

## REVIEW

# Sleep-Wake Disturbances After Traumatic Brain Injury: Synthesis of Human and Animal Studies

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Sleep-wake disturbances following traumatic brain injury (TBI) are increasingly recognized as a serious consequence following injury and as a barrier to recovery. Injury-induced sleep-wake disturbances can persist for years, often impairing quality of life. Recently, there has been a nearly exponential increase in the number of primary research articles published on the pathophysiology and mechanisms underlying sleep-wake disturbances after TBI, both in animal models and in humans, including in the pediatric population. In this review, we summarize over 200 articles on the topic, most of which were identified objectively using reproducible online search terms in PubMed. Although these studies differ in terms of methodology and detailed outcomes; overall, recent research describes a common phenotype of excessive daytime sleepiness, nighttime sleep fragmentation, insomnia, and electroencephalography spectral changes after TBI. Given the heterogeneity of the human disease phenotype, rigorous translation of animal models to the human condition is critical to our understanding of the mechanisms and of the temporal course of sleep-wake disturbances after injury. Arguably, this is most effectively accomplished when animal and human studies are performed by the same or collaborating research programs. Given the number of symptoms associated with TBI that are intimately related to, or directly stem from sleep dysfunction, sleep-wake disorders represent an important area in which mechanistic-based therapies may substantially impact recovery after TBI.

**Keywords:** TBI, sleep, EEG, animal models, pediatric, orexin, glutamate, BCAA.

## INTRODUCTION

Traumatic brain injury (TBI), defined as an alteration in brain function or other brain pathology caused by an external force, is a common injury and results in 2.5 million emergency room visits annually.<sup>1,2</sup> Even in its mildest form (generally known as “concussion”), individuals with TBI can suffer from persistent sequelae that prevent the return to normal physical, cognitive, and emotional functioning—all of which are important components of overall recovery. Sleep-wake disturbances are among the most prevalent and persistent symptoms following TBI.<sup>3–5</sup> Sleep-wake disturbances have been reported in ~30–70% of individuals with mild, moderate, or severe TBI up to 3 years postinjury.<sup>6–22</sup> Furthermore, disrupted sleep contributes to several other complications, including memory and cognitive complaints, chronic pain, and psychological distress.<sup>23–28</sup>

Although sleep-wake disturbances after TBI have long been recognized in humans, the underlying neurologic mechanism(s) have yet to be clearly established. Only recently have studies utilized animal models of TBI that are capable of providing mechanistic insight into these sleep-wake disturbances. Thus, this review begins with a brief introduction to the epidemiology of sleep-wake disturbances in humans after TBI. We follow with a summary of the clinically relevant sleep-wake disturbances observed in humans after TBI and then present a working overview of the pathophysiology of these sleep-wake disturbances. This human clinical and pathophysiological background is then followed by a synthesis of the current literature on sleep-wake disturbances in animal models of TBI. Finally, we discuss the relationship between sleep and recovery from TBI as well as treatment options for sleep-wake disturbances after TBI. For additional in-depth discussion of relevant research concerning sleep-wake disturbances in humans after TBI, we refer the reader to previous reviews on the topic.<sup>29–41</sup>

This review presents a scoping overview of relevant literature to date, as an alternative to a strictly systematic approach. The advanced search function in PubMed was used to identify 243 publications with “TBI” and “Sleep” in the title and/or abstract

as potentially relevant literature to include in this review. Studies from this literature search were excluded ( $n = 95$  in total) on the basis of being unrelated ( $n = 41$ ), or only peripherally related to sleep-wake disturbances following TBI (e.g., studies with a primary focus of neuropsychiatric and behavioral conditions ( $n = 18$ ), surgical approaches and treatments ( $n = 10$ ), cognitive function/memory ( $n = 6$ ), headache ( $n = 4$ ), rehabilitation ( $n = 4$ ), epilepsy/seizure management ( $n = 3$ ), nutrition and metabolic function ( $n = 3$ ), posttraumatic stress disorder ( $n = 2$ ), relationship with spinal cord injury ( $n = 2$ ), and editorials/commentaries ( $n = 2$ )). In addition, literature outside this search was included where appropriate, usually identified from references from primary literature identified by the initial PubMed search. Of the 243 identified publications on this topic, 181 of them were published between 2010 and the present time, indicating a nearly exponential rise in the number of manuscripts published on this emerging and important topic.

## EPIDEMIOLOGY

TBI is typically classified using the Glasgow Coma Scale (GCS)<sup>42</sup> as mild (GCS 13–15), moderate (GCS 9–12), and severe (GCS  $\leq 8$ ). While widely used since the 1970s, this scale has well-documented limitations for classifying TBI severity.<sup>43,44</sup> Clinically, we know that individuals who have abnormal computed tomography scans with intracranial hemorrhage are at risk of hemorrhage expansion and/or neurological deterioration regardless of admission GCS score.<sup>45</sup> Based on the World Health Organization criteria published in 2004, individuals with head trauma are classified as “mild TBI” if these lesions are nonoperable and GCS  $\geq 13$ , although some authors and clinicians would consider these individuals to have a “moderate” injury that warrants a higher level of clinical monitoring in the hospital and often in an intensive care setting.<sup>46,47</sup> Mild TBI, on the other hand, has been used interchangeably with term “concussion” to imply an innocuous and self-limited injury, although we now understand that these injuries too can lead to prolonged symptoms and sequelae.<sup>48</sup>

Studies indicate that 30–70% of TBI survivors across the entire injury spectrum experience disordered sleep after injury,<sup>6–22</sup> a finding unique to traumatic cerebral injury, as traumatic spinal cord injuries do not cause similar sleep–wake disturbances.<sup>49</sup> Numerous studies have demonstrated that the severity of the inciting head injury does not predict the degree of sleep–wake disturbances;<sup>6</sup> individuals with traumatic brain insults of all severities are at risk. Reported rates vary widely due to methodological variances in many studies, including sample bias (i.e., samples referred to sleep laboratories), varied assessment methods (i.e., subjective self-report versus objective polysomnography or actigraphy), and poor recognition or underreporting by patients and clinicians. In a population-based study of 346 patients with mild TBI (concussion) in New Zealand, 40% of patients experienced sleep difficulties 1 year after injury, more than 3 times the incidence seen in the general population.<sup>50</sup> Female gender, poor preinjury sleep quality, and symptoms of poor sleep/cognition within 2 weeks after injury were predictive of persistent sleep disturbance. In patients with moderate–severe TBI evaluated during acute rehabilitation, 66% had sleep–wake disturbances (evaluated using the Delirium Rating Scale-Revised-98) at 1-month postinjury.<sup>51</sup> The severity of sleep–wake disturbances in this population predicted hospital length of stay and the duration of posttraumatic amnesia, even after controlling for injury severity.<sup>51</sup> Baumann et al. studied 65 patients who required hospital admission with their first-ever moderate–severe TBI and found that more than 70% had sleep–wake disturbances in the first 6 months after TBI.<sup>6</sup> In 51 of those patients who were available for follow-up 3 years later, less than 20% felt that their sleep symptoms had improved.<sup>7</sup> Similarly, Imbach and Büchele et al. reported sleep–wake disturbances persisting for 18 months postinjury.<sup>52</sup> A recent meta-analysis of 21 studies with 1706 participants across the spectrum of TBI severity showed a 50% prevalence of sleep–wake disturbances in TBI survivors, a number much higher than that seen in the general population.<sup>9</sup> Taken together, these data suggest that sleep–wake disturbances are common, can persist, and impact recovery regardless of TBI severity.

## SLEEP–WAKE DISTURBANCES IN HUMANS AFTER TBI

TBI is strongly associated with several clinically recognized sleep–wake disturbances. The most common sleep–wake disturbances are insomnia and hypersomnia/pleiosomnia, followed by sleep-related breathing disorder, circadian rhythm disorder, and parasomnia/movement disorders. Due to symptomatic overlap and high prevalence, we also summarize reports of fatigue after TBI.

