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Insomnia in the context of traumatic brain injury

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Abstract—Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality in the United States. One of the most common comorbidities of TBI is the disruption of normal sleep. While often viewed as a nuisance symptom, sleep disruption can delay TBI recovery and negatively affect many of the psychological (e.g., anxiety, depression) and neuromuscular (e.g., pain) sequelae of TBI, decreasing quality of life. Treatment of sleep disruption in the context of TBI is complicated by issues of an altered neuronal milieu, polypharmacy, and the complex relationship between the various comorbidities often found in patients with TBI. Given the growing number of veterans returning from combat with TBI and the elevated risk of comorbid disrupted sleep, both caused by and independent of TBI, a comprehensive review of sleep disruption and its treatment is of great relevance to the Department of Veterans Affairs.

Key words: cognitive behavioral therapy, comorbidity, insomnia, pharmacotherapy, rehabilitation, sleep, sleep disorder, sleep disruption, traumatic brain injury, veterans.

SLEEP DISTURBANCES IN TRAUMATIC BRAIN INJURY: RELEVANCE TO VETERANS

Sleep disturbances, such as insomnia, are very common following traumatic brain injury (TBI) and have been reported in frequencies up to 84 percent (**Table**). Sleep disruption can be related to the TBI itself but may also be secondary to neuropsychiatric (e.g., depression, anxiety) or neuromuscular (e.g., pain) conditions associated with TBI or to the pharmacological management of the injury and its consequences (**Figure**). Sleep disturbances in TBI may affect or exacerbate psychiatric problems, memory, mood, behavior, and social functioning. Sleep disruption has been shown to hinder overall rehabilitation from TBI and is suggested to have a negative effect on the neural remodeling necessary for recovery from many types of brain injuries [1]. Although increased awareness of the potential negative contribution of sleep disorders to poorer outcome in TBI exists, further studies are necessary to generate additional objective data on these patients in terms of the prevalence, clinical features, types of sleep problems, and relationships between the severity of the TBI and sleep disorders and between sleep disorders and other psychiatric problems, as well as the appropriate treatments for these conditions.

This review focuses on insomnia in the context of TBI. Thus, we will consider insomnia directly caused by TBI (e.g., secondary to neural damage), insomnia indirectly caused by TBI (e.g., secondary to depression), and insomnia unrelated to TBI but occurring in individuals with TBI as being in the context of TBI. In the TBI and sleep literature, these three etiologies are generally not clinically parsed. Insomnia is the most common disorder

Abbreviations: CBT = cognitive-behavioral therapy, CBT-I = CBT for insomnia, EEG = electroencephalography, PTSD = posttraumatic stress disorder, REM = rapid eye movement, TBI = traumatic brain injury, VA = Department of Veterans Affairs.

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Table.
Survey studies of insomnia in traumatic brain injury (TBI). On average, 40 percent of individuals (1,119 of 2,816) in these studies were reported to have symptoms of insomnia. Methodologies for determination of insomnia in these publications vary widely from surveys to electroencephalography recordings, likely adding to variability in percentage of individuals reported to have insomnia. References are presented in chronological order.

Reference	No. Subjects with TBI	% with Disrupted Sleep	TBI Severity (Physician Rating)	Time Since Injury (time, range, or mean ± SD)
Rutherford, 1977 [1]	145	15	Mild, moderate, severe	6 wk
Keshavan et al., 1981 [2]	60	70	Mild, moderate, severe	1.5 mo
Keshavan et al., 1981 [2]	60	37	Mild, moderate, severe	3 mo
McLean et al., 1984 [3]	120	36	Mild, moderate, severe	1 mo
Dikmen et al., 1986 [4]	19	41	Mild	1 mo
Cohen et al., 1992 [5]	22	73	Mild, moderate, severe	3–5 mo
Cohen et al., 1992 [5]	77	52	Mild, moderate, severe	24–36 mo
Segalowitz and Lawson, 1995 [6]	346	29	Mild	Unknown
Beetar et al., 1996 [7]	202	56	Mild, moderate, severe	23.9 ± 21.2 mo
Perlis et al., 1997 [8]	39	53	Mild	24.1 ± 26.8 mo
Clinchot et al., 1998 [9]	86	50	Mild, moderate, severe	1 yr
Deb et al., 1998 [10]	148	29	Mild, moderate, severe	1 yr
Hibbard et al., 1998 [11]	338	58	Mild, moderate, severe	10.2 yr (1–49 yr)
Fichtenberg et al., 2002 [12]	50	30	Mild, moderate, severe	4 mo (0.5–53 mo)
Mahmood et al., 2004 [13]	87	37	Mild, moderate, severe	<1 yr
Lundin et al., 2006 [14]	102	21	Mild	3 mo
Ouellet et al., 2006 [15]	452	29	Mild, moderate, severe	7.85 yr
Parcell et al., 2006 [16]	63	80	Mild, moderate, severe	230 d (20–1,194 d)
Worthington and Melia, 2006 [17]	135	47	Mild, moderate, severe	119.3 ± 108.8 mo
Baumann et al., 2007 [18]	96	3	Mild, moderate, severe	6 mo
Lew et al., 2007 [19]	62	84	Mild	Unknown
Schwab et al., 2007 [20]	94	37	Mild, moderate, severe	Unknown
Bushnik et al., 2008 [21]	73	40	Moderate, severe	1 yr

