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A Brief and Selective Review of Treatment Approaches for Sleep Disturbance following Traumatic Brain Injury

Mareen Weber*, Christian A Webb and William DS Killgore

McLean Hospital, Harvard Medical School, USA

Abstract

Sleep disturbance often presents as a clinically significant symptom of Traumatic Brain Injury (TBI). Poor sleep may delay recovery, exacerbate psychiatric comorbidities, and even increase suicidal risk among TBI patients. Thus, effective and efficient treatment of sleep disturbance in this population is critical. This review provides a brief, selective, and focused synopsis of several of the more common and empirically tested pharmacological and behavioral approaches and their efficacy in the treatment of sleep disturbance following TBI. Depending on the nature of the injury and the specific sleep-related problems, there may be appropriate uses for pharmacologic interventions such as hypnotic or wake-promoting agents, cognitive-behavioral therapy, sleep hygiene, circadian rhythm modification, or even alternative medicine approaches. Overall, the literature on this important topic is sparse, and existing studies are hampered by relatively small sample sizes, under representation of youth and females, inconsistencies across reports in both time since injury and injury severity. Existing methodological limitations do not currently allow for definitive conclusions regarding the effectiveness of particular treatment approaches. Future research will not only need to address these limitations, but also develop treatment options for children and adolescents, who are currently underrepresented in the literature.

Keywords: Sleep; Traumatic brain injury; Treatment; Therapy; Melatonin; Modafinil; CBT-I; Blue light; Sleep-hygiene

Introduction

Sufficient sleep, both in terms of quantity and quality, is essential for cognitive performance and emotional wellbeing [1], and plays an important role in an individual's overall subjective quality of life [2]. Without sufficient restorative sleep, a person's reaction time is slowed, attentional lapses are more frequent [3,4], and there is an increased risk of work-related injuries and motor vehicle accidents [5]. Lack of sleep affects mood [6], emotional coping capacities [7], and even leads to increased symptoms of anxiety and depression among healthy individuals [8]. At the highest cognitive and emotional levels, sleep loss can degrade decision-making [9,10] and impair complex judgment and reasoning capacities [11,12]. Moreover, insufficient restorative sleep can lead to a number of health-related problems, including greater risk of weight gain and obesity, type 2 diabetes, metabolic problems, and hypertension [13,14]. Thus, regardless of the factors involved, chronically disturbed sleep can have adverse effects on health, emotional wellbeing, and normal cognitive functioning. It is therefore essential for medical practitioners and other clinicians to be aware of the presence of sleep disorders and to provide effective and efficient treatment of these problems when they are identified.

Whereas patients who present with primary sleep complaints, such as insomnia or sleep-related breathing problems, may be easy to identify, there are often clinical situations in which a patient may also have a sleep disorder that goes undiagnosed and untreated because it is not the primary presenting problem. This may often be the case among patients recovering from Traumatic Brain Injury (TBI). Following a TBI, physicians and other practitioners may focus on more overt problems associated with the injury and fail to adequately assess the presence of sleep-related problems in these patients. In fact, recent studies suggest that sleep problems may actually be some of the most common complaints among patients with TBI, with nearly half reporting some insomnia-related problems following their injury [15]. This is particularly troublesome, as sleep may be a vital component of the brain repair and recovery process. For instance, recent animal research suggests that sleep may play a critical role in neural plasticity. Lack of sleep appears to suppress the proliferation of new hippocampal neurons in the dentate gyrus of laboratory animals independent of its effects on circadian disruption or stress hormones [16,17]. Perhaps even more importantly, sleep appears to be essential in the process of neural re growth and regeneration following experimentally induced brain lesions in animals [16,18-20]. For example, rats subjected to experimentally manipulated sleep disturbance following an induced cerebral ischemic stroke showed significantly poorer recovery of function in the post-stroke period compared to those with normal sleep [19]. Thus, emerging evidence suggests that sleep is an important factor in healthy brain development, and plays a vital role in the growth and regeneration of neurons following brain damage.

