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Sleep, Sleep Disorders, and Circadian Health following Mild Traumatic Brain Injury in Adults: Review and Research Agenda

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Abstract

A rapidly expanding scientific literature supports the frequent co-occurrence of sleep and circadian disturbances following mild traumatic brain injury (mTBI). Although many questions remain unanswered, the preponderance of evidence suggests that sleep and circadian disorders can result from mTBI. Among those with mTBI, sleep disturbances and clinical sleep and circadian disorders contribute to the morbidity and long-term sequelae across domains of functional outcomes and quality of life. Specifically, along with deterioration of neurocognitive performance, insufficient and disturbed sleep can precede, exacerbate, or perpetuate many of the other common sequelae of mTBI, including depression, post-traumatic stress disorder, and chronic pain. Further, sleep and mTBI share neurophysiologic and neuroanatomic mechanisms that likely bear directly on success of rehabilitation following mTBI. For these reasons, focus on disturbed sleep as a modifiable treatment target has high likelihood of improving outcomes in mTBI. Here, we review relevant literature and present a research agenda to 1) advance understanding of the reciprocal relationships between sleep and circadian factors and mTBI sequelae and 2) advance rapidly the development of sleep-related treatments in this population.

Keywords: circadian; concussion; insomnia; sleep; sleep disorders; traumatic brain injury

Introduction

Every year in the United States, at least 2.5 million Americans seek medical attention for traumatic brain injury (TBI).[1] Most of these injuries are classified as mild (mTBI), defined as a Glasgow Coma Scale score of 13 to 15.[2,3] Most sequelae resolve without treatment within 3 months following injury. However, symptoms such as fatigue, poor cognitive performance, difficulties performing activities of daily living, depressed mood, post-traumatic stress, and chronic pain can develop and persist for years.

Importantly, insufficient and disturbed sleep are among the most common complaints following mTBI, reported by 50% (range: 30 to 85%) of patients.[4] Sleep disturbances can develop during the acute, subacute, or chronic phase post-mTBI. Not only can poor sleep cause further neurodegeneration, but insufficient and disturbed sleep also likely independently contribute to morbidity and long-term sequelae of mTBI.[4] Evidence from epidemiologic, clinical, and experimental non-TBI cohorts demonstrates that insufficient and disturbed sleep worsens outcomes in depression,[5] post-traumatic stress disorder,[6] and chronic pain,[7] and impairs cognitive and functional performance,[8] to name several. Poor sleep can precede, exacerbate, and prolong each of these conditions, with profound negative impact on health-related quality of life (HrQOL) and increased economic costs, including health-care utilization and disability.[9]

For these reasons, the past decade has seen an explosion of interest in the relationship between sleep and mTBI.[10–13] Although there is consensus regarding the frequent co-occurrence and clear adverse outcomes associated with sleep complaints in mTBI, less is known about the mechanisms by which mTBI impacts sleep and circadian health or the natural history of sleep complaints following

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mTBI. These relationships are complex and bidirectional; advancing understanding will require serial assessment during the acute, subacute, and chronic phases following brain injury. To date, few longitudinal studies have been conducted and those typically assess sleep at only two time-points.

Preliminary findings suggest that focused sleep interventions can improve not only disturbed sleep but also HrQOL and functional outcomes following mTBI.[14,15] These findings are consistent with results reported from non-mTBI samples, suggesting that targeted sleep treatments can improve sleep as well as other key outcomes in patients suffering depression,[5] post-traumatic stress disorder (PTSD),[16] and chronic pain.[17,18]

This review synthesizes key findings regarding sleep and mTBI in adults, with emphasis on advancing understanding of the temporal and interactive relationships between sleep and mTBI sequelae, to guide treatment development. Sleep physiology, measurement of sleep, and sleep disorders occurring in the context of mTBI are briefly discussed. Next, the salience of sleep for several common and debilitating consequences of mTBI (depression, PTSD, and chronic pain) are explored. Finally, a research agenda is presented, with the synergistic aims of elucidating the temporal and interactive relationships between sleep and mTBI outcomes, and identifying strategies and time-points for sleep-focused targeted prevention and treatment in mTBI.

Sleep Physiology

Trauma to the brain can disrupt multiple aspects of sleep-wake function. Sleep and wakefulness follow a natural, endogenous rhythm that is regulated by the interaction between a homeostatic process (Process S) and a circadian timing process (Process C).[19]

Process S is a homeostatic drive that decreases alertness and increases with each hour of wakefulness, then dissipates during sleep. It is believed to be mediated, at least in part, by the extracellular biochemical substrate adenosine, which is known to increase with prolonged wakefulness. Process C is a circadian alerting signal and is regulated primarily in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. This intrinsic pacemaker confers circadian rhythmicity of approximately 24.2 h to sleep, wakefulness, and all physiologic functions that vary across the day, including body temperature, blood pressure, and hormone secretion, including cortisol and melatonin.[20,21] As homeostatic pressure for sleep increases throughout the day, the circadian alerting signal rises in parallel to facilitate wakefulness.[22] Then, like homeostatic pressure toward sleep, the circadian alerting signal also subsides during the biologic night.[22] Process C is modulated partly by melatonin secreted by the pineal gland. Melatonin secretion is itself regulated by exposure to light, particularly short-wavelength (i.e., blue) light. When light enters through the eyes (including transmission through closed eyelids), photic stimuli are transmitted via retinohypothalamic and retinogeniculohypothalamic pathways to the SCN; in turn, melatonin secretion is suppressed.[23,24] Melatonin levels are low during the day then rise in the evening, which suppresses central nervous system arousal and sets the stage for sleep onset.[25] The single most accurate marker for assessing circadian phase is the onset of melatonin secretion under conditions of low light (i.e., dim-light melatonin onset [DLMO]). As evidenced throughout this review, sequelae of mTBI can include alterations in homeostatic sleep drive and/or circadian rhythmicity, thus altering the propensity for sleep and wakefulness during the 24-h day.

Sleep is defined by cortical-electrical activity or other physiologic parameters (e.g., electrooculography) and is comprised of two distinct states. Consensus recommendations and standardized criteria for defining different stages of human sleep have been published elsewhere.[26] In adult humans, non-rapid eye movement (NREM) sleep comprises 75–80% of sleep, with the remainder in rapid eye movement (REM) sleep. NREM and REM sleep are distinct and mutually exclusive physiological states. During NREM sleep (subdivided into stages N1, N2, and N3, or slow wave sleep [SWS]), electroencephalogram (EEG) activity becomes increasingly synchronized, and the arousal threshold increases, resulting in progressive difficulty in forced awakening. Conversely, REM sleep is characterized by EEG activation similar to or higher than waking levels for many brain regions, excluding the frontal cortical structures, rapid eye movements, and skeletal muscle atonia. NREM and REM sleep are believed to perform independent yet complementary physiologic and mental restorative functions.[27] Table 1 summarizes key characteristics of sleep stages in adults, as well as results of a recent meta-analysis of sleep architecture in patients with TBI compared with non-TBI controls.