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Table. (Continued)

Survey studies of insomnia in traumatic brain injury (TBI). On average, 40 percent of individuals (1,119 of 2,816) in these studies were reported to have symptoms of insomnia. Methodologies for determination of insomnia in these publications vary widely from surveys to electroencephalography recordings, likely adding to variability in percentage of individuals reported to have insomnia. References are presented in chronological order.

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SD = standard deviation.

of sleep in the general population and has even higher prevalence in those who have experienced a TBI [2]. Sleep apnea (i.e., sleep-disordered breathing) is also a prevalent disorder in the general population that leads to disruption of nocturnal sleep and to daytime sleepiness. Given the demographics of veterans, sleep apnea exists commonly in this population [3]. A direct connection between sleep apnea and TBI is unlikely, though sleep apnea will likely compound the difficulties in TBI rehabilitation. Several case studies and reports have also described narcolepsy, another sleep disorder found in <5 percent of the general population, in those with TBI [4–6]. These TBI-induced narcolepsy cases are likely due to a disruption of the hypocretin neurotransmitter system localized in the lateral hypothalamus [7]. An extended discussion of narcolepsy, however, is beyond the scope of this review.

INSOMNIA

Sleep can be characterized by both subjective and objective measures. However, inconsistency between these two measures often characterizes sleep pathology. For example, sleep apnea, present in about half the Department of Veterans Affairs (VA) patient population, can be readily characterized using objective measurements of breathing and electroencephalography (EEG) during an overnight sleep episode [8]. Yet many individuals who, on objective measures, have severely disturbed

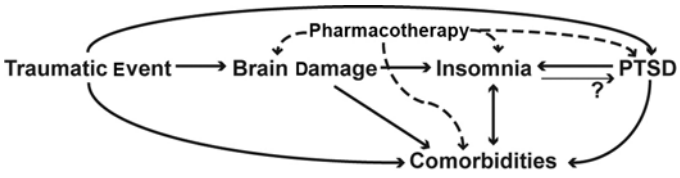

Figure.
Schema of complex relationship between traumatic brain injury, insomnia, and posttraumatic stress disorder (PTSD), as well as associated comorbidities and pharmacotherapy. Single-ended arrows show directional relationships; double-ended arrows show reciprocal relationships. Question mark ("?") indicates possible, though not proven, causal relationship.

sleep because of sleep apnea often fail to realize that their sleep is disturbed; more often they describe poor daytime alertness. Likewise, many individuals who complain of insomnia have normal sleep when measured by EEG. According to the International Classification of Sleep Disorders, insomnia is defined as a subjective complaint of difficulty initiating or maintaining sleep, waking up too early, or having nonrestorative sleep despite adequate opportunity for sleep [9]. The dichotomy between the complaint of insomnia and a laboratory finding may result from a failure of recording and analytic techniques to accurately describe the physiologic abnormality that underlies this feeling of insomnia. Alternatively, insomnia might be an inherently subjective experience that, in most cases, objective techniques cannot adequately capture. Take, for example, two individuals with, theoretically, identical sleep. One complains of insomnia, the other does not. Because, by definition, insomnia is a subjective complaint, the former individual would be categorized with insomnia and the latter without, despite their "identical" sleep. This frame of reference issue is critical in understanding and interpreting studies of sleep medicine.

Most laboratory studies fail to detect significant differences in the sleep architecture or sleep EEG power spectrum when comparing the sleep of individuals with mild TBI with those without TBI (both with or without the complaint of insomnia). Limited findings indicate possible increased sleep fragmentation (i.e., more transitions between sleep and wakefulness) [10], increased wakefulness during attempted sleep [11], decreased time spent in rapid eye movement (REM) sleep [11], and greater amounts of stage 2 ("lighter") sleep [12]. The inconsistency in specific objective findings may be because of the varied types and causes of TBI under study. In cases of severe TBI, disturbed EEG is often found during both waking hours and sleep. During sleep in those with severe TBI, the EEG during REM sleep is often the most disturbed [11,13–14]. Recovery of normal REM sleep during EEG often parallels and can even precede recovery of general cognitive function [14]. Whether this reflects a common etiology or a beneficial effect of having normal REM sleep is unknown but worthy of future research.

