Sleep and Wake Disorders Following Traumatic Brain Injury: A Systematic Review of the Literature

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ABSTRACT: Traumatic brain injury is a leading cause of death and disability in both Canada and the United States. Disorders of sleep and wakefulness are among the most commonly reported sequelae postinjury, across all levels of severity. Despite this, sleep and wakefulness are neither routinely, nor systematically, assessed and are only recently beginning to receive more clinical and scientific attention. *Objectives:* This review aims to systematically appraise the literature regarding sleep and wake disorders associated with traumatic brain injury according to the following domains: epidemiology, pathophysiology, neuropsychological implications, and intervention; to summarize the best evidence with a goal of knowledge translation to clinical practice; and to provide recommendations as to how the field can best be advanced in the most scientifically rigorous manner. *Methods:* Systematic review and rating of the quality of evidence. *Results:* Forty-three articles were reviewed for levels and quality of evidence. Fifty-six percent of the literature was classified as Level III, and 24 percent were Level IVA. Overall, 89 percent of the studies were rated as moderate quality. A separate summary was provided for the pediatric literature. *Conclusions:* A comprehensive review of the emerging literature revealed wide ranges in estimates for incidence and prevalence of sleep disorders following TBI depending on characteristics of patients, measures used, and length of follow-up. Few treatments have been found to be effective, and as such more research is recommended. Our overview of the pediatric literature shows that this is an important issue for survivors of all ages. Overall, further work is needed to fully understand this complex disorder and to identify appropriate and timely interventions.

KEY WORDS: traumatic brain injury, mild traumatic brain injury, sport-related concussion, sleep, sleep disorders, insomnia, hypersomnia, excessive somnolence, treatment

I. BACKGROUND AND INTRODUCTION

A. Overview and Objectives

Traumatic brain injury (TBI), defined as an acquired nondegenerative, noncongenital insult to the brain from an external mechanical force, is a leading cause of death and disability in both Canada and the United States for both adults and children.¹ Furthermore, although the literature re-

viewed in this paper is truly international in scope, at this time in the United States, “the nature of modern tactical engagement...in the current Iraq and Afghanistan conflicts has resulted in the largest proportion of identified traumatic brain injuries in any conflict in the nation’s history.”^{2(p. 1004)} In fact, the US Department of Defense reported an incidence of 10,963 diagnosed conflict-related TBIs in the year 2000. However, this incidence was reported as 27,862 by December 31, 2009,

which represents an increase of 145%.³ TBI can result in significant impairments in physical, neurocognitive, and psychosocial/emotional function, as well as impairments in communication and sleep. Regardless of injury severity, these impairments may be transient or permanent, resulting in profound disruption for survivors and their families.

Disorders of sleep and wakefulness are among the most commonly reported sequelae postinjury, across all levels of severity.^{4,5} Despite this, sleep and wakefulness are neither routinely, nor systematically, assessed postinjury, and are only recently beginning to receive more clinical and scientific attention. Previous reviews by Ouellet and colleagues,⁶ Orff and colleagues,⁷ and most recently by Zeitzer and colleagues⁸ indicate that the field is still in a developmental stage and a body of literature is beginning to emerge. These previous reviews focused primarily on the prevalence and nature of sleep disorders and, to a lesser extent, on implications and effective treatment strategies among adult TBI survivors.

As of yet, there has been no systematic appraisal of the literature, nor has there been a review that has included literature pertaining to a pediatric population. The literature on pediatrics is of particular relevance given the fact that approximately 500,000 children aged younger than 17 years are hospitalized each year with TBIs in the United States.^{9,10} This statistic does not include those children with minor TBIs who were either seen by their family physician/pediatrician or remained undiagnosed. Furthermore, TBI is the leading cause of disability in those under the age of 24 years, and the peak age of occurrence for TBI is 15–24 years.¹¹ Thus, the unique contributions of this paper are: 1) to systematically update and extend previous reviews on sleep and brain injury^{6–8} by conducting a thorough critical appraisal of the methodological quality of the literature that includes both children and adults and then, based on the identified strengths, weaknesses, and inconsistencies in the current literature; 2) to summarize the best evidence that currently exists with a goal of translating knowledge to clinical practice; and 3) to provide specific recommendations as to how the field can best be advanced in the most scientifically rigorous manner, given the unique complexities of this disorder.

In summary, the objectives of this review are to systematically appraise the literature regarding sleep and wake disorders associated with TBI according to the following domains: epidemiology (including sports-related concussion), pathophysiology, neuropsychological implications, and intervention. Furthermore, we will identify practice points and provide recommendations for a research agenda, based on the current body of literature.

In order to provide readers with a clearer understanding of the importance of sleep (and wakefulness) in the rehabilitation and recovery process, we begin with a brief definition of sleep and an overview of the role and functions of sleep.

B. Definition of Sleep and Its Functions

To fully grasp the significance of the impact of sleep disturbances postinjury, it is important to have a clear understanding of the actual definition of sleep and the critical roles and function it plays in human (and animal) physiology and homeostatic regulation. In 1995, Tobler¹² defined sleep as a physiological, complex, and integrated behavior characterized by a significant reduction of the response to external stimuli, by a characteristic posture usually in a special environment, by a characteristic change in the neurophysiological recordings of brain activity, and by a homeostatic increase after its restriction. Sleep is a critical function that serves to reverse and/or restore biochemical and/or physiological processes that are progressively degraded during prior periods of wakefulness.

Sleep is believed to be essential for optimal immune function by influencing cellular (T-cell) immunity. Furthermore, an increase in growth hormone secretion is observed immediately following sleep onset, concurrently with a rise in cortisol in the latter half of sleep. This is critical for growth and development and is also important from the perspective of recovery from trauma, because not only does human growth hormone stimulate growth and cell reproduction, it also plays a critical role in cell regeneration. Furthermore, cortisol plays a crucial role in facilitating the body's adaptation to physical and mental stress, in the suppression of inflammation, enhancement

of wound healing, modulation of plasma glucose, and increased production of erythrocytes (red blood cells).¹³

Sleep is divided into non-REM (rapid eye movement) and REM sleep. Studies of non-REM and REM sleep and the importance of their temporal succession in both animals and humans reveal that these stages have been found to play key roles in certain types of memory and learning, as well as cerebral plasticity.^{14–16} REM sleep, which occurs at the end of each sleep cycle, and the overall length of the REM cycle peaks prior to wakening also play a key role in aspects of memory consolidation and new learning. Furthermore, REM sleep during the neonatal period plays an important role in brain growth, neuronal maturation, connectivity, and synaptic plasticity in infants.¹⁷ Thus, recognition of the critical role that sleep plays in endocrine and immune function, thermoregulation, cognition, and behavior underscores the need to evaluate and optimize sleep during recovery from brain injury.

II. METHODOLOGY

An extensive and iterative literature search was conducted using the Ovid, Medline, PsychInfo, CINAHL, and EMBASE databases to ensure the capture of any relevant studies pertaining to the assessment of sleep after TBI. Medical subject heading terms included: brain injuries or brain concussion or brain hemorrhage, traumatic or brain injury, chronic or diffuse axonal injury/sleep disorders/insomnia, and hypersomnia. The search was limited to articles published in English from 1998–2009. Only peer-reviewed full-text articles were considered for this study.

The search was initially exhaustive to include titles relating to both acquired brain injury and TBI, as the terms are sometimes used synonymously. This allowed us to ensure that we captured all relevant studies. Each article abstract was then reviewed to further ensure relevance. Additional search strategies were also employed and as such, the reference lists of all articles were scanned for additional studies that may be relevant for review. Because the literature on the relationship between sleep disturbances and TBI is still developing,

our inclusion criteria were quite broad and all identified articles were reviewed.

We then subdivided the articles into five different domains of scientific inquiry, including epidemiology, pathophysiology, pediatrics, intervention, and neuropsychological implications. Because there are a limited number of articles in the different subcategories of focus, all identified articles from Level II to Level V were included. In all, 68 articles were evaluated and 43 articles were included for the purposes of this review. We excluded only those that we deemed to be opinion papers or consensus papers not based on the results of a specific scientific study.

To critically appraise and stratify the quality of the evidence, the articles were evaluated on their research design and scientific rigor. Although it was not our intention to conduct a meta-analysis such as those undertaken by the Cochrane Collaboration Group, the ranking criteria were selected from the literature on evidence-based practice in rehabilitation, with a goal of providing guidance to end users about the studies likely to be most valid. Thus, the articles were categorized according to the scientifically validated hierarchy developed by Holm and edited by Boschen and colleagues (Table 1).^{18,19} Other rating systems are available;^{20–22} however, the Holm hierarchy^{18,19} was chosen in order to better differentiate among the published studies that exist at this point in the development of the literature on sleep and TBI. Given the early stage of development and the inherent complexities of the field, few randomized control trials (RCTs) have been conducted. It is, therefore, necessary to use a hierarchy that gives weight to non-RCT designs and also has a place for well-designed qualitative studies. Although the Holm hierarchy is an appropriate choice, it still did not fully differentiate the literature for our purposes. Thus, the edited and published version used by Boschen and colleagues¹⁹ was used for this systematic review.

Boschen and colleagues added two additional levels to the Holm hierarchy: the first is Level IIA, which was added to evaluate review papers that did not meet the criteria for Level I as they included non-RCT designs, and the second is Level IVA, which was added to separate out the well-designed non-experimental research designs such as cost analyses and the qualitative designs

TABLE 1
Total Number of Articles Retrieved by Level of Evidence

Level of Evidence	No. of Articles	Article Type
Level I ^a	0	Systematic reviews of randomized controlled trials (RCTs)
Level II	2	Properly designed individual RCTs of appropriate size
Level IIA ^b	2	Systematic reviews of case-controlled, cohort, or other experimental designs (including RCTs reviewed together with other experimental designs)
Level III	25	Well-designed trials without randomization, single group pre-post, cohort, time series, or matched case-controlled studies (also cross-sectional studies and case series)
Level IV	0	Well-designed non-experimental studies from more than one center or research group
Level IVA ^b	10	Well-designed individual non-experimental studies, cost analysis studies, and case studies
Level V	6	Reports of expert committees, descriptive studies, clinical observations, opinions of respected authorities, or testimonials
Total Reviewed	45	Total

^aBased on Holm.¹⁸

^bAdapted from Boschen and colleagues¹⁹ to further differentiate the evidence.

from the purely opinion and descriptive studies classified as Level V articles.

To fully capture the literature in its current state of evolution, we also considered review articles of multiple well-designed studies (called Level I and Level IIA studies in this hierarchy) in our article inclusion criteria. These review articles were considered separately from the single-study articles because they gave us a better perspective of the historical development of research in the field of sleep and TBI. Single studies were classified into levels based on the extent to which they met the criteria of the individual designated levels within this published hierarchy.

The process of assigning articles to levels was completed independently by two of the authors. Discrepancies were discussed and consensus was reached. Articles categorized as Level I or Level IIA were read and summarized but were not critically reviewed, as they were review articles in and of themselves. Published hierarchies do exist for the evaluation of systematic reviews; however, because none of the review articles identified for this systematic review were systematic in nature, these hierarchies were not applicable.

Each of the articles was evaluated using a template generated for use in this study. The templates addressed the purpose, study design, sample, outcome measures, significant findings, relevant conclusions, and comments made by the authors of the articles, as well as any special notes from the article reviewers. Two of the authors and an undergraduate student completed the templates for the articles.

In order to critically appraise the quality of the articles, information was abstracted from the templates in regard to the following seven questions:

1. Were baseline characteristics described and equivalence of groups evaluated?
2. Was the intervention/methodology described in detail, that is, sufficient for replication?
3. Was blinding employed?
4. What was the sample size per group used for data analysis?
5. What was the attrition rate?
6. Were the outcome measures used for the study standardized?
7. Was there a follow-up data collection point?

This latter question was added specifically for the purposes of this review. The authors attempted to assess whether the intervention/methodology was described in sufficient detail to allow for understanding of the key elements and to allow for replication. These items were identified based on the items used in meta-analytic and other systematic reviews.²³ The presence of the above-listed seven quality elements and their description in the articles was further rated on a three-point scale developed by Boschen and colleagues¹⁹ (Table 2). The classification of the quality rating - the sum of the scores of each of the six elements - was made using a trichotomous scheme representing “low” (summed score of <3), “moderate” (summed score of ≥3 and <5), and “high” (summed score ≥5) quality determined by the developers, based on the previous work of Boschen and colleagues. The abstraction and rating were performed independently by two of the authors and discrepancies were discussed and consensus was reached.

In addition, the articles on intervention were assigned a rating using the Downs and Black Rating System.²⁰ As the Downs and Black system is widely known and accepted, we attempted to use this for the evaluation of all of the articles included. However, although it is an excellent

tool for the assessment of the quality of evidence specific to intervention studies, we encountered a number of difficulties in applying it to the nonintervention studies reviewed in this article. Thus, the Downs and Black System was applied only to the intervention studies. The use of these two quality assessment methodologies for the intervention studies allowed for comparison and a more thorough description of the literature.

III. RESULTS

A. Previous Reviews of Sleep Disorders and Insomnia Following TBI: A Historical Overview of the Literature to Date

To date, three reviews of the literature pertaining to sleep and/or insomnia following TBI have been published (Ouellet and colleagues,⁶ Orff and colleagues,⁷ and Zeitzer and colleagues⁸). The thorough Ouellet review,⁶ which we consider to be Level IIA, was the first to be conducted on the topic of sleep disturbance following TBI. This review made a number of important contributions to our understanding of the early adult literature on this complex topic. The authors aimed to re-

TABLE 2
Criteria Used to Assess the Quality of the Studies

Rating of Assessed Characteristic	Baseline Characteristics: Described, “Equivalence”	Blinding	Sample Size (per group)	Attrition	Standardized Outcomes	Description of Intervention	Length of Follow-Up
1	Both elements present in the article	Double	>75	<15%	All	Sufficient to replicate	>3 months
0.5	Either characteristics were described or equivalence was noted, but not both	Single	30-75	15-25%	Some	Some description	0-3 months
0	Neither presented	No blinding or not stated	<30	>25%	None	No sufficient description	None

view the evidence on epidemiology, etiology, and treatment of insomnia in the context of TBI, and to propose areas for future research.

