melatonin in circadian rhythm regulation, this finding provides additional evidence that a disruption of the sleep/wake cycle may be central to the pathogenesis of GAD.

Panic Disorder

Panic disorder (PD), characterized by sudden, recurrent panic attacks, occurs in approximately 5% of the U.S. population [5]. Sleep architecture in PD has been reviewed elsewhere [1,2], with mixed findings that range from a minimal reduction in sleep time and slow wave sleep (SWS) to a substantial increase in sleep onset latency. The core feature of sleep disturbance in PD, however, is nocturnal panic attacks (NP). These occur in 44-71% of individuals with PD [25]; they have been found to emerge from the transition between stage 2 (N2) and SWS [26]. NP, abrupt awakenings from sleep in a state of panic,

usually accompanied by subjective fear and discomfort and physiological symptoms, including racing heart, shortness of breath, and chest tightness, are a major cause of insomnia in PD. This sleep disruption can result from the attacks themselves, from cognitive distortions about sleep, or from a conditioned fear of sleeping.

Correlates of Sleep Disturbance in PD

Recent studies have uncovered other factors associated with sleep disturbance in PD in addition to NP. In one study, anxiety sensitivity, defined as the belief that anxiety-related sensations are harmful and cause for fear, was associated with increased sleep latency in PD patients [27]. Such sensitivity may relate to difficulties with cognitive inhibition, i.e., the ability to “tune out” irrelevant stimuli, and there is some evidence that poor cognitive inhibition may lead to sleep disturbances in PD. A recent study in PD patients measured cognitive inhibition using the inhibition condition of the Stroop task. In this task, color names are printed in differently colored ink (e.g., the word “blue” printed in red ink), and participants are required to say the name of the ink color, inhibiting the natural response, which is to read the color word. In this study, difficulties with cognitive inhibition were associated with increased sleep latency and reduced sleep quality [28]. Impaired cognitive inhibition may be related to PD patients’ inability to ignore the internal physiological sensations from which panic attacks evolve.

Treatment of PD Sleep Disturbances

An adaptation of CBT designed for NP was found to be more effective than a waitlist control, with efficacy persisting over a 9-month follow-up period [29]. However, a more recent study comparing this adapted CBT protocol to traditional CBT for PD found that both were associated with significant reductions in NP that lasted through a one-year follow-up period [30]. Generalizability of these findings is limited by small sample sizes and lack of randomization. Randomized controlled trials (RCTs) comparing CBT adapted for NP and standard CBT for PD are warranted. Given research demonstrating an association between increased anxiety sensitivity and increased sleep onset latency, pharmacotherapy addressing anxiety sensitivity may be helpful in individuals with PD and insomnia, sleep onset insomnia in particular. For example, paroxetine and clonazepam have been shown to decrease anxiety sensitivity in patients with panic disorder and could, via this mechanism, improve insomnia symptoms [31].

Sleep in Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is characterized by intrusive, unwanted, repeated, and uncontrollable thoughts, feelings, impulses or images, and repetitive behaviors that are aimed at reducing the associated anxiety. Sleep disturbance in OCD is often characterized by increased sleep onset latency, reduced overall sleep duration, and reduced sleep efficiency [32]. Greater severity of OCD symptoms has been associated with more severe sleep disturbance [32].

The Specific Effect of Obsessional Thinking on Sleep

Recent research suggests that obsessions, rather than compulsions, may play a larger role in generating the insomnia often observed in OCD. For example, Timpano and colleagues [33] found that insomnia was significantly associated with obsessions but not with compulsions; depression, which, frequently is comorbid with OCD, did not explain the relationship between OCD and disturbed sleep. This finding is particularly compelling in the context of the previously reviewed research on worry and rumination in GAD, both of which have been associated with increased sleep disturbance (see Dimensions of Psychological Contributions to Sleep Disturbance in GAD, above). Taken together, there is evidence of an association between sleep disturbance and aspects of what could be termed “cognitive interference.” Future research on this dimension of cognition across psychiatric disorders could be highly useful for treatment development.

Circadian Rhythms in OCD

There is evidence that circadian rhythms influence vulnerability to, and presentation of, OCD. For example, a growing literature supports the importance of delayed sleep phase in OCD [32]. One study of inpatients with OCD revealed that 17.6% met criteria for delayed sleep phase [34], compared to a rate of 0.17% to 8.9% (depending on the exact definition) in the general population [35]. A recent meta-analysis of sleep and circadian rhythms in OCD reported a higher overall prevalence of delayed sleep phase in OCD patients than controls, a finding that was not affected by the exclusion of individuals with comorbid depression [36]. Therefore, circadian rhythm disruption appears to be a salient

feature of OCD that cannot be explained completely by comorbid depression, in which circadian dysregulation is well documented.