Population-based studies indicate that insomnia occurs in approximately 40 percent of individuals with a TBI of any severity (**Table**) and is often the most prevalent somatic complaint in this population [15]. We must note, however, that these studies generally relied on survey data and did not adequately control for time since TBI, severity of injury, or the presence of premorbid insomnia. However, we have consistently observed that a greater incidence of subjective insomnia exists in individuals with TBI of any severity than in controls without head trauma. Some studies show, perhaps paradoxically, that those with less severe TBI have higher rates of insomnia than those with more severe TBI [16–18]. This may be because of the underreporting of sleep disturbances in those with severe TBI as these individuals may be unaware of their sleep problems because of impaired memory or cognitive function. Those with mild trauma may be more aware of their sleep issues because of their more acute awareness and sensitivity to post-TBI neurological and neuropsychiatric changes. In general, those with severe TBI report fewer posttraumatic symptoms than those with lesser injuries [19].

A general model of insomnia etiology postulates that two components exist: a general predisposition to developing insomnia and an acute stressor [20]. A TBI can possibly influence both parts of this equation. First, the injury itself could change brain biochemistry or anatomy such that an individual will be more predisposed to develop insomnia. Various neurotransmitters involved in the generation or modulation of sleep and wakefulness have been reported to be disrupted in TBI, including hypocretin-1 [21], dopamine [22], and serotonin [23]. Most of these studies, however, focused on damage secondary to moderate or severe TBI. Little available data exist on the effects of mild TBI on the neurotransmitter systems involved in the generation of sleep and wakefulness. However, even a mild TBI can cause shearing damage to long axons and most of the aforementioned neurotransmitter systems use long axons potentially

vulnerable to such an insult [24]. We need more data to determine whether mild TBI can cause disruptions in the neurotransmitters critical for sleep and wakefulness. Given the variety of ways in which TBI can occur and the redundancy of sleep- and wakefulness-generating mechanisms, it is quite unlikely that any single biochemical disruption would be responsible for the all of the insomnia observed in those with TBI [25].

TBI can also affect the other part of the insomnia equation because numerous acute stressors commonly associated with a TBI exist that could increase insomnia symptoms. These nonsleep comorbidities include an elevated prevalence of depression (15.6%–61.0%) [26], pain (43.1%) [27], and anxiety (23.0%) [28]. While direct neural damage resulting from the TBI may cause some of these morbidities, the events surrounding the TBI may cause others. Some could have been premorbid to the TBI or occurred postmorbid to the TBI. The TBI comorbidity with the most notoriety is posttraumatic stress disorder (PTSD), which is characterized by three symptom clusters (reexperiencing, avoidance, hyperarousal) that can all manifest in disrupted sleep. The relative contributions of TBI and PTSD to psychiatric and neuromuscular comorbidities, and likely sleep disruptions such as insomnia, are controversial and not well delineated [29–30]. A distinctive aspect of the relationship between sleep disruption and other TBI-related comorbidities is that they frequently reciprocate. For example, depression can lead to insomnia and, conversely, insomnia can initiate or worsen depression [31]. Treatments of comorbidities can also interact. For example, patient use of opioids for daytime pain management can lead to daytime somnolence and disruption of nocturnal sleep. In turn, disturbed nocturnal sleep can lower pain thresholds [32]. Patients must take care with pharmacotherapy so that treatment of one comorbidity minimally disrupts another comorbidity of the TBI (**Figure**). Unfortunately, no literature specifically addresses the effect of psychiatric comorbidities on the occurrence or severity of insomnia in the context of TBI. Research in this area will be critical to help guide the physician in treating insomnia as a primary or secondary pathology.

Pharmacological Treatment

The results of only a few clinical studies of pharmacological treatment of sleep disruption in the context of mixed-severity TBI have been published. Li Pi Shan and Ashworth examined zopiclone (nonbenzodiazepine-benzodiazepine receptor agonist) and lorazepam (traditional benzodiazepine) and found them to be equally effective in treating insomnia in TBI [33]. Kemp et al. found that neither melatonin (sleep-promoting hormone) nor amitriptyline (tricyclic antidepressant) was successful in treating insomnia in TBI [34]. Similarly, an administration of sertraline (selective serotonin reuptake inhibitor) found negative results [35]. These studies were small and not well controlled; both positive and negative findings need to be taken with caution. Further, use of medication to treat sleep disruptions associated with TBI generally may not be the most appropriate therapy because concerns often exist about the possibility of interactions with other medications prescribed to these individuals, as well as about the potential side effects of these medications. The benzodiazepines, newer nonbenzodiazepine-benzodiazepine agonists, tricyclic antidepressants, and antihistamines, all of which are commonly used or prescribed to treat sleep disruption, have significant cholinergic side effects that may interfere with neural remodeling and lower seizure threshold. While these side effects may be especially important in individuals with moderate or severe TBI, we must still consider them in individuals with mild TBI. Most pharmacotherapy for sleep is generally recommended for acute, rather than chronic, insomnia [36], and relatively few studies have been published that validate the continuous use of a single pharmacological agent for >6 months [37].

