

Clinical Importance of Sleep Disturbance as a Treatment Target in PTSD

Abstract: In this review, evidence for the importance of sleep-related disturbances in PTSD as a target for treatment is presented. Examination of efficacy studies of the first-line treatments for posttraumatic stress disorder (PTSD)—selective serotonin reuptake inhibitors and cognitive behavior therapy—indicates that neither adequately treats PTSD nightmares and insomnia. The published guidelines that recommend these treatments do not provide advice on treating posttraumatic sleep disturbance, suggesting a possible lack of awareness of the problem. Based on clinical reports, imaging, and polysomnographic studies, a theoretical model in which REM dysregulation in PTSD plays a key role in the development and persistence of PTSD will be presented. Finally, evidence regarding the beneficial effects of prazosin and other agents in the treatment of PTSD-related sleep disturbance will be highlighted.

CLINICAL CONTEXT: SLEEP DISTURBANCE AS A CORE SYMPTOM IN PTSD

Persistent and severe posttraumatic nightmares and sleep disturbance are reported by more than 70% of combat veterans and civilians with posttraumatic stress disorder (PTSD) (1). It is surprising that there has been relatively little research in this area. In 1989 Ross et al. (2) speculated that sleep disturbance and nightmares in particular were relatively specific for the disorder, a “hallmark” symptom of PTSD. Individuals with severe PTSD-related nightmares often develop conditioned fear of going back to sleep or going to sleep (3). Germain et al. (4) studied 367 individuals with PTSD of 6 months’ to more than 30 years’ duration and found that PTSD severity was most closely associated with the severity of sleep disturbances.

Other sleep-related problems that are common in PTSD have been described. Periodic limb movement disorder, a condition characterized by repetitive movements of the arms and legs during sleep (5), occurs in 30%–70% of individuals with PTSD. Sleep-disordered breathing (SDB) disorders such as obstructive sleep apnea occur in 40%–91% of individuals with PTSD, far exceeding the rates in demographically similar individuals without PTSD or in the general population (6). Both of these disorders cause miniarousals during sleep and contribute to sleep disturbance (Figure 1). Finally, the cumulative sleep deprivation resulting from the above problems acts as an additional stressor that contributes to allostatic load by increasing inflammatory cytokine levels and promoting sympathetic activation (7). Even brief experimental sleep deprivation in normal subjects has clear-cut adverse effects on cognition, mood, and frontal lobe function (8, 9).

PTSD-related sleep disturbance has been viewed by many as an accompanying or secondary symptom that should improve with successful treatment of PTSD (10, 11). The prevalence of this perspective is apparent in published expert consensus statements and treatment guidelines intended to advise clinical practice but do not mention sleep (12). In the DSM-IV-TR diagnostic criteria for PTSD (Table 1), nightmares and insomnia appear in different symptom clusters and neither is required for a diagnosis of PTSD. This fact may also reflect the complexity of the disorder or insufficient information about which symptoms are most fundamental.

CME Disclosure

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It is not widely recognized that in the aftermath of a traumatic event, sleep disturbance appears before the onset of PTSD (13) as does polysomnographic evidence of sleep disruption; both are predictors for PTSD (14, 15).

TREATMENT STRATEGIES AND EVIDENCE

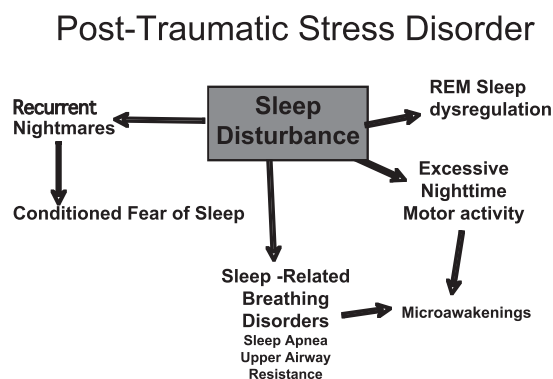
DO FIRST-LINE TREATMENTS FOR PTSD EFFECTIVELY TREAT SLEEP DISTURBANCE?