Sleep Architecture in OCD

Sleep architecture in OCD has been thoroughly reviewed elsewhere [1,2], with variable results. Some studies reveal increased sleep discontinuity and reduced REMS latency while others report little abnormality. Thus far, PSG studies have been unable to parse the differential effects on sleep of OCD and comorbid depression. In one study, non-depressed OCD patients, relative to healthy controls, demonstrated a moderate disturbance in sleep continuity but no abnormalities of SWS or REMS timing or amount, which have been described in depression [37]. However, another controlled study of a similar sample reported only a reduction in stage 4 sleep, which is often seen in depression [38]. Given these conflicting results and the relatively small number of studies of sleep architecture in OCD, future research is needed to understand the sleep disturbances that are intrinsic to OCD and to distinguish these from others associated with comorbid depression.

Treatment of Sleep Disturbances in OCD

Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are frequently prescribed for the treatment of OCD; however, many of these drugs may have deleterious effects on sleep [39]. Given the relationship between obsessional thinking and sleep quality, CBT for OCD may have positive effects on sleep as well as waking symptoms. Exposure and Response Prevention therapy (ERP) is an empirically

supported treatment for OCD [40]. Future studies should address whether targeting obsessional thinking via ERP improves sleep in individuals with OCD.

Posttraumatic Stress Disorder

The vast majority of individuals with PTSD report the two sleep disturbances included in the DSM-5 classification of the disorder, recurrent nightmares as a form of re-experiencing the traumatic event and insomnia. Insomnia is a symptom of many mental disorders, but recurrent nightmares of a traumatic experience are quite specific to PTSD, perhaps pathognomonic [41]. We review here recent developments in our understanding of the phenomenology and pathophysiology of PTSD sleep disturbances and current strategies to treat these frequently disabling sleep problems.

An increased prevalence of obstructive sleep apnea (OSA) in PTSD was not confirmed in one controlled study; however, there was evidence that OSA could increase PTSD severity [42]. The authors recommended further research on the implications of these findings for treating PTSD comorbid with OSA. This topic will not be discussed further here.

Tonic REM Sleep Alterations in PTSD: the Importance of Time Post-trauma

There is considerable evidence for fundamental REMS alterations in PTSD. In one study, REMS fragmentation in the early aftermath of trauma predicted the development of PTSD [43]. Fragmented, preserved, and enhanced REMS continuity following trauma all have been described [44,45]. Mellman et al. [44] have helped to reconcile these seemingly discrepant observations by noting the importance of the time elapsed post-trauma as a moderating variable. In a

non-clinical community sample of young adults, they found that both REMS percentage (REMS time/total sleep time) and REMS segment length increased with PTSD duration, as assessed retrospectively. They suggested that increases in REMS amount and REMS continuity over time could reflect successful adaptation to a stressor, a hypothesis that they viewed as broadly consistent with a current view that REMS is essential to the successful processing of emotional memories [46]. An equally compelling hypothesis is that the reconstituted REMS observed long after a traumatic experience may be the outcome of maladjustment to a stressor and the neurobiological substrate of the recurrent nightmares that severely disrupt sleep in PTSD [44].

Phasic REM Sleep Alterations in PTSD: Basic and Clinical Studies

A comprehensive description of REMS architecture in PTSD should include phasic as well as tonic REMS measures, the latter indicating REMS amount and REMS continuity vs. fragmentation [44]. Phasic REMS processes are transient brain macropotentials and peripheral physiological events, with rapid eye movements the best studied phasic event in humans. In their meta-analysis of 20 PSG studies of PTSD, Kobayashi et al. [47] found an increased REM density (number of rapid eye movements/REMS time). The significance of this finding may best be understood in the context of the animal literature on the role of REMS phasic mechanisms in the processing of fearful stimuli.

In the rat, the pontine-wave (P-wave), recorded in the pons, is the prototypical REMS phasic event. Datta [48] observed that P-wave density increased following 2-way active avoidance training in rats and hypothesized that

P-wave generation is essential for effective REMS-dependent memory processing. Ross [44] suggested that severe psychological stress initiates a phasic REMS response that either facilitates successful emotional adaptation or, alternatively, lays the groundwork for the development of PTSD. Based on a study of fear conditioning in two rat strains with different levels of stress sensitivity, DaSilva et al. [49] proposed that the inability to mount a strong phasic REMS response following exposure to a severe stressor could lead eventually to the increase in phasic activity that characterizes sleep in chronic PTSD.