With regard to the early literature on prevalence, Ouellet and colleagues⁶ reviewed nine studies and concluded that there were significant methodological issues in many of them, including the lack of an operational definition of insomnia, and heterogeneous approaches (lack of consistency) to the assessment measures used to evaluate the presence and clinical significance of the insomnia. Furthermore, they identified that most of the studies varied in terms of the time of evaluation postinjury and the level of severity of the brain injury, making it difficult to draw any specific conclusions regarding prevalence.

Among the studies reviewed by Ouellet and colleagues, they identified a range of reported symptoms of insomnia from 30–70% in patients with TBI, with symptoms of poor sleep initiation and maintenance being the most prevalent.⁶ They also noted a range of time postinjury that symptoms (of insomnia) were present from 6–12 weeks postinjury up to several years. This was an important conclusion/observation because Ouellet and colleagues identified that “insomnia appears to develop a chronic course in a significant proportion of TBI patients.”^{6(p. 188)}

In addition, Ouellet and colleagues also identified a number of potential etiological factors that may be associated with the development of insomnia following TBI, including predisposing, precipitating, and perpetuating factors.⁶ Finally, they reviewed the literature on potential psychological and behavioral consequences of insomnia, and summarized the few studies on intervention, including pharmacotherapy and psychotherapies. The authors concluded the article with some basic practical recommendations based on the literature to date. They felt comfortable concluding that insomnia is a common problem after TBI, the etiology and maintenance of which is complicated. They further concluded that the presence of insomnia in patients with TBI likely has detrimental consequences; however, more research is needed to identify effective treatments. They suggested that because insomnia can be chronic, combinations of pharmacological and psychological treatment options should possibly be used. Data collected from non-TBI patients

suggest that cognitive behavioral therapy (CBT) has promise.

In 2009, Orff and colleagues⁷ conducted an in-depth review of the literature, which we also identified as being Level IIA. This review, which builds on the previous work by Ouellet and colleagues,⁶ included a clearly defined search strategy, key search terms, and methodology. This review aimed to address “the etiology and implications of sleep problems in TBI, particularly mild TBI (mTBI), across 4 general domains of current scientific inquiry and observation: subjective impressions of poor sleep; objective changes in sleep-related parameters; alterations in circadian rhythms; and neurophysiologic and/or neuropsychologic abnormalities associated with TBI.”^{7(p. 155)}

In the five years since the Ouellet review, the prevalence of sleep disturbances following TBI (both subjectively reported and objectively measured, although the latter has some contrary findings) has been further established, and the literature has thus evolved to more closely look at this complex disorder. With regard to subjective impressions of poor sleep, Orff and colleagues⁷ identified that the majority of studies surveyed had reasonably large sample sizes and provided replicable findings of insomnia in TBI patients, particularly those with mild TBI (mTBI). Results of the studies surveyed on the topic of objective changes in sleep parameters were not quite so conclusive. The authors identified several studies with objective evidence of changes in sleep quantity and quality, as well as other sleep disorders such as obstructive sleep apnea (OSA), periodic limb movements (PLM), and narcolepsy. However, they also cited a number of studies in which objective changes in sleep parameters were not found, despite subjective complaints of the subjects. The authors cited similar methodological concerns as those previously addressed by Ouellet and colleagues, and further cited the lack of, or inconsistent reporting on, other important factors such as prior TBIs and past/current medical and psychiatric status, “making it difficult to evaluate the role of these variables in sleep-related outcomes and complicating comparisons between studies.”^{7(p. 163)}

Orff and colleagues⁷ reviewed the literature on TBI and circadian changes, and reported that

although the literature is relatively sparse and somewhat conflicting at this time, there is a growing body of evidence to suggest that sleep disturbances following TBI may be due to alteration in the timing and rhythms of sleep (i.e., circadian rhythm sleep disorders) in a subset of patients. In addition, they reviewed the literature on neurophysiologic and neuropsychological disturbances associated with sleep. They reported endocrine changes that may explain sleep disturbances in this population and also highlighted the limited but important research that suggests that deficits in cognitive performance after TBI may be related, in part, to the degree of sleep disturbance.

Consistent with the Ouellet review, Orff and colleagues also summarized the literature on interventions to date, which remains limited to a few studies addressing pharmacotherapy and CBT. Finally, they discussed limitations of the literature and identified that although the body of work has grown since the Ouellet review in 2004,⁶ there remain similar methodological limitations such as small sample sizes, considerable variation in age, time since injury, level of severity, and measures used to assess sleep. Orff and colleagues recommend that future research needs to focus on uncovering the specific types, causes, and severity of TBI that most often lead to sleep problems; the consequences of sleep disturbance; and the most effective treatment strategies.

The final review studied for this article is by Zeitzer and colleagues.⁸ This review, which we identified as being a Level V and lacking the methodological strength of the previous two reviews, was conducted for the US Department of Veterans Affairs (VA). As such, its focus seems to consider insomnia in the context of TBI from the perspective of those assessing and treating veterans diagnosed with mTBI, hampered by a co-morbid sleep disorder. (Note: Sleep apnea may in fact be preexisting because it is, interestingly, present in about half of the Department of VA patient population⁸(p. 829)). This review lacks a clearly defined objective and systematic review approach; however, the authors state that they will “consider insomnia directly caused by TBI (e.g., secondary to neural damage), indirectly caused by TBI (e.g., secondary to depression), and unrelated to TBI but occurring within individuals with TBI.”⁸(p. 827)

Consistent with previous reviews, Zeitzer and colleagues cited studies of TBI populations of varying severities (mild-moderate) and varying lengths of time postinjury from 6 weeks to greater than 10 years. They reported that insomnia occurs in approximately 40% of individuals with a TBI of any severity, even though it is more commonly reported among patients with mTBI, and is the most prevalent somatic complaint across all levels of severity. The authors also postulated two components of TBI-related insomnia. First, there is a general predisposition to develop sleep disturbance as a result of alterations or disruptions in neurotransmitters involved in the regulation of sleep (and they state further that the literature on this topic is for the most part limited to those with moderate-severe TBI). Second, acute stressors may trigger insomnia. They highlighted non-sleep comorbidities such as depression, pain and post traumatic stress disorder, all of which are of particular relevance to individuals with TBI in general and to veterans with mTBI. From this discussion, they highlighted two future research questions. First, can mTBI cause disruptions in the regulation of sleep? The authors stated further that the literature on this topic is, for the most part, limited to those with moderate-severe TBI. Second, can acute stressors trigger the insomnia? They highlighted non-sleep comorbidities such as depression, pain, and posttraumatic stress disorder, all of which are of particular relevance to individuals with TBI in general and to veterans with mTBIs. They also identified two additional research questions: Can mTBI cause disruptions in the neurotransmitters critical for sleep and wakefulness?; and, What is the effect of psychiatric comorbidities on the occurrence or severity of insomnia in the context of TBI? The latter question aims to assist the physician in treating insomnia as a primary or secondary pathology.

Finally, Zeitzer and colleagues⁸ briefly summarized the literature on pharmacological and non-pharmacological treatments. As per the previous two reviews, the literature on treatment remains limited. As a result, these authors identified some cautionary caveats in the use of pharmacotherapy and described nonpharmacological interventions such as CBT plus various combinations of sleep hygiene, sleep restriction, and relaxation training. The authors highlighted the critical need for further

nonpharmacological studies as viable alternatives to treatment of insomnia in patients with mTBI. The authors concluded that more systematic research is required to “provide a foundation for an evidence-based medical approach to treatment of insomnia in the context of mTBI.”^{8(p. 832)}

B. Single Study Papers

As shown in Table 1, the majority of the literature (56%) is classified as Level III (Well-designed trials without randomization, single group pre-post, cohort, time series, or matched case-controlled studies [also cross-sectional studies and case series]). The next largest level is Level IVA, with 24% of the categorized articles (well-designed individual non-experimental studies, cost analysis studies, and case studies). The published literature is getting stronger as there are fewer Level V studies than Level III or IVA studies, but is still clearly in development as there are no Level I studies and few Level II or IIA studies.

Single study papers were organized into the following categories: epidemiology (comparison group studies or single group/cohort studies), pathophysiology, pediatrics, neuropsychology, and intervention (see Tables 3, 4, and 5). It is important to note that there are Level III studies in each of the above categories, but as of yet the Level II

studies are only with regard to pharmacological interventions. Only one of the studies reviewed was considered of low quality, the majority were of moderate quality (89%), and only a few were of high quality (10%). Each of the studies is summarized in detail in Table 5, which lists the level, quality, and key details relating to the conduction of the reported study. Each category of studies will be discussed below in the order in which they appear in the table. Following each summary there will be an in-text box summarizing the research agenda and practice points identified with the authors of the reviewed studies, followed by our recommendations.

1. Epidemiology

The evidence relating to the epidemiology of sleep and wake disturbances following TBI has historically been the primary focus of the literature, comprising 23 of the 43 articles across the five subtopics we identified for this review. Epidemiological investigation of a phenomenon is a necessary starting point as it provides a solid foundation for all further investigations to follow. We subdivided the studies on epidemiology, all of which were rated as Level III study designs, to include nine papers with a comparison group, all of moderate quality, and 12 articles that used a

TABLE 3
Article Scope and Level of Articles

Article Scope	Total No. of Articles	Level II/IIA	Level III	Level IVA	Level V
Epidemiology - Comparison group	9		9		
Epidemiology - Single group/cohort	14		5	6	3
Pathophysiology	3		2	1	
Pediatrics	6		6		
Neuropsychology	4		1	2	1
Intervention	6	2	3	1	
Review	3	2			1
Total	45	2/2	26	10	5

TABLE 4
Article Scope and Quality of Articles

Article Scope	Total	Moderate Quality				High Quality	
		3	3.5	4	4.5	5	6.5
Epidemiology - Comparison group	9			6	3		
Epidemiology - Single group/cohort	14	1	3	4	4	2	
Pathophysiology	3		1	1	1		
Pediatrics	6 ^a		2	1	1	1	
Neuropsychology	4		1	2	1		
Intervention	6		1	1	2	1	1
Review	3						
Total	45	1	8	15	12	3	1

^aOne article was of low quality with a rating of 2.5.

single group design, 10 of which were moderate quality, and two were of high quality.^{24,25} Both of these studies were also classified as Level III. Among the single group studies, there were five rated as Level III, five rated as Level IVA, and two rated as Level V. The use of a comparison group is a stronger design; however, our quality rating scheme studies included several elements, weighted equally, to assess overall quality so that a study weak in one area can be strong in other areas.

There are several important elements that should be addressed in a good quality epidemiological study. Recruitment is a key issue and recruitment methods must be carefully considered to make sure that any selection bias is eliminated. Recruitment from the perspective of time postinjury is also a factor for consideration in that it allows us to observe the developmental time course of the disorder. Among the articles we reviewed, 65% of the studies (15/23) used consecutive recruitment; however, only 13% (3/23) used consecutive recruitment directly from the acute setting. Twenty-six percent were consecutively recruited as patients entered rehabilitation and the remaining 26% were recruited while in rehabilitation or upon discharge from rehabilitation. Parcell and colleagues²⁶ recruited all patients with TBI, with no preference for those

with sleep complaints, thus reducing bias in their sample. The remainder of the studies included retrospective chart review or recruitment by advertising. In contrast to the Parcell study, the study by Ouellet and colleagues,⁴ with the largest sample size of 452, recruited participants with reported symptoms of insomnia via mailings sent to 1500 prospective participants from archives of Québec City's largest rehabilitation center, local brain injury associations, and support groups. The authors specifically reported using liberal inclusion criteria to try and capture a "broad portrait of the TBI population."^{24(p. 201)}

It is also important to consider possible confounders or variables that influence interpretation of the findings, such as preexisting, concurrent, and secondary comorbidities; age at onset of injury; time since injury; severity of injury; etiology of injury; and gender. In an "ideal" study, the sample population would be large enough to allow stratification on some or all of these variables, so that the findings would be more generalizable and create a more thorough picture of the phenomenon.

Overall, the objective of the epidemiological studies reviewed for this article was to document the incidence, prevalence, and nature of sleep disturbances following TBI, primarily "insomnia" per se, with the inclusion of the most recent data relating specifically to sports-related concussion.