From a neurophysiologic perspective, transitioning between sleep and wake is highly complex. Numerous interactions take place among several hypothalamic and brainstem nuclei. Among the most studied regions are the ventrolateral preoptic (VLPO)

Table 1. Sleep-Related EEG Activity Stage

	EEG frequency	*Features*	*Key neural pathways*	*Hypothesized function*	*% of TST in healthy adults*
Wakefulness	Alert- beta Relaxed- alpha (8–13 Hz)				
N1	Theta (4–7 Hz)	Lightest sleep stage, slow eye movements	Cortex	Transitional state	2–5%
N2	Theta (4–7 Hz)	K-complex, spindles	Thalamo-cortical circuit		45–55%
N3	Delta (0.5–2 Hz)	Hypersynchronized slow wave activity	Thalamus	Physical repair (growth hormone)	15–20%
REM	Low-amplitude, mixed frequency	Sawtooth waves, atonia, sharply peaked eye movements	PPT/LDT	Memory consolidation	20–25%**

*REM sleep is reduced in traumatic brain injury relative to matched controls.[56]

EEG, electroencephalogram; TST, total sleep time; REM, rapid eye movement; PPT, pedunculopontine tegmental nucleus of pans and midbrain; LDT, laterodorsal tegmental nucleus of pans and midbrain.

Table 2. Sleep-Related Neurotransmitters

Neurotransmitter	*Site of origination*	*Wake promoting or sleep promoting*	*Relative activity*	*Comments*
Adenosine	Extracellular space	Sleep	NREM>REM>>Wake	Metabolized during NREM sleep
GABA	VLPO	Sleep	NREM>>REM>Wake	Main NREM neurotransmitter
Melatonin	Pineal gland	Sleep	NREM>REM>Wake	Converted from serotonin in the pineal gland
Glutamate	Cortex	Wake	Wake = REM>NREM	Main CNS excitatory neurotransmitter
Dopamine	Substantia nigra	Wake	Wake = REM>NREM	Neither wake nor sleep promoting; active in dreams
Orexin (hypocretin)	Hypothalamus	Wake	Wake>>REM = NREM	Regulates REM-on and REM-off
Acetylcholine	Basal forebrain	Wake	Wake> = REM>>NREM	Most active wake, but also REM sleep (REM-on)
Norepinephrine	Locus ceruleus	Wake	Wake>NREM>>REM	Suppresses REM (REM-off)
Serotonin	Dorsal raphe nucleus	Wake	Wake>NREM>>REM	Suppresses REM (REM-off)
Histamine	Tuberomamillary nucleus	Wake	Wake>>NREM>REM	

>> connotes a greater difference than >
NREM, non-rapid eye movement; REM, non-rapid eye movement; VLPO, ventrolateral preoptic; CNS, central nervous system.

nucleus, where sleep is regulated, and the posterior lateral hypothalamus, where wakefulness is regulated. Table 2 highlights key neurotransmitters and brain centers implicated in sleep-wake transitions. Although sleep and wakefulness exist on a continuum, in healthy individuals sleep inhibits wakefulness, and vice versa. Similarly, NREM and REM sleep are mutually exclusive, inhibitory processes reflecting discrete neurophysiologic states.[28] In light of this complex neurophysiology, it is perhaps not surprising that mTBI can result in injury to sensitive neuronal structures and the essential connections that they exhibit. As discussed below, alterations in normal sleep or wakefulness can develop, as can frank sleep-wake disturbances and circadian dysregulation.

Measurement of Sleep

Sleep is typically measured via overnight polysomnography (PSG), objective actigraphy, subjective sleep diaries, and self-report questionnaires (Table 3). PSG includes assessment of electrical activity via EEG, muscle tone via electromyogram (EMG), and eye movements via electrooculogram, along with cardiac and respiratory measures. In addition, daytime sleep studies such as the maintenance of wakefulness test and more commonly, the multiple sleep latency test (MSLT), can provide valuable objective insight into the ability to maintain wakefulness and objective daytime sleepiness, respectively. The MSLT is considered the measurement standard for sleepiness and consists of a series of planned daytime naps roughly 2 h apart. Latency to sleep is recorded and averaged across naps. Despite the utility of these tests for measuring sleepiness, such laboratory testing is resource-intensive and may not always be necessary to achieve a research objective. As a result, investigators seeking an objective measure of rest-activity cycles have also employed actigraphic monitoring in adult[29–35] as well as adolescent mTBI samples.[36] An actigraph is a small, wristwatch-size device that is typically worn on the non-dominant hand. Models range from relatively inexpensive, typically non-validated commercial activity monitors to those with research-grade triaxial processors. Among healthy adults[32] and individuals with sleep disorders,[37] actigraphy is an accepted proxy for some sleep and circadian patterns and parameters and a frequently used outcome measure in sleep-related clinical trials.

Table 3. Objective and Subjective Differences in Sleep between TBI and Non-TBI Controls

Measure	*TBI vs. non-TBI control*	*n*
Polysomnography		
Sleep onset latency	*SMD* = 0.29 (CI: 0.08, 0.51)	342
Wake after sleep onset	*SMD* = 0.60 (CI: 0.33, 0.87)	224
Sleep efficiency	*SMD* = –0.47 (CI: –0.89, –.06)	298
Total sleep time	*SMD* = –0.37 (CI: –0.59, –0.16)	348
Questionnaire		
PSQI	*SMD* = 1.02 (CI: 0.65, 1.39)	703
ESS	*SMD* = 0.40 (CI: 0.17, 0.62)	858

Data from Sommerauer and colleagues.[56]
TBI, traumatic brain injury; SMD, standard mean difference, PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale.

Although not an objective measure, subjective sleep diaries are a standard approach to measuring self-reported sleep patterns over time, and sleep diaries have been utilized as an outcome measure in patients with mTBI.[14,38,39] Only two questionnaires have been validated against objective measures of sleep in patients with TBI[40–42]: the Pittsburgh Sleep Quality Index (PSQI)[43] and the Epworth Sleepiness Scale (ESS).[44] Finally, high-density EEG (hd-EEG) and sleep neuroimaging methods also have provided insight into localized and neural underpinnings of healthy and disrupted sleep and have advanced understanding of circadian variation in brain function.[45–47]

Each of these approaches to measuring sleep has strengths and weaknesses. The optimal measurement strategy for any given scientific endeavor should be guided by the research question, population of interest, feasibility, and other considerations. Readers are referred elsewhere for a detailed discussion regarding pros and cons of various approaches to research measurement of sleep in mTBI.[10] Unfortunately, the quality of the literature regarding sleep in TBI is variable and difficult to interpret because studies have used inconsistent measurement of sleep. There is yet no consensus regarding standardized sleep assessment nor a set of sleep-related common data elements in mTBI research, as has been developed for other aspects of TBI.[48] Nonetheless, multi-method assessment of sleep and circadian patterns, including both objective and subjective measures, should be included whenever possible.[10]

Poor Sleep Quality in TBI

The literature consistently reports that TBI is associated with reports of poor subjective sleep quality as well as impairments in objectively measured sleep continuity. For example, between 30–70% of patients with mixed-severity TBI report subjective complaints of sleep-wake disturbances.[49–53] Indeed, a recent meta-analysis of controlled studies ($N=16$) found that relative to non-TBI controls, patients with mixed-severity TBI report poorer subjective sleep quality as measured by the PSQI, including the global score as well as all subscale scores.[54] Similarly, relative to non-TBI controls, patients with mixed-severity TBI also report greater levels of daytime sleepiness, with increased scores on the ESS.[54] On PSG, relative to non-TBI controls, patients with mixed-severity TBI demonstrate longer sleep onset latency (SOL), increased wake after sleep onset, poorer sleep efficiency (i.e., total time asleep/total time in bed), and reduced total sleep time (TST).[54]

Unfortunately, as is common throughout the literature, this study aggregated findings across studies of varying TBI severity (Table 4). Unfortunately, studies of sleep disturbances among individuals with well-characterized mTBI have been limited. Several recent studies specific to mTBI are presented below. On the whole, extant literature suggests that subjective complaints of poor sleep quality and insomnia are more common among patients with mTBI, whereas hypersomnia is more common and more persistent among individuals with moderate and severe TBI. Future studies will benefit from more refined classification of TBI severity and injury characteristics.