Maher et al. (16) recently reviewed the empirical evidence for efficacy of pharmacotherapy and certain cognitive behavior treatments for PTSD and concluded that the recommended first-line treatments do not effectively resolve PTSD-related sleep disruption. Recommendations made for PTSD pharmacotherapy by several expert consensus groups (17) were in unanimous agreement that the selective serotonin reuptake inhibitors (SSRIs) should be considered as first-line pharmacotherapy for PTSD. Improvements in all three symptom clusters (B, C, and D) (Table 1) were reported in the pivotal studies of the three Food and Drug Administration-approved SSRIs (fluoxetine, paroxetine, and sertraline). However, there were minimal effects on insomnia and no evidence for clinically meaningful reduction of nightmares (16) in these studies. In summary, the evidence to date suggests that the SSRIs have some beneficial effects on PTSD, minimal effects on insomnia, and no effect on nightmares in PTSD.

Cognitive behavior therapy (CBT) with exposure has been shown to benefit PTSD and is recommended as the first-line non-drug treatment (18, 19) but only a few studies provided sleep outcome data. In one report, 48% of 24 of individuals completing treatment with CBT for civilian PTSD and no longer meeting the DSM-IV-TR criteria still had clinically significant sleep disturbance (primarily insomnia) (3); some of these patients derived a benefit from additional insomnia-targeted CBT (20). In one open label (21) and one controlled trial (22) of imagery rehearsal therapy (IRT) focused on PTSD-related nightmares and insomnia, there were clinically significant improvements in sleep measures and PTSD, but most participants continued to have at least moderately severe insomnia, nightmares, and PTSD at the end of the study.

These data indicate that neither of the first-line PTSD treatments—SSRIs or CBT with exposure—is particularly effective for normalizing sleep. SSRIs are ineffective for nightmares and have only minimal benefit on other sleep disturbances. The few data available suggest that there is residual sleep

Figure 1. PTSD Sleep-related Disturbances.



disturbance after standard CBT. Importantly, the IRT studies that targeted sleep disruption provide evidence suggesting that targeting sleep disturbance appears to reduce PTSD severity.

NEUROBIOLOGICAL SUBSTRATES OF PTSD RELEVANT TO SLEEP DISTURBANCE

One reason for reconsideration of the importance of sleep disruption in PTSD is that sleep is regulated in part by brain areas in which PTSD-related changes occur, suggesting that the stress response, arousal, fear conditioning/extinction, emotional memory, and, importantly, sleep may be biologically linked. Exaggerated activity of the amygdala in conjunction with reduced activation in the medial prefrontal cortex (mPFC) and hippocampal dysfunction have been most consistently reported (23). These changes are thought to interfere with extinction of the fear response (24, 25). Imaging studies show that exposure to trauma-related stimuli results in excessive activation in the amygdala and decreased activation in the mPFC/anterior cingulate and hippocampus (25). The magnitude of these changes correlates with the clinical severity of PTSD symptoms (26) and appears to increase with repeated reexposure (27). Persistently increased release of norepinephrine (NE), a monoamine that plays a critical role in fear conditioning/extinction and in part mediates stress-related deficits in hippocampal function, may not only interfere with extinction but also could actually promote fear conditioning (23, 28). Excessive NE activity is also thought to mediate in part symptoms of reexperiencing, hyperarousal, vigilance, and, importantly, sleep disturbance in PTSD (15, 29–33).

POLYSOMNOGRAPHY IN PTSD

Normal human sleep is characterized by cycles of REM sleep and non-REM (NREM) sleep, each

Table 1. DSM-IV-TR Criteria for PTSD

Criterion A: A traumatic event in which

1. The person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others.
2. The person's response involved intense fear, helplessness, or horror.

Criterion B: intrusive recollection (at least 1)

1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions
2. Recurrent distressing dreams of the event
3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated)
4. Intense psychological distress at exposure to internal or external trauma-related cues
5. Physiologic reactivity upon exposure to internal or external trauma-related cues

Criterion C: avoidant/numbing (at least 3, not present before the trauma)

1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
3. Inability to recall an important aspect of the trauma
4. Markedly diminished interest or participation in significant activities
5. Feeling of detachment or estrangement from others
6. Restricted range of affect (e.g., unable to have loving feelings)
7. Sense of foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal lifespan)

Criterion D: hyperarousal (at least 2, not present before the trauma)

1. Difficulty falling or staying asleep
2. Irritability or outbursts of anger
3. Difficulty concentrating
4. Hypervigilance
5. Exaggerated startle response

Criterion E: Duration of the disturbance (symptoms in B, C, and D) is more than one month.