The behavioral response threshold in healthy individuals has been reported to be elevated during phasic compared to tonic REMS [50]. Elevated REMS phasic activity in PTSD could explain the increased arousal threshold during REMS that has been observed in patients compared to controls [51].

Neurocircuitry of REM Sleep Alterations in PTSD

Although the neurocircuitry responsible for REMS changes in PTSD remains to be fully elucidated, there is much evidence for the involvement of the limbic system, and more specifically, the amygdala. This structure plays an essential role in emotion and in the regulation of arousal states [52]. Amygdalar activation during REMS has been observed in healthy humans [52].

Schwartz and Maquet [53] have proposed that, using functional neuroimaging (fMRI) techniques, there could be demonstrated a relationship of “common fear experience in dreams to the activation of the limbic system, in particular the amygdala.” As a disorder characterized by recurrent nightmares, PTSD deserves to be studied with complementary fMRI and dream content

analysis methods. Increased activation of the amygdala has been demonstrated during waking in some studies of PTSD [54]. It can be predicted that the investigation of amygdalar function across the sleep-wake cycle will provide important insights into the brain mechanisms of the PTSD sleep disturbance. As an example, using FDG PET neuroimaging, Germain et al. [55] have observed hypermetabolism in “brain regions involved in arousal regulation, fear responses, and reward processing” during REMS as well as waking in Operations Enduring Freedom and Iraqi Freedom Veterans with PTSD compared to controls.

Circadian Rhythm Abnormalities in PTSD

Hasler et al. [56] observed that self-reported evening chronotype (referring to the propensity for an individual to sleep later in the 24-hour period) in combat-exposed military Veterans with a varying level of posttraumatic stress symptoms was associated with greater sleep disturbance and lifetime posttraumatic stress severity. Nielsen [57] has reviewed the evidence that PTSD is characterized by “an apparent phase advance in dreaming such that vivid nightmares, which usually occur in late REM sleep, occur in PTSD patients also early in the sleep episode...” This raises the question whether individuals with PTSD may purposefully delay their sleep onset to avoid sleeping when nightmares are most distressing. However, van Liempt et al. [42] measured mean melatonin onset time and found no evidence of a phase advance in small samples of PTSD compared to control subjects.

Sleep Movement Disturbances in PTSD

Individuals with PTSD frequently describe excessive movement during sleep, reports that often are corroborated by bed partners. These movements could be a result of the prominent muscle activation that occurs during spontaneous awakenings from sleep [58]. An early PSG study in “trauma survivors” noted extreme motor activity, sometimes violent, during REMS [59]. This suggests that the pathophysiology of PTSD could involve neural circuitry that also is disrupted in REM behavior disorder (RBD). Although RBD typically is not associated with psychopathology [60], Husain et al. [61] reported that 56% of a sample of RBD patients had comorbid PTSD. Complicating the consideration of any association between PTSD and RBD is the well-known relationship between antidepressant medications used to treat PTSD (see Treatment of PTSD Sleep Disturbances: Pharmacotherapy, below) and the occurrence of RBD symptoms [62].

Compared to healthy controls, combat Veterans with PTSD may show phasic motor dysregulation during non-REMS, in the form of periodic limb movements (PLMs, [63]). Cantor and Ross [63] have suggested a potential link between the neural mechanisms of PLMs and those of PTSD. This is based on the observation that a group of individuals with PLMs had an abnormal blink reflex, one component of the startle reflex which is characteristically exaggerated during wakefulness in PTSD [63]. Another potential link between the pathophysiology of PLMs and that of PTSD is provided by the evidence that sympathetic nervous system activity, which is elevated in PTSD [64], has an essential role in producing PLMs [65]. PLMs can be associated with partial

arousal or awakening [66], and might thereby contribute to insomnia in PTSD. The antidepressant medications used to treat PTSD (see Treatment of PTSD Sleep Disturbances: Pharmacotherapy, below) can increase PLMs, thereby promoting arousal and exacerbating insomnia [66].

Apparently paradoxically, Woodward et al. [67] observed that, compared to healthy controls, a group of combat Veterans with PTSD showed a reduction in sleep movement time. Noting the uncertain relationship between movement time and brief body movements, they saw no incompatibility between their finding and reports of elevated phasic motor activity in PTSD.