Traditional methods of assessing for sleep–wake disturbances in individuals with TBI include polysomnography (PSG) and multiple sleep latency/maintenance of wakefulness testing. PSG and multiple sleep latency/maintenance of wakefulness testing are based upon scalp electroencephalogram (EEG) and therefore, beyond their use in clinical sleep staging, may have limited capabilities to capture functional neurobiological changes, especially in the subcortical regions that potentially contribute to sleep–wake disturbances. However, as we describe subsequently, promising quantitative EEG (qEEG) approaches may reveal additional insights into brain function beyond

conventional sleep staging. There may also be a future role for novel neuroimaging techniques such as magnetic resonance spectroscopy for neurotransmitter content (e.g., glutamate and gamma-aminobutyric acid; GABA) in the cortex that might elucidate mechanisms underlying sleep–wake disturbances in TBI.<sup>53</sup>

## Insomnia

Insomnia is characterized by difficulty in initiating and/or maintaining sleep. Symptoms include difficulty falling asleep, sleep fragmentation, and/or early morning awakenings, resulting in associated daytime sensations of fatigue, sleepiness, and mood/performance deficits.<sup>54</sup> Insomnia in the context of TBI<sup>55</sup> is reported in 30–60% of individuals following TBI of all severities,<sup>56</sup> although insomnia may be more common following mild injuries.<sup>8,50</sup> Repetitive traumatic head injuries may increase the risk of developing insomnia. Among military personnel, rates of self-reported insomnia were 6% in those with no history of TBI, 20% after a single TBI, and 50% in those who had experienced multiple TBIs.<sup>57</sup> Because insomnia is generally diagnosed using structured interviews and/or questionnaires, some caution is advised in interpreting these studies, as individuals have a tendency to either over- or underreport symptoms compared to findings from objective PSG studies.<sup>58</sup>

## Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) is characterized by daily or near-daily episodes of irrepressible need to sleep or unintentional lapses into sleep at potentially inappropriate times. In contrast to fatigue, which more commonly manifests during physical exertion, EDS is characterized by sleepiness during sedentary activities. While insomnia tends to be overreported by patients after head injury,<sup>58</sup> EDS may actually be underreported. Imbach et al. found that 57% of TBI survivors had objective evidence of EDS as determined by multiple sleep latency testing, considerably higher than the prevalence of EDS in a control population without brain injury (<20%).<sup>59</sup> Survivors, but not controls, markedly underestimated their sleepiness when subjective self-reports were employed.<sup>59</sup> Similarly, in a rehabilitation setting, 50% of individuals with moderate to severe TBI were found to have objective evidence of EDS, but these difficulties were not detected on self-report questionnaires.<sup>60</sup>

## Pleiosomnia

Following TBI, individuals may exhibit pleiosomnia, that is, an increased need for sleep.<sup>61</sup> In fact, actigraphy monitoring 6 months after TBI showed that individuals with TBI required 1–2 hours more sleep/24 hours over a 2-week monitoring period compared to healthy controls.<sup>59</sup> In this cohort, pleiosomnia positively correlated with TBI severity and was exacerbated in individuals who had intracranial hemorrhage. In a prospective electrophysiological study of 65 patients studied 6 months after TBI, 22% reported that they needed two more hours of sleep in a 24-hour period than prior to their injury.<sup>6</sup> In both of these studies, similar to EDS symptoms, patients with TBI also underestimated pleiosomnia on self-report questionnaires compared to objective measures.<sup>6,59</sup>

### Sleep-Related Breathing Disorders

Obstructive sleep apnea and central sleep apnea are reported more frequently in individuals after TBI than in the general population. Several small studies have reported a prevalence of 25–35% of obstructive sleep apnea following TBI of any severity, which is higher than most general population studies.<sup>5,62–64</sup>

### Circadian Rhythm Sleep Disturbances

Circadian rhythm sleep disturbances, most commonly identified by delayed sleep phase syndrome and irregular sleep–wake pattern, may be easily overlooked following TBI. Complaints of difficulty falling asleep, staying asleep, and difficulty awakening at standard wake times may be misconstrued as insomnia rather than circadian rhythm sleep disturbances. For example, in a previous study by Ayalon et al. 15 (36%) of 42 patients with mild TBI who had insomnia, in fact, had a circadian rhythm sleep disturbance (either delayed sleep phase syndrome or irregular sleep–wake pattern).<sup>65</sup> This distinction is important, as treatment approaches differ depending on whether the patient has insomnia versus a circadian rhythm sleep disturbance. In an observational study of 23 patients with TBI roughly 1-year postinjury by Shekleton et al., evening salivary melatonin production was reduced and was associated with decreased sleep efficiency, increase wake after sleep onset, and higher rates of anxiety and depression.<sup>66</sup> Circadian rhythm sleep disturbances may be especially prominent in the acute phase after TBI. Duclos et al. studied 16 patients with moderate–severe TBI in the first 10 days after injury and found severe fragmentation of the rest–activity cycle using actigraphy recordings.<sup>3</sup> Further studies are needed, as the confounding effects of acute hospitalization, pain, and anxiety complicate interpretation of these results.

### Abnormal Movements and Behaviors During Sleep

Abnormal movements and behaviors during sleep have also been reported. In a study of adolescents with a history of chronic mild head injury, parasomnias were reported by 42% of head injured patients (compared to 19% of controls). Adolescents reported increased rates of sleep enuresis (involuntary urination; 21% versus 0%) and sleep bruxism (teeth grinding; 42% versus 6%) in head-injured subjects compared to noninjured control subjects.<sup>67</sup> In this population, there was also an increased fear of falling asleep, fearful awakenings, and frightening dreams, which were not seen in control subjects. In a similar adolescent cohort followed after mild head injury (0.5–6 years from injury), there were more complaints of poor sleep and bruxism, although there were no group differences in total sleep time, bedtimes, or wakeup times.<sup>68</sup>

In 60 adult patients with chronic TBI (3 months–2 years from injury), 25% presented with parasomnia as their primary sleep complaint, the most frequent of which was REM sleep behavior disorder (RBD).<sup>17</sup> While RBD has not been traditionally associated with TBI in clinical practice, the literature on this association is scant and has not been systematically examined. As RBD is widely considered to be a harbinger of synucleinopathy-related disorders such as Parkinson's disease, and TBI increases lifetime risk of Parkinson's disease, there may be a

pathophysiological link between TBI and RBD, although this is still yet to be defined.

There is also emerging evidence that trauma exposure (e.g., TBI and/or post-traumatic stress disorder) is associated with a greater risk of dream enactment and disruptive nocturnal behaviors along with increased electromyographic (EMG) tone during both REM and NREM sleep, especially among the military population.<sup>69</sup> While trauma-associated sleep disorder shares a number of features with RBD, it may encompass a separate nosologically defined parasomnia. It is not known whether trauma-associated sleep disorder carries an increased risk of neurodegeneration, although a recent report may indicate that the isolated finding of REM sleep without atonia carries an increased risk of synuclein-associated neurodegeneration.<sup>70</sup>

### Fatigue

General physical and mental fatigue during the waking hours has long been recognized as a common and debilitating complication following TBI,<sup>71–73</sup> that undoubtedly contributes to subjective measures of sleepiness, yet appears to be independent of pain, depression, and disrupted sleep.<sup>74,75</sup> Not surprisingly, fatigue has been shown to impair quality of life.<sup>76</sup> Symptoms of fatigue have been shown to extend at least 2 years postinjury.<sup>13,77,78</sup> Although the cause remains unknown, neuroendocrine dysfunction, specifically deficiencies in basal cortisol levels and in the growth hormone response to glucagon stimulation, may contribute to symptoms of fatigue in patients with TBI.<sup>79</sup>

### Sleep–Wake Disturbances in Children After TBI

Pediatric, children, and adolescent survivors of TBI also experience sleep–wake disorders postinjury reported either independently or from parental/caregiver observation.<sup>80–83</sup> In an early study, Kaufman et al. reported an increase in subjective and objective markers of impaired sleep in adolescents (~13 years of age at the time of the study) ~3 years postinjury.<sup>67</sup> These data were confirmed in a later, larger study ( $n = 98$ ) of similarly aged adolescents in which 28% exhibited sleep–wake disturbances 6 months to 6 years postinjury.<sup>68</sup> Three additional studies also reported continued impairment in sleep in adolescents (ages ~8–15 years) up to 1 year<sup>84,85</sup> or 5 years<sup>86</sup> postinjury.

Milroy et al. were unable to recapitulate this finding in a group of children who experienced head injury at an earlier age (~7 years old).<sup>87</sup> Similarly, sleep–wake disturbances were largely absent in children who experienced a mild TBI early in life (~5 years of age) by 12 and 18 months postinjury.<sup>88</sup> This raises the possibility that the age at which head injury is experienced may be an important factor in determining the long-term prognosis of sleep–wake disturbances after TBI. Indeed, Hooper et al. reported that, although sleep–wake disturbances were common acutely (1–4 months post-injury), they were absent by 10 months postinjury.<sup>81</sup> This study spanned infancy to 18 years of age (average age = 8.7 years) in a large sample ( $n = 681$ ), which may be broad enough to statistically obscure the presence of a developmental/aging effect. However, data from another study with a similarly large sample size ( $n =$



729) and broad age range (2–17 years of age) showed persistent sleep–wake disturbances at 3, 12, and 24 months postinjury based on a single parent report question.<sup>89</sup>

These available studies highlight the unsolved questions on the nature of sleep–wake disturbances in the acute, subacute, and chronic periods after pediatric TBI. Larger and better designed pediatric observational trials are needed to understand the influence of age on sleep–wake disturbances across the recovery continuum. Perhaps even more intriguing, though, are how these disruptions impact cognitive and psychological development in the developing brain. Emerging evidence from animal models has implicated the role of sleep in synaptic plasticity,<sup>90,91</sup> toxin clearance,<sup>92</sup> and memory consolidation.<sup>93</sup> Clarifying these roles for sleep in humans, both in the healthy and in the injured states, will be important to better appreciate how therapies targeting sleep–wake disturbances might impact long-term recovery.