TABLE 5

Sleep and Wake Disorders following Traumatic Brain Injury: Summary of Reviewed Articles

Reference	Study Objective	Research Design	Sample Size Inclusion/Exclusion	Subjects	Data Collection Methods/Measures	Significant Findings	Comments	Quality ^a
Epidemiology/Prevalence/Description: Comparison Group								
Fitchnerberg et al. 2002 USA	Type: Epi/Prev/Disc Establish frequency of insomnia (diagnosis using DSM-IV) in TBI and compare it with insomnia rates in other rehab outpatients	Level III Recruitment: Prospective cohort Consecutive OR; Cross-sectional; Comparison group (Controls): rehabilitation outpatients (same # SCI and MSK)	TBI ^b = 50 Controls = 50 MSK = 25 SCI = 25 Inclusion: • Galveston Orientation and Amnesia (GOAT) score >75 • ≥ Rancho Los Amigos Level VI Exclusion: • not in PTA state	Age, yrs: (P<.05) TBI: 36.5 ± 14.5; SCI: 38.2 ± 13.5; MSK: 47.3 ± 12.2 Gender: (P<.05) TBI: 44% F SCI: 24% F MSK 80% F GCS: sTBI 42% modTBI: 18% mTBI: 40% Time since: 3.8 ± 7.4 mos.	PSQI BDI Sleep diaries (TBI only) Insomnia diagnosis using DSM-IV criteria	TBI: ↓ sleep quality (initiation problems 2x during problems); ↑ sleep duration TBI: 30% insomnia diagnosis (DSM-IV) TBI: ↓ PSQI global scores TBI: < insomnia rate than controls	Prevalence of insomnia is 1/3 of TBI population First paper to use formal diagnosis of insomnia Limitations: Did not stratify results by severity, reliability of self-report sleep diaries	Moderate: 4.5/7 Baseline: 1 Blinding: 0 Sample size: 0.5 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0
Parcell et al. 2006 Australia	Type: Epi/Prev/Disc Explore subject sleep reports from persons with TBI	Level III Recruitment: Consecutive PR (≥ 2 wks post discharge) Longitudinal survey design Controls: general community,	TBI = 63 Controls = 63 Inclusion: • 16-65 yrs • Facility in English • No transmeridian travel > 1 time zone in previous 12 mos • No preinjury sleep disorder • No benzodia-	Age, yrs: TBI 32.5 ± 1.7; Controls: 30.5 ± 1.2 Gender: Both groups: 43% F GCS: 9.6 ± .57 PTA: 19.8 ± 2.7; used for severity mTBI = 8	7-day self report sleep-wake diary (sleep and wake times, sleep onset latency, frequency, and duration of nocturnal awakenings and daytime	TBI: > sleep changes; > night-time awakenings and longer sleep onset latency; more frequently reported by mTBI; ↑ anxiety and depression	Strengths: Follow-up and used a 7-day diary; Considered other potential factors impacting sleep; Limitations: Difference in time used to note changes (TBI, 8 mos; Controls 3 mos)	Moderate: 4.5/7 Baseline: 1 Blinding: 0 Sample size: 0.5 Attrition: 0 Standardized outcomes: 1 Description: 1 Follow-up: 1

TABLE 5 (CONTINUED)

TABLE 5 (CONTINUED)									
Watson et al. 2007 USA	Type: Epi/Prev/Desc Evaluate the prevalence of sleepiness following TBI	Level III Recruitment: Prospective cohort Consecutive A Longitudinal 2 comparison groups; C1 non-crani- al trauma admissions; C2 trauma free selected from friends of TBI Data collection: 1 mo and 1 yr postinjury	age and gender matched TBI reflect on changes since injury and controls reflect on changes in the last 3 mos Data collection: initial and 3 mos	zepam or other sleeping medications • No previous BI, neurological disorder, or major psychiatric disorder Screened by neuropsychologist to determine eligibility	modTBI = 13 sTBI = 27; vsTBI = 14 Time since: mean 230 days	naps) General sleep questionnaire to evaluate sleep changes and quality ESS HADS	associated with ↑ reporting of sleep changes		
				TBI = 512 (n = 346 at 1 mo; n = 410 at 1 yr) C1 = 132 (n = 131 at 1 mo; n = 124 at 1 yr) C2 = 102 (n = 101 at 1 mo; n = 88 at 1 yr) Inclusion: • Any period of LOC • PTA ≥ 1 hr • Other objective evidence of head trauma • Hospitalization ** Some had pre-existing conditions: prior TBI, alcohol abuse, significant psychiatric disorder	Age, yrs: TBI: 30 ± 14 C1: 31.4 ± 13.5 C2: 24.5 ± 8.1 Gender: TBI: 27% F; C1: 28% F; C2: 56% F GCS: ≤ 10 at admission Injury severity: time from injury to a consistent GCS score of 6 Time since: 1 mos and 1 year at follow-up	Sickness Impact Profile (SIP): sleep and rest subscale consisting of 4 questions	TBI: 55% endorsed ≥ 1 sleepiness items 1 mo postinjury vs C1 41% and C2 3% TBI 27% endorsed ≥ 1 sleepiness items 1 yr postinjury vs C1 23% and C2 1% TBI: sleeper than C1 at 1 mo but not 1 yr TBI are sleeper particularly those with more severe injuries; sleepiness	Strengths: Good follow-up Limitations: Weak outcome measure; not separately validated; just descriptive data, large attrition Majority were mTBI as sTBI not able to complete the SIP; may lead to underestimate of the true sleepiness pattern in TBI	Moderate: 4.5/7 Baseline: 1 Blinding: 0 Sample size: 1 Attrition: 0 Standardized outcomes: 0.5 Description: 1 Follow-up: 1

TABLE 5 (CONTINUED)

Beetar et al. 1996 USA	Type: Epi/Prev/Desc: Compare the incidence of sleep and pain in TBI and comparative neurologic populations	Level III Recruitment: OR (neurophysiology service) Cross-sectional Case-control study Consecutive chart review Comparison group: general neurologic patients referred for neurophysiological assessment	mTBI = 127 mod to sTBI = 75 Controls = 123 Used Mild TBI Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine	Age, yrs: TBI: 36.1 ± 11.7; Controls: 43.3 ± 13.6 Gender: TBI: 32% F; Controls: 42% F GCS: NI Time Since: TBI: 23.9 ± 2.2 mos (injury); Controls: 35.5 ± 23.3 mos (symptom)	Chart review Patient report of sleep and or pain problems	Sleep maintenance most common sleep problem; TBI: 55% had insomnia complaints vs Controls <33%; TBI: > insomnia and pain complaints (2.5 x more); presence of pain ↑ insomnia report 2 x; TBI without pain: > sleep complaints than Controls and mTBI > mod/sTBI; mTBI > pain than mod/sTBI; Complaints ↓ with > time since injury	Strengths: One of earliest studies to document incidence Limitations: Retrospective and subjective data collection	Moderate: 4/7 Baseline: 1 Blinding: 0 Sample size: 1 Attrition: 1 Standardized outcomes: 0 Description: 1 Follow-up: 0
Ouellet & Morin 2006	Type: Epi/Prev/Desc:	Level III Recruit-	TBI = 14 m to sTBI Controls = 14	Age, yrs: TBI: 30.4 ± 9.7	Diagnostic Interview for	TBI: PSG showed 71%	Results similar to those with primary	Moderate: 4/7

TABLE 5 (CONTINUED)

Canada	Compare subjective and objective measures of sleep in TBI	LC Rehabilitation centers and advertisements sent to TBI associations and support groups mailing lists); Cross-sectional; Comparison group: healthy good sleepers matched on age and gender to TBI; recruited through advertisements and acquaintances of the authors; 2 nights of PSG	Inclusion: <ul style="list-style-type: none"> • 18-50 yrs • TBI $\leq$ last 5 yrs • Stable physical health • No longer an inpatient • Have an insomnia syndrome Exclusion: <ul style="list-style-type: none"> • Major untreated or unstable comorbid condition • Sleep difficulties before TBI • Evidence of another sleep disorder • Significant pain • Unable to complete the questionnaires 	Controls: 30.0 $\pm$ 10.0 Gender: 56% F GCS: 4 mild, 1 mild-mod, 4 mod, 3 moderate, 2 severe (criteria in article) Time since: 21 mos	Insomnia Sleep diary PSG Sleep survey ISS MFI BDI Beck Anxiety Inventory	with insomnia Large effect sizes for total sleep time wake after sleep onset, awakenings longer than 5 min, and sleep efficiency TBI: > portion of stage 1 sleep When those using psychotropic meds excluded, TBI had > awakenings lasting longer than 5 min and a short REM sleep onset latency	insomnia or insomnia-related to depression Limitations: Small sample size and a lot of variability in TBI group and presence of sleep problems in Control group Multiple comparison and lack of statistical power	Blinding: 0 Sample size: 0 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0
Parcell et al. 2008 Australia	Type: Epi/Prev/Disc Evaluate changes in sleep quality and changes in objective recorded sleep parameters after TBI and	Level III Recruitment: AI (mod to sTBI); Cross-sectional; Survey and lab-based nocturnal PSG;	TBI = 10 Controls = 10 Inclusion: <ul style="list-style-type: none"> • 16-65 yrs • English facility • Normal body mass index • No transmeridian travel across > 1 time zone in 	Age, yrs: TBI: 38.8 $\pm$ 4.3; Controls: 37.8 $\pm$ 44.4 Gender: 40 % F GCS: 10.9 $\pm$ 1.0 40% mod TBI; 40% sTBI; 20%	Demo-graphic and medication details at recruitment and injury details from medical records; Sleep-wake	TBI: poorer sleep quality and higher levels of anxiety and depression; TBI: $\uparrow$ in deep (slow wave) sleep, $\downarrow$ in REM, >	Documents of importance of subjective report as central to diagnosis and treatment but need to consider objective data as well Provides many important practice	Moderate: 4/7 Baseline: 1 Blinding: 0 Sample size: 0 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0

TABLE 5 (CONTINUED)

Schreiber et al. 2008 Israel	investigate the relationship between mood state and injury characteristics	Comparison group age- and gender-matched controls in general community; PSG over 2 nights within 1 wk; evaluated in TBI and control pairs	<ul style="list-style-type: none"> • previous 12 mos • No preinjury sleep disorder • No benzodiazepines or other sleeping medications • No previous BI, neurological disorder, or major psychiatric disorder 	vsTBI; PTA 16.44 ± 4.3 days Time since: 516 ± 124 days	diary for 7 days; ESS Sleep quality questionnaire (TBI changes since injury and Controls changes in last 3 mos); PSQI; nocturnal PSG; HADS	> night-time awakenings; TBI: > anxiety and depression, which co-varied with the observed sleep changes	points; is a strong contributor to clinical and research literature	
	Level III	Recruitment: Retro-spective; Consecutive OR (where sleep lab data available); Cross-sectional	mTBI = 26 Controls = 20 (apparently healthy) Inclusion: • 21-50 yrs • Documented (≥ 1 yr since mTBI) • Normal brain CT, MRI • Negative EEG • No past history of CNS pathology • No pre-morbid or present major psychiatric diagnosis • No sleep apnea or restless leg syndrome	Age, yrs: TBI: 31.6 ± 8.8 Controls: 33.8 ± 7.8 Gender: NI GCS: NI Time since: 12 mos to 21 yrs	PSG MSLT	TBI: sleep patterns disturbed; sleep architecture altered; < REM sleep scores and > NREM scores TBI: MSLT documented significant EDS	Important to identify those who need treatment for sleep problems Limitations: Controls were not all within the normal values Possible issues of recall bias Wide range of time postinjury Difference in data collection strategy between the 2 groups	Moderate: 4/7 Baseline: 1 Blinding: 0 Sample size: 0 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0

TABLE 5 (CONTINUED)

Williams et al. 2008 Canada	Type: Epi/Prev/Disc Characterize the extent and nature of dis- rupted sleep in individuals with long- term sleep complaints subsequent to mTBI (i.e., sport-related concussion) To determine whether sleep disturbances in mTBI are more char- acteristic of psychological, psychiatric, or idiopathic insomnia	only 1 night MSLT on day between the 2 nights	Level III Recruitment: LC (univer- sity setting) Cross-sec- tional Comparison group Face-to-face interview and labora- tory PSG	TBI = 9 Controls = 9 Inclusion: • 18-26 yrs TBI: • Between 6 mos and 6 yrs post- injury • Symptoms of Post Concussion Syndrome (PCS) at the time of injury • Clearly distin- guish between sleep patterns before and after injury • Sleep difficulties within 1 mo of injury • Sleep complaints characterized by sleep onset of > 30 min on ≥ 4 or days in a week Controls: • No previous BI • No sleep difficul- ties	Age, yrs: TBI: 21.4 ± 2.4 Controls: 20.7 ± 2.1 Gender: TBI: 33% F; Controls: 56% F GCS: mild range; LOC for ≤ 5 min Time since: TBI 27.8 ± 15.5 mos	Personality Assessment Inventory (PAI): de- pression and anxiety Brock Adaptive Function- ing Ques- tionnaire (BAFQ) PSQI Sleep Disor- ders Question- naire (SDQ) Brock sleep and insom- nia question- naire Sleep log for 2 wks PSG for 3 consecutive nights Power spec- tral (FFT) analysis of the sleep onset period	TBI: long- term trouble with initiating/ maintaining sleep with attention and memory and affective (depression and anxiety) abnormalities; significant difference shown in PAI, BAFQ, PSQI TBI: 4% less efficient sleep, shorter REM onset latencies, longer sleep onset laten- cies (vari- ability within sample); FFT revealed greater intra-subject variability in sigma, theta, and delta power during sleep onset TBI different	Sleep disturbanc- es can persist well after injury; Strengths: Very thorough study Limitations: Small sample, sample of con- venience (stu- dent volunteers); Confirmation of subjective self- reports with PSG; Highlights need to look at sport- related concussion	Moderate: 4/7 Baseline: 1 Blinding: 0 Sample size: 0 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0

TABLE 5 (CONTINUED)

Gosselin et al. 2009 Canada	Type: Epi/Prev/Disc Investigate the effects of sport-related concussion on subjective and objective sleep quality	Level III Recruitment: LC (independent of the nature of reported symptoms) Cross-sectional Used concussion diagnostic criteria Comparison group: No history of concussion; matched on age, gender, education, and age started playing the sport PSG on 2 consecutive nights in the lab	ABI = 10 Controls = 11 Inclusion: • ABI: history of at least 2 concussions Exclusion: • Presence of neurological or psychiatric diseases • Extremely early or late habitual bed times • Use of drugs known to affect sleep or daytime sleepiness • Work the night shift • Travel to another time zone in last 2 mos	Age, yrs: ABI: 24.3 ± 6.1 yrs; Controls: 22.6 ± 2.4 Gender: ABI: 30% F Controls: 34% F GCS: ABI all 13-15 # concussions: 4.6 ± 2.1 with at least 1 in last yr Time since: NI	PSG QEEG: assessment of 10-min period of wakefulness 30-min after sleep offset; Post Concussion Symptom Scale (PCSS); PSQI; ESS; BDI; Locally developed questionnaire on sleep quality; Cog Sport computer battery: short neuropsychology evaluation adapted from NFL battery	ABI: > symptoms, worse sleep quality; > delta activity and < alpha activity during wakefulness; Concussion seems to be associated with a wakefulness problem, rather than sleep disturbance; Athletes with worse sleep quality (PSQI) and symptoms (PCSS) > relative delta power during daytime; ABI lower PSQI associated with ↓ in REM sleep efficiency PSQI and PCSS correlated with	Discrepancy between subjective and objective findings; not explained by depression nor hyperarousal Limitations: Small sample with exclusions the sample became even smaller, however, highlights need to assess sleep and wakefulness following sport-related concussion Only a pilot study	Moderate: 4/7 Baseline: 1 Blinding: 0 Sample size: 0 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0
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TABLE 5 (CONTINUED)