Despite gross differences in subjective and objective measures of sleep quality, findings regarding differences in sleep architecture have been less consistent. In the recent meta-analysis by Grima and colleagues,[54] only a non-significant trend toward increased latency to REM was detected; no other differences in sleep stages were observed between TBI and non-TBI controls. Nonetheless, it is important to appreciate that the literature is plagued by lack of measurement standardization of sleep, inconsistent operational definitions of sleep disorders, and heterogeneous samples with varying levels of TBI severity. For example, the controlled studies included in the aforementioned meta-analysis included participants of mixed TBI severity, including multiple injury subtypes and mechanisms of injury. When combined with small sample sizes, this limitation makes it difficult to detect subtler but potentially important changes in sleep neurophysiologic activity in mTBI, such as increased SWS, which has been associated with regenerative effects such as axonal sprouting and synaptic remodeling. Several studies not meeting inclusion criteria for the Grima and colleagues meta-analysis[55–57] have reported increased SWS in TBI patients relative to matched healthy controls, suggesting a potential neurorecuperative role for SWS following TBI.

Sleep disturbances in mTBI

As emphasized throughout this review, ample evidence supports the high prevalence of sleep complaints following mTBI. For example, Theadom and colleagues[58] conducted a study among adults >16 years with mTBI ($N=341$) and measured sleep at baseline (< 4 days), and 1, 6, and 12 months post-injury. At 1 year follow-up, 41.4% of participants reported poor subjective sleep quality, and 21.0% screened positive for insomnia disorder. Further, sleep complaints at baseline were associated with worsened outcomes at 12 months, including post-concussive symptoms, mood, cognition, and community integration. Finally, results indicated that sleep troubles can emerge early or late within the first year following injury. Although 44.9% of participants reported improved sleep between 6 and 12 months, an additional 38.9% reported worsened sleep.[58]

Table 4. Objective and Subjective Measures of Sleep

Measure	*Description*
Overnight polysomnography	Considered the measurement standard of sleep. Includes assessment of electrical activity via electroencephalography (EEG), muscle tone via electromyogram (EMG), and eye movements via electrooculogram (EOG), along with cardiac and respiratory measures.
Daytime polysomnography	Multiple sleep latency test (MSLT) and Maintenance of wakefulness test (MWT) can provide valuable insight into objective sleepiness and ability to maintain wakefulness, respectively. MSLT is required for diagnosis of narcolepsy.
Actigraphy	Small, wristwatch-size device that is typically worn on the non-dominant hand. Models range from relatively inexpensive, non-validated commercial activity monitors to those with research-grade processors. Actigraphy has been employed in TBI.[36]
Sleep diary	Standardized approach to measuring self-reported sleep patterns over time, and sleep diaries have been utilized as an outcome measure in patients with mTBI.[14,40,41]
Advanced sleep measurement methods	High-density EEG (hd-EEG) and sleep neuroimaging have advanced understanding of localized and neural underpinnings of healthy and disrupted sleep, including circadian variation in brain function.[47–49]
Questionnaire	
Pittsburgh Sleep Quality Index (PSQI)	Nineteen-item self-report questionnaire that assesses sleep quality and disturbances over a 1-month time interval. The PSQI has adequate psychometric properties and has been validated for insomnia in TBI.[45,201]
Insomnia Severity Index (ISI)	Seven-item self-report questionnaire that assesses perceived sleep disturbance and daytime consequences. The ISI possesses excellent psychometric properties and is the most commonly used insomnia measure.[202]
Epworth Sleepiness Scale	Eight items assess likelihood of falling asleep in common daytime situations, for example watching television or as a passenger in a car. Scores are summed to determine subjective sleepiness.[203]

TBI, traumatic brain injury; mTBI, mild traumatic brain injury.

Others also have reported that subjective sleep complaints are common and associated with worsened outcomes following mTBI. For example, in a cross-sectional study using online questionnaires, Towns and colleagues[59] found that 92% of 158 individuals with history of mTBI reported poor sleep quality, which was positively associated with post-concussive symptoms. Sullivan and colleagues[60] administered online questionnaires to 61 individuals with self-reported mTBI within the past 6 months. After controlling for confounding variables, only current sleep-related impairment (as measured by the Patient-Reported Outcomes Measurement System; PROMIS) was significantly associated with current neurobehavioral symptoms.[60] Similarly, Mollayeva and colleagues[61] found 69.2% of employed individuals with delayed recovery from mTBI to suffer insomnia. Insomnia was associated with pain, depression, anxiety, and wake time variability.[61] In a separate investigation, Mollayeva and colleagues[62] conducted a cross-sectional study of insomnia among employed individuals with mTBI ($N=92$). Compared with workers with low disability, those with high disability reported more insomnia, depression, anxiety and pain. Moreover, in a fully adjusted model, only insomnia was predictive of work disability, highlighting the adverse economic consequences of insomnia in this population.[62]

Subjective sleep complaints are more common among individuals with mTBI than among matched controls and patients with more severe injuries. For example, Sullivan and colleagues[63] administered questionnaires to patients with mTBI ($n=33$) and matched controls ($n=33$). Individuals with mTBI reported more sleep disturbances, more severe insomnia complaints, greater wake after sleep onset, and greater sleep-related impairment. However, no differences in TST, SOL, SE, excessive daytime sleepiness, or sleep timing were observed.[63] In a study among 112 patients in a Veterans Affairs Polytrauma Rehabilitation Center, Farrell-Carnahan and colleagues[64] found 29% of patients met diagnostic criteria for insomnia, which was significantly more common among those with mTBI (43%) than among those with moderate-severe TBI (22%).