Criterion F: The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Acute: if duration of symptoms is less than 3 months

Chronic: if duration of symptoms is 3 months or more

Adapted, with permission, from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision. Washington, DC, American Psychiatric Association, 2000.

of which takes 70–120 minutes (1). NREM sleep includes four stages (1 through 4) in which stages 3 and 4 represent deep sleep. In healthy young adults, stages 3 and 4 are most prevalent during the first one third of the 8- to 9-hour night. REM episodes occur mostly during deeper stages 3 and 4 and are characterized by rapid ocular movements and motor paralysis. REM episodes typically increase in length as the night progresses. During REM and NREM sleep in normal subjects, there are changes in activation and deactivation of different brain areas as measured by regional cerebral blood flow

(rCBF) (4). During REM sleep there is a relative increase in rCBF in the amygdala, paralimbic areas, and wake-promoting areas (medial pons and thalamus) and reduced rCBF in lateral prefrontal, parietal, and sensory cortices compared with wakefulness. During NREM sleep, rCBF is decreased in the pons, midbrain reticular and thalamic areas, and associated cortices and increased in areas that promote sleep (dorsal pontine tegmentum and basal forebrain) (34). On the basis of their respective patterns of brain activation and deactivation, NREM sleep is hypothesized to be a restorative,

low-activation state and REM sleep may be related to learning, memory consolidation, and/or emotional processing (1, 11).

Despite such consistent and high rates of subjective reports of sleep problems (35), results of polysomnographic studies in PTSD were surprisingly inconsistent and inconclusive (36) and failed to reflect the severe sleep disturbances reported. In 2007, Kobayashi et al. (37) completed a metaanalysis of 20 polysomnography studies in PTSD that used control groups for a total of 772 patients. This analysis revealed that there were, in fact, characteristic polysomnographic abnormalities in individuals with PTSD than in those without PTSD: more light (stage 1) sleep, less deep (stages 3 and 4), slow-wave sleep, and greater REM density. Sleep abnormalities in PTSD were modulated by age, comorbid depression, sex, and substance abuse.

Nightmares in PTSD. A number of researchers have speculated that nightmares are a core feature of PTSD (2, 10, 11) that predict chronicity of sleep disturbance (38). Compared with those without PTSD, PTSD nightmares are more frequent, occur earlier in the sleep cycle, are consistent in content or theme, and may replicate real events (35). Fear nightmares may generate further sleep-disruptive behaviors such as fear of going to sleep or going back to sleep after checking or other safety behaviors, nighttime eating, sleeping in lounge chairs, and others (3, 10), thus contributing to overall sleep deprivation.

REM sleep disruption in PTSD. As more is learned about REM disruption in PTSD, several investigators have suggested that disordered REM sleep may be important in the genesis and maintenance of PTSD (2, 10, 11, 15). In addition to increased REM density, others have reported more REM-to-stage-1 transitions (39), more awakenings from REM sleep (6), and more frequent but shorter REM episodes (14) in subjects with PTSD than in control subjects. This REM fragmentation (14) may theoretically be caused by excessive NE activity (15), prematurely terminating REM episodes or perturbing the normal rhythm of cholinergic REM-on and aminergic REM-off signals (10, 11, 31, 32, 40). REM fragmentation may effectively mimic REM deprivation with consequences resembling the behavioral aspects of REM sleep behavior syndrome (41) and possibly the metabolic effects of REM deprivation (7).

PERIODIC LIMB MOVEMENTS IN PTSD

Excessive motor movements during sleep in PTSD have been described by a number of inves-

Table 2. REM Fragmentation Sleep Disturbances in PTSD

Increased REM density
More frequent, shortened REM episodes
More awakenings from REM sleep
More REM to stage 1 transitions
Shorter latency to move from REM to stage 1
More REM-preceded awakenings with panic, startle and physiological arousal

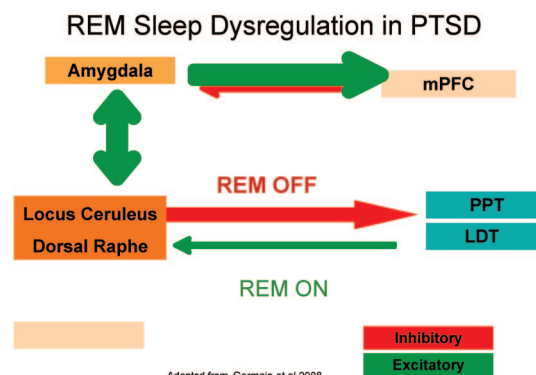
tigators (4–6, 42, 43). Because nightmares in PTSD tend to emerge just after REM episodes, during which there is normally motor paralysis, Ross et al. (42) investigated motor behavior during REM sleep in war veterans via electromyographic recording of anterior tibialis muscle movements. Prolonged anterior tibialis twitches were more frequent in subjects with PTSD than in control subjects during REM sleep. Periodic limb movements also occurred more often during NREM sleep in subjects with PTSD (6); these were similar to symptoms of REM sleep behavior disorder (41), leading to speculation that disturbed REM-NREM phasic mechanisms may play a role in sleep-motor behavior (6, 10, 11, 42).