The role of sleep in recovery from brain injury suggests that treating sleep disturbance in neurological conditions such as TBI might be particularly important in facilitating maximal recovery. Indeed, poor sleep, one of the most frequently reported TBI-related symptoms [21], was shown to complicate recovery from brain injury [22]. The need for effective and efficient treatment protocols in the context of TBI can be assumed to be substantial given the high prevalence and incidence of TBI in both civilian and military personnel – approximately 1.7 million TBIs occur annually in the United States alone [23]. Moreover, approximately 50% of TBI patients report some type of subjective sleep disturbance following their injury [15]. In fact, irrespective of injury

***Corresponding author:** Mareen Weber, McLean Hospital, Harvard Medical School, 115 Mill St, Belmont, MA 02178, USA, Tel: 617 855 2231; Fax: 617 855 2770; E-mail: mweber@mclean.harvard.edu

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severity, subjective complaints of poor sleep such as difficulty falling or staying asleep, increased need for daytime naps, excessive daytime sleepiness, or increased fatigue may emerge at any stage following TBI [24]. Furthermore, these complaints appear to increase for up to six weeks following the injury [25] and are often still apparent even 3 years later [26]. Notably, for those patients still in the hospital, sleep maintenance difficulties were most common (81%), while problems with excessive daytime sleepiness were most frequently reported among patients following discharge (73%). In addition to high rates of subjective complaints of insomnia and other sleep problems, TBI patients also show some evidence of objective sleep changes, such as reduced Rapid Eye Movement (REM) sleep and increased stage 2 Non-Rapid Eye Movement (NREM) sleep compared to healthy controls [27]. Another study reported greater slow wave NREM sleep among military veteran patients with TBI compared to veterans with other clinical conditions, and also showed that these patients spent significantly less sleep time awake compared to other groups [28]. However, the evidence for objective sleep problems identified via polysomnography is considerably less consistent than that for subjective complaints [24]. While it is possible that a preexisting subjective sleep problem might worsen following a TBI, a substantial proportion of the sleep disturbances seen following TBI are believed to be a direct result of the injury itself [29].

Matters are complicated by the fact that neither TBI nor sleep disturbance are uniform constructs. The manifestation of TBI can vary greatly depending on the severity of the injury (i.e., mild, moderate, severe), the type of injury (e.g., blunt trauma; open head wound; blast-related; etc.), and the direction of force and location of damage within the brain. Furthermore, these factors may also contribute to the heterogeneous expression of sleep disruption among TBI patients. Some patients may experience higher rates of obstructive sleep apnea, narcolepsy, or periodic limb movements [30,31], while others may experience circadian rhythm disruption such as delayed sleep phase disorder [32]. A recent prospective study using clinician ratings reported that 84% of TBI patients showed evidence of sleep-wake cycle abnormalities at admission to a rehabilitation unit within days after injury, which declined to 66% within one month following their TBI [33]. Interestingly, the severity of sleep disturbance also predicted duration of post-traumatic amnesia. Some patients may experience symptoms consistent with sleep onset insomnia, while others may fall asleep relatively easily but have difficulty maintaining sleep throughout the night. For many, excessive daytime sleepiness or fatigue may be the primary problem [24]. Depending on the nature of the specific sleep disorder, some treatments will be more or less effective, so it is imperative that the clinician conduct a thorough assessment to identify the idiosyncratic sleep problems presented by the patient and tailor treatments to address their particular symptoms or underlying causes.

Within the context of TBI, poor sleep may also exacerbate comorbid psychiatric disorders such as depression or anxiety, or even the experience of pain [25,34]. Of note, insomnia following combat-related mild TBI was shown to predict suicidality [35], highlighting the vital importance of treating sleep disturbance following TBI. These injuries may also be associated with changes in sleep micro- and macro architecture, reduced sleep efficiency, more nighttime awakenings, prolonged sleep onset latency, and increased sleep fragmentation [24], although the clinical significance and reproducibility of many of these changes is uncertain due to the large inconsistencies and methodological limitations across much of the existing literature. Likewise, the empirical evidence of neuropsychological and neurophysiologic correlates of subjective or objective sleep disturbance following TBI is inconsistent at best, and does not allow for the formation of robust conclusions presently [24]. Despite the high prevalence and incidence of subjective sleep disturbance following TBI, the current literature provides little consistent guidance on effective treatment options. Consequently, many clinicians may be generally unaware of the magnitude of the problem of sleep disturbance following TBI and have little information regarding currently accepted treatment approaches. To address this dearth of information, we provide a brief and selective review of the most widely explored treatments for sleep problems following TBI. The present review is not meant to be an exhaustive description or comprehensive evaluation of the scientific literature on sleep treatments. Rather, we selectively reviewed the literature and present a concise overview of the most well-accepted and potentially promising treatments, while highlighting some of the major gaps in the current knowledge about these approaches. These are covered briefly below in the following sections: hypnotic interventions, wake-promoting interventions, Cognitive Behavioral Therapy (CBT) & sleep hygiene, circadian rhythm interventions, and alternative approaches.