### Quantitative EEG Findings in Sleep After TBI

Diagnosis of these sleep–wake disturbances are heavily reliant on subjective symptoms and observational analysis performed as part of a comprehensive sleep evaluation. To determine if there are common objective electrophysiological changes that lead to disordered sleep after TBI, several studies have performed qEEG analyses obtained during PSG (Table 1). The overarching rationale of in-depth qEEG analyses stems from the fact that gross examination of sleep stages from in-lab PSG may be highly variable between subjects, and, therefore, changes in sleep staging after TBI may be difficult to discern. Accordingly, more detailed examination of specific EEG frequency bands (i.e., alpha, theta, beta, and delta power spectral analyses), coherence and cross-frequency coupling across channels, and other such measures may increase the ability to illuminate changes in brain activity after TBI.

In the acute stage following mild TBI, patients may show longer sleep latency and lower sleep efficiency, along with lower delta power, but higher alpha and beta power, during non-REM (NREM) sleep.<sup>94,95</sup> In the subacute to chronic stages following TBI, others have reported an increase in NREM sleep and higher delta power compared to matched controls.<sup>52</sup> Concussed athletes reported worse sleep quality and greater sleep–wake disturbances and daytime dysfunction.<sup>96</sup> However, there were no differences in PSG-derived variables or in qEEG analysis of NREM or REM sleep. In the waking qEEG, concussed athletes (compared to non-concussed athletes) exhibited increased delta and reduced alpha activities, potentially coinciding with self-reported daytime dysfunction. Similarly, in a small study of 8 patients with acute and subacute TBI, no differences in PSG-derived variables were observed, but qEEG analysis showed an increase in delta, theta, and alpha-1 power at 72 hours postinjury that progressively decreased across the 12-week time point.<sup>97</sup>

However, these studies have not been consistent. Several studies have found no or decreased delta power in patients with mild TBI who similarly reported poor quality sleep.<sup>77,78,81–83</sup> The discrepancies may be because most qEEG studies to date have utilized power spectral analyses of frequency bands averaged over long time periods. Many human studies are plagued by

small sample sizes, and any meaningful differences may be washed out by averaging spectra over long time durations (e.g., the entire night of sleep), when sleep quality may be very different at specific time points during the night. More sophisticated analyses that take into account phasic sleep events and examine qEEG in smaller temporal windows (e.g., cross-frequency coupling or coherence) may help to better identify signal from noise.<sup>98</sup> In addition, examining more temporally precise features of sleep such as spindles, K-complexes, and local slow waves may be of greater utility. Cote et al. examined 20 subjects with chronic TBI (mean time since injury: 6.7 years) compared to controls and found more spindles during slow wave sleep, and a lower density of spontaneous K-complexes/fewer evoked K-complexes in response to stimulus presentation in subjects with TBI compared to controls.<sup>98,99</sup> Modarres et al. quantified individual slow waves during the waking EEG and calculated the coherence of these slow waves across multiple channels and found that subjects with TBI had more slow waves during wakefulness and decreased coherence of waves across channels.<sup>100</sup> Notably, in the Modarres study, striking parallels were seen in their highly controlled animal model of TBI as in their human subjects with TBI, indicating a shared neurophysiology of TBI between species.

The results of the Modarres et al.<sup>100</sup> study highlight the value of employing qEEG analyses in human and animal models of TBI in parallel, using similar methodology, calculations, time spans, and other controllable parameters. Indeed, part of the challenge of unifying disparate qEEG findings across studies stems from heterogeneity in the acuity and severity of, duration elapsed since, and age at the time of injury. For this reason, studies that can combine animal and human data using similar qEEG approaches will increase the specificity and help refine the relevant biology to TBI that is fundamentally conserved between species. In this way, qEEG may eventually provide us with a reliable and quantitative biomarker for sleep–wake disturbances after TBI.

### PATHOPHYSIOLOGY OF SLEEP–WAKE DISTURBANCES IN HUMANS AFTER TBI

The functional neuroanatomy and neuropharmacology of both normal and disordered sleep are active areas of investigation in which rapid progress is being made. Generalized electrographic, autonomic, and behavioral activation during waking emerges from specific arousal systems located in the brain stem, posterior and lateral hypothalamus, and basal forebrain. These networks utilize a variety of neurotransmitter/neuropeptide systems, including histamine, serotonin, norepinephrine, acetylcholine, dopamine, glutamate, and orexin/hypocretin (ORX). Each of these neuronal networks has specific roles in cognition, behavior, sensory processing, and/or autonomic control during waking and contributes to overall arousal. These arousal systems impact cortical activity indirectly through projections through the thalamus, lateral hypothalamus, and basal forebrain or via direct projections to the cortex. Differences in the pattern and intensity of neuronal activity across sleep–waking states among these various systems likely account for the varied manifestations of sleep–wake disorders after brain injury.

**Table 1**—Summary of Relevant Literature Reporting qEEG Data in TBI Patients.

Publication	Ref	Sample size and sex	Mean time post injury	Injury Severity	Control	Polysomnogram data	Quantitative EEG data
Parsons et al, 1997, <i>J Neurotrauma</i>	97	8 (2)	72 hours, 6 weeks, and 12 weeks	Mild	None	• No differences	• Increase in delta, theta, and alpha-1 power at 72 hours post-injury that decreased across the 12 week time point
Williams et al, 2008, <i>Clin Neurophysiol</i>	239	9 (3)	27.8 months	Mild	Healthy non-TBI	• Decreased sleep efficiency and REM latency	• No differences
Gosselin et al, 2009, <i>Sleep Medicine</i>	96	10 (7)	6.2 months	Mild	Healthy non-TBI	• No differences	• No differences in NREM or REM sleep qEEG data, • Increased delta and reduced alpha power in the waking qEEG
Rao et al, 2011, <i>J Neuropsych Clin Neurosci</i>	94	7 (1)	≤1 week	Mild	Healthy non-TBI	• Increased sleep latency and lower sleep efficiency	• Decreased delta power, but increased alpha and beta power, during NREM sleep
Khoury et al, 2013, <i>J Neurotrauma</i>	95	24 (9)	48.7 days	Mild	Healthy non-TBI	• Increased sleep latency and lower sleep efficiency	• Decreased delta power, but increased alpha and beta power, during NREM sleep
Arbour et al, 2015, <i>Sleep Medicine</i>	240	34 (11)	10.5 weeks	Mild	Healthy non-TBI	• No differences	• Increased beta power, with no differences in absolute delta, theta, alpha, or sigma power
Cote et al, 2015, <i>AIMS Neuroscience</i>	99	20 (11)	6.7 years	6, Mild; 8, Mod; 6, Severe	Healthy non-TBI	• Increased sleep latency	• Decreased density of spontaneous K-complexes and fewer evoked K-complexes
Imbach and Büchele et al, 2016 <i>Neurology</i>	52	31 (11)	18 months	21, Mild; 2, Mod; 8, Severe	Healthy non-TBI	• Increased sleep time • Decreased sleep latency	• Increase in NREM sleep and higher delta power
Modarres et al, 2016, <i>Neurobiol Sleep Circ Rhythm</i>	100	8 (0)	58.4 months	Mild	Healthy non-TBI	• Decreased sleep latency • Decreased % REM sleep	• Increased slow waves during wakefulness, and decreased coherence across channels

Value in parentheses next to sample size denotes number of female subjects.

Abbreviations: qEEG, quantitative electroencephalography; EMG, electromyography; NREM, non-rapid eye movement; REM, rapid eye movement; TBI, traumatic brain injury.