Treatment of PTSD Sleep Disturbances: Psychotherapy for PTSD

Existing meta-analyses of the effectiveness of psychotherapies for PTSD have paid little attention to sleep outcomes [68]. The VA/DoD 2010 Clinical Practice Guideline [69] supports the use of exposure-based therapies, prolonged exposure (PE) in particular, and cognitive processing therapy (CPT). Galovski and colleagues (2009) [70] found that both PE and CPT were somewhat effective in reducing global sleep disturbance in adult, female rape survivors; however, sleep impairment remained clinically significant despite an overall improvement in PTSD symptoms. Examining long-term changes in sleep symptoms after CPT and PE, Gutner et al. [71] found no improvement in sleep disturbance, again in the context of a remission of the waking symptoms of PTSD.

Treatment of PTSD Sleep Disturbances: Psychotherapy for Insomnia

There is some evidence that cognitive-behavioral therapy for insomnia (CBT-I) is effective for insomnia related to PTSD [68]. Talbot and colleagues [72]

conducted a randomized clinical trial (RCT) of CBT-I in a community sample with PTSD. Compared to waitlist controls, the CBT-I group had a superior response on sleep diary measures, on Pittsburgh Sleep Quality Index (PSQI) scores, and on PSG-derived total sleep time, effects that remained significant at 6-month follow-up. However, both the CBT-I and waitlist control groups had reductions in PTSD symptom severity and posttraumatic nightmares, indicating that trials with an active treatment control group will be essential to demonstrating the efficacy of CBT-I specifically.

Treatment of PTSD Sleep Disturbances: Psychotherapy for Recurrent Nightmares

Imagery rehearsal (IR; [73,74]) the best studied psychotherapeutic intervention for recurrent nightmares, may promote increased mastery of nightmare content [75]. A variety of protocols exist, all having these essential components: choosing a recurrent nightmare, rescripting it during waking, and rehearsing the new dream script imaginally at bedtime. Most forms of IR include additional potentially active treatment elements, such as CBT-I techniques. Only one RCT of IR has included a potentially active psychotherapy control [76]. In a study of Vietnam War Veterans with chronic, severe PTSD and recurrent nightmares, there was no significant difference in reducing nightmare frequency and PTSD severity and improving sleep quality between IR and a comparison treatment that included components of CBT-I [76]. Harb and colleagues [74] have emphasized the limitations of the extant IR literature and identified strategies to advance the field. Exposure, Relaxation and Rescripting Therapy (ERRT) is a

variant of IR that has shown promise for reducing nightmares and insomnia in predominantly civilian samples with posttraumatic symptoms [77].

Treatment of PTSD Sleep Disturbances: Pharmacotherapy for PTSD

The selective serotonin reuptake inhibitors (SSRIs) have the strongest evidence base among pharmacotherapies for PTSD [69]. However, there is remarkably little evidence that insomnia and recurrent nightmares in PTSD respond to these drugs [68]. To the best of our knowledge, only a small open-label trial of fluvoxamine in Vietnam War combat Veterans demonstrated an improvement in subjective sleep quality and a decrease in dreams related to combat trauma [78].

The use of selective serotonin and norepinephrine reuptake inhibitors (SNRIs), in particular venlafaxine, is supported by clinical guidelines for treating PTSD [69]. However, in a pooled analysis of two controlled trials, there was no advantage of venlafaxine ER in reducing distressing dreams as assessed with the CAPS-SX17 [79]. Accordingly, the “Best Practice Guide for the Treatment of Nightmare Disorder in Adults” does not recommend venlafaxine for treating PTSD-associated nightmares [73].

The tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have not been studied in large clinical trials in PTSD [79]. Currently there is only weak support for the usefulness of the TCAs and the MAOIs in controlling recurrent nightmares [73]. This is particularly interesting in light of the prominent REMS suppressant effect of the MAOIs, given that most nightmares emerge from REMS [73].

The atypical antipsychotic drugs have been investigated as a treatment for PTSD. One controlled trial of olanzapine monotherapy found a greater reduction in the total CAPS score with the medication, but only the decrease in the avoidance and numbing sub-score achieved significance [80]. A small placebo-controlled trial of adjunctive olanzapine for combat-related PTSD unresponsive to SSRI treatment showed a greater improvement in sleep, as measured by the PSQI, in the olanzapine group [81]. The largest study of an atypical antipsychotic drug in PTSD showed no significant effect of risperidone in Veterans [82]. No completed RCTs of quetiapine, ziprasidone, or aripiprazole have been carried out in PTSD populations.