SDB in PTSD. There are numerous reports of SDB, especially sleep apnea in individuals with PTSD (37, 43–49). A survey of 256 sexual assault survivors showed that 51% exhibited SDB and 61% exhibited sleep-related movement disorders. The literature suggests a complicated interaction between trauma and disordered sleep. Whether sleep-related airway obstruction contributes to the etiology of PTSD, is a result of PTSD, or is related more generally to sleep deprivation remains unclear.

QUESTIONS AND CONTROVERSY: IS REM DYSREGULATION A MODEL FOR SLEEP DISTURBANCE IN PTSD?

During normal sleep, REM sleep is initiated in the ventral part of the oral pontine reticular nucleus (40) by firing of cholinergic neurons (31). This can occur only during requisite “silence of the locus ceruleus” (32) (i.e., inhibition of locus ceruleus and raphe activity). REM sleep is terminated by increased aminergic input from sleep-off nuclei including the raphe and locus ceruleus, thereby creating a dynamic, alternating cycle of cholinergic-aminergic activity. In PTSD, the persistently overactive noradrenergic system has been hypothesized to escape normal inhibitory processes, resulting in

Figure 2. Schematic Model of REM Sleep Dysregulation in PTSD.



The combined effects of increased activity in the amygdala and reduced inhibitory input from the mPFC results in adrenergic hyperactivity. This promotes increased activity of brainstem REM-off centers (locus ceruleus and dorsal raphe) during sleep. These in turn exert more inhibition of REM-on centers in the pontopedunculopontine tegmentum (PPT) and laterodorsal tegmentum (LDT). As a result, the usual rhythm of REM-NREM sleep is disrupted, and REM sleep is fragmented. Red line, inhibitory pathway; green line, excitatory pathway. Adapted from Germain et al. (11).

early termination or disruption of REM episodes as evidenced by increased REM density and more frequent REM awakenings (10, 11) (Figure 2). With perturbation of the normal cadence of REM-on and REM-off cycles, periodic limb movements during REM episodes could theoretically result from disrupted timing or incomplete termination of noradrenergic signaling in or near REM episodes. In addition, the occurrence of nightmares during REM episodes may be related to amygdala hyperactivity with incompletely inhibited, intrusive α -adrenergic signals during REM episodes. This hypothesis is consistent with pharmacologic induction of nightmares with α -agonists (50, 51) and indirectly supported by recent preclinical evidence that membrane potential changes related to REM sleep deprivation are mediated via an α_1 -adrenergic mechanism (52). This model suggests that agents which block central postsynaptic nor-epinephrine receptors or decrease central NE release (33, 53) and/or otherwise normalize REM sleep might have benefits in PTSD-related sleep disturbances.

RECOMMENDATIONS: IMPLICATIONS FOR TREATMENT SLEEP DISTURBANCE IN PTSD

The focus of this brief review was to examine the importance of sleep disturbance in PTSD and discuss the importance of treating disrupted sleep. There is accruing evidence that some agents may be specifically useful for treating patients with PTSD who have residual sleep disturbance.

PRazosin

Prazosin, a centrally and peripherally acting α_1 -receptor antagonist, was shown to meaningfully reduce or eliminate PTSD-related nightmares in veterans (54, 55) and civilians (56) in three placebo-controlled studies. Target doses of 10–15 mg at bedtime in the first two studies in veterans with combat PTSD were well tolerated with only a few terminations due to orthostatic hypotension (54, 55). The third study was a placebo-controlled crossover study in 13 civilians with PTSD. In addition, this study included sleep measures. Treatment periods were 3 weeks (random assignment to prazosin or placebo) separated by a 1-week washout; the average dose was approximately 3 mg nightly. Prazosin treatment was superior to placebo in improving sleep disturbance and nightmares and was associated with increased total sleep time, total REM time, and increased duration of REM episodes (56). In one small study of subjects for whom nightmares were controlled well with prazosin, adding small daytime doses reduced reactivity to trauma cues during the day (57). These findings lend support to the model linking noradrenergic overdrive and REM dysregulation for PTSD-related nightmares, sleep disturbance, and perhaps other PTSD symptoms.