Baumann et al. indicated that the wake-promoting neuropeptide hypocretin-1 (orexin A) is abnormally low in the cerebrospinal fluid of individuals in the acute stage post-TBI [21]. Levels of hypocretin-1, however, return to normal within 6 months post-TBI. Thus, future drug development that targets enhancement of the hypocretin system may produce a useful treatment of the daytime sleepiness and nighttime sleep disruption that immediately follow a TBI, but we doubt that it will be useful in treating the long-term sleep disruption that often occurs in the months or years after TBI. Given the wide range of types of neural damage that occurs in the context of TBI, it is unlikely that any single pharmacological treatment, such as enhancement of the hypocretin system, will be appropriate in all circumstances.

Nonpharmacological Treatment

Although administration of pharmaceuticals is the most widely used treatment of insomnia, meta-analyses derived from studies of patients without TBI have indicated that

nonpharmacological treatment can be as good, if not better, for the treatment of chronic insomnia [36]. In the population without TBI, various types of nonpharmacological treatments have been tested, including relaxation training, stimulus control, sleep restriction, cognitive therapy, sleep hygiene education, and cognitive-behavioral therapy (CBT) (cognitive therapy plus varying combinations of the previously listed treatments). Relaxation training uses methods such as progressive muscle relaxation for reducing bodily tension or imagery training for curtailing intrusive thoughts to promote good sleep [38]. Stimulus control is based on the concept that following a set of instructions that limits bed use to only sleep or sex will reassociate the bed and bedroom with sleep and reestablish a consistent sleep/waking pattern in the individual [39–42]. Sleep restriction is designed to reduce the amount of nonsleeping excess time a person with insomnia spends in bed to the actual amount of time spent asleep. It thereby creates a mild sleep deprivation that leads to higher quality sleep [43–46]. Cognitive therapy for insomnia focuses on changing maladaptive thinking, which in the context of insomnia focuses on intrusive thoughts often associated with insomnia [47–48]. Cognitive therapy challenges maladaptive and/or inaccurate cognitions about sleep and insomnia [39,49]. Sleep hygiene provides subjects with basic education about daily behaviors (e.g., no evening caffeine), environmental conditions (e.g., sleep in a dark room), and other sleep-related factors (e.g., regular bed and waking times) that have the potential to interfere with or support good sleep [50–51]. CBT for insomnia (CBT-I) combines cognitive therapy with one or more of the behavioral therapies, such as sleep restriction, sleep hygiene, or stimulus control. Although no standardization of the components of CBT-I exists, the combined approach has well-documented efficacy [36,38,52–60]. A single published report indicates the effectiveness of CBT-I associated with TBI [61]. In this study, individuals with mild to severe TBI and a complaint of insomnia undertook an 8-week course of CBT-I, after which there was a >10 percent gain in sleep efficiency. We critically need more studies of nonpharmacological interventions to treat insomnia specifically in mild TBI to establish them as viable alternatives to pharmacotherapy.

CONCLUSIONS

Both the literature and press have noted the increasing number of veterans diagnosed with mild TBI. Recovery from TBI is often lengthy and difficult and may be hampered by the presence of a comorbid sleep disorder. Primary among these comorbidities is insomnia. Disruption of normal sleep by insomnia can also exacerbate neuropsychiatric and neuromuscular sequelae of TBI that can, in turn, worsen the insomnia. Further complicating treatment is that the drugs commonly used to treat the comorbid psychiatric and neuromuscular problems may also interfere with sleep. Conventional pharmacological treatment of insomnia may also be inappropriate in the context of TBI because of issues of polypharmacy, chronicity of the disorders, and drug dependency. Nonpharmacological treatment, such as CBT-I, has only been recently explained as an alternative and needs further validation. We must understand the interrelationship of common comorbidities such as depression, pain, anxiety, and insomnia to better treat each of these issues. We need more systematic research to provide a foundation for an evidence-based medical approach to the treatment of insomnia in the context of mild TBI.

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