Treatment of PTSD Sleep Disturbances: Pharmacotherapy for Insomnia

Few studies have examined the benefits of pharmacotherapy for insomnia in individuals with PTSD. There was no significant advantage of the benzodiazepine clonazepam in a small, single-blind, placebo-controlled trial [83]. However, clonazepam, the mainstay of pharmacological treatment for RBD, could have a place in the treatment of excessive movement during sleep in PTSD, a topic for future research. In a RCT, Pollack and colleagues [84] found that a 3-week treatment with eszopiclone, a non-benzodiazepine that acts at the benzodiazepine receptor, led to greater improvements in PTSD symptoms, including sleep disturbance.

There is some evidence that the 5-HT₂ antagonist/SSRI trazodone, an antidepressant drug with prominent sedative properties, may be useful in treating insomnia and recurrent nightmares in individuals with PTSD [85]. Nefazodone,

an antidepressant with a similar pharmacological mechanism, showed some utility in open-label trials [78], but concerns about hepatotoxicity have limited further investigation with this medication.

Treatment of PTSD Sleep Disturbances: Pharmacotherapy for Recurrent Nightmares

There is low level evidence for the usefulness of topiramate, low dose cortisol, and gabapentin in treating recurrent nightmares. There are conflicting data on the benefit of the antihistamine cyproheptadine [73]. The introduction of the alpha-1 adrenoceptor antagonist prazosin is arguably the most important advance in the pharmacotherapy of the nightmare disturbance in PTSD.

Two placebo-controlled trials of prazosin in U.S. military Veterans reported a decrease in nightmares [65]. A placebo-controlled trial in civilians with PTSD also showed an advantage of prazosin in reducing trauma nightmares [65]. Additionally, Raskind and colleagues [86] reported a decrease in combat-related nightmares in active duty U.S. service members treated with prazosin compared to placebo; sleep quality and overall PTSD symptoms were improved as well. Notably, prazosin has also been found to reduce non-nightmare distressed awakenings, i.e., those awakenings from sleep accompanied by extreme psychological distress without any recall of dream mentation [87]. Other drugs that reduce central noradrenergic activity could also be expected to ameliorate the nightmare disturbance in PTSD. There are positive case reports for clonidine, an alpha-2 adrenoceptor agonist that inhibits the firing of noradrenergic locus coeruleus neurons [88], but no clinical trial of this drug has been conducted.

Conclusion: Directions for Future Research

The past decade has seen numerous advances in our understanding of both the mechanisms of sleep disturbance in anxiety disorders, OCD, and PTSD, and in their treatment. Research in GAD, PD, and OCD has uncovered common dimensional processes at the interface of sleep disturbance and anxiety disorders. Many of these processes cluster around difficulties with cognitive control (e.g., worry, rumination, anxiety sensitivity, obsessional thinking, impaired cognitive inhibition). Together, this research suggests that treatments for sleep disturbance in these disorders may benefit from the utilization of cognitive strategies aimed at reducing mental activity prior to sleep onset and during mid-sleep waking periods. Cognitive restructuring of negative beliefs about sleep is already an important component of CBT-I. Individuals with GAD, PD, and OCD may benefit from the addition to CBT-I of anxiety-specific cognitive strategies.

The brain mechanisms underlying the sleep disturbance in PTSD are increasingly understood. These advances have depended in part on the translation from basic research in animals. Although non-REMS can be affected in PTSD, e.g., in the form of PLMs, attention has focused on REMS processes. Abnormalities of REMS control may evolve with the passage of time post-trauma. Neuroimaging during sleep will likely provide important insights into the underlying neural circuitry. The alpha-1 adrenoceptor antagonist prazosin has assumed an important role in the treatment of recurrent nightmares in PTSD.

Identifying effective psychotherapies for the sleep disturbance in PTSD is a field poised for further investigation.

Circadian rhythm disturbances have been observed in GAD and OCD, and there is reason to suspect the presence of circadian abnormalities in PTSD. Although research in this area is still in its early stages, identifying the ways in which circadian rhythm abnormalities contribute to sleep disturbances in anxiety disorders, PTSD, and OCD could lead to important developments in both pharmacotherapy and psychotherapy. An example is the reported benefit of agomelatine in treating GAD and associated insomnia .

Finally, although the DSM-5 no longer considers GAD, PD, OCD, and PTSD under the umbrella of “anxiety disorders,” this review has highlighted areas of overlap in the pathophysiology and treatment of the sleep disturbances in these disorders. Dimensional approaches to the study of sleep across psychiatric disorders is likely to be key in introducing new treatments and improving the quality of life for affected individuals.

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