Baumann et al. 2007 Switzerland	Type: Epi/Prev/Desc Determine the frequency and clinical characteristics of posttraumatic SWD; assess CSF hypocretin levels 6 mos after TBI and risk factors for posttraumatic SWD	Level III Recruitment: Prospective study; Consecutive A; (within 4 days of injury); Longitudinal; Single group Baseline: laboratory tests; 6 mos; other outcomes, subsample repeated laboratory tests	TBI = 65 (96 enrolled; 76 available for follow-up) Inclusion: • Acute, first ever TBI Exclusion: • Sleep-wake or psychiatric disorders diagnosed prior to TBI	Age, yrs: 16-72, mean 38 ± 16 yrs Gender: 14% F GCS: mean 10.2, mTBI: 40% modTBI: 23% sTBI: 37% Time since: 6 mos after TBI	CT scan; CSF hypocretin-1 levels; Human leukocyte antigen (HLA) typing Interview: social status and residual symptoms postinjury, including sleep habits; Neurological examination using a standard protocol, with the Folstein MMSE BDI; Medical Outcomes Study Form - 36; ESS;	SWD are common after TBI, EDS/fatigue = 55%; Posttraumatic hypersomnia = 22%; Low hypocretin levels found in 19% 6 mos after injury vs 93% in first days after injury; 6 mo hypocretin levels were lower in those with posttraumatic SWD; No other significant relationships were found; Hypocretin	Strengths: Very thorough Limitations: Attrition was large and not all available for laboratory follow-up	High: 5/7 Baseline: 0.5 Blinding: 0 Sample size: 1 Attrition: 0.5 Standardized outcomes: 1 Description: 1 Follow-up: 1

related; Absorbate spectral power showed high inter-subject variation in ABI; therefore analyze on the relative spectral power

TABLE 5 (CONTINUED)

Castriotta et al. 2007 USA	Type: Epi/Prev/Desc Determine the prevalence and consequences of sleepiness and sleep disorders after TBI Explore the relationship between presence of sleep disorders, injury characteristics and subject variables	Level IV A Recruitment: Prospective study AI (3 centers); Single group; Cross-sectional	TBI = 87 Inclusion: • >18 yrs old • ≥ 3 mos post-injury Exclusion: • Presence of circadian rhythm disorder • Use of sedating medications • Unable to give informed consent	Age, yrs: 38.3 ± 15.1 Gender: 28% F GCS: NI Severity: mild 8%, moderate 175, moderate-severe 6%, severe 33%, unknown 36% Time since: 64.3 ± 117.7 mos	PSG; MSLT; ESS; PVT; POMS; FOSQ	Sleep Apnea Scale of the Sleep Disorders Questionnaire; Ullanlinna Narcolepsy Scale; PSG; MSLT; Actigraphy	system possible contributor to pathophysiology of posttraumatic SWD	Strengths: First study to show that a sleep disorder adds an additional cognitive burden Limitations: No objective measure of daily functioning	High: 5/7 Baseline: 1 Blinding: 0 Sample size: 1 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0
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TABLE 5 (CONTINUED)

Fitchenberg et al. 2000 USA	Type: Epi/Prev/Desc Relationship between insomnia and demographics, injury, and psychological variables in post-acute TBI	Level IV A Recruitment: Prospective study; Consecutive OR; Cross-sectional; Single group	TBI = 91 Inclusion: • Diagnosis of TBI on basis of examination • Recovery to post-acute phase • Medical determination of need for outpatient neuro-rehabilitation Exclusion • In state of PTA • Rated below Level VI on Levels of Cognitive Functioning Scale (LCSF) • Using sleep medication	Age, yrs: 33.8 ± 14.5 Gender: 41% F GCS: 13-15: 33% 9-12: 21% 3-8: 46% Time since: mean 3.3 mos	PSQI; BDI; GOAT; LCFS	Strong relationship between insomnia and depression; Pain disturbance of sleep was significantly associated with insomnia; BDI: 68% depressed were suffering from insomnia	better NSI POMS: no differences	Moderate: 4.5/7 Baseline: 0.5 Blinding: 0 Sample size: 1 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0	Strengths: Identifies a developmental pattern that may progress from a physiological basis to a secondary disorder associated with depression
Ouellet, Beaulieu-Bonneau & Morin 2006 Canada	Type: Epi/Prev/Desc; To determine the frequency of insomnia according to DSM-IV and International Classification of Sleep Disorders (ICSD) criteria. To describe clinical and sociode-	Level IV A Recruitment: LC (French-speaking from rehabilitation center archives and on mailing lists of TBI associations in Quebec); Mailed questionnaire	TBI = 452 Inclusion: • ≥ 16 yrs • TBI: minor, mild, moderate or severe	Age, yrs: 40.2 ± 13.1 Gender: 35% F GCS: NI Severity: 59.9% sTBI 23.3% modTBI 13.7% mTBI (criteria includes GCS) Time since: mean 7.8 yrs	Questionnaire booklet entitled "Quality of sleep and level of fatigue following a TBI": Locally developed questions ISS Multi-dimensional	Insomnia prevalent after TBI, 64.3% with sleep onset insomnia, 76.6% with sleep maintenance insomnia; Predictors of insomnia: lesser severity of BI,	Limitations: Only subjective data Underrepresentation of mTBI Those with insomnia problems may have been more motivated to respond Not able to determine insomnia subtypes	Moderate: 4.5/7 Baseline: 1 Blinding: 0 Sample size: 1 Attrition: 1 Standardized outcomes: 0.5 Description: 1 Follow-up: 0	

TABLE 5 (CONTINUED)

<p>mographic characteristics of insomnia in TBI</p> <p>Cross-sectional; Single group; Significant others completed a brief parallel evaluation</p> <p>fatigue inventory Indices de détresse psychologique de L'Enquête Santé Québec (French adaptation of Psychiatric Symptom Index) Significant Other's Evaluation Questionnaire (significant other versions of ISS and other above questions)</p>		
<p>Rao et al. 2008 USA</p> <p>Type: Epi/Prev/Desc</p> <p>To assess the prevalence of and risk factors for sleep disturbances in acute posttraumatic TBI</p>	<p>Level III</p> <p>Recruitment: PAC (within 3 mos of trauma); Longitudinal observational study; Single group; Data collection: 1) within 2 wks of injury to assess history of</p> <p>TBI = 54</p> <p>Inclusion:</p> <ul style="list-style-type: none"> • ≥ 18 yrs • Able to provide informed consent • Admitted to hospital with expectation of LOC • GCS ≤ 15 • Positive CT findings <p>Exclusion:</p> <ul style="list-style-type: none"> • Prior TBI • Open head injury • History of other 	<p>Age, yrs: 43.2 ± 17.7</p> <p>Gender: 41% F</p> <p>GCS: mean 12.5 ± 3.6; 65% mild, 11% moderate, and 19% severe</p> <p>Time since: ≥ 3 mos</p>
	<p>Worse on most sleep measures after TBI compared to before TBI; Anxiety disorder secondary to TBI was most consistent significant risk factor to be associated with worsen-</p>	<p>Strengths: Assess sleep problems in the acute period; Participants had a range of severities</p> <p>Limitations: Subjective data and recall bias might be an issue</p> <p>Lack of info on other potential influencing factors (pain, medical problems and</p> <p>Moderate: 4.5/7</p> <p>Baseline: 0.5</p> <p>Blinding: 0</p> <p>Sample size: 0.5</p> <p>Attrition: 1</p> <p>Standardized outcomes: 1</p> <p>Description: 1</p> <p>Follow-up: 0.5</p>

TABLE 5 (CONTINUED)

TABLE 5 (CONTINUED)								
psychiatric and sleep problems 2) within 1-3 mos of injury; for some both at the same time	type of illness		ing sleep status	medications				
Clinchot et al. 1998 USA	Type: Epi/Prev/Desc Define and correlate the incidence and type of sleep disturbances that occur after BI	Level V Recruitment: Prospective study Consecutive AI Single group Longitudinal Baseline and 1 yr follow-up post discharge via telephone interview	TBI = 145 Inclusion: • ≥ 14 yrs with sustained BI Exclusion: • Not acute injury • Primarily the result of anorexia	Age, yrs: 31 Gender: 23% F GCS: Median = 4 Time since: mean 20 days	Direct observation; Medical record extractions; Agitated Behaviour Scale; FIM; Wechsler Memory Scale; Halstead Reitan Neuropsychological Battery; Follow-up interview; Community Integration Questionnaire; Sleep difficulties, medical problems, medications, services used	50% difficulty with sleep, 25% sleeping more and 45% difficulty falling sleep GCS ≤ 7 less likely to have problems with sleep than GCS > 7; 64% with sleep difficulty waking up too early; Sleep complaints correlated with presence of fatigue, > GCS, better immediate memory, positive substance abuse history, > age, and being female	Limitation: Large number lost to follow-up; those lost more likely to have a history of substance abuse Self-report of sleep difficulties	Moderate: 4/7 Baseline: 0.5 Blinding: 0 Sample size: 1 Attrition: 0 Standardized outcomes: 1 Description: 0.5 Follow-up: 1
Webster	Type:	Level IV A	TBI = 28	Age, yrs:	Overnight	Sleep-related	Strengths:	Moderate:

TABLE 5 (CONTINUED)

et al. 2001 USA	Epi/Prev/Desc Determine the occurrence and nature of sleep-related breathing disorders in adults with TBI	Recruitment: Prospective observational study Consecutive AI; Single Group	Inclusion: • 18-65 yrs • <3 mos postinjury • Rancho ≥ 3 Exclusion: • Previously documented sleep apnea, narcolepsy or habitual snoring • Tracheostomy • History of other premorbid neurologic or pulmonary conditions	34.5 Gender: 25% F GCS: lowest during the first 24 hrs; 71% GCS ≤ 8 , 25% GCS 9-12, 4% GCS > 12 PTA > 1 day Rancho 95% Level VI or VII Time since: <3 mos	sleep study using portable 6-channel monitoring system; calculated a respiratory disturbance index	breathing disorders defined by a respiratory index of 5 or greater seem to be common in adult subjects with TBI; Evidence of sleep apnea was found in 36% of subjects	Prospective and consecutive design; New info regarding the occurrence of sleep apnea in early recovery phase; Attempt to eliminate confounding factors Limitations: Low power; Homogeneous sample; Not able to collect EEG data	4/7 Baseline: 0.5 Blinding: 0.5 Sample size: 0 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0
Masel et al. 2001 USA	Type: Epi/Prev/Desc Determine prevalence, demographics, and causes of EDS in adults with BI and investigate relationship between subjective and objective data	Level III Recruitment: Consecutive AI Case series Cross-sectional Single group 2 overnight sleep evaluations 1 wk apart; actigraphy for 2 wks after 2nd PSG	TBI = 71 Complete medical history and physical examination; Inclusion: None Exclusion: None	Age, yrs: 32 $\pm$ 11 Gender: 38% F GCS: only for 56%: Non hypersomnia (NH): 6 $\pm$ 4; Post traumatic hypersomnia (PTH): 7 $\pm$ 5; Hypersomnia with abnormal indices (HAI): 8 $\pm$ 5 Rancho $\geq$ Level IV Time Since: 38 $\pm$ 60 mos	Actigraphy PSG; MSLT; ESS; PSQI; Millon Clinical Multiaxial Inventory-II (MCM-II); Neuropsychologic battery; Diagnosis of narcolepsy and post-traumatic hypersomnia using the ICSD	Hypersomnia was common with high presence of sleep apnea hypopnea syndrome, periodic limb movements, and PTH; NH: n = 38; PTH: n = 21; HAI: n = 12; No relationship between hypersomnia groups and GCS, psychopathology, time postinjury and demographic	Suggest maybe that patients with TBI have an inability to perceive their hypersomnolence Limitation: Wide range of time postinjury; Self-selection bias	Moderate: 4/7 Baseline: 0.5 Blinding: 0 Sample size: 0.5 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0

TABLE 5 (CONTINUED)

Verma et al. 2007 USA	Type: Epi/Prev/Desc Determine the spectrum of sleep disorders in patients with chronic TBI and determine if the severity of sleep disorder is related to severity of chronic TBI	Level V Recruitment: Retrospective LC (referred for evaluation for sleep disorder); Cross-sectional; Single group; One overnight PSG	TBI = 60 Inclusion: NI Exclusion: NI	Age, yrs: 20-69, mean 41 Gender: 37% F GCS: NI Severity assessed by GAF: mild 40% moderate 20% severe 40% Time since: 3 mos to 2 yrs	Detailed medical history, neurological exam, neck size, chin size and position, jaw alignment, and oropharyngeal examination; PSG; MSLT; ESS; BDI; Hamilton Anxiety Scale	A full spectrum of sleep disorders occur in patients with chronic TBI. Complicated relationship with severity of injury. EDS was most common presenting symptom, which may lead to other problems like insomnia, anxiety and depression	Strengths: Identifies and describes the spectrum of sleep disorders; Sleep disturbances can compromise rehab process and return to work; Limitations: Retrospective; 1 night of PSG; Lack of exclusion of possible effects of meds and pain; HAS and BDI not collected on all participants; GAF may not be best evaluation of severity	Moderate: 4/7 Baseline: 0.5 Blinding: 0 Sample size: 0.5 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0
Castriotta & Lai 2001 USA	Type: Epi/Prev/Desc Determine the frequency of sleep disorder	Level III Recruitment: Prospective cohort study; Consecutive	TBI = 10 Inclusion: • Subjective excessive sleep • ≥ 18 yrs or older	Age, yrs: 56.3 ± 5.3 Gender: 60% F; GCS: sTBI 60%	Clinical interview; ESS; PSG; MSLT	Sleep disorder breathing was found in 7 subjects;	Strengths: Prospective Limitations: Small sample	Moderate: 3.5/7 Baseline: 0.5 Blinding 0 Sample size: 0

variables; no significant differences of note on the neurologic tests; No significant correlation between ESS or PSQI and MSLT

TABLE 5 (CONTINUED)