In addition to subjective sleep complaints, individuals with mTBI also demonstrate objective sleep disturbances. Mollayeva and colleagues[65] administered PSG to individuals diagnosed with mTBI ($N=40$). Compared with established norms, individuals with mTBI demonstrated more nocturnal wakefulness and less N2 and REM sleep. Other studies have included control participants. For instance, Arbour and colleagues[66] administered 2 nights of PSG to patients with mTBI ($n=34$) and matched healthy controls ($n=29$). Based on power spectral analyses, patients with mTBI demonstrated significantly worse sleep quality and increased beta power during NREM, consistent with physiologic hyperarousal. However, no differences in SWS or sleep spindles were observed.[66] Williams and colleagues[67] also administered multiple questionnaires and 1 night PSG to patients with mTBI ($n=9$) and controls ($n=9$). Compared with controls, patients with mTBI demonstrated lower sleep efficiency, shorter REM-onset latency, and longer and highly variable sleep latencies. Further, quantitative EEG (qEEG) power spectral analyses revealed higher sigma, theta, and delta power among patients with mTBI. Importantly, intra-subject variability was high in the mTBI group, highlighting the heterogeneous nature of the condition.[66]

Perhaps the heterogeneity of mTBI partially explains observed differences in subjective and objective measures of sleep in patients with mTBI. Gosselin and colleagues[68] administered 2 nights PSG to athletes ($n=11$) with multiple concussions (range = 2–9) and matched controls ($n=11$). Relative to controls, athletes with multiple mTBI demonstrated worse self-reported sleep and poorer mood, but no differences in PSG or qEEG were observed.[66] Similarly, Allan and colleagues[69] administered 14 days of actigraphy, as well as questionnaires and sleep diaries, to patients with recent mTBI ($n=14$) and non-TBI controls ($n=34$). Compared with controls, patients with mTBI reported significantly higher sleep-related impairment, poorer nightly sleep quality, and higher rates of clinical insomnia. However, the only difference in actigraphically measured sleep was that individuals with recent mTBI demonstrated phase advance, going to bed and arising approximately 1 h earlier than controls.[69]

In addition to discrepancies between subjective and objective measures of sleep, high within-subject sleep variability has been observed following mTBI. Raikes and Schaefer[70] administered two 5-day sessions of actigraphy and sleep diaries, 30 days apart, to young adults with acute concussion ($n=6$) and matched controls ($n=10$). Individuals with mTBI demonstrated greater nocturnal sleep duration as well as a higher coefficient of variation as measured via actigraphy and sleep diary. Further, variability in sleep duration persisted for 30 days.[70] In non-TBI samples, such night-to-night variability has been associated with a broad range of adverse health consequences and warrants further study among mTBI samples.

In light of the frequent occurrence and adverse consequences of sleep disturbances in mTBI, investigators have sought to identify a causal link between sleep and mood outcomes. Mantua and colleagues[71] conducted a study to examine sleep-dependent emotional processing among individuals with chronic mTBI ($n=40$) and controls ($n=41$). Participants viewed negative and neutral images both before and after a 12-h period including or not including sleep, and memory recognition was assessed at session two. Based on PSG and compared with controls, mTBI participants had less REM sleep, longer latency to REM sleep, and more subjective sleep complaints. Consolidation of negative images was only observed in the non-mTBI group, and only non-mTBI participants habituated to negative images. These results suggest sleep and wake-dependent emotional processing might underlie poor emotional outcomes associated with chronic mTBI.[71]

Sleep Disorders in mTBI

Sleep pathologies are described in terms of insufficient sleep quantity, altered sleep architecture, clinical sleep disorders, and circadian misalignment. Sleep and circadian disturbances are associated with numerous and potentially severe daytime consequences. Data from epidemiologic, clinical, and experimental studies of poor sleep demonstrate diminished psychomotor performance and increased accident risk; poor cognitive function; irritability and depressed mood; and impaired endocrine, metabolic, immune, inflammatory, and cardiovascular function.[72,73] Although a detailed discussion is beyond the scope of this review, recent guidelines suggest 7–8 h of sleep per night is required for optimal health and functioning among adults.[74,75] Table 5 presents common sleep and circadian disorders common in mTBI, and outlines standard treatments.

Clinical assessment of sleep complaints

Although there is no standardized sleep assessment battery following mTBI, a recent national working group recommended multi-method assessment of sleep and sleep disturbances whenever possible.[10] In addition to the standardized subjective and objective measures described above, a careful clinical history is essential.

Table 5. Common Sleep and Circadian Disorders in TBI

Disorder	*General prevalence*	*Prevalence in TBI*[4]	*Description*	*Treatments*
Insomnia	10–15%	29%	Difficulty initiating or maintaining sleep, generally characterized as ≥ 30 min sleep latency and/or ≥ 30 min wake after sleep onset, including early morning awakening, with daytime impairment, occurring ≥ 3 nights per week for ≥ 3 months.	Cognitive behavioral treatment for insomnia (CBTI) is considered first-line treatment for primary and comorbid insomnia. Pharmacotherapy and benzodiazepines in particular should be avoided in TBI due to risks of cognitive side effects.
Sleep apnea	(Age 30–60) Men: 24% Women: 9%	25%	Sleep-related breathing disorder characterized by repeated breathing pauses during sleep. Majority is obstructive in nature (i.e., obstructive sleep apnea [OSA]) and caused by partial or total closure of the upper airway. OSA is associated with oxyhemoglobin desaturation and sleep fragmentation due to cortical arousals and increased effort to breathe. Less common is central sleep apnea, characterized by transient reduction in respiratory effort. Sleep apnea can also be mixed.	For moderate or severe OSA, positive airway pressure (PAP) therapies are recommended first-line treatment. PAP uses positive pressure as a pneumatic splint, to gently inflate the airway. Mandibular advancement dental devices can also be effective, particularly in mild-moderate disease. When indicated, weight loss is a cornerstone recommendation. A range of tertiary treatment options exist.
Hypersomnias	Narcolepsy: 0.05% Idiopathic hypersomnia: 0.002–0.005%	Post-traumatic narcolepsy: 4% Post-traumatic hypersomnia: 28%	Neurologic disorder characterized by excessive daytime somnolence and rapid eye movement (REM) intrusion during wakefulness, as well as cataplexy, sleep paralysis, and hypnogogic hallucinations. Trauma to hypocretin-producing neurons has been shown to induce cataplexy. Hypersomnia that is not due to specific central nervous system abnormality. Trauma can cause non-specific damage to wake producing regions of the brain.	Treatment is based on symptoms clusters and differential response. Wake promoting agents are classified as either amphetamines or non-amphetamine (e.g., modafinil/ armodafinil). Sodium oxybate is used for narcolepsy with and without cataplexy. Noradrenergic antidepressants such as venlafaxine and duloxetine can also help reduce cataplexy.
Periodic limb movement disorder	3.9%	19%	Neurologic disorder characterized by involuntary twitching or jerking of limbs during sleep, most often including legs. Frequently overlaps with restless legs syndrome.	Treatment options include benzodiazepines, dopaminergic agents or neuroleptics, or less frequently, anticonvulsants or GABA agonists. When comorbid with OSA, PAP can eliminate PLMs.
Circadian rhythm sleep disorders	Unknown	Unknown	Trauma to the circadian pacemaker in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus can disrupt ''process C.'' Experimental lesions of the SCN have resulted in a complete loss of the circadian rhythm and randomly distributed sleep-wake periods during the 24-hour cycle.	Treatment to modify circadian rhythm includes timed bright light therapy and melatonin. Light therapy is the most potent circadian modulator. A regimented sleep-wake schedule is vital.

TBI, traumatic brain injury; PLM, periodic limb movements.

Table 6. Elements of Clinical Sleep History Conducted by Fictitious Nurse, Ms. BAMS-RN

B	Bedtime	• Time in bed • Time lights out • Perceived sleep latency
A	Awakenings	• Number • Timing • Perceived duration • Reasons (e.g., nocturia, rumination)
M	Maladaptive sleep behaviors	• Alcohol within 2 h of bed • Caffeine within 6 h of bed • Inconsistent pre-sleep routine or engaging in stimulating activities before bed: planning, worry, professional activities, housework, finances, computer • TV/electronics in bed or bedroom
S	Snoring	• Loud snoring • Snorting/gasping • Witnessed apneas
R	Risetime	• Time awake • Time out of bed • Feel refreshed • Dry mouth • Headache
N	Naps	• Timing • Duration • Other daytime sleepiness

From Wickwire and colleagues.[218] Reprinted with permission.