The underlying neuropathological and neurophysiological changes contributing to sleep–wake disturbances that occur after TBI are not well understood. Most individuals who suffer mild TBI do not exhibit abnormal radiographic findings and direct pathological examination is rarely possible. In patients with more severe traumatic injuries, case reports have identified structural brain injuries thought to contribute to secondary sleep–wake disturbances after TBI, including the suprachiasmatic nucleus and optic chiasm<sup>101</sup> and the hypothalamus, amygdala, and brain stem.<sup>102</sup> However, the vast majority of cases do not have an obvious structural abnormality contributing to sleep–wake dysfunction.<sup>103</sup> Some have hypothesized that brain stem injury may contribute to arousal dysfunction after TBI,<sup>104,105</sup> but a recent postmortem examination of 8 patients with TBI showed only mild changes in the number of brain stem neurons in patients with TBI when compared to controls.<sup>106</sup>

### Hypothalamic Regulation of Sleep–Wake Disturbances After TBI

Given the lack of a structural correlate with sleep–wake disturbances after TBI and clinical features mimicking narcolepsy (including EDS and nighttime sleep fragmentation), several groups have now looked at the role of the ORX system in sleep–wake disturbances after TBI. ORX is a neuropeptide expressed by neurons in the perifornical lateral hypothalamus that have extensive projections to other hypothalamic nuclei, the limbic system, thalamus, cortex, and spinal cord, exciting several monoaminergic and cholinergic wake-promoting systems.<sup>107</sup> Circadian oscillations in ORX within cerebrospinal fluid (CSF) correlate with arousal cycles,<sup>108,109</sup> and exogenous administration of ORX promotes wakefulness.<sup>110,111</sup> Interestingly, the phenotypes of human and canine narcolepsy and associated neurochemical imbalances, notably with respect to ORX expression deficiency,

are strikingly similar.<sup>112</sup> Using positional cloning, narcoleptic Doberman pinschers have been identified to be deficient in ORX neurotransmission, due to an ORX receptor gene mutation.<sup>113</sup> In contrast, although the cause of human narcolepsy remains unknown, human narcoleptic patients have been shown to be deficient in ORX, as determined by ORX immunoreactivity from CSF samples.<sup>114</sup> ORX knockout mice results in a condition of fragmented wakefulness similar to human narcolepsy.<sup>115</sup> Additionally, ORX receptor antagonism<sup>116</sup> promotes sleep in mice, rats, rabbits, dogs, monkeys, and humans.<sup>117</sup>

In humans, Baumann et al. measured CSF ORX levels of 44 patients in the first several days after moderate–severe TBI and showed CSF ORX levels were decreased in 95% of patients.<sup>6</sup> Although CSF ORX levels recovered in the majority of patients 6 months after injury, low CSF ORX levels were associated with sleep–wake disturbances, including narcolepsy and a narcolepsy-like syndrome, in 3 of 4 patients in whom low CSF ORX levels persisted at 6 months. In a related study, autopsy examination of brains from 4 patients who died after severe TBI showed a reduction in ORX neurons in the hypothalamus compared to matched controls.<sup>118</sup> Of note, autopsy examination of patients with narcolepsy also show a reduction in ORX neurons.<sup>119</sup> Other injuries to the hypothalamus may also influence sleep following TBI. In a study of 12 TBI patients and 16 matched controls, 7 TBI patients had neuropathological abnormalities of the hypothalamus, particularly loss of wake-promoting histaminergic neurons (41%), whereas ORX neurons were decreased by 21%.<sup>120</sup> Thus, there may be multiple mechanisms by which hypothalamic injury contributes to sleep–wake disorders after TBI.

### Brain Stem and Pineal Dysregulation of Sleep After TBI

Recent work from Valko et al. examined the midbrain and pons in 8 patients on autopsy from fatal TBI.<sup>106</sup> Severe TBI was associated with a 17% loss of serotonergic dorsal raphe nuclei neurons and a 29% loss of noradrenergic locus coeruleus neurons, while other arousal promoting neurons appeared less injured (e.g., median raphe nuclei, pedunculopontine, and laterodorsal tegmental nuclei).

Melatonin is produced by the pineal gland and regulates the sleep–wake cycle following a circadian pattern of release into the bloodstream. Although melatonin release may be disrupted following TBI,<sup>121</sup> melatonin supplementation did not improve sleep yet does produce improvements in daytime alertness.<sup>122</sup> Exogenous melatonin can be used to induce phase shifts in the sleep–wake cycle. In a study of 23 patients with chronic TBI (>6 months since injury), there was a decrease in evening melatonin production when compared to age- and sex-matched controls.<sup>66</sup> Seifman et al. studied patients with acute TBI as well as other critically ill patients admitted to the hospital and found that both populations had decreased levels of serum melatonin compared to healthy controls.<sup>123</sup> Recent work from Grima et al. extend these findings by demonstrating that patients with TBI produced 42% less salivary melatonin as well as a shift toward a later onset of melatonin synthesis.<sup>124</sup>

### Glutamate Dysfunction as a Contributor to Sleep–Wake Disturbances After TBI

The excitatory neurotransmitter glutamate regulates the sleep–wake cycle across species. Homer proteins, which bind to metabotropic glutamate receptors and alter Ca<sup>2+</sup> sensitivity, are involved in sleep–wake processes in both *Drosophila* and mice.<sup>125</sup> Genetic deletion of the homer 1a protein in *Drosophila* (which is upregulated during sleep) results in fragmented sleep and the failure to sustain long bouts of sleep, despite increased sleep pressure.<sup>125</sup> In contrast, genetic deletion of the homer 1a protein in mice (which is upregulated during wakefulness) produces fragmented sleep and failure to sustain long bouts of wakefulness.<sup>125</sup> Simultaneous real-time measurements of sleep and glutamate concentration in the prefrontal cortex of healthy mice demonstrate that the concentration of extracellular glutamate increases during wakefulness, decreases during periods of extended sleep, and spikes during REM sleep.<sup>126</sup> These data reveal a close temporal link between sleep/wake state and extracellular glutamate concentrations. Glutamate dysfunction, specifically an increase in glutamate signaling, has been described in rat cortex within the first hour after TBI induced via controlled cortical impact (CCI)<sup>127,128</sup> and in humans 24 hours after TBI.<sup>129</sup> Additionally, increases in cortical glutamate network activity can be attributed to impaired GABAergic control in a murine TBI model.<sup>53</sup> Thus, it follows that TBI-induced changes in cortical glutamate could be one potential mechanism underlying sleep–wake dysfunction. We recently reported decreased glutamate within the presynaptic terminals synapsing onto ORX-positive cells in the hypothalamus after TBI, suggesting decreased excitatory inputs onto this critical wake-promoting system.<sup>130</sup>

In summary, sleepiness after TBI is likely the result of multiple factors, including direct damage to some arousal-promoting neurons, injury/inflammation in the cortex, thalamus and hypothalamus, diffuse axonal injury, and alterations in cerebral energy metabolism. It is possible that intervention in this early setting on these or other signaling pathways may help to ameliorate later sleep disturbance, but these approaches require further study.

### ANIMAL MODELS OF SLEEP–WAKE DISTURBANCES AFTER TBI

Animal models of TBI recapitulate several sleep–wake disturbances seen in humans after TBI, including insomnia, EDS, and pleiosomnia. However, there are no well-defined animal models of TBI that accurately model sleep-related breathing disorder, circadian rhythm disorder, or abnormal movements during sleep. The majority of work using animal models of TBI have utilized rats and mice, although several have used larger animals such as swine or nonhuman primates. Experimentally inducing TBI is accomplished by subjecting the brain, with or without craniotomy, to an external mechanical force. In this section, we briefly summarize the most common approaches used to study sleep–wake disturbances in animal models of TBI, which include fluid percussion injury (FPI; midline and lateral), CCI injury, and the weight drop injury model (Table 2). We refer the reader to comprehensive reviews on the general topics of animal models of TBI,<sup>131,132</sup> the translational and strategies of

**Table 2**—Summary of Animal Models Used in Work Assessing sleep–wake Disturbances After TBI.

Model	Type of injury	Strengths	Weaknesses	Species
FPI	· Mixed global/focal insult	· Very common model used	· Requires craniotomy	· Mouse, <sup>100,164,169–171</sup> Rat <sup>165</sup>
	· Midline or lateral	· Highly reproducible · Mild regarded as the most translation model of TBI	· Does not replicate clinical TBI in terms of skull fracture · Limited mechanical control over neurological insult	
CCI	· Predominantly focal	· Single or repetitive insults	· Requires craniotomy	· Mouse, <sup>155,167,168,173</sup> Piglet <sup>172</sup>
		· Highly reproducible		
		· Severity of neurological insult easily controlled		
Weight Drop	· Mixed global/focal insult	· Representative of human conditions · Does not require craniotomy	· Not highly reproducible · High mortality without post-injury 100% O <sub>2</sub> ventilation	· Mouse, <sup>157</sup> Rat <sup>158,159</sup>