Hypnotic interventions

Because patients with TBI often complain of symptoms of insomnia (i.e., problems with sleep onset, sleep maintenance, or delayed sleep phase disorder), there may be occasions where sleep-inducing medications may be prescribed. Such medications may be useful for short-term treatment of sleeplessness. However, the use of sedative-hypnotic agents to promote sleep in adults with TBI is controversial and even discouraged by some, as TBI is often associated with an already high medication burden [36]. More importantly, however, it has been suggested that sleep inducers may potentially delay cognitive recovery from TBI [37] and leave subjective complaints of poor sleep unaffected [38]. In particular, Larson and Zollman [37] reported that typical sleep inducers such as benzodiazepines and atypical gamma-aminobutyric acid (GABA) agonists may be problematic due to their effects on cognitive functioning during peak plasma concentrations and may even impair neuroplasticity. This raises concern that such agents might adversely affect optimal recovery from brain injury. Clearly, patients prescribed such medications should be routinely followed and monitored for safety, effectiveness, and potential effects on recovery. Further research on this topic is greatly needed.

Wake-promoting interventions

For many TBI patients, their primary complaint is fatigue or excessive somnolence during daytime hours. Excessive daytime sleepiness can have a major effect on quality of life and increases the potential for work-related injuries and automobile accidents. Consequently, there may be times when wake-promoting agents might be prescribed to a TBI patient with associated excessive somnolence problems. Modafinil is a wake-promoting agent that is approved for the treatment of excessive daytime sleepiness in narcolepsy, obstructive sleep apnea, or sleep disorder due to shift work. Presumably, modafinil (or its longer acting enantiomer armodafinil) would have a similar wake promoting effect in TBI patients suffering from excessive daytime somnolence. Indeed, a small sample of patients with chronic TBI (severity not reported) and excessive daytime sleepiness showed improved daytime vigilance and normalized nighttime sleep via self-report following five to 13 months of 100-400 mg modafinil administered each morning [39]. In a randomized clinical trial including a small (mostly male) adult sample of individuals with mild and severe TBI at the chronic recovery stage and with subjective excessive daytime sleepiness or fatigue, six weeks of 100-200 mg of morning modafinil significantly reduced subjective daytime sleepiness, but not reports of

fatigue compared to placebo [40]. The intervention also improved the objective ability to stay awake in sleep-inducing conditions (i.e., the Maintenance of Wakefulness Test, MWT) and increased sleep latency compared to placebo. Of note, neither the modafinil nor the placebo group produced a clear improvement in subjective ratings of vigilance, suggesting restrictions in modafinil's efficacy in restoring some aspects of cognitive functioning in patients with TBI. This limitation is further supported by two studies in chronic mild to severe TBI and comorbid sleep disturbance (i.e., either narcolepsy, posttraumatic hypersomnia, subjective daytime sleepiness or fatigue) that could not replicate modafinil's beneficial effect on daytime sleepiness, daytime alertness, nighttime sleep or cognitive functioning [30,41]. However, even in healthy individuals, modafinil is often less likely to lead to subjective feelings of arousal (e.g., nervousness, excitation, jitteriness, pounding heart) compared to other types of stimulants such as caffeine [42], potentially leading to a discrepancy between objective and subjective alertness. Thus, there is some limited evidence to support the use of modafinil in aiding objective daytime alertness in TBI patients, but the findings have been inconsistent and further study is clearly needed. More evidence regarding the effects of the longer acting enantiomer, armodafinil, are needed before clear guidelines can be established.