TABLE 5 (CONTINUED)							
orders associated with TBI; investigate relationship between posttraumatic sleep disorders and pretraumatic sleep disorders	yet timing post-injury unclear; Cross-sectional; Single group; Use criterion standard to diagnose sleep disorders; Those with overt sleep apnea had a 2nd PSG with titration of nasal CPAP	<ul style="list-style-type: none">Alert and orientedExclusion:<ul style="list-style-type: none">Medications to cause hypersomnolencePregnancyPatients with cardiopulmonary and recent abdominal and thoracic injuries	mTBI: 40% Time Since: ≥ 72 hrs; 110 191 mos	Overt OSA in 5 subjects Narcolepsy in 2 subjects Treatable sleep disorders seem to be common in sleepy TBI population All 10 had treatable sleep disorders; 3 had symptoms of hypersomnia before injury	Attrition: 1 Description: 1 Follow-up: 0		
Chaput 2009 Canada	Type: Epi/Prev/Disc Assess the relationships among sleep complaints, headaches, and mood alteration in mTBI	Level III Recruitment: Retrospective chart review; Consecutive ER; Single group; Longitudinal; Data retrieval at 10 days and 6 wks; Self-report: in order to prevent selection bias, those patients assessed by self-report	TBI = 443 At 10 days: 87.8% At 6 weeks: 64.1% Inclusion <ul style="list-style-type: none">Seen for ≥ 1 visit where post-injury symptoms were not due to alcohol or other illegal substance, or medication, or other injuries, or 2° to treatment of other injurymTBI diagnosis by neurosurgeon based on task force criteria Exclusion: <ul style="list-style-type: none">≤ 16 yrsLanguage barrier	Age, yrs: mean 46.9 Gender: 31.8% F Severity: mTBI GCS: scene: mean 13.2 (10-day group) and 15 (6-wk group) Emergency department: 13.9 (10 day group) and 15 (6-wk group) 42% abnormal CT-scan Time since: <10 days post-trauma and <6 wks	Review of past medical history including current medications, known allergies, as well as smoking, alcohol and drug intake habits; CT scans were reviewed if present; Rivermead post-concussion symptom assessment questionnaire	Limitations: Did not assess current stressors; Subjective nature of data collected	Moderate: 3.5 Baseline: 0.5 Blinding: 0 Sample size: 1 Attrition: 0 Standardized outcomes: 0.5 Description: 0.5 Follow-up: 1

TABLE 5 (CONTINUED)

Makley 2009 USA	Type: Epi/Prev/Desc Investigate whether im- provements in sleep efficien- cy correlate with duration of PTA after closed head injury	and history were not excluded but rated for presence or absence of 6 types of sleep com- plaints	Known history of mental retarda- tion, diagnosis dementia or learning dis- ability impairing the cognitive and reasoning process, or co- existing psychiat- ric illness	may in- crease risk of chronicity of symptoms Seem to indicate an alteration in sleep homeostat- sis following mTBI despite absence of physical pain as presented at 10 days	Moderate: 3.5 Baseline: 0.5 Blinding: 0.5 Sample size: 0 Attrition: 0 Standardized outcomes: 0.5 Description: 1 Follow-up: 1
	Level IV A Recruitment: Prospective; Consecutive AI; Single group; Longitudinal; Actigraphy within 72 hrs of admis- sion and for duration of stay (min of 7 days); Daily mea- surement of PTA; cleared when O- LOG score of ≥ 25 on 2 cons- cutive days; Follow-up	CHI = 14 Exclusion: • Known history of a sleep disorder, anoxic injury, active psychiatric illness, obesity, untreated thyroid disease, degen- erative neurologic condition, signifi- cant tetraparesis or immobility	Age: 24-45 yrs Gender: NI GCS: NI Time since: 15 days (9-23)	Complete neurologic and physical examination on admis- sion; FIM at admis- sion and discharge; Actigraphy; O-LOG to measure PTA by SLPs blind- ed to sleep scores; Bed- side sleep logs kept by nursing staff; Follow-up: DRS; Super- vision Rating Scale	Actigraphy a good method to mea- sure sleep pat- terns in immediate post-acute Strengths: Effort made to measure/eliminate potential con- founding variables Limitations: Small sample with large attrition (only 9 available for analysis)

TABLE 5 (CONTINUED)

Worthington & Melia 2006 UK	Type: Epi/Prev/Disc Investigate the impact of disorders of arousal and sleep disturbance on everyday living and participation in rehabilitation	3 mos	SWLS; PSQI	lated with 1 unit ↑ in O-LOG score Association between improve-ment in sleep efficiency and return of awareness > for those admitted with PTA	Strengths: First sizeable study to address the impact and management of arousal disorders after BI	Moderate: 3/7 Baseline: 0.5 Blinding: 0 Sample size: 1 Attrition: 1 Standardized outcomes: 0 Description: 0.5 Follow-up: 0
	Level V Recruitment: Retro-spective naturalistic observation; Recruitment AI (7 centers); Cross-sectional; Single group	ABI = 135 Inclusion: • Admission to service on grounds of significant cognitive and/or behavior disorder • Severe BI • All able to participate in rehab Exclusion: NI	Age, yrs: 38 ± 11.4 Gender: 25% F GCS: range, 3-7 Time since: 119.3 ± 108.8 mos	Structured rating form: 5 key features including delayed sleep onset, frequent waking at night, early morning waking, delayed morning waking, and EDS	47% disturbance of arousal and sleep patterns; Significant adverse effect on activity in 66% of 47%; Disordered arousal could persist up to 10 yrs post-injury; Concurrent psychiatric illness, but not epilepsy, was associated with arousal and sleep disorder; Nonpharmacological interventions	

TABLE 5 (CONTINUED)

<p>used in 34% of cases benzodiazepine/hypnotic drugs 20% Long-term outcome from SBI affected by enduring disturbance of arousal, most commonly noted as sleep disorder</p>		
<p>Ayalon et al. 2007 USA</p>	<p>Type: Pathophysiology Describe the physiologic and behavioral characteristics of CRSDs following mTBI in patients complaining of insomnia</p> <p>Level III Recruitment: LC; Descriptive; Cohort; Cross-sectional; Data collection every 2 hrs for 24 hrs</p> <p>TBI = 42</p>	<p>Pathophysiology Age, yrs: mean 26 (range, 17-45) Gender: 20% F GCS: mTBI Time since: NI</p> <p>Actigraphy; Saliva melatonin; Oral temperature; PSG; Self-report questionnaire to determine circadian preference: morning-eveningness questionnaire</p> <p>36% had CRSD; 19% had DSPS; showed ↑ temp, rhythm, amplitude; 17% had irregular sleep-wake pattern; had weaker circadian rhythmicity - account for behavior differences in sleep-wake pattern? Distinct profiles of 24-hr periodicity of melatonin rhythm and</p> <p>mTBI might contribute to emergence of CRSDs; Important to have correct diagnosis or can inappropriately treat for insomnia</p> <p>Moderate: 4.5/7 Baseline: 0.5 Blinding: 0 Sample size: 1 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0</p>

TABLE 5 (CONTINUED)

Baumann et al. 2005 Switzerland	Type: Pathophysiology Assess the CSF hypocretin-1 levels in patients with TBI	Level III Recruitment: Consecutive A; Cohort; Cross-sectional; Data collection 1-4 days post-TBI	TBI = 44 Controls = 20 (no neurologic problems) Inclusion: • Acute TBI, 1-4 days post-injury Exclusion: NI	Age, yrs: mean 36 (range, 17-69) Gender: 73% F GCS: 31 sTBI; 8 mod TBI; 5 mTBI Time since: 1-4 days	TBI: Hypocretin-1 levels assessed venotricular CSF (n = 37) and spinal CSF (n = 8) by radioimmunoassay Controls: levels assessed via spinal anaesthesia and some ventricular Used Marshall to categorize the CT	24-hr periodicity of oral temperature Hypocretin-1 levels abnormally low in 95% of mod-severe TBI and in 97% of those with posttraumatic brain CT changes; Site of CSF sample did not matter; Marshall I: 8, II-IV: 36 n = 9 comorbid diseases	Change in levels may reflect hypothalamic damage and may be linked to SWD May also reflect loss of consciousness Limitation: Small sample	Moderate: 4/7 Baseline: 0.5 Blinding: 0 Sample size: 0.5 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0
Quinto et al. 2000 USA	Type: Pathophysiology Describe the experience of DSPS in ABI	Level IV A Recruitment: LC; Single subject case study	TBI = 1 Sleep onset insomnia: not responsive to pharmacological treatment	Age, yrs: 48 Gender: Male GCS: NI Time since: NI	Sleep logs Actigraphy	Sleep onset insomnia with frequent awakenings; Chronotherapy unsuccessful declined; Phototherapy declined	Authors hypothesize lesion to suprachiasmatic nucleus, which is the site of human circadian clock Emphasized need to be aware of DSPS as potential consequence of ABI when diagnosing sleep problems	Moderate: 3.5/7 Baseline: 0.5 Blinding: 0 Sample size: 0 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0

TABLE 5 (CONTINUED)

	Type:	Pediatric					Limitations:	Moderate:
		Level III	mod TBI = 56 sTBI = 35 Controls = 80 Inclusion: • 1 night in hospital for all 3 groups • No evidence of abuse or previous neurological disorder • English-speaking	Age at injury, yrs: 9.5 ± 2.0 Gender: 33% F GCS: used lowest post-resuscitation/injury score Time since: 3 wks post Other: 68% Caucasian	Child Behaviour Checklist: 7 items only (assessed stability in comparison to full scale)	modTBI worse pre-injury sleep modTBI and Controls: small ↓ in sleep from pre to post; sTBI: ↑ in postinjury problems: daytime sleepiness and nocturnal sleep duration		
Beebe et al. 2007 USA	Pediatric Determine the effect of mod and severe TBI on sleep of school-aged children	Recruitment: Concurrent prospective cohort A (children aged 6-12 yrs); Longitudinal 3 groups: modTBI, sTBI, orthopaedic injury; Baseline (retrospective parental report of preinjury sleep at 3 wks post), and 6, 12, and 48 mos post-injury					Timing of follow-ups varied; Retrospective data collection; Weak instrument (only 7 items and part of larger scale)	4.5/7 Baseline: 1 Blinding: 0 Sample size: 1 Attrition: 0 Standardized outcomes: 0.5 Description: 1 Follow-up: 1
Kaufman et al. 2001 Israel	Pediatric Subjective and objective characterization the long term effects of mHI on sleep in adolescents	Level III Recruitment: Prospective cohort A (archives); Cross-sectional; mHI: subjective and objective measures C1, C2: objec-	mHI = 19 C1 (healthy) = 16 C2 (healthy) = 15 Inclusion • 10-18 yrs • Hospital admission with mHI (ICD-10 codes) • GCS ≥ 13 • 3 yrs postinjury • Complained of sleep disturbance	Age, yrs: 13.5 ± 1.7 Gender: mHI 21% F; C1 19% F C2 20% F GCS: ≥ 13 Time since: 3 yrs post-injury	Locally developed questionnaire: medical history, details of the injury, sleep habits, and sleep disturbances: pre and post sleep	mHI: significant ↓ in sleep period time, total sleep time and sleep efficiency; mHI: significant ↑ min awake and number of awakenings >3 min	Strengths: Thorough evaluation; Use of healthy controls; Subjective corroborated objective for the most part; Participants 3 yrs post-injury so identifies/confirm long-term sleep problems	3.5/7 Baseline: 1 Blinding: 0 Sample size: 0 Attrition: 1 Standardized outcomes: 0.5 Description: 1 Follow-up: 0

TABLE 5 (CONTINUED)

TABLE 5 (CONTINUED)									
Milroy et al. 2007 UK	Type: Pediatric Obtain ob- jective and subjective re- ports of sleep disturbances in school-aged children with mTBI	Level III Recruitment: A (from database); Cross- sectional; 2 groups: mTBI and orthopaedic controls with injury to wrist or arm	Exclusion: NI tive only; C1, C2 matched for age, gender; recruited by advertisement, word of mouth; One data collection, including 5 days of actigraphy	mTBI = 18 (43% of admissions) Controls = 30 (61% of admissions) Inclusion: • 7-12 yrs • ≥ 6 mos since last hospital at- tendance • Admission < 48 hrs Exclusion: • Developmental delay, epilepsy, psychiatric, or sleep disorders • Attends a special school • Other recent hospitalization • History of nonac- cidental injury	Age, yrs: mean TBI: 9.7 ± 1.5 Controls: 9.7 ± 1.5 Gender: TBI 56% F, Controls 40% F GCS: GCS of 15 = 16 GCS of 13 = 1 GCS of 14 = 1 2% recorded PTA Time since: 23.9 mos; Con- trols 25 mos	Actigraphy for 5 nights; Parental and self-report question- naires: Chil- dren's Sleep Habits; Self- report Sleep Scale Strengths and difficul- ties; Demo- graphic and injury-related questions	mHI: subjec- tive report difficulty falling asleep, difficulty waking in the morning, day- time sleepi- ness, restless sleep, fearful awakenings from sleep, parasomnias	Limitations: Small sample but reflective of the realities of this type of research	Moderate: 4/7 Baseline: 1 Blinding: 0 Sample size: 0 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0
Necajaus- kaite et al.	Type: Pediatric	Level III Recruitment:	TBI = 102 Controls = 102	Age, yrs: 4-16	Locally de- veloped	16.7% of par- ents reported	Limitations: Criteria measured	Moderate: 3.5/7	

TABLE 5 (CONTINUED)

2005 Lithuania	Investigate the clinical features and prevalence of symptoms of PCS in children with mTBI and evaluate changes over time	A; Cross-sectional; Two groups: TBI: single mTBI; Controls: mild body injury; 2 questionnaires mailed separately; first, for period during the last year and during the last month with no referral to trauma (to reduce bias); second (just TBI group) for period shortly after the trauma Compared those <2 yrs post-injury to those 2-5 yrs post-injury	Groups matched on gender, age, date of admission	Gender: 28% F GCS: NI Time since: 1-5 yrs post admission	standardized question-naire addressing: health and symptoms (irritability, fears, sleep disorders, learning problems, concentration problems, memory disorders, headaches, and comitant symptoms prior to trauma)	sleep problems shortly after head trauma	were not reliable estimates of long-lasting PCS; Weak measures; Only 1 data collection from Controls; Retrospective; possible issues of recall bias	Baseline: 1 Blinding: 0 Sample size: 1 Attrition: 1 Standardized outcomes: 0 Description: 0.5 Follow-up: 0
Korinthenberg et al. 2004 Germany	Type: Pediatric Investigative predictors of post-	Level III Recruitment Prospective cohort Consecutive A	mHI = 98 Inclusion: • LOC <10 or none • Able to answer questions at	Age, yrs: 3-5 (n = 26), 6-9 (n = 42), 10-13 (n = 30) Gender:	EEG Protocol of "examination of child with minor neuro-	At follow-up: 23% presented with somatic and psychiatric	Strengths: Large sample size Thorough investigation with follow-up	Moderate: 5/7 Baseline: 0.5 Blinding: 0 Sample size: 1