Abbreviations: FPI, fluid percussion injury; CCI, controlled cortical impact injury; TBI, traumatic brain injury.

animal models of TBI,<sup>133</sup> and neuroinflammation associated with TBI.<sup>134</sup>

### Fluid Percussion Injury

FPI is induced by a pendulum swinging and striking a piston of a fluid reservoir to generate a pressure pulse (i.e., percussion) to the exposed and intact dura.<sup>135–137</sup> The percussion produces a brief displacement and deformation of brain tissue, with the severity of the injury determined by the strength of the pressure pulse. The two most common injury locations are centrally around the midline<sup>138</sup> or laterally between bregma and lambda over the parietal bone.<sup>139</sup> Although FPI does not replicate clinical TBI with associated skull fracture, it does replicate intracranial hemorrhage, brain swelling, and progressive gray matter damage. Historically, lateral FPI is one of the most common TBI animal models,<sup>137</sup> despite limited mechanical control over the neurological insult (i.e., the height of the pendulum is the only modifiable parameter). The advantages of FPI over other rodent models of TBI is the high reproducibility and wide acceptance across dozens of laboratories worldwide, resulting in hundreds of publications over the past 3 decades that describe in detail the brain histological changes (e.g., markers of apoptosis and gliosis), electrophysiological changes, and behavioral deficits resulting from FPI.<sup>137</sup> Furthermore, neurological testing for righting reflex time immediately after brain injury is highly predictive of histological severity of injury.<sup>140,141</sup> Recent work has advanced this technique by utilizing a computer-controlled pneumatic instrument with precisely controlled impact pressure and dwell time, resulting in improved reproducibility.<sup>142</sup>

Mild FPI is widely regarded as the most translational model for nonpenetrating concussive injury,<sup>143,144</sup> as the percussion injury (e.g., injected under the skull surface atop the intact dura) results in a mixed global/focal insult spanning both hemispheres.<sup>137</sup> FPI also affects subcortical structures including hippocampus, prefrontal cortex, and amygdala electrophysiology, even if there is little structural damage to these distant sites.<sup>145–149</sup> Although severe TBI induced by FPI has been performed

in pigs<sup>150</sup> and rats,<sup>151,152</sup> researchers have not yet studied sleep–wake disturbances after severe FPI.

### Controlled Cortical Impact Injury

The CCI injury model uses a pneumatic or electromagnetic impact device to drive a rigid impactor onto the exposed dura to create a cortical lesion.<sup>153</sup> CCI causes a more focal insult compared to the mixed focal/global insult from FPI. The major advantage of CCI over other models of TBI is the extent to which mechanical factors (e.g., time, velocity, depth of impact) can be controlled. Furthermore, the severity of injury can be manipulated by adjusting the impact velocity, with increasing velocities leading to increasing TBI severity.<sup>154</sup> However, the generalizability of CCI injury to human concussion is somewhat limited by the nature of the focal, cortically penetrating lesion. CCI is a useful model for mild, moderate, and severe focal TBI. Similar to FPI, the injury is not limited to cortical damage and can also affect subcortical structures.<sup>155</sup>

### Weight Drop Injury

Weight drop injury can be either closed head or performed through an open craniotomy. Only closed head weight drop models been studied with regard to sleep–wake disturbances, and thus, most studies closely resemble the Shohami<sup>156</sup> (mixed focal diffuse) model. Sleep–wake phenotypes from these models are summarized in [Table 3](#). Sabir et al.<sup>157</sup> utilized a closed head weight drop model in mice similar to what has been previously described,<sup>156</sup> in which a 329-g rod is dropped from a 1-cm height that induces a mild TBI. Büchele et al.<sup>158</sup> and Morawska et al.<sup>159</sup> utilized a weight drop model in rats that was slightly modified from the classic Marmarou<sup>160,161</sup> approach by allowing the weight to fall from a steep angle (rather than vertically). The weight drop model benefits from not requiring a craniotomy to be performed and, therefore, more closely resembles the human condition. Although this approach is easily implemented and well characterized, the severity of inciting injury is not highly reproducible yet can span the spectrum of mild to severe



**Table 3**—Summary of Relevant Literature Examining Sleep in an Animal Model of TBI.

Publication	Ref	Species	TBI model	Injury severity	Control	Time between injury and sleep recording	Measure of sleep	Sleep or qEEG phenotype
Willie JT and Lim MM et al, 2012, <i>J Neurotrauma</i>	155	Mice	CCI	Moderately severe	Sham surgery	0–3 days	EEG and EMG	<ul style="list-style-type: none"> <li>Increased sleep and shorter wake bouts</li> <li>Increased sleep–wake fragmentation</li> </ul>
Lim MM et al, 2013, <i>Sci Trans Med</i>	164	Mice	Lateral FPI	Mild	Sham surgery	8–13 days	EEG and EMG	<ul style="list-style-type: none"> <li>Increased sleep</li> <li>Increased sleep–wake fragmentation</li> </ul>
Skopin MD and Kabadi SV et al, 2014, <i>J Neurotrauma</i>	165	Rats	Lateral FPI	Moderate	Sham surgery	6, 19, and 29 days	EEG and EMG	<ul style="list-style-type: none"> <li>Increased sleep–wake fragmentation</li> </ul>
Rowe RK et al, 2014, <i>PLoS ONE</i>	169	Mice	Midline FPI	Mild and moderate	Sham surgery	0–7 days continuous	Piezoelectric cage system	<ul style="list-style-type: none"> <li>Increased sleep for first 6 hours post injury</li> </ul>
Rowe RK et al, 2014, <i>SLEEP</i>	170	Mice	Midline FPI	Moderate	Sham surgery	0–7 days continuous	Piezoelectric cage system	<ul style="list-style-type: none"> <li>Increase in sleep only during first hour of dark phase (~10 hours post injury)</li> </ul>
Rowe RK and Harrison JL et al, 2014, <i>Brain Inj</i>	171	Mice	Midline FPI	Moderate	Sham surgery	0–7 days continuous	Piezoelectric cage system	<ul style="list-style-type: none"> <li>Increased sleep for first week post injury with no change between weeks 2–5</li> </ul>
Petraglia AL et al, 2014, <i>J Neurotrauma</i>	173	Mice	Single and repetitive closed head CCI	Mild (single and repetitive)	Non-surgery control	1 month	EEG and EMG	<ul style="list-style-type: none"> <li>Decreased sleep</li> <li>Increased sleep–wake fragmentation</li> <li>Decreased NREM</li> </ul>
Hazra A et al, 2014, <i>J Neuroscience Res</i>	168	Mice	CCI	Mild	Sham surgery	28 days	CageScan Software	<ul style="list-style-type: none"> <li>Increased sleep–wake fragmentation</li> <li>Increased latency to reach peak sleep</li> </ul>
Sabir M and Gaudreault PO et al, 2015, <i>Brain Behavior Imm</i>	157	Mice	Closed head weight drop	Mild	Sham surgery	0–2 days	EEG and EMG	<ul style="list-style-type: none"> <li>Shorter bouts of wakefulness – state instability</li> <li>Spectral changes - delta power</li> </ul>
Bücheler F and Morawska MM et al, 2016, <i>J Neurotrauma</i>	158	Rats	Closed head weight drop	Not specified	Sham surgery	1, 7, and 28 days	EEG and EMG	<ul style="list-style-type: none"> <li>No change in the proportion of time spent in wakefulness, NREM, and REM</li> </ul>
Thomasy HE et al, 2016, <i>Neurobiol Sleep Circ Rhythm</i>	167	Mice	CCI	Mild and moderate	Sham surgery	7 and 15 days	EEG	<ul style="list-style-type: none"> <li>Increased sleep</li> </ul>
Morawska MM and Bücheler F et al, 2016, <i>J Neuroscience</i>	159	Rats	Closed head weight drop	Not specified	Sham surgery	5 days	EEG and EMG	<ul style="list-style-type: none"> <li>Increased in sleep</li> <li>Increase in sleep–wake fragmentation</li> <li>Spectral changes - delta power</li> </ul>
Olson E et al, 2016, <i>J Neurotrauma</i>	172	Piglets	CCI	Not specified	Non-surgery control	4 days	Actigraphy	<ul style="list-style-type: none"> <li>Increased lethargy</li> </ul>
Modarres et al, 2016, <i>Neurobiol Sleep Circ Rhythm</i>	100	Mice	Lateral FPI	Mild	Sham surgery	8–13 days	EEG and EMG	<ul style="list-style-type: none"> <li>Increased slow waves during wakefulness</li> <li>Spectral changes – theta:alpha ratio</li> </ul>

All mice were C57BL/6 and all rats were Sprague-Dawley. All studies used male animals with the exception of Hazra et al where the sex was not clearly identified, and Olson et al where piglets were all female.