Clinical assessment should seek to establish the temporal relationship between sleep complaints and mTBI. The assessment should also account for the mechanism and severity of injury, as blast injuries have been associated with insomnia whereas blunt trauma injuries have been associated with sleep-disordered breathing and hypersomnolence.[49] It is also crucial to identify factors that can influence sleep, such as depression, PTSD, and chronic pain, as well as medication use. Table 6 includes recommended domains to include in a clinical sleep history.

Insomnia

Insomnia, defined as difficulty falling asleep and/or difficulty staying asleep with associated daytime consequence, is the most common sleep disorder following mTBI,[4] reported by between 30–65% of patients with chronic mTBI. Features of insomnia include prolonged sleep onset latency, increased wake after sleep onset, and poor sleep quality.[49,76,77] Interestingly, insomnia is also more common in those with mTBI relative to those with moderate or severe TBI.[49,76,77] Although sleep disturbances can develop during the acute (0–7 days), subacute (7–90 days), and chronic phase (> 90 days) of mTBI, it is often difficult to determine the cause(s) of insomnia, in part because insomnia has well-documented bidirectional relationships with the most common sequelae of mTBI, including depression,[78] PTSD,[6] and chronic pain.[7] Often a symptom of these or other so-called ''primary'' disorders, it is now widely recognized that insomnia can quickly take on a life of its own and warrant independent treatment even after the underlying disorder is treated. Reflecting this evolved understanding, the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) nosology eliminated conceptualizations including ''primary'' and ''secondary'' insomnia in favor of the more accurate ''insomnia disorder.''[79]

The National Institutes of Health,[80] American College of Physicians,[81] and American Academy of Sleep Medicine,[82] along with other leading organizations agree that cognitive behavioral treatment of insomnia (CBTI) should be considered first-line treatment for chronic insomnia.[82–87] CBTI is a time-limited, behaviorally focused treatment that has demonstrated effectiveness for improving not only sleep but also comorbid conditions[88,89] including but not limited to depression,[5] PTSD,[16] chronic pain,[17,18] and alcohol and substance dependence.[90,91] A small uncontrolled study[14] as well as case reports[15] have found CBTI to improve sleep in TBI patients of mixed severity,[14] and a Department of Veterans Affairs sleep health program that incorporated multiple components of CBTI was found to improve outcomes in patients with persistent TBI symptoms.[92] Nonetheless, additional studies are needed. CBTI is of particular interest for mTBI because it is highly amenable to telehealth approaches,[93] thus enabling remote provision of services following discharge from Level 1 trauma centers, where many mTBI are initially diagnosed. Table 7 presents common treatment components of CBTI.

In addition to CBTI, there are a number of Food and Drug Administration (FDA)–approved insomnia medications (i.e., sedative hypnotics).[94] Non-benzodiazepine receptor agonists such as zolpidem, zopiclone, and eszopiclone are commonly prescribed. However, no randomized studies have assessed the safety or efficacy of these or other medications in persons with TBI, and hypnotics have been found to increase risk for dementia among TBI patients.[95] Similarly, current TBI treatment guidelines recommend avoiding benzodiazepines when possible due to the risk of myriad adverse effects including disinhibition and cognitive dysfunction

Table 7. Common Components of Cognitive-Behavioral Treatment for Insomnia

Sleep restriction therapy[205]	Sleep restriction seeks to relieve insomnia by improving sleep efficiency (SE). Patients are instructed to reduce their time in bed to slightly above their total sleep time. Once patients have achieved 90% SE (i.e., 90% of time in bed is spent asleep), time in bed is systematically increased.
Stimulus control[206]	Stimulus control seeks to restrict bedroom activity to sleep and sex. Patients are also instructed to decrease the impact of potential environmental distractions, for example, by wearing earplugs to reduce ambient noise.
Cognitive therapy[207]	Cognitive therapy for insomnia seeks to correct erroneous beliefs and worry regarding the amount of sleep one requires and the potential consequences of poor sleep.
Relaxation or mindfulness[208,209]	Relaxation has an extensive empirical basis as an effective intervention for numerous psychophysiological and stress-related disorders. More recent efforts have included mindfulness in insomnia protocols, as an alternate strategy to reduce physiologic hyperarousal and cognitive rumination.
Sleep hygiene	Sleep hygiene seeks to eliminate sleep-interfering behaviors such as excessive or poorly-timed caffeine consumption.

(outcomes independently associated with mTBI), as well as physiologic dependence.[96,97] Sedative hypnotics including in particular benzodiazepines should be used with great caution among patients with mTBI, and appropriate counseling and careful monitoring are essential.

Circadian dysregulation

Circadian dysregulation is common following mTBI.[29] Careful assessment of circadian rhythmicity will accurately distinguish insomnia from circadian rhythm sleep disorders (CRSDs). Possible mechanisms for the increase in CRSDs post-TBI include altered melatonin production, which has been observed in humans,[55] and/or decreased melatonin receptors, which have been observed following experimental TBI in animal models.[98] These alterations are highly salient not only due to changes in circadian rhythmicity following TBI but also because melatonin affords protection from neurotrauma, at least in animal models.[99] Surprisingly, to date only one study has evaluated the impact of melatonin on sleep in TBI. In a small study of patients with mixed-severity TBI, Kemp and colleagues found 5 mg melatonin to be associated with within-subject improvements in daytime alertness, but no changes in sleep onset latency, sleep duration, or sleep quality were observed.[100] More recently, in a small study ($N = 13$) of patients with mixed TBI and compared with placebo, 3 weeks of nightly administration of 8 mg ramelteon, a melatonin-receptor agonist, significantly increased TST and mildly increased SOL.[35] Importantly, significant improvements in neurocognitive performance also were detected.[35] Further investigation of melatonin therapy in mTBI is warranted.

Fatigue

In addition to disturbed sleep, daytime fatigue is a common and potentially disabling consequence of mTBI. Up to 70% of mTBI patients experience significant daytime fatigue, which negatively impacts numerous functional domains, including workplace productivity. Preliminary evidence supports the use of blue-wavelength light (BL) to reduce daytime fatigue among patients with TBI of mixed severity. Sinclair and colleagues observed large reductions in daytime fatigue and moderate reductions in daytime sleepiness following 4 weeks of timed morning BL exposure (45 min in the morning; λ max = 465 nm, 84.8 μW/cm^2, 39.5 lux, 1.74 Å$\sim$ 1014 photons/cm^2/sec).[101] Similar findings have been reported regarding the impact of BL on sleepiness and improved physical balance following 6 weeks of timed (30 min) BL among patients with mTBI.[102,103] Interestingly, despite the fact that morning light exposure is known to suppress melatonin and thus help entrain the circadian rhythm, none of the BL studies to date have detected changes in sleep quality subsequent to administration of BL.[101–103]

Heterogeneous injury characteristics and small sample sizes may explain these non-significant findings. Regardless, because BL is safe, inexpensive, and known to increase positive affect and neurocognitive performance, it is a particularly appealing combination target for incorporating a fatigue management component to sleep-related interventions in mTBI.