TABLE 5 (CONTINUED)

traumatic syndrome in children with mHI	(used specific criteria); Longitudinal; Objective and subjective measures	admission	40% GCS: NI Time since: <24 hrs since admission	logical dysfunction"; Structured validated interview	complaints including sleep disturbance and fatigue, which did not correlate with somatic, neurologic, or EEG findings immediately postinjury	Limitations: Better with a further follow-up	Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0.5
Pillar et al. 2003 Israel	Type: Pediatric Assess the prevalence and risk factors of long-term sleep disturbances in adolescents after mHI	Level III Recruitment: Retrospective cohort A "random" selection from archives); Cross-sectional; Matched controlled comparison group (healthy)	mHI = 98 Controls = 80 Inclusion: • 7-15 yrs at injury • Admitted to hospital with mHI • ICD-10 codes 506.0 • GCS ≥ 13 on admission to ER Exclusion: NI	Age, yrs: 13.5 $\pm$ 2.3 (range, 8-18) Gender: 32% F GCS: 14.7 $\pm$ 0.6 on admission Time since: 0.5-6 yrs	Detailed 60-item questionnaire	Strengths: Large sample Comprehensive questionnaire; Large range post-injury; Comparison group Limitations: 2/3 response rate No information on BMI at time of injury	Low: 2.5/7 Baseline: 1 Blinding: 0 Sample size: 1 Attrition: 0 Standardized outcomes: 0 Description: 0.5 Follow-up: 0
Mahmood et al. 2004.	Type: Neuropsychology	Level IVA Recruitment:	TBI = 87 Inclusion:	Age, yrs: NI	PSQI, BDI; Global scale	PSQI better at identifying insomnia	Moderate: 4.5/7

TABLE 5 (CONTINUED)

USA	chology Examine the relationship between sleep disturbances and neurocognitive ability post-TBI	Consecutive AI (archival records) Correlational Cross-sectional	<ul style="list-style-type: none"> TBI based on medical exam, recovery to post-acute phase, medically determined need for rehab, cognitive function at Level VI (Levels of Cognitive Function Scale) Indication of at least a concussion (LOC or confusion or positive neuroimaging) Exclusion: NI	<p>Gender: 43.7% F GCS: mild: 24; mod 19; sev 44 Time since: 97% within a year of injury; 89.7% within 6 mos; 70.1% within 3 mos</p>	<p>form; Memory Assessment; Scales; Neuropsychology tests: Wide range; Achievement test; (WRAT-3) - estimate of premorbid IQ; Digit Span; Digit Symbol; Grooved Peg Board; Block Design; Trail making-B; Controlled Oral Word Association Test (COWAT)</p>	<p>bances mTBI more sleep disturbed than severe Performance on selected measures of cognitive function ↑ prediction of sleep disturbance accounting for 14% of variance beyond that accounted by injury severity and gender (17%); Executive functioning and speed of information processing difficulties may be associated with sleep disturbances</p>	<p>nia but may have not have captured hypersomnia Need a reliable indicator better able to detect and report sleep disturbances Need to further assess the influence of gender; explore the threshold level and changes over time</p>	<p>Baseline: 0.5 Blinding: 0 Sample size: 1 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 0</p>
Wilde et al. 2007 USA	Type: Neuropsychology Examine the impact of comorbid OSA on cognitive	Level III Recruitment: PA (3 centers, sleep disorder centers, and a rehab	<p>TBI = 35 OSA = 19 No OSA = 16 Inclusion: • > 18 yrs • ≥ 3 mos post-injury</p>	<p>Age, yrs: >18 Gender: OSA: 11% F No OSA: 25% F GCS: OSA 53% unknown, 16%</p>	<p>Neuropsychological performance: Psychomotor Vigilance test</p>	<p>OSA ↓ on verbal and visual delayed-recall measures and > attention lapses</p>	<p>Strengths: First study to address this issue OSA associated with more impairment of sustained attention and</p>	<p>Moderate: 4/7 Baseline: 1 Blinding: 0 Sample size: 0 Attrition: 1 Standardized</p>

TABLE 5 (CONTINUED)

function of persons with TBI	program) Case controlled; Cross-sectional; 2 TBI groups: OSA and No OSA; Controlled using age, education, time postinjury, and severity of injury and GCS (when available); OSA diagnosed by nocturnal PSG	Exclusion: NI	mod, 5% mod-sev, 26% sev; No OSA: 50%; unknown, 12% mod, 19% mod-sev, 19% sev Time since: ≥ 3 mos post-injury	Rey Complex Figure Rey Auditory-Verbal Learning; Digit Span from WMS-R; Finger tapping; ESS on night of PSG and MSLT	Effect sizes using Cohen's <i>d</i> medium and large	memory; Treatment of OSA did not improve outcomes Limitations: Lacked data on levels of severity, difficult to generalize findings; Small sample but effect sizes good	outcomes: 1 Description: 1 Follow-up: 0
Wiseman-Hakes et al. 2010 Canada	Type: Neuropsychology Assess aspects of cognition and communication over a course of treatment for PTH Recruitment: LC Single case study Treatment: 17 wks 1) Baseline: 12 mos postinjury, lorazepam 1 mg and citalopram 20 mg for 1 mo 2) At 1 yr 1 mo, citalopram ↑ 40 mg 3) At 1 yr 2 mos:	TBI = 1	Age, yrs: late teens Gender: male GCS: initial 3, hospital 5 PTA > 1 mo Time since: 11 mos	Daily Cognitive-Communication and Sleep Profile (D-CCASP) ESS Stanford Sleepiness Scale PSG Maintenance of Wakefulness Testing (MWT) (at follow-up)	Relationship between quality of sleep and language processing Prolonged REM latency Positive relationship between sleep and language processing, sustained attention/vigilance, memory and changes in medication	Limitations: Single case study and exploratory in nature	Moderate: 4/7 Baseline: 0.5 Blinding: 0 Sample size: 0 Attrition: 1 Standardized outcomes: 0.5 Description: 1 Follow-up: 0

TABLE 5 (CONTINUED)

Study	Intervention	Comparison	Outcomes	Notes
Henry et al. 2000 USA	Type: Neuropsychology To investigate neuropsychological, psychological and behavioral functioning following non-impact BI	add methylphenidate 20 mg; 4) 1 week later methylphenidate ↑ 40 mg daily 5) Sleep Study 2: modafinil replaced methylphenidate and mirtazepine was added Baseline, 17 wks daily data collection, follow-up at 3 yrs 8 mos	Able to improve daily functioning and resume attendance at school	Moderate: 3.5/7 Baseline: 0.5 Blinding: 0 Sample size: 0.5 Attrition: 1 Standardized outcomes: 1 Description: 0.5 Follow-up: 0
	Non impact TBI = 32 Inclusion: • History of whiplash with brief or no LOC and no evidence of cranial trauma • No physical evidence that head struck windshield/headrest • Subjective report of an alteration in mental status at accident with no objective evidence Exclusion:	Age, yrs: mean 41.8 (range, 8-64) Gender: 53% F GCS: NI Time since: 1 wk to 5 yrs	Clinical interviews corroborated via interviews with significant others/co-workers Neuro-psychology battery: Wechsler Adult Intelligence Scale - revised (WAIS-R), WMS-R, Rey figures, Hooper,	Whiplash can produce wide-ranging circuitry dysfunction (similar to mTBI) Cognitive deficits observed particularly with executive functioning (attention and concentration); PASAT most sensitive test; Some experience of mild depression; Problems observed with behavioral control, sleep and sexuality; EEG showed

TABLE 5 (CONTINUED)

Jha et al. 2008 USA	Type: Intervention Test the efficacy of modafinil in treating fatigue and EDS	Level II Downs and Black: 23/28 Recruitment: PA; Double-blind, placebo-controlled crossover trial: 4 wk, washout period, 4 wk open label trial at end of modafinil: 2 x 100 mg twice a day for 8 wks with 2 wks graduated in (manufacturer provided) Data collection: base-	Previous whiplash or closed BI, neurological disorder seizure, psychiatric problem substance abuse or medical condition or medication that compromise nervous system integrity	<p>front-central slowing and ↑ in spike activity</p> <p>Boston naming and verbal fluency, Trails A and B Wisconsin Card Sort, Stroop, auditory, consonant trigrams, PASAT</p>	<p>Intervention</p> <p>Age, yrs: 38.25 ± 12.20 Gender: 31.4% F GCS: severe: 3-8 (51%); moderate 9-12 (23.5%); mild 13-25 (25.5%); Time since: 5.77 ± 4.97 yrs</p>	<p>ESS: E1>E2 at week 4 but not at week 10: only short-term benefit</p> <p>Insomnia reported more often with drug than placebo; Safe and well tolerated; There were no significant differences between modafinil and placebo and no consistent and persistent clinically significant differences</p>	<p>Strengths:</p> <p>Thorough complete information with demographics, methodology; Acknowledged complexity of fatigue and relationship with sleepiness</p> <p>Limitations:</p> <p>All sleep measures self-report; Standard dosage, therefore not able to tailor to individual (modify to meet individual responses (ex. taper)); Single center; Multiple stat tests, Clinical significance complicated as most did open label</p>	<p>High: 6.5/7 Baseline: 1 Blinding: 1 Sample size: 0.5 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 1</p>
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TABLE 5 (CONTINUED)

Castriotta 2008 USA	Type: Intervention Determine whether treat- ment of sleep disorders identified in BI adults results in resolu- tion of those disorders and improvement of symptoms and daytime function	line, week 4, week 10, weeks 4 and 10 after crossover	psychiatric or be- havior symptoms • Non-English • Pregnant females or potential child- bearing unless using contracep- tives	TBI = 57 Inclusion: • > 18 yrs • ≥ 3 mo post- injury Exclusion: • Presence of circadian rhythm disorder • Unable to give informed consent • Use of sedating medications	Age, yrs: 38.6 ± 14.8 Gender: 25% F GCS: used with CT findings ac- cording to crite- ria to establish severity 30% sTBI; 5% mod- sTBI; 18% mod TBI; 9% mTBI; 38% missing Time since: 67.8 ± 126.3 mos	Sleep: NPSG; MSLT; ESS; Neuropsy- chological; PVT; POMS; FOSQ; Urine sam- ple to test for drugs/ medications; Treatment: CPAP for OSA; Modafinil for narcolepsy and PTH Pramipexole for Peri- odic Limb Movement Syndrome (PLMS)	39% had abnormal sleep studies; 23% OSA; 3% PTH, 5% narcolepsy, 7% PLMS; 21% EDS; GCS ↓ for sleep disor- dered; Sleep disordered > reductions in tension and anger and ESS than non- disordered; Apnea/hy- popnea Index improved with treatment ↑ Amount of REM Treat- ment may result in NPG resolu- tion without change in sleepiness of	Strengths: Rigorous meth- ods; used estab- lished criteria as much as possible Limitations: Medications not titrated; Large missing severity data; Subsamples small; MSLT not the right mea- sure as it seems that sleep and wakefulness are 2 separate active processes	Moderate: 5/7 Baseline: 1 Blinding: 0 Sample size: 0 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 1

TABLE 5 (CONTINUED)

Francisco & Ivanhoe 1996 USA	Type: Intervention Effects of methylphenidate on posttraumatic narcolepsy	Level IVA Downs and Black: 11/28 Recruitment: LC; Single case study; Methylphenidate: 10 mg 2x/day then ↑ to 30 mg 2x/day over 4 mos	TBI = 1 Classic tetrad of narcolepsy (cataplexy, EDS, sleep paralysis hypnagogic hallucinations); diagnosis confirmed by PSG and MSLT; No structural, metabolic, or cardiac abnormalities that explain the symptoms	Age, yrs: 27 Gender: Male GCS: 3 at injury site but 7 at ED; mod TBI Time since: 22 mos	PSG; MSLT	1 mo after initiation cataplexy and EDS started to improve 6 mos after the start of treatment the patient is asymptomatic At 12 mos medication was involuntarily withdrawn and symptoms returned	Drugs leading to norepinephrine release may be helpful in reversing the symptoms of narcolepsy	Moderate: 4.5/7 Baseline: 0.5 Blinding: 0 Sample size: 0 Attrition: 1 Standardized outcomes: 1 Description: 1 Follow-up: 1
Ouellet and Morin 2007 Canada	Type: Intervention Determine the efficacy of cognitive behavior therapy (CBT) in TBI	Level III Downs and Black: 16/28 Recruitment OR: Single case design with multiple baselines across subjects 8 wk CBT addressing stimulus control, sleep restriction cognitive	TBI = 11 Inclusion: • 18-50 yrs • TBI in last 5 yrs • Not an inpatient • Insomnia syndrome (operational definition) • If taking meds for 6 mos and stable Exclusion: • Major untreated or unstable medical or psychiatric comorbidity • Meds known to	Age, yrs: 27.3 Gender: 46% F GCS: 3-14; 2 no data; mTBI to sTBI as evaluated by multidisciplinary team using standard criteria Time since: 25.64 mos	Sleep diary (Total wake time, Sleep efficiency); Diagnostic Interview for Insomnia; ISI; MFI; Dysfunctional Beliefs and Attitudes About Sleep Scale; BDI; BAI; 2-night PSG; Short telephone	Baseline results showed variability as expected; clinical and significant reductions in total wake time and sleep efficiency for 8/11 (74%); Progress generally well maintained at follow-up; Sleep effici-	Strengths: Good baseline table; CBT seems promising Limitations: Needed to include description of CBT; Did not assess cognitive functioning; Women were overrepresented; Self-selected so may be more motivated to change	Moderate: 4.5/7 Baseline: 0.5 Blinding: 0.5 Sample size: 0 Attrition: 1 Standardized outcomes: 1 Description: 0.5 Follow-up: 1