Abbreviations: CCI, controlled cortical impact injury; FPI, fluid percussion injury; EEG, electroencephalography; EMG, electromyography; NREM, non-rapid eye movement; REM, rapid eye movement.



TBI (potentially with skull fracture). The weight drop model, particularly in more severe models with skull fracture, often requires ventilating the animal postinjury with 100% oxygen. The potential effects of administering supplemental oxygen postinjury are unknown, but considering the known increase in oxidative stress with supplemental oxygen,<sup>162,163</sup> this is a notable methodological difference compared to FPI and CCI.

### Comparison to Sleep–Wake Disturbances in Humans After TBI

Researchers have only recently begun to explore sleep physiology in these animal models of TBI (Table 3). One of the earliest reports of sleep–wake abnormalities in an animal model of CCI-induced moderate TBI demonstrated a trend for brain injured mice to show less wakefulness during the dark phase (when mice are typically more awake) and increased sleep fragmentation.<sup>155</sup> Hypothalamic ORX levels, examined via in vivo microdialysis, were reduced in injured mice compared to uninjured control animals. Indeed, hypothalamic ORX levels in uninjured animals followed a normal diurnal fluctuation according to sleep–wake state and activity. These data suggest that TBI-related impairment in ORX neurotransmission may underlie the presence of sleep–wake disturbances after TBI.

More recent work using rodent models<sup>164,165</sup> of lateral FPI-induced mild TBI have not only reproduced the phenotype of increased sleep–wake fragmentation and decreased levels of overall activity observed after moderate TBI but also support the hypothesis that TBI-related impairment in ORX neuron activation, at least in part, drives sleep–wake disturbances after TBI. In the mouse model of lateral FPI-induced mild TBI, increased sleep–wake fragmentation coincides with impaired ORX neuron activation, examined via cFOS activation, while restoration of ORX neuron activation restores normal sleep–wake state patterns.<sup>164</sup> Restoration of ORX neuron activation was accomplished via dietary supplementation with branched chain amino acids (BCAAs), which are essential amino acids required for de novo cerebral glutamate and GABA synthesis that also ameliorate TBI-related cognitive impairment in mice.<sup>166</sup> We recently reported decreased glutamate within the presynaptic terminals synapsing onto ORX-positive cells in the hypothalamus after TBI, suggesting decreased excitatory inputs onto this critical wake-promoting system.<sup>130</sup> Accordingly, BCAA supplementation, via increasing glutamate synthesis, is likely restoring normal cortical excitability and thereby ORX neuron activation. Furthermore, in a mouse model of CCI-induced TBI there is both a reduction in the overall number of ORX positive cells in the perifornical region of the lateral hypothalamus as well as a reduction in the number of cholinergic neurons in the basal forebrain corresponding increased TBI-related NREM sleep time.<sup>167</sup>

Also, possibly consistent with a TBI-induced change in the ORX system, Hazra et al. reported increased awakenings from sleep and shorter bouts of sleep during the light phase at 28 days post-CCI induced TBI in mice.<sup>168</sup> Astrocytosis, a histological marker of brain injury, occurred immediately in the cortex but was delayed in subcortical structures (e.g., the thalamus). Localized thalamic microglial activation also increased over time, suggesting a distinct temporal and spatial neurodegenerative response to TBI that may parallel the changes in sleep over the temporal course of TBI recovery.

More recent work using a midline FPI model of TBI in mice shows a similar increase in sleep-like activity acutely post-TBI. First, Rowe et al. reported an increase in sleep (>50%) during the first 6 hours post-TBI that was accompanied by increases in proinflammatory cytokines (i.e., IL-1 $\beta$ ) and IBA-1 positive microglia.<sup>169</sup> Subsequently, the same group investigated the effect of disrupting sleep for 6 hours following TBI.<sup>170</sup> Sleep disruption acutely after injury increased sleep during the first hour of the dark period (~10 hours post-TBI). Mice that sustained TBI but were not subjected to sleep disruption did not exhibit an increase in sleep. Later, Rowe and Harrison et al. investigated the effect of TBI on chronic sleep disturbance (out to 5 weeks post-TBI).<sup>171</sup> Total sleep, sleep during the dark cycle, and sleep bout length were increased in mice that sustained TBI in the first week after injury but did not extend to the more chronic period. These findings have also been supported in large animal models of TBI. In a CCI piglet model, alterations in daytime and nighttime activity levels corresponded to an increase in lethargy.<sup>172</sup> Notably, these studies quantitated sleep-like activity using either actigraphy, or specialized noninvasive piezoelectric recording chambers and an algorithm based on respiration signals, rather than EEG/EMG recordings.

Several studies have utilized a closed head model of TBI such that no craniotomy is required to induce the injury. Petraglia et al. subjected mice to either a single impact or repetitive impacts in an attempt to mimic chronic traumatic encephalopathy.<sup>173</sup> These authors reported a decrease in sleep 1 month postinjury, specifically manifested by less time spent in NREM sleep. No difference was observed in the total time spent in REM sleep; however, injured animals exhibited an increase in EMG activity during REM sleep, indicative of REM sleep disturbance. In contrast, Sabir et al. observed shorter bouts of wakefulness (indicating state instability) after a similar closed head model of TBI during the first 24 hours postinjury.<sup>157</sup> However, more recent work found no differences in the proportion of time spent in wakefulness, NREM, and REM sleep during the light period between injured and control groups.<sup>158</sup>

Taken together, the majority of studies suggest a hypersomnolence phenotype in animal models of TBI that resembles reports of EDS and insomnia (e.g., manifesting as sleep fragmentation) in humans. Nevertheless, subtle differences in this finding are clearly present in the literature. Regardless of the experimental model of TBI and time course, 5 studies reported an acute increase in sleep,<sup>155,157,159,169,171</sup> 3 studies report a chronic increase in sleep,<sup>164,165,167</sup> and 5 studies report an increase in sleep fragmentation.<sup>155,159,164,168,173</sup> However, 2 studies did not demonstrate sleep–wake changes after TBI,<sup>158,170</sup> and 1 study reported a decrease in total sleep time at a chronic time point after TBI.<sup>173</sup> Several possibilities may explain these discrepancies. Methodological differences in the type and severity of injury (CCI versus lateral FPI versus midline FPI, mild versus moderate), the time point at which sleep is examined (acute versus subacute versus chronic), and the method of determining sleep (e.g., EEG versus activity-based surrogate) likely all contribute to these inconsistencies. Variation between individual animals and heterogeneity of response in this inherently heterogeneous disease also likely play a role. Notably, only 4 studies have examined animals pre- and postinjury, allowing for repeated measures testing and addressing the issue of individual

heterogeneity in response to TBI.<sup>155,159,167,169</sup> Furthermore, subtle differences may be expected based on the species, strain, sex, and potentially the age of the animals. Indeed, there is an increased appreciation for the importance of utilizing young-adult animals that are sufficiently mature to avoid potential contamination by early systemic maturation on a studies primary outcome variables.<sup>174</sup> For example, although 8-week-old mice are frequently considered to be “adult,” recent work reported a marked change in respiratory mechanics by 6 months of age (when body weight stabilizes<sup>175</sup>) which was hypothesized to be attributable to continued systemic maturation.<sup>176</sup> Other factors, such as inflammatory and cellular responses in the brain to injury, are strongly affected by age.<sup>177-179</sup> Thus, it remains possible that the physiological response to TBI differs based on the animal’s age.

### **SLEEP AS AN EXACERBATING FACTOR AND PREDICTOR OF TBI RECOVERY**

It is generally accepted that sleep is a critical neurophysiological process that is necessary for cognitive and behavioral functioning<sup>180</sup>; however, a clear consensus regarding the precise physiological function of sleep remains inconclusive.<sup>181</sup> Impairments in cognition and physical functioning following sleep deprivation have been well documented.<sup>182-184</sup> Mild disruption of even a single 24 hour sleep–wake cycle is associated with behavioral changes and emotional lability<sup>185</sup> that resolve when normal sleep patterns resume.<sup>180</sup> Given the impact of sleep disruption on the healthy brain and the pathophysiological mechanisms implicated in the studies described earlier, there has been much interest and speculation over the role that sleep disruption might impact recovery after TBI. Improved understanding of sleep disruption in TBI recovery is of particular interest, as there are numerous treatment options available.

### **Relationship of Sleep and Recovery Across the TBI Spectrum in Humans**

Sleep–wake disturbances have long been recognized following moderate–severe head injury based on observations in the acute care and rehabilitation settings. More recently, the impact of sleep–wake disturbances in those with mild TBI is being increasingly recognized and appreciated for its impact on quality of life and recovery after mild TBI.