Post-traumatic increased sleep need

Several studies demonstrate increased total sleep time among TBI patients post-injury, which persists for years.[51] Further, relative to non-TBI controls, TBI patients underestimate their need for sleep post-injury. For example, Sommerauer and colleagues found that patients with TBI of mixed severity slept an additional 2.5 h per 24 h period while concurrently underestimating their need for sleep.[56] This increased need for sleep has been termed ''pleiosomnia''[104] and has been hypothesized to result from loss of wake-promoting, histamine-producing neurons in the tuberomammillary nucleus.[105] Among patients with mTBI, however, the picture is less clear. A recent study by Suzuki and colleagues[106] found that 29% of mTBI patients with moderate-to-severe pain at 1 month post-injury demonstrated increased sleep need, including sleeping >8 h at night and napping during the day. Although this prevalence of increased sleep need is notable, it is lower than the prevalence rates reported in samples among individuals with mixed severity TBI. In aggregate, these findings highlight the need for advanced understanding of mechanisms of sleepiness post-mTBI and suggest routine assessment of TST and estimated sleep need in people with mTBI.

Post-traumatic hypersomnolence and post-traumatic narcolepsy

Daytime sleepiness is a common and frequently disabling consequence of TBI, including mTBI. Between 50–85% of TBI patients report hypersomnolence.[49,50] A hypothesized central mechanism involves damage to essential neural wakefulness circuits including orexin (hypocretin) producing cells in the hypothalamus.[11] In a seminal study of patients with mixed TBI severity, Baumann and colleagues found cerebrospinal fluid (CSF) hypocretin to be low or undetectable within 4 days following injury.[107] However, CSF hypocretin levels had normalized for most patients by 6-month follow-up.[107] Similarly, although most hypersomnolence remits over time following mTBI, between 10–53% of patients experience persistent symptoms.[49–51,53,107–109] In addition to the increased sleep need described above, clinical sleep disorders that might occur include post-traumatic hypersomnia (PTH) and post-traumatic narcolepsy (PTN) can occur and should be evaluated when excessive daytime sleepiness persists for 3 months or more. Both PTH and PTN require objective documentation of sleepiness as evidenced by the MSLT, described above. Among U.S. adults, the mean daytime latency to sleep is 11.4 min.[110,111] By contrast, among patients with TBI, PTH is diagnosed with a mean sleep latency <8 min on the MSLT. Similarly, PTN is diagnosed by mean sleep latency <8 min with the occurrence of >2 sleep onset REM periods (SOREMs) during the MSLT.

During the acute and subacute phases of mTBI, treatment of daytime sleepiness should focus on ensuring adequate sleep and restoring and optimizing the sleep-wake cycle. Once daytime sleepiness becomes chronic, interferes with rehabilitation, or PTH or PTN is diagnosed, targeted treatment is warranted. To date, there are no FDA-approved medications for PTH or PTN, highlighting a clear research need. Psychostimulant (e.g., methylphenidate, amphetamines) and non-amphetamine wake-promoting medications (e.g., modafinil, armodafinil) are often prescribed off-label for the treatment of excessive daytime sleepiness, but only a small number of studies have evaluated their safety and efficacy among patients with TBI. Double-blind randomized controlled trials have found modafinil as well as its newer R isomer, armodafinil, to reduce subjective and objective measures of sleepiness in patients with TBI of mixed severity.[112,113] However, no improvements in daytime fatigue were observed, highlighting the complex and multifactorial nature of daytime complaints in this population.

Obstructive sleep apnea

Although the prevalence of obstructive sleep apnea (OSA) is higher among patients with TBI than in the general population, the true prevalence of OSA in this population is not yet known.[4,11]

Nonetheless, evidence suggests that OSA worsens neurocognitive performance including memory and attention among patients with TBI, even after controlling for TBI severity.[114] Standard of care treatment for OSA remains positive airway pressure (PAP) therapy. Among non-TBI patients, PAP improves neurocognitive performance and executive functioning, but not all individuals overcome pre-treatment cognitive deficits despite successful treatment of OSA. Importantly, the impact of OSA treatment on neurocognitive recovery in mTBI has not been studied. Maximizing PAP adherence among people with TBI is of particular and timely interest. Although PAP is highly effective when used properly, it is well-documented that many patients struggle to adjust to the therapy.[115] Future investigations must consider patient preferences and other potential barriers to PAP adherence among persons with mTBI. For example, in addition to physical injuries, many patients with mTBI suffer comorbid insomnia and/or PTSD, both of which can negatively impact PAP adherence.[116,117–119] Alternatives to PAP such as oral appliance therapy should be explored in patients with mild-moderate OSA.[120] In summary, considering the hypoxemia associated with OSA and its known impact on neurocognitive function, treatment of OSA in people with mTBI represents an important area for future research.

Sleep and Neuropsychiatric Comorbidities in mTBI

Sleep and depression in mTBI

Depressive disorders are common among persons with TBI, with an estimated first-year post-TBI depression frequency in the range of 25% to 50%.[121] For example, among 559 patients with TBI followed for 1 year post-injury, 53% met diagnostic criteria for major depressive disorder (MDD).[122] Impressively, 73% of these individuals had no prior history of depression. Although the low rate of prior depression suggests a causal relationship between TBI and depression in this sample, the issue is far from resolved.

Studies have generally focused on at least two independent but potentially synergistic mechanisms through which TBI could result in MDD. The first is situational. There is a clear relationship between post-TBI depression and poorer functional and health-related outcomes.[121,122] The depressive symptoms reflect an adjustment disorder related to the stress of the TBI and subsequent difficulties and disability that result from the injury. A second possible mechanism through which TBI could contribute to mood symptoms could be ''organic,'' in that damage to specific neural systems might directly influence changes in mood. For example, TBI often results in disruption of the neuroendocrine system, which can contribute to cognitive and affective dysfunction.[123,124] Another way in which specific neurological damage associated with TBI can influence mood regulation is through the presence of microbleed lesions. In a study utilizing susceptibility-weighted imaging, the distribution and range of microbleeds in the frontal, parietal, and temporal lobes was significantly correlated with post-TBI depression.[125] Similarly, CT scans positive for intracranial lesions have been associated with depression at 3-months post injury.

A robust scientific literature spanning many decades highlights the centrality of sleep complaints to depressive and other mood disorders. For example, sleep disturbance is one of the nine core symptoms of MDD,[79] and there is evidence that changes in sleep often precede and even contribute to a depressive episode.[126] Among patients with TBI, a relatively small prospective study ($N = 101$) demonstrated that poor sleep within the first 3 months of a first-time closed-head injury predicted increased neuropsychiatric symptoms (depression, apathy, anxiety) over the subsequent 12 months.[127] Nonetheless, the causal relationship between sleep and depression remains unclear.[78] Thus, considering the effects of TBI on sleep as evidenced throughout this review, it is important to understand how changes in sleep might create vulnerabilities to mood disorders following TBI. Because sleep and mood difficulties are often co-occurring conditions following TBI,[128] understanding how these relationships might impact treatment in people with TBI is another essential research objective.