Prazosin was originally marketed as an antihypertensive agent (Minipress) in doses up to 20 daily. Dosage forms are 1-, 2-, or 5-mg capsules. For nightmares, bedtime dosing is used, with an initial dose of 1–2 mg with monitoring for postural hypotension and with advancement every few weeks to 10–15 mg unless improvement occurs earlier. Clinical experience indicates that suppression of nightmare symptoms can occur at doses as low as 1 mg nightly within 1–2 weeks. The most common side effects are postural dizziness in about 10% of patients, to which most develop tolerance. Sedation occurs in about 10% of patients, but for sleep disturbance this is desirable for most patients. Prazosin is also used off-label to treat benign prostatic hypertrophy (2 mg b.i.d.) and Raynaud's disease (0.5–3 mg b.i.d.).

OTHER ANTIADRENERGIC AGENTS

The evidence for efficacy of other antiadrenergic agents is much less well-developed than that for prazosin. Both clonidine, an α_2 -adrenergic agonist, and guanfacine have been reported to improve symptoms of PTSD in children and in adults (33, 53). In one controlled study guanfacine, an α_2 -adrenergic agonist that is less selective for the α_2 -receptor than clonidine, was not found to be

efficacious for PTSD-related nightmares (58). Propranolol, a β -adrenergic antagonist, modestly reduced the percentage of traumatized individuals who develop PTSD (59) and is anecdotally helpful in children with PTSD, but there are no reports on sleep effects.

GABAPENTIN

Gabapentin is an anticonvulsant that also exerts anxiolytic, antinociceptive, and sleep-promoting effects in humans (60). The broad actions of gabapentin in the central and peripheral nervous systems, as well as those of its derivative pregabalin, are thought to be effected via its high affinity for and binding to the $\alpha 2\delta$ subunit of voltage-gated neuronal Ca^{2+} channels. This results in reduced release of norepinephrine, serotonin (5-HT), glutamate, and substance P from neurons with pathologically rapid firing rates (60). In normal subjects and sample patients with epilepsy, gabapentin enhances slow-wave sleep, increases total sleep time, reduces arousals and awakenings, and reduces periodic motor movements during sleep (61, 62). Hamner et al. (63) reported the off label effects of adjunctive gabapentin (300–2100 mg daily) added to the existing drug treatment regimen of 30 veterans with PTSD to reduce nightmares and sleep disturbance. Twenty of these had been receiving SSRIs shown to have efficacy in PTSD. Of 30 patients, 24 (77%) showed moderate to marked improvement in sleep disturbance and global PTSD severity after the adjunctive gabapentin treatment. It is unclear whether these therapeutic effects are mediated via antiadrenergic or other mechanisms such as effects on γ -aminobutyric acid (GABA) neurotransmission. In controlled studies, gabapentin showed clinically and (nearly statistically) significant benefits in the treatment of panic disorder and social anxiety disorder (64, 65). Both gabapentin and its derivative pregabalin promote nonsynaptosomal glial uptake and release of GABA (66). There is presumed dysregulation of GABA functioning in both panic disorder and PTSD as evidenced by reduced GABA_A-benzodiazepine receptor binding (67, 68). In addition, preclinical evidence suggests that gabapentin normalizes GABA function in the central nucleus of the amygdala and in laboratory models using human neocortex synaptosomal preparations, which may be relevant to its therapeutic effects in humans (69, 70). In summary, the existing human data and interesting preclinical evidence support the hypothesis that gabapentin and probably pregabalin show

promise as potential alternative or adjunctive treatments for SSRI-treated patients with PTSD who have residual sleep disturbance.

SUMMARY

The evidence presented supports the concept that disturbed sleep is an important issue in PTSD treatment. More research is needed to confirm whether normalizing REM abnormalities in PTSD is consistently associated with improvement. The findings that generated this hypothesis and the recently reported effects of prazosin on sleep architecture are certainly encouraging, and the convincing controlled data on the effects of prazosin on sleep disturbance are of immediate clinical utility. Gabapentin and its derivative pregabalin should be studied in controlled trials as monotherapy and as adjunctive treatments in prospective clinical trials. The benefit of CBT treatment, which targets nightmares (IRT), also supports the theory that targeting sleep in PTSD is clinically relevant. It is hoped that further studies will clarify this understudied area.

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