Following mild TBI in humans, there is frequently a period of hypersomnolence, which can last for a week or more.<sup>61,186</sup> The role of this in TBI recovery and how interference during this time might impact healing is not well understood. Patients in whom sleep–wake disturbances persist beyond this acute period tend to have worse outcomes when followed longitudinally. In sports-related concussion, athletes who reported sleep–wake disturbances exhibited higher symptom burden on postconcussive questionnaires that persisted during clinical follow-up.<sup>187</sup>

It is long recognized that sleep and mental well-being are interrelated and mutually affect each other. Thus, sleep disruption after TBI may simply be a reflection of underlying psychiatric comorbidities such as depression and anxiety.<sup>188</sup> However, several studies suggest that sleep–wake disturbances impact clinical outcome independent of these associated conditions. Workers with chronic mild TBI who reported sleep–wake disturbances/insomnia more than 6 months after injury were more

likely to report marked/extreme global disability, even after controlling for depression, anxiety, and pain.<sup>189,190</sup> In 374 patients who sustained mild TBI, 71% of patients reported sleep–wake disturbances at baseline assessment; at 1 year, 50% had persistent sleep disturbance.<sup>188</sup> When analyzed in a multivariable model, sleep disruption was a predictor of poor functional outcome at 1 year while a measure of psychological distress was not. These data suggest that sleep–wake disturbances may represent a therapeutic target following mild TBI to promote recovery from other postconcussive symptoms.

In more severe forms of TBI, sleep disturbance following TBI has been best studied in the rehabilitation setting. Holcomb et al.<sup>191</sup> prospectively examined the relationship between sleep disruption and cognitive recovery in 106 patients admitted to an acute rehabilitation center following TBI. They found that persistent sleep disruption was associated with poorer cognitive recovery over a 3-week period of admission. Importantly, this was not influenced by injury severity. Persistence of sleep–wake disturbances is associated with a longer length of stay in the acute rehabilitation setting<sup>51</sup> while restoration of sleep is associated with recovery from the posttraumatic confusion state<sup>192</sup> and return of memory.<sup>193</sup> In the first 3 months following moderate to severe head injury, sleep–wake disturbances actually predicted the development of neuropsychological sequelae, including depression, anxiety, and apathy, at 6 and 12 months after injury.<sup>194</sup> Whether treatment of sleep–wake disturbances could impact these long-term outcomes remains to be studied.

Much less is known about how sleep disruption in the acute setting might predict or impact long-term outcome after TBI. In the acute phase immediately after injury, Duclos et al. used actigraphy to monitor patients hospitalized after TBI.<sup>3</sup> Rest episodes were highly fragmented in the acute period following moderate–severe TBI, correlating with poor sleep–wake cycles. Consolidation of rest and activity phases, which corresponds with restoration of sleep–wake cycles, was associated with a shorter length of acute hospitalization and lower disability rating scale scores at hospital discharge. Patients with a more rapid return to consolidated rest–activity patterns also exhibited more rapid resolution of posttraumatic amnesia. Others have examined sleep EEG to predict emergence from coma in disorders of consciousness (e.g., in some cases resulting from severe brain injury) and found that the amount of spindles and REM sleep are good prognostic indicators.<sup>195</sup>

We recently examined sleep characteristics in severely injured patients ( $n = 65$ ) who underwent continuous EEG monitoring for a mean time of 51 hours during their acute hospitalization in the neurological intensive care unit for severe TBI.<sup>196</sup> We found that objective evidence of sleep was present in 30% of patients with severe TBI and was associated with an improved outcome at hospital discharge. Importantly, the presence or absence of sleep characteristics was not predicted by injury severity as assessed by GCS score or Rotterdam neuroimaging score on admission. While much more work needs to be done, these studies raise the important possibilities that (1) sleep characteristics in the acute period following brain injury may provide prognostic information for patients and families and (2) optimization of sleep in the early period after moderate-to-severe TBI may impact brain recovery.<sup>196</sup>

## Relationship of Sleep and Recovery Across the TBI Spectrum in Animals

Similar to humans, most reports of animal models of TBI indicate that they exhibit a period of hypersomnolence following TBI, although, just as in humans, the role this plays in recovery is not well understood. Morawska and Büchele et al. demonstrated in a rat model of TBI that slow oscillatory activity in the delta frequency range is key to facilitating cognitive improvement following TBI.<sup>159</sup> In this study, both sleep induction with the drug gamma-Hydroxybutyric acid (GHB), and sleep restriction via gentle handling, prevented the development of cognitive impairment that was observed in animals that received TBI alone. Although these results may at first seem contradictory, the authors attributed these findings to an increase in delta power (slow wave sleep) in both experimental groups. Indeed, GHB increases oscillatory activity in the delta frequency.<sup>197,198</sup> Similarly, sleep restriction results in more frequent and larger slow waves during subsequent sleep recovery periods in humans<sup>199</sup> and rats.<sup>200</sup> These data support previous work by the same group utilizing GHB to accelerate recovery after ischemia/brain damage, in light of their findings that sleep disruption exacerbated histological injury and delayed recovery after stroke.<sup>201</sup> GHB administration in mice after focal cerebral ischemia accelerated stroke recovery as determined by increased body weight and motor grip strength, compared to control animals.<sup>202</sup> Similar findings have been reported in rat models of cerebral ischemia, where GHB administration improved sensorimotor activities and memory.<sup>203,204</sup> Previous work showing a neuroprotective effect from sleep deprivation on TBI in rats may be partially explained by the increase in delta power.<sup>205</sup> Similarly, sleep deprivation prior to induction of focal cerebral ischemia in the rat<sup>206</sup> or TBI<sup>207</sup> is neuroprotective or at least does not increase neuronal susceptibility to injury.<sup>208</sup> Interestingly, there is also evidence that acute sleep deprivation induces neurogenesis in the hippocampus<sup>209,210</sup> and increases the expression of neurotrophins in the cortex.<sup>211</sup>

The mechanism underlying the delta power-associated improvements in neurocognition could be relevant to the recently described brain glymphatic system, which shows enhanced clearance of toxins and waste products from cerebral interstitium during sleep.<sup>212</sup> This phenomenon may be relevant to the development of neurodegenerative disorders such as Alzheimer's disease and chronic traumatic encephalopathy resulting from TBI.<sup>213,214</sup> Interestingly, a recent study by Plog et al. show biomarkers of TBI are transported from the injured brain, to the blood, via the glymphatic system.<sup>92</sup> To date, sleep modulation of the brain glymphatic system has only clearly been demonstrated in rodents, therefore much still remains to be determined with regard to glymphatics and TBI in humans.

## TREATMENT OPTIONS FOR SLEEP-WAKE DISTURBANCES AFTER TBI

Given the paucity of empiric treatment options to facilitate TBI recovery, the prevalence of sleep disturbance following TBI, and the association of poor clinical outcomes with disturbed sleep, it is reasonable to consider therapies to optimize sleep early in the TBI recovery process. While current treatment options vary for individual patients according to the specific sleep disorder or dominant symptomatology, emerging data from preclinical

models suggest that there are unique mechanisms to sleep-wake disturbances after TBI that may be amenable to therapy to improve clinical outcomes.

### Symptom-Directed Therapy

Current therapies for sleep-wake disturbances after TBI are extrapolated from therapies used for non-TBI sleep-wake disturbances. Therefore, the lowest dose of medications for the shortest duration possible should be used whenever feasible, particularly in those with cognitive impairment who may be more sensitive to medication-related side effects.<sup>215</sup> Any underlying condition, such as obstructive sleep apnea, restless legs syndrome, depression, thyroid dysfunction, and anemia, should be evaluated and treated.