Although previous research has demonstrated changes in neural systems following both TBI and depression independently, little research has examined the possible mediating relationship of sleep between TBI and depression. One potential mechanism through which sleep might influence depression in TBI is through the negative impact of sleep disruption on cognitive function.[129] Disruptions of sustained attention are common in mild and moderate TBI and are negatively correlated with long-term outcome and quality of life.[130,131] At the same time, insufficient and disturbed sleep adversely impact cognitive function, including sustained attention. Although the extent to which poor sleep might contribute to alterations in attention in TBI remains poorly understood,[132] evidence suggests that attention control mediates the relationship between sleep and depressive symptomatology. In a study assessing sleep patterns among college students across a 3-week period, poorer sleep quality was associated with greater increase in depressive symptoms, and that the relationship between sleep and mood changes was mediated by changes in attention control.[133] Specifically, increased sleep difficulties and changes in the stability of circadian rhythms influenced attention control, which subsequently resulted in increased depressive symptoms. Thus, changes in sleep quality might contribute to the development of depression through cognitive impairments such as reduced attention control. An additional indirect pathway through which sleep might influence depression is via chronic pain, which is common in TBI (see below).[134] Indeed, a recent study tested a related hypothesis.[135] Among a large pool ($N = 2622$) of chronic pain patients, new sleep disturbances were found to triple the probability of the development of depression. Although the specific mechanisms remain unclear, this research supports the potential mediating role of sleep between physical pain/disability and the development of mood symptoms in TBI.

Sleep and PTSD in mTBI

Substantial evidence demonstrates that physical trauma can cause TBI and concurrently trigger development of subsequent PTSD.[136–144] In military samples the prevalence estimates of PTSD in individuals with chronic mTBI vary between 18% and 79%,[145] compared with 11% to 30% in individuals without mTBI.[146] Similarly, veterans who screen positive for TBI are 3.3 times more likely to meet criteria for PTSD than veterans with a negative TBI screen.[147] The increased prevalence of PTSD is important because PTSD can worsen outcomes in people with mTBI. For example, comorbid PTSD and TBI result in higher prevalence of cognitive and functional impairments[148] including reduced attentional performance,[149] more frequent and severe headaches,[150] other pain-related complaints, mood disorders, other anxiety disorders, and substance use disorders,[13,151,152] than either condition alone.[153–155]

Sleep disturbances are common in both PTSD and mTBI and are more common among those with comorbid PTSD and mTBI than among those with either condition alone. Further, they demonstrate complex reciprocal relationships. For example, sleep disturbances that precede or develop shortly after mTBI are a known risk factor

for development of subsequent PTSD, as well as for development of multiple neuropsychiatric conditions.[156–158] Chronic sleep disturbances also contribute to other types of emotional, cognitive, social, and functional impairments including increased suicidality, increased mood lability and impulsivity, impaired cognitive performance and vigilance, absenteeism, and motor vehicle and work-related accidents,[159–161] which are also hallmarks of both PTSD and TBI. The convergence of these observations suggests that sleep disturbances independently and synergistically contribute to poor functional outcomes and psychiatric comorbidity in PTSD and TBI. Treating sleep disturbances and sleep and circadian disorders in patients with PTSD can improve not only sleep but also as daytime PTSD symptoms and mood disturbances.[6,16,88,162–164] In TBI samples, preliminary evidence also suggests that sleep-focused treatments targeting insomnia can alleviate cognitive and mood symptoms, as well as fatigue.[14,15,165] There are promising early reports that prazosin, a noradrenergic alpha-1 antagonist used in the treatment of PTSD-related nightmares, may improve both sleep quality and cognitive performance in adults with mTBI.[166] In aggregate, these findings provide further support for the viability of sleep-focused treatments in comorbid PTSD and TBI.

Sleep and chronic pain in mTBI

Chronic pain, most commonly headache, is among the most prevalent, persistent, and disabling sequelae of TBI, impacting 15 to 75% of patients in months and years following the initial injury.[135,167,168] As with sleep disturbances, chronic headache is significantly more prevalent among individuals with mTBI than among those with moderate or severe TBI.[135,169] The pathophysiology of headache disorder in mTBI, however, remains poorly understood and somewhat controversial.[134,169,170] It has been proposed that headache complaints in mTBI might be more closely associated with secondary psychiatric sequelae, especially PTSD,[171] than with mTBI itself. Nonetheless, numerous studies demonstrate that compared with individuals with mTBI but without chronic pain, those with mTBI and persistent headaches and other pain conditions report increased rates and more severe neuropsychiatric sequelae, including PTSD, depression, and sleep disturbances.[172–174] Further, on the whole, the data suggest that associations between mTBI and headache do not appear to be fully mediated by these conditions.[134,175]

Headache complaints might be due to unique injury-related pathophysiology or share a common underlying pathophysiology with neuropsychiatric symptoms, such as aberrant brainstem-related hyperarousal. Complex mutually interacting relationships among headaches, anxiety, sleep disturbances, and mood alterations are likely and have yet to be adequately studied in mTBI.[175] To date, minimal data describe the temporal relationship between sleep and pain symptoms in mTBI. Cross-sectional studies, however, indicate that the presence of pain significantly increases the risk of comorbid insomnia in mTBI.[176,177] This is consistent with the general chronic pain literature demonstrating that from 50–88% of patients with chronic pain report clinically significant and objective sleep disturbances.[7,178] Although little is known about the effects of pain on sleep in mTBI, a case-control qEEG study demonstrated that mTBI patients with pain demonstrated increased fast frequency EEG activity over multiple frequency bands during REM sleep (i.e., alpha-gamma), reduced slow wave activity in both REM and NREM sleep, and increased NREM beta activity.[179]

These finding suggest that pain in mTBI may associated with abnormal sleep microstructure, indicative of cortical hyperarousal during sleep. Similar abnormalities have been found in patients with insomnia disorder and are linked with the perception of poor sleep continuity, despite relatively normal gross sleep architecture findings.[180] Although few prospective studies have evaluated the evolution of sleep and pain symptoms in mTBI, several epidemiological studies demonstrate that self-reported poor sleep quality confers an approximately 2- to 3-fold risk for developing a new onset chronic insomnia over 1 to 3 years, even after controlling for traditional psychosocial risk factors.[181–184]

These studies also demonstrate that poor sleep predicts pain persistence, increased pain severity, and the progression of emergent musculoskeletal pain and from regional to widespread pain.[181–184]

Conversely, a chronic widespread pain study found that patients who report good sleep quality spontaneously remit at three times the rate of patients reporting poor sleep.[185] Similarly, several acute non TBI-related injury studies also have demonstrated that poor sleep predicts the transition from acute to chronic pain after injury.[186,187]

A recent chart review study determined that relative to mTBI patients without sleep complaints, those reporting poor sleep quality at 10 days were three times more likely to develop concomitant headaches within the first 6 weeks of injury.[188]

These and similar data strongly suggest that sleep disruption should be independently targeted in mTBI and future research is needed to determine if such interventions improve pain and other neuropsychiatric outcomes. It is important to note that headaches are not the only type of pain experienced by patients with mTBI, as many patients sustain other bodily injuries (15–28%) at the time of the mTBI,[189] which might contribute to sleep disruption and subsequent increased risk for pain chronification.