TABLE 5 (CONTINUED)

restructuring, sleep hygiene, education and fatigue management; Sleep diary for 2 wks at follow-up and 3, 5, or 7 wks randomly determined across subgroups of 3; 1-mo and 3-mos follow-up	produce insomnia <ul style="list-style-type: none"> • Sleep disturbances before TBI • Another sleep disorder • Unable to complete questionnaire • Experience significant pain 	interview at follow-up by independent interviewer	ciency augmented; ↓ fatigue symptoms
Level III Downs and Black: 10/28 Recruitment OR; Single case study; 8 wkly individual manualized CBT sessions (adapted for TBI) addressing stimulus control, sleep restriction, cognitive restructuring,	Age, yrs: late 30s Gender: male GCS: 13/15, no coma, PTA 5-7 days, moderate TBI Time since: NI	Sleep diary for 5 wks of baseline, 8 wks CBT, 2 wks post treatment and follow-up at 1 and 3 mos PSG (5 nights: 3 pre and 2 post) Insomnia Severity Index (ISI) Dysfunctional Beliefs and Attitudes about Sleep Scale	Sleep onset ↓ from 47 min to 18 min and nocturnal awakenings ↓ from 85 to 28 min; both below clinical criteria Sleep efficiency ↑ from 58% to 83% PSG corroborated data Majority of gains were maintained at follow-up (tapering of
Level III Downs and Black: 10/28 Recruitment OR; Single case study; 8 wkly individual manualized CBT sessions (adapted for TBI) addressing stimulus control, sleep restriction, cognitive restructuring,	Age, yrs: late 30s Gender: male GCS: 13/15, no coma, PTA 5-7 days, moderate TBI Time since: NI	Sleep diary for 5 wks of baseline, 8 wks CBT, 2 wks post treatment and follow-up at 1 and 3 mos PSG (5 nights: 3 pre and 2 post) Insomnia Severity Index (ISI) Dysfunctional Beliefs and Attitudes about Sleep Scale	Moderate: 4/7 Baseline: 0.5 Blinding: 0 Sample size: 0 Attrition: 1 Standardized outcomes: 0.5 Description: 1 Follow-up: 1

TABLE 5 (CONTINUED)

TABLE 5 (CONTINUED)							
Shan & Ashworth 2004 Canada	Type: Intervention Assess the effects of lorazepam versus zopiclone on cognition	and sleep hygiene education given by a clinical psychologist 5 wks of baseline, 8 wks CBT, 2 wks post-treatment and follow-up at 1 and 3 mos	MFI BAI	medication was occurring) ISI dropped from clinical to subclinical score			
	Level II Downs and Black: 23/28 Recruitment: Consecutive AI; Double-blind, crossover trial Self-regulate (0, 0.5 or full tablet) of lorazepam (0.5-1.0 mg) or zopiclone (3.75-7.5 mg) at bedtime for 7 days Start-ing dose randomly generated At 2 wks	ABI and stroke = 18 (ABI: 6) E1 = 9 E2 = 9 Inclusion: • >18 yrs • Secondary causes of insomnia okay: depression, apnea, restless legs Exclusion: • Acutely ill • Non-English/French speaking • Unable to read questions • Severe cognitive impairment	Age, yrs: 56.6 Gender: 44% F GCS: NI Time since: NI	Folstein MMSE: baseline, during week 1 and week 2; Rate quality of sleep from night before (2 of 7 days but not the first 3 days) - locally developed Total sleep time recorded by nursing staff questionnaire every 30 min or 1 hr Nurses rated restfulness	The medications seem to be equally effective	Limitations: Nonpharmacological interventions used Criteria participants used for self-dosing not clear Weak measures: locally developed, as convenience, thought more sensitive than Morning Sleep Questionnaire and no gold standard Excluded severe impairment	Moderate: 3.5/7 Baseline: 0.5 Blinding: 1 Sample size: 0 Attrition: 1 Standardized outcomes: 0 Description: 1 Follow-up: 0

TABLE 5 (CONTINUED)

state which intervention prefer	and drowsi- ness on a 1-4 scale testing for ataxia
^a Overall quality (sum across all the elements above; 0.5 rounded down): 5, 6, or 7 indicate high quality; 3 or 4 indicate moderate quality; and 1 or 2 indicate low quality. ^b "TBI", refers to the traumatic brain injury group; "ABI", refers to the acquired brain injury group; "Controls", "C1", "C2" refers to the control/comparison group(s). Abbreviations: ↑, increase; ↓, decrease; A, acute; AI, acute inpatient rehabilitation; BDI, Beck Depression Inventory; CPAP, continuous positive airway pressure; CRSDs, circadian rhythm sleep disorders; CSF, cerebral spinal fluid; CT, computerized tomography; CVA, cardiovascular accident; DSPS, delayed sleep phase syndrome; EEG, electroencephalogram; ER, emergency room; ESS, Epworth Sleepiness Scale; F, female; FOSQ: Functional Outcome of Sleep Questionnaire; GCS, Glasgow Coma Scale score; HADS, Hospital Anxiety and Depression Scale; HI, head injury; ISS, Insomnia Severity Index; LC, long-term community-residing; LOC, Loss of consciousness; mTBI, mild brain traumatic injury; modTBI, moderate TBI; MFI, Multidimensional Fatigue Inventory; mHI, mild head injury; MMSE, Mini-Mental State Exam; MSK, musculoskeletal injury; MSLT, Multiple Sleep Latency Test; MVC, motor vehicle collision; NFL, National Football League; NH, nonhypersomnia; NI, Not Indicated; NREM, non-REM; O-LOG, orientation log; OR, outpatient rehabilitation; PA, postacute; PAC, postacute community; POMS, Profile of Mood States; PR, postrehabilitation; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; PTA, posttraumatic amnesia; PTH, post-traumatic hypersomnia; PVT, Psychomotor Vigilance Test; REM, rapid eye movement; SCI, spinal cord injury; sTBI, severe TBI; vsTBI, very severe TBI.	

It has been consistently reported in the literature that individuals with TBI experience symptoms of insomnia and other sleep disturbances across the spectrum of recovery from the acute stage and beyond, across all levels of severity, with some patients continuing to report sleep disturbances for many years postinjury.^{4,6,29–37}

Thus, in order to try and present the literature in a manner that might further elucidate our understanding of the developmental course of posttraumatic sleep disturbances over time, we attempted to discuss the studies from the perspectives of sleep in the acute stage, early recovery/rehabilitation (to 1 year), and 1–3 years and beyond. However, consistent with the reports of Ouellet and colleagues⁶ and Orff and colleagues⁷ in their previous reviews, we experienced difficulties in doing so, particularly for those studies (the majority of which we identified) that were cross sectional, that is, evaluating sleep at only one time period.

Most studies clearly identified the average time postinjury of their participants and the range/standard deviation, but the ranges were, in fact, quite wide. Among the studies that utilized a comparison group (these studies were methodologically stronger than studies that did not involve a comparison group), the ranges of time postinjury were the following (in chronological order from publication date): from 2.7 months to 5 years, average 2 years post;³⁵ 2 weeks to 53 months, average 3.8 months post;³² 7 to 41 months, average 20.96 months post;⁴ 20 to 1194 days, average 230 days;²⁹ 12 months to 21 years, mean not given;³⁶ 74 to 1194 days, average 516 days;²⁶ 12.3 to 43.3 months, average 27.8 mos;³⁷ and up to 1 year post, specifics not given.²⁷ Thus, among these studies, we identified an overall 21-year range in time postinjury of subjects. The results, however, were not stratified in any of the studies by time postinjury, thus making it extremely difficult to draw any definitive conclusions regarding the developmental time course of the sleep disorders.

Furthermore, sleep disorders may well be confounded over time by the subsequent development of depression, anxiety, reduced activity and weight gain, again making it difficult to draw specific conclusions about the etiology of these disorders. It is necessary to acknowledge and mitigate potential factors that may confound the results,

whether these are factors that were preexisting to the brain injury or have developed secondary to the brain injury. However, from the perspective of recruitment at various times postinjury, there were studies that reported on sleep findings, including both prevalence and nature, at specific time points across different levels of severity. Thus, we have attempted to summarize the literature regarding the prevalence and nature of sleep disorders following TBI based on the source of patient recruitment: acute/postacute, rehabilitation, and community. Only those studies that delineated recruitment by time postinjury and level of severity, as well as stratified results according to the source of patients (e.g., acute care, rehabilitation settings) and level of severity, are included below. Thus, those studies that did not stratify their findings by level of severity are not included in our analysis. In addition, we only included studies that had substantial measures of sleep versus a single item documenting sleep problems.

a. Patients Recruited From Acute and Post-acute Care

We identified five studies that recruited participants from acute care settings.^{26,28,30,32,39}

Acute mild. Chaput and colleagues³⁸ conducted a retrospective chart review to determine the prevalence of sleep complaints in a sample of 443 patients diagnosed with mTBI. The authors used two time points: 10 days postinjury and again at 6 weeks postinjury. Of this sample, 13.3% reported sleep changes at 10 days postinjury, and this increased to 33.5% at 6 weeks postinjury with a smaller sample. Furthermore, the prevalence of sleep complaints at 6 weeks was 2.9 times more likely if such a symptom was present at 10 days ($P = .004$) and was associated with concomitant headaches, depressive symptoms, and irritability. Given the large sample size and the fact that they recruited all of those patients within the diagnostic category rather than just those with sleep complaints, the sample bias is minimized and the results are more generalizable to the whole mTBI population. The nature of the sleep complaints, however, was not delineated.

Acute and postacute moderate-severe. Makley and colleagues²⁸ followed a sample of 14 patients

with moderate-severe injuries recruited at 9 to 23 days postinjury from acute care, and reported that 78% had severely impaired mean sleep efficiency (<63%), as measured by actigraphy. These patients were subdivided into two groups, those with ongoing posttraumatic amnesia (PTA) and those whose PTA had resolved. Of significance, they reported that sleep efficiency improved once patients were no longer in a state of PTA ($P = .032$). Baumann and colleagues²⁴ consecutively recruited 96 patients within the first 4 days after TBI; at 6 months following TBI, 65 patients were evaluated using a combination of polysomnography (PSG), Multiple Sleep Latency Test (MSLT), actigraphy and clinical interview. The authors determined that at 6 months postinjury, among patients across all levels of severity (60% moderate-severe), 72% had sleep problems, 28% had subjective daytime sleepiness, 25% had objectively measured daytime sleepiness, 17% reported fatigue, and 22% reported “*sensu strictu*” (an increased sleep need over 24 hours). An additional 5% had insomnia. The authors further noted that in 43% of patients, the only possible cause of these problems was directly attributed to the TBI.

Rao and colleagues³⁰ recruited a sample of 54 patients within 3 months of trauma across all levels of severity; however, all had experienced a loss of consciousness. Results of the Medical Outcome Scales for sleep indicated significantly increased sleep disturbance ($P = .018$), decreased sleep adequacy ($P = .023$), and increased daytime sleepiness ($P = .0002$) in comparison to self-reports of preinjury sleep. Watson and colleagues³⁹ looked specifically at the prevalence of hypersomnia in a consecutive sample of 346 patients with TBI recruited from admissions to a Level 1 trauma hospital, in comparison with trauma controls (without TBI) and trauma-free controls. Data on sleepiness were collected at 1 month postinjury, with follow-up at 1 year. The level of severity was determined by the time taken to follow commands according to the motor component of the Glasgow Coma Scale (GCS). Although 78% of subjects took less than 24 hours to follow commands, they presented with serious enough symptoms in the emergency room that they were admitted to hospital and as such we have included them in our discussion of patients with moderate-severe TBI. At 1 month postinjury, 55% of all TBI subjects endorsed one

or more sleepiness items on the Sickness Impact Profile, in comparison with 41% of trauma controls and 3% of trauma-free controls ($P < .001$).

b. Patients Recruited From Rehabilitation Populations

Mild. We identified only four recent studies in which mild subjects from a rehabilitation outpatient population were recruited. Beetar and colleagues³⁵ conducted a retrospective chart review to determine the prevalence of sleep complaints in a consecutive series of 202 patients with TBI referred for neuropsychological assessment. The sample included 127 mTBI patients, 75 moderate-severe TBI patients, and 123 non-TBI controls. The authors found that, overall, 56.4% of the TBI patients had significantly more complaints of insomnia in comparison with controls (30.9%; $P < .001$), and the mTBI group reported approximately 50% more insomnia complaints than those with moderate-severe injuries ($P < .001$). This study was an important early contribution to the literature on sleep and TBI. Even though the authors did not use an operational definition of insomnia, their large sample size, use of a control group, and delineation of results by severity provided a strong foundation for future research. With regard to prevalence, Clinchot and colleagues⁴⁰ also reported on a sample of patients recruited from consecutive admissions to rehabilitation and contacted at 1 year postinjury. The authors found that approximately 75% of subjects (GCS score of 13–15) subjectively reported sleep disturbance.

Schreiber and colleagues³⁶ studied the nature of sleep disturbance, conducting a retrospective study of 26 patients with mTBI and sleep disturbance who were consecutively admitted to ambulatory rehabilitation. In comparison with healthy age- and sex-matched controls (who had routine sleep evaluations as part of a preemployment assessment procedure), the mTBI group had objective changes in sleep architecture, including increased light sleep (nREM) in 54.5% of subjects in comparison with controls (46.6%), and significantly lower total sleep time ($P < .05$). They also reported increased excessive daytime sleepiness objectively measured by MSLT in comparison with controls (higher number of falling asleep

episodes ($P \leq .05$) and shorter time to fall asleep ($P < .0005$). Baumann and colleagues²⁴ (also discussed in the section above on acute and postacute moderate-severe TBI) reported objectively measured sleep efficiency of 92% among their mild subjects; however, they identified 2 subjects (13%) with sleep efficiency well below the age-adjusted 25% percentile values. It is important to consider that the findings of these three studies may not be generalized to the population of mTBI as a whole. Despite the fact that the subjects were classified as mild, they all required rehabilitation and/or were referred for neuropsychological evaluation, thus placing them in a more “involved or severe/complicated” category of “mild” injury.