Cognitive behavioral therapy for insomnia (CBT-I)& sleep hygiene

A range of effective non-pharmacological approaches to treating insomnia have been developed, including sleep hygiene education, sleep restriction, stimulus control therapy and relaxation-based interventions [21,43]. One particularly promising approach is Cognitive Behavioral Therapy for insomnia (CBT-I) [44]. CBT-I is a four-to-eight session multi component intervention, which targets factors maintaining insomnia, including both sleep-interfering behaviors and cognitions. CBT-I combines behavioral (e.g., stimulus control, sleep restriction) and cognitive (i.e., restructuring of maladaptive sleep-related cognitions and intrusive pre-sleep thoughts) interventions, as well as incorporating psycho-education regarding sleep. A growing body of evidence supports the efficacy of CBT-I in the treatment of insomnia. Findings from a recently published meta-analysis of randomized controlled trials (RCTs) comparing CBT-I to sleep inducing medications (zopiclone, zolpidem, temazepam, and triazolam) for insomnia suggests that, on average, CBT-I is at least as effective as medications in the treatment of insomnia [45]. Moreover, Mitchell and colleagues reported results indicating that the benefits of CBT-I may be more durable than those of medication.

Given the elevated prevalence of insomnia among individuals who have experienced TBIs, coupled with the growing body of research supporting the efficacy of CBT-I for insomnia, it is surprising that, to our knowledge, only two studies have tested the efficacy of CBT-I associated with TBI [46,47]. These studies provided preliminary evidence that CBT may be an effective intervention for post-TBI insomnia. Although they yielded promising findings, both of these studies were limited by the fact that they relied on single-case experimental designs.

Sleep hygiene approaches may also prove effective for patients with TBI. A recent study from the Department of Veterans Affairs Palo Alto Health Care System (VA PA HCS) reports on the implementation of newly developed sleep hygiene guidelines at their institution [48]. More specifically, the new sleep hygiene program incorporated CBT, exercise, relaxation training, sleep restriction, and stimulus control. A convenience sample of 67 individuals with TBIs admitted to the 18–bed Poly trauma Rehabilitation unit at the VA PA HCS between 2009 (prior to the implementation of the new sleep hygiene guideline) and 2010 (post-implementation) were included in the study. Although not statistically significant, average sleep duration increased slightly from 2009 (M=7.3) to 2010 (M=7.7). However, no change was observed in disability as assessed by a measure of functional independence. Larger, well-designed RCTs are needed to test the efficacy of CBT approaches against credible comparison conditions controlling for placebo-related factors (e.g., treatment outcome expectancies, the passage of time) [49]. Moreover, to the extent that CBT is shown to be an effective treatment for post-TBI insomnia, research will be needed to examine what aspects of this multi component treatment drive improvement (e.g., comparing the full CBT-I package versus a CBT-I intervention which excludes cognitive techniques to examine the incremental benefits, if any, of the cognitive components of treatment). Similar to psychopharmacological interventions, there are no data available on pharmacological interventions in pediatric populations with TBI.

Circadian rhythm interventions

An individual's level of alertness is affected by a number of factors including light exposure, food consumption, and the diurnal fluctuation of melatonin. In healthy individuals, melatonin, a pineal hormone regulated by the hypothalamus, has been shown to influence the timing of the sleep-wake rhythm [50]. Normally, melatonin secretion increases dramatically with the onset of darkness and is believed to prepare the brain for sleep. Melatonin is produced naturally by the body and normally increases in the evening hours as light levels decrease [51]. During sleep, melatonin levels decrease slowly, dropping to their lowest levels in the early morning hours just before natural awakening. For individuals with delayed sleep phase disorder or other problems with sleep onset that may stem from circadian misalignment (i.e., biological circadian phase is out of sync with natural day/night or work schedules), melatonin supplementation may prove beneficial. Timing of melatonin administration is critical, however. Evening administration (i.e., before bedtime) of melatonin leads to an advance in the circadian rhythm (i.e., the person falls asleep earlier in the evening and wakes earlier in the morning), whereas morning administration produces a phase delay (i.e., the person falls asleep later in the night and wakes later in the morning) [52]. For healthy individuals wishing to fall asleep earlier in the evening (i.e., phase advancement), a dose of melatonin (0.3 or 3 mg) taken about 6 to 7 hours before bedtime appears to be effective at producing a phase advance in the circadian rhythm [53].