In a study of 70 military personnel with TBI, initiation of behavioral therapy, medications, and continuous positive airway pressure (CPAP), as applicable based on individual patient characteristics, led to an improvement in measures of depression and PTSD in those who responded to treatment.<sup>216</sup> Similar results were seen in a small, community-based study in patients with chronic TBI (1–22 years after injury).<sup>217</sup>

Cognitive-behavioral therapy for insomnia (CBT-I) is quite efficacious in general populations with insomnia.<sup>218,219</sup> However, the efficacy of CBT-I after TBI has only been examined in small studies.<sup>186,187</sup> In one such study, insomnia symptoms persisted after CBT-I, but depression and anxiety improved.<sup>186</sup> In a study of 11 patients with TBI, CBT-I was effective in 73% of patients, resulting in a reduction in total wake time of >50%.<sup>220</sup> This effect persisted over 3 months of follow-up and was accompanied by an improvement in related symptoms such as fatigue. Acupuncture was associated with an improvement in perception of sleep and cognition in a small sample of patients with TBI having insomnia, though it did not increase sleep duration.<sup>221</sup> Blue light therapy has been shown to be helpful in a small study of patients with TBI.<sup>222</sup> Additionally, moderate intensity aerobic exercise has been shown to be effective in improving sleep quality, cognitive function, and neurobehavioral function in patients with TBI.<sup>223,224</sup>

Both benzodiazepine and nonbenzodiazepine medications can be efficacious for treatment of insomnia after TBI,<sup>225</sup> although these medications have not been studied in comparative trials in this patient population. It should be noted that benzodiazepines have been reported to suppress slow wave sleep, the stage of sleep which has recently been hypothesized to be important for recovery after TBI.<sup>35,159</sup> Further research on the important role of slow wave sleep and TBI will inform the potential need to change our current clinical management of sleep-wake disturbances in patients with TBI. ORX receptor antagonists are the newest agents to become available for the treatment of insomnia. Three randomized controlled trials have shown that these agents are well tolerated and efficacious in the treatment of insomnia.<sup>226–228</sup> Other pharmacologic treatment options for EDS include agents that, rather than optimize sleep, promote wakefulness (modafinil and armodafinil) and stimulants (methylphenidate). Four randomized trials investigating the use of modafinil and armodafinil in patients with TBI<sup>229–232</sup> showed improvement in some, but not all, measures of subjective sleepiness. Finally, a pilot study employing a melatonin receptor agonist, ramelteon, that targets melatonin receptors 1 and 2 located in the suprachiasmatic nucleus of the hypothalamus, has shown promise in treating insomnia in patients with



TBI.<sup>233</sup> For review of additional pharmacotherapeutic options for sleep–wake disorders after TBI and other neurologic sequelae, we refer the reader to a previous review on the subject.<sup>234</sup>

### Emerging Data on Novel Therapies for Sleep–Wake Disturbances After TBI

Emerging data from preclinical models suggests that there may be other options for the treatment of sleep after TBI. For example, we recently established a mouse model of mild TBI with sleep–wake disturbances that exhibited improved sleep through dietary supplementation of BCAAs, which are essential amino acids required for de novo glutamate, and subsequently GABA, synthesis in brain.<sup>164</sup> Mice administered BCAA therapy ad libitum in the drinking water showed improvements in TBI-induced sleep–wake disturbances, maintenance of wakefulness, and ORX neuron activation. More recent work from our group demonstrated that BCAA supplementation is required for at least 5 continuous days of administration in order to successfully treat cognitive impairment after TBI.<sup>235</sup> Interestingly, withdrawal of the BCAA therapy caused mice to revert back to the injured phenotype, suggesting that BCAA needs to be on board for efficacy. This time course and dependency is consistent with the purported mechanism of TBI causing decreased substrate required for glutamatergic synaptic neurotransmission. Indeed,

recent data from our laboratory showed that mice with TBI on BCAA supplementation showed a restoration of glutamate within presynaptic terminals synapsing onto ORX-positive cells in the hypothalamus, compared to mice with TBI not on therapy.<sup>130</sup> These data provide evidence that BCAA therapy may prove beneficial in enhancing the cognitive recovery of human subjects after mild TBI. In two small studies on patients with severe TBI, subjects given intravenous BCAA supplementation for 15 days showed improvement in the modified Rankin Scale score at hospital discharge, although sleep was not examined as an outcome in these studies.<sup>236,237</sup> A clinical trial is currently underway to examine the efficacy of BCAA therapy after sports-related concussion in cognition and sleep as measured by actigraphy ([www.clinicaltrials.gov](http://www.clinicaltrials.gov), NCT01860404).

Another potential therapy may be to enhance sleep directly using agents that promote sleep and/or delta power during sleep, such as sodium oxybate or GHB.<sup>238</sup> As discussed earlier (see Section 7.2), the cognitive impairment observed in rats after TBI can be attenuated by sleep modulation using GHB, through increasing delta power, and reducing posttraumatic amyloid precursor protein accumulation in the cortex and hippocampus.<sup>159</sup> While early in the pipeline, these potential therapies are promising, mechanistic-based alternatives to current symptomatic treatment of sleep–wake disturbances after TBI.

Human	Shared Findings	Animal
<b>Neuropathology</b> ↓ Serum and salivary melatonin <sup>66,123,124</sup> ↓ Serotonin in dorsal raphe <sup>106</sup> ↓ Norepinephrine in locus coeruleus <sup>106</sup> ↑ Metabolic glutamate in injured cortex <sup>129</sup> ↓ Histaminergic neurons in hypothalamus <sup>120</sup> ↓ MCH in hypothalamus <sup>120</sup>	↓ Orexin in hypothalamus <sup>6,118,120,155,165,168</sup>	↓ Acetylcholine in basal forebrain <sup>168</sup> ↓ Synaptic glutamate in injured cortex <sup>127,128,130</sup> ↑ Thalamic microglial activation <sup>169</sup> ↑ Astrocytosis <sup>169</sup> ↑ Pro-inflammatory cytokines <sup>170</sup> – Histaminergic neurons in hypothalamus <sup>168</sup> – MCH in hypothalamus <sup>155</sup>
<b>Neurophysiology (EEG)</b> ↓ Number of K-complexes <sup>99</sup> ↑ Sleep spindles during slow-wave sleep <sup>99</sup> –/↑ NREM sleep time <sup>52,96</sup> ↑/↓ Delta power <sup>52,94-97,240</sup>	↑ Slow-waves during wakefulness <sup>100</sup>	↓ Theta:Alpha ratio <sup>100</sup> –/↓ NREM sleep time <sup>161</sup> ↑ Delta power <sup>160</sup>
<b>Sleep-Wake Phenotype</b> ↓ Sleep efficiency <sup>94,95,239</sup> ↑/↓ Sleep latency <sup>52,100,94,95,99</sup> ↓ REM sleep latency <sup>239</sup>	↑ Sleep fragmentation <sup>155,162,165,169,174</sup> ↑ Sleep time <sup>52,155,160,162,165,167,168,170,172</sup>	↑ Number of sleep bouts <sup>155,160</sup> ↓ Duration of wake bouts <sup>160</sup>
<b>Treatment Options</b> CBT for insomnia <sup>187,188,220</sup> Bright light therapy <sup>222</sup> Melatonin/Ramelteon <sup>233</sup> Modafinil/Armodafinil <sup>229-232</sup> Benzo/non-benzodiazepines <sup>225</sup> Aerobic exercise <sup>223,224</sup> Acupuncture <sup>221</sup>	<i>None</i>	Branched chain amino acids <sup>165</sup> gamma-Hydroxybutyric acid <sup>162</sup>

**Figure 1**—Summary table showing the findings from animal and human studies with regard to several levels of analysis: neuropathology, neurophysiology, sleep–wake phenotype, and treatment options. Findings that are shared between animal and human studies are depicted in the center “Shared Findings” column. An absence of any Shared Findings in the Treatment category suggests that there is opportunity to move potential treatments identified in animal studies into the human condition. Abbreviations: EEG, electroencephalography; NREM, nonrapid eye movement sleep; REM, rapid eye movement; MCH, melanin-concentrating hormone; CBT, cognitive–behavioral therapy.



## SUMMARY

There are few disorders as heterogeneous and complex as TBI. The collective work described herein highlights the importance and value of clinicians and basic scientists working closely together to improve our understanding of this complex human condition. A summary figure that synthesizes what is known about the pathology, physiology, sleep–wake phenotype, and treatment options from both the human and the animal literature is shown in [Figure 1](#). In this review of the existing literature, we showcase the ability of preclinical animal models to recapitulate many aspects of human sleep–wake disturbances, including hypersomnolence, sleep fragmentation, increased slow wave activity, and decreased orexin function in the hypothalamus. Animal studies have offered important insights into the pathophysiological mechanisms of TBI sleep–wake disturbances that had remained elusive from human studies plagued by injury heterogeneity and methodological variability. While this research is still early, it is clear that there is a dearth of treatments in use as a result of bench to bedside translation of findings from animal models. These models have led to the identification several sleep-targeted therapies with potential to improve recovery after TBI. Further work using quantitative metrics, both biochemical (ORX, other biomarkers) and electrophysiological (qEEG), will help to refine the diagnosis, prognosis, and treatment of sleep–wake disturbances after TBI. Finally, an implication of this review is that longitudinal/prospective studies with high-risk populations (in conjunction with parallel pre-post injury studies in animal models) are needed, to advance our understanding of the role of different aspects of sleep in TBI and recovery.

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## DISCLOSURE STATEMENT

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