Although the pathophysiology of mTBI headache and other chronic pain disorders remains poorly understood, emerging data suggest the possibility that impaired descending pain modulatory systems, which are with linked with pain chronification in the non-TBI literature, may play a role similar role in mTBI.[190–192] For example, in a case control study by Defrin and colleagues,[191] mTBI patients with headache exhibited impaired adaptation to tonic heat pain and deficient conditioned pain modulation (i.e., reduced endogenous pain inhibitory capacity)[193–195] compared with healthy controls and to well-matched mTBI patients without headaches. Although this finding requires replication, it suggests a possible pathway through which sleep disturbances might directly contribute to pain persistence in mTBI, as sleep fragmentation has been shown to impair conditioned pain modulation (CPM) in healthy females.[196] Deficient CPM 1) predicts the development and trajectory of chronic pain[197–200]; 2) is associated with enhanced clinical pain[201,202]; and 3) has been identified as a central feature of several idiopathic chronic pain conditions including chronic tension headache.[203–208] Several clinical studies have demonstrated that the associations between CPM and chronic pain are at least partially modulated by objective[209] and subjective measures of poor sleep.[209–213] Nonetheless, although deficient CPM is one plausible pathway by which sleep disruption may contribute to chronic pain in the context of mTBI, investigation of other mechanistic pathways through which sleep may confer risk for chronic pain in mTBI are warranted.

Role of Sleep in Rehabilitation From mTBI

Sleep almost certainly plays an important role in recovery from mTBI. Sleep is necessary for somatic growth and restoration and is

directly linked to anabolic processes, including the release of growth hormone during deep sleep. Further, sleep is vital for neural growth and neural synaptic plasticity, as well as learning and memory consolidation.[214] Perhaps most interesting, it also has been demonstrated that among mice, sleep is associated with a significant increase in interstitial space and subsequent β-amyloid clearance.[215] These findings suggest an essential neuroprotective role for sleep by eliminating neurotoxic waste. This process is posited not only to improve neural growth and synaptic plasticity following mTBI, but also to help ameliorate subsequent neurodegeneration.

The Way Forward: A Research Agenda

As evidenced throughout this review, insufficient and disturbed sleep, as well as clinical sleep and circadian disorders, are highly common following mTBI and associated with clear adverse consequences. More important, these modifiable treatment targets have potential to improve outcomes in mTBI, a complex condition with few successful clinical trials, guidelines, or evidence-based practices. In spite of this promise, essential questions remain unanswered. To develop actionable recommendations to improve clinical practice and patient outcomes, advanced understanding is required within six key research domains (Table 8).

First, it is vital to delineate more clearly the natural course of sleep and sleep disturbances following mTBI. Despite strong evidence that sleep and circadian disturbances are common, little is known about the onset, remission, or persistence of these complaints. This will require multi-method assessment of sleep including subjective and objective measures. To this end, validation of instruments used to measure sleep and sleep disturbances in mTBI is needed. Standardized measures of sleep should be incorporated into mTBI common data elements, which would help to ensure large sample sizes and to advance understanding of a vitally important outcome following mTBI.

Second, there is a dearth of information regarding the mechanisms associated with sleep and circadian disturbances in mTBI. Understanding the functional and/or neuroanatomic and behavioral changes associated with sleep and circadian disturbances will help facilitate the development of novel treatment approaches. Future studies should make an effort to measure TBI severity and mechanism, and to perform analyses that take these variables into account.

Third, greater insight is needed regarding the impact of sleep and circadian disturbances on key short-term and long-term mTBI outcomes of interest. This includes the interaction of sleep with other common sequelae of mTBI, such as depression, PTSD, and chronic pain. Indeed, a seminal 2013 report from the Institute of Medicine concluded that there ''dramatic need to understand short- and long-term effects of concussion.''[216]

Literature suggests that among mTBI patients, sleep disturbances are associated with worsened neurocognitive function, PTSD, depression, pain, and health economic outcomes including increased disability and health care utilization. However, long-term follow-up is lacking. Future research should investigate the relationship of sleep to long-term recovery and development of additional comorbidities following mTBI. Relatedly, little is known about the impact of mTBI on other conditions, especially chronic medical conditions involving inflammatory processes, such as diabetes and cardiovascular disease, which are known to be highly comorbid with sleep disorders.

Fourth, in order to advance indicated prevention initiatives, it is necessary to identify which individuals are at greatest risk for developing chronic sleep disorders following mTBI. Pre-injury patient-level factors including neuroanatomy, genetic makeup, comorbid disease conditions, medication usage, and sleep patterns

Table 8. Research Agenda for Sleep and Circadian Disturbances following mTBI

Domain	*Research Questions*
Measurement	1. What subjective and objective measures of sleep should be included in mTBI common data elements?
Natural history	2. How do subjective and objective measures of sleep change following mTBI? 3. What is the prevalence of sleep and circadian disorders following mTBI, including onset, remission, and persistence? 4. How do mechanism of injury and mTBI injury severity impact development of sleep and circadian disorders?
Short and long-term outcomes	5. What is the relationship between changes in sleep and circadian patterns and key mTBI outcomes of interest, including health and economic outcomes? 6. How do sleep disturbances interact with other common sequelae of mTBI?
Risk stratification	7. Which pre-injury and clinical factors place individuals at risk for developing chronic sleep and circadian disorders following mTBI? 8. Can an algorithm identify individuals at risk for chronic sleep and circadian disorders following mTBI?
Treatment development	9. What modifications are required to adapt and optimize evidence-based sleep and circadian treatments for mTBI populations? 10. How can evidence-based treatment approaches be combined to address multiple sleep and circadian comorbidities following mTBI? 11. Can sleep architecture be manipulated to expedite and/or optimize recovery from mTBI? 12. What is the optimal temporal sequence for targeted prevention and/or intervention efforts?
Implementation	13. What are priorities for key stakeholder groups regarding sleep and circadian disorders following mTBI? 14. What are barriers and facilitators of adoption and integration of evidence-based practices for assessment, diagnosis, and treatment of sleep and circadian disorders following mTBI?

mTBI, mild traumatic brain injury.

are all candidate predictors of risk for developing chronic sleep disorders. Treatment-related factors such as time from injury, comorbid injury and illness, and hospital care are likely to impact outcomes and warrant investigation. In addition, identifying post-injury disease trajectories is likely to provide not only additional insight into the disease process and but also temporal guidance regarding targeted prevention and intervention efforts. This will require large, well-characterized samples of people with mTBI who undergo serial assessment of clinical, imaging, and outcomes characteristics.[217]

Fifth, there is dramatic need for adaptation, development, refinement, and testing of sleep-focused treatments among people with TBI, to address sleep and circadian disorders once they have become chronic. Because of their demonstrated effectiveness in other populations and favorable risk-benefit profiles, non-drug therapies such as CBT for insomnia and fatigue management hold particular promise. In terms of sleep medications, randomized controlled trials are needed to ensure efficacy and safety among mTBI populations. Further, research is needed to evaluate the impact of other sleep disorders in mTBI, including treatments for circadian rhythm sleep disorders (i.e., bright light therapy, melatonin) and obstructive sleep apnea (i.e., PAP and oral appliances). Notably, sleep disorders are highly amenable to telehealth approaches, and this modality might be particularly useful for increasing access to care for mTBI patients initially seen in trauma centers far from home. Nonetheless, evidence among mTBI patients is needed.

Finally, the successful adoption and integration of evidence-based sleep and circadian practices will require incorporation of implementation science. Little is known about methods to promote assessments, treatments, and policies for mTBI in clinical and public health settings. Implementation science approaches can help identify barriers and facilitators of sleep-focused treatments in mTBI populations.

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