Moderate-severe. Although we identified seven studies that examined the prevalence and/or nature of sleep disturbances in samples recruited from a moderate-severe rehabilitation population,^{25,31,32,40–43} only the most recent (and higher quality) study stratified or reported results according to severity,²⁵ with the exception of the earlier work by Clinchot.⁴⁰ Clinchot and colleagues⁴⁰ (recruitment described above) found that approximately 57% of patients with a GCS score of 8–12, 24% of patients with a GCS score of 5–7, and 40% of patients with a GCS score of 3–4, reported subjective sleep complaints. Castriotta and colleagues²⁵ conducted an objective evaluation of sleep in 87 patients who were at least 3 months postinjury and were recruited from the rehabilitation services at three academic medical centers. Abnormal sleep studies were found in 46% of subjects. With regard to the nature of the sleep disturbances, 20% had OSA, 11% had posttraumatic hypersomnia, 6% had narcolepsy, and 7% had PLM. Among all subjects, 22% had objective excessive daytime sleepiness as measured by the MSLT. Interestingly, they identified no differences in injury severity and/or time postinjury between sleepy and non-sleepy subjects with TBI.

Finally, we identified two studies that recruited patients from rehabilitation, and although they identified objectively measured sleep and wake disturbances among participants, neither study identified any significant differences in injury severity or time postinjury between sleepy and non-sleepy subjects.^{25,31} Castriotta and colleagues²⁵ examined the prevalence of sleep disorders in a prospective sample of 87 patients with TBI who

were recruited from the rehabilitation services at three academic medical centers. Abnormal sleep studies (PSGs) were found in 46% of participants, including 23% with OSA, 11% with posttraumatic hypersomnia, and 7% with PLMs. Objective excessive daytime sleepiness was found in 25% of participants. Consistent with the findings of Verma,³¹ OSA was more common in obese participants (body mass index [BMI] ≥ 30). Furthermore, these investigators did not find any differences in severity of injury or time postinjury between sleepy and nonsleepy participants ($P < .05$).

c. Patients Recruited From the Community

We identified eight articles in which samples of individuals with TBI who had returned to the community were recruited.^{4,26,27,29,31,37,39,44}

Mild. Williams and colleagues³⁷ studied the extent and nature of sleep complaints in a sample of nine university students with previous mTBIs (range, 1.4–3.6 years postinjury) in comparison with age- and gender-matched controls. They identified 4% less efficient sleep, shorter REM onset latencies, and longer sleep onset latencies in comparison with controls, objectively measured by PSG. Although this study is quite thorough and rigorous in design, the small sample size and “sample of convenience” (i.e., student volunteers), weakens the generalizability of the findings. Schreiber and colleagues³⁶ characterized the nature of sleep disturbances in a sample of 26 chronic mTBI patients with sleep complaints who were at least 1 year postinjury. They reported changes in sleep architecture (as measured by PSG), including increased light non-REM sleep, in 54.5% of patients ($\pm 13.4\%$) in comparison with controls ($46.6\% \pm 10.4\%$).

Moderate-severe. Parcell and colleagues²⁹ reported on a sample of 63 participants with TBI consecutively recruited after discharge from rehabilitation, in comparison with 63 age- and sex-matched controls. Eighty percent of patients reported subjective changes in sleep relative to controls (23%), including more nighttime awakenings, and longer sleep-onset latency. In another study,²⁶ Parcell and colleagues recruited 10 community-based participants with TBI and 10 age- and sex-matched controls. The authors

reported objectively measured increases in slow-wave sleep, reductions in REM sleep, and reduced sleep efficiency in comparison with controls, as well as subjective reports of poorer sleep quality.

Ouellet and colleagues⁴ recruited a sample of 452 participants from mailings distributed to 1500 people with TBIs identified through the archives of the rehabilitation center, as well as TBI associations and support groups. Their sample included 59.9% with severe injuries, 23.3% with moderate injuries, 13.7% with mild injuries, and 3.1% with “minor” TBIs. Participants completed a detailed questionnaire that was then mailed back to the authors, who identified that 50.2% of their sample reported insomnia symptoms and 29.4% fulfilled the diagnostic criteria for an insomnia syndrome. This study continues to have the largest sample size of all of the literature to date pertaining to the prevalence of insomnia following TBI. In addition, it is one of the few that actually delineated between those who presented with symptoms of insomnia and those who met the diagnostic criteria for insomnia, thus providing a more reliable and valid estimate of the true prevalence. It is not possible, however, to completely eliminate sample bias without having information regarding the 1000 others who chose not to participate.

In another study, Ouellet and Morin⁴⁴ examined the nature of insomnia in the context of TBI by recruiting a sample of 14 adults with TBI who presented with an insomnia syndrome (nine of whom were moderate-severe), and 14 healthy, age- and sex-matched controls. It was not clear from the article how or where the participants were recruited. The authors reported that 71% of subjects had objective findings of insomnia, including more awakenings and shorter REM onset latencies. Furthermore, in comparison with controls, those with TBI had significantly more awakenings lasting longer than 5 minutes ($P = .059$), as well as significantly shorter REM latency (for those with TBI taking no medications) ($P = .050$). In the 1-year follow-up to their study of the prevalence of hypersomnia in the acute stage following TBI, Watson and colleagues³⁹ found that 27% of participants continued to endorse subjective symptoms of sleepiness, in comparison with 23% of trauma controls and 1% of nontrauma controls ($P < .001$). However sleepiness did im-

prove in 84–100% of participants with TBI, with the smallest improvement being 84% in the mildest group (≤ 24 hours to respond to commands). Verma and colleagues³¹ objectively examined the nature and spectrum of sleep disorders in chronic TBI by recruiting a sample of 60 patients who presented with postinjury sleep complaints. It is not clear where or how the participants were recruited. Sixty percent of patients in the sample had moderate-severe injuries. Hypersomnia was the presenting complaint in 50% of all participants, which the authors reported was “mostly due to” underlying sleep apnea, narcolepsy, and PLMs. Of interest, 45% of the sample exceeded a BMI of 30, which is considered to be obese. Insomnia was the presenting complaint in 25% of participants, and half of those had difficulties with sleep onset.

Sport-related concussion. New to the literature is a 2009 study that evaluates sleep following sport-related concussions. Gosselin and colleagues²⁷ examined both subjective and objective sleep quality in 10 subjects/athletes with a sport-related concussion, and compared their findings to those of 11 nonconcussed control athletes from noncontact sports. The concussed group had a history of 4.6 (± 2.1) concussions on average, sustaining at least one in the previous year. Objective measures of sleep included two consecutive nights of PSG, and electroencephalography (EEG) spectral power; subjective measures of sleep included the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and Post Concussion Symptom Scale, as well as a subjective questionnaire that was developed specifically for the study. The authors reported that although the concussed athletes identified more symptoms and worse sleep quality than controls, this was not corroborated by any polysomnographic variables, or REM and nREM sleep quantitative EEG variables. However, concussed athletes showed considerably more relative delta activity, and reduced alpha activity and relative alpha power, during wakefulness than controls. Based on these findings, the authors concluded that sport-related concussions are thus associated with wakefulness problems, rather than sleep disturbances per se. Although this study has a small sample size and as such the Gosselin and colleagues’ findings are preliminary, their strong methodological design is

such that this is an important first step in examining this population. Their findings are relevant and timely, given that sport-related concussions occur at a predictable rate in “high-risk” sports (i.e., football, hockey, etc.), ranging from 7–12% of the participant population in any given year, and that the sequelae of sport-related concussion is currently receiving much attention.^{45–47}

d. Prevalence

As the literature has continued to evolve, we have attempted (as have others before us) to identify ranges of the prevalence of sleep disturbances identified among the studies based on time postinjury of recruitment. The results of these studies confirm that disorders of sleep and wakefulness are prevalent across all stages of recovery from TBI, from the early acute stage until many years postinjury, and across all levels of severity. However, defining conclusive “ranges” continues to be problematic due to the heterogeneity within and between samples, inconsistencies in the measures used, different study objectives, and variations in reporting. Some studies utilized percentages for reporting findings; alternatively, others reported on regression analysis of sleep, along with various associated phenomenon (i.e., depression, anxiety); identified changes in sleep architecture; looked specifically at insomnia as a global phenomenon; reported on the symptoms of insomnia; or, looked at other types of sleep disorders such as hypersomnia in and of itself, or secondary to apnea. As such, a valid synthesis of prevalence rates among studies remains elusive, and larger epidemiological studies across levels of severity and varying time points are warranted.

e. Methodological Limitations

Although the studies continue to become more scientifically rigorous as the literature evolves, the results to date are representative of methodological limitations in study design, as most of the literature is based on a clinical subset of TBI survivors who: a) present with sleep complaints, therefore introducing bias into the sample; and b) have received rehabilitation and therefore represent a subset of

this patient population with likely more severe injuries, even those who are classified as “mild”. Thus it is likely that the data are skewed and are not fully representative of the TBI population as a whole. However, Parcell and colleagues²⁶ specifically identified that their sample of 10 included “the first ten willing participants, with no preference for patients with sleep complaints,” and Fichtenberg and colleagues³² recruited a prospective sample of 50 consecutive admissions to an outpatient rehabilitation program. The advantage of recruiting consecutively upon admission to the acute setting or from the emergency room is that all patients diagnosed with TBI are included in the study sample and followed regardless of whether they require postacute care. By following patients from the acute stage the issue of time since injury becomes negated, as all of the sample will be entered into the study at time of injury. As soon as recruitment takes place after the acute stage, researchers are already introducing forms of selection bias into the sample that should be addressed when discussing the generalizability of the findings. Given that such a small percentage of the studies were able to recruit consecutively from the acute setting the epidemiological understanding of this phenomenon is going to be fraught with issues of generalizability and difficulty in making clear conclusions.

An ideal study would follow a large sample consecutive series of patients from acute care for at least three years to understand how sleep problems manifest themselves, or not, and how these change over time, considering natural recovery by levels of severity.

Confounds. Some of the researchers made sure to exclude concurrent potential confounders, whereas others collected data on potential confounders (usage of caffeine, alcohol, medications, or drugs, BMI, and emotional state). However, with the exception of emotional state, which is also identified as a concurrent risk factor, the results were not stratified according to any of these confounds, nor were they addressed in discussion. Thus, we are only able to comment that these confounders exist, but are not able to make any definitive comments regarding their influence.

Risk factors. Ten studies identified risk factors specifically associated with insomnia following TBI, and two studies identified risk factors for

other types of posttraumatic sleep and wake disorders. Beetar and colleagues³⁵ identified pain and mTBI as being risk factors for insomnia complaints in a case-controlled sample of 200 TBI patients of mixed severity. Among a sample of 91 consecutive patients admitted to an outpatient rehabilitation program, Fichtenberg and colleagues⁴¹ identified three risk factors associated with insomnia including milder injuries, the presence of pain, and depression. Of the three factors, depression had the strongest association with insomnia. Consistent with Fichtenberg's findings, Ouellet and colleagues⁴ reported that among a sample of 460 survivors recruited from the community (averaging 7.85 years postinjury, 83.2% of whom with moderate-severe injuries), risk factors for insomnia included milder injuries, depression, and pain. They also identified high levels of fatigue as a further risk factor.

Among a sample of 60 patients with varying levels of severity, ranging from 3 months to 2 years postinjury, Verma and colleagues³¹ noted that those with complaints of insomnia had elevated Beck Depression Inventory (BDI) scores and Hamilton Anxiety scores, thus further confirming that depression and anxiety are risk factors for insomnia following TBI across all levels of severity. They also identified 45% of their sample as having a significantly high BMI. Chaput and colleagues³⁸ identified headaches, depressive symptoms, and irritability as co-occurring with sleep complaints in a sample of 443 patients with mTBI, at both 10 days and 6 weeks. Rao and colleagues³⁰ also identified depression and anxiety as coexisting risk factors for symptoms of insomnia. Clinchot and colleagues⁴⁰ was the only study to identify gender (female) as a risk factor for symptoms of insomnia ($P = .033$), in addition to older age ($P = .035$), milder injuries, and a GCS score greater than 7 ($P = .034$). Baumann and colleagues²⁴ identified that severe TBI (sTBI) was associated with the development of posttraumatic hypersomnia ($P = .02$), but not with the presence, characteristics, and severity of other posttraumatic sleep disorders. The association between more severe TBI and the development of hypersomnia was also confirmed by Watson and colleagues.³⁹ Castriotta and colleagues²⁵ identified that among the 46% of their sample with abnormal sleep studies (with five different types of sleep and/or wake disorders),

the sample participants were significantly older than the nonsleep-disordered subjects ($P < .01$) and had a significantly higher BMI ($P < .05$).

Sample size. TBI is very heterogeneous and as a result it is complicated to conduct research that is generalizable. Ideally, studies would be able to recruit a large number of patients so that stratification on a number of variables would be possible: age at injury, gender, etiology of injury, severity of injury, and time since injury. Only 39% (9/23) of the studies reviewed used sample sizes of greater than 75. Thirty-five percent (8/23) of the studies involved studies with sample sizes of less than 30 and thus were compromised in their statistical analysis and their ability to generalize to the different subgroups of brain injury.

Definition of insomnia. Another methodological limitation, also identified by Ouellet and Morin,⁴⁴ is the lack of an operational definition of insomnia. Among the five comparison group studies that evaluated subjective reports of insomnia, sleep, and hypersomnia postinjury,^{29,32,35,39,44} only two utilized an operational definition of insomnia, the International Classification of Sleep Disorders and the DSM-IV.^{32,44} Related to this is the lack of consistency in or development of an operational framework for assessing severity of brain injury. Many studies use the GCS score to assess severity but the GCS score is not always available and other factors are included: length of PTA, period of loss of consciousness, cerebral computed tomography (CT) findings, and neuropsychological findings. One study³⁹ determined injury severity based on time taken to follow commands. Baumann and colleagues,²