There may be a role for melatonin in sleep problems in TBI. Some evidence suggests that melatonin may itself be neuro protective in animal models [39,54,55]. Unfortunately, brain injury may affect the cycling or production of melatonin [51]. Due to its involvement in sleep onset, sleep-wake regulation [56], and its putative neuro protective effects, melatonin supplementation has been posited to improve sleep, subsequent daytime alertness, and recovery following TBI in humans. Indeed, one month of daily 5 mg melatonin (time of administration not specified) improved subjective ratings of daytime alertness, sleep quality and sleep onset latency in a small sample of adult men with chronic mild to severe TBI and subjective sleep disturbance [57]. However, objective cognitive functioning did not change, and melatonin did not prove superior to 25 mg tricyclic antidepressant that served as the control intervention. Because these data have not yet been replicated, definitive conclusions are not possible at this stage. To our knowledge, there have been no controlled trials examining the effectiveness of these types of treatments for TBI-related sleep complaints in pediatric samples.

Another method that has recently shown potential efficacy in regulating the circadian rhythm and sleep-wake cycle is morning bright

light exposure. Exposure to bright light during the morning hours, especially light in the blue wavelengths, has been shown to suppress daytime melatonin production and produce a phase advancement of the circadian rhythm. Carter et al. combined morning blue-wavelength light therapy with physical exercise and evening melatonin administration to successfully improve the sleep-wake rhythm in a 20-year old veteran who developed major depressive disorder and circadian rhythm sleep disorder following a mild to moderate TBI [58]. Bright light seems particularly promising given its demonstrated ability to improve subjective sleep quality and to increase alertness [59-61]. Comprehensive empirical evidence for its effectiveness in the context of TBI is pending, but emerging evidence by Ponsford et al. [62] suggests that this technique may be effective for improving fatigue in patients with mild to severe TBI. Studies in our own lab are currently ongoing to examine the effectiveness of bright light therapy in improving sleep and post-concussive symptoms in patients with mild TBI. As with most interventions, there are no known studies of light treatment with pediatric populations.

Alternative approaches

Similar to CBT, there are surprisingly few data on other non-pharmacological treatments in the literature. Acupuncture proved to be of some effectiveness in one recent study, as subjective sleep quality and objective cognitive functioning associated with chronic TBI (severity not disclosed) improved compared to pre-treatment, but not for the control group who did not receive the intervention [63]. Similarly, single-case studies suggest biofeedback to be effective to treat insomnia following TBI with comorbid posttraumatic stress disorder [64]. However, as systematic clinical trials are pending, there are currently not enough data to argue in favor of routine application of either acupuncture or biofeedback.

Conclusion and Future Directions

Overall, there is surprisingly little data on the efficacy of pharmacological and non-pharmacological treatment options for sleep disturbance following TBI. Published data have thus far focused exclusively on adult populations. Given that TBI is highly prevalent in children and adolescents [65], this is particularly problematic. The existing research literature in adult TBI is scant and fraught with methodological limitations. Most studies have included predominantly male populations and tend to ignore TBI severity. There are several reasons why it is imperative that future research begins to include information about TBI severity as a matter of course. In particular, brain damage and its behavioral correlates, including cognitive functioning, disability status, and awareness of TBI-related deficits have been shown to vary with TBI severity. This means that some treatment protocols might be more appropriate, and potentially more effective, for individuals with mild than severe TBI. For example, severe TBI may significantly affect meta cognition and self-reflection, which in turn may impede an efficient and effective implementation of CBT. In contrast, TBI severity may be less likely to moderate the efficacy of non-pharmacological approaches such as bright light therapy, although this currently remains an open question. Clearly, systematic studies are needed to establish the extent to which TBI severity might influence therapy outcome. Thus, for the field to move forward, treatment protocols need not only be developed for children and adolescents with sleep disturbance following TBI, but also tested in more balanced samples representing both sexes and carefully considering TBI severity.

In sum, the present brief and very selective review suggests that the extant literature on treatments for sleep problems among individuals with TBI is extremely limited. Non-pharmacologic approaches such as CBT, sleep hygiene, light therapy, and perhaps circadian influencing supplements such as melatonin appear to have some potential to improve sleep in this population. Comprehensive animal models of the effects of TBI on sleep disruption and larger, well-designed placebo controlled trials in humans are greatly needed before firm treatment recommendations can be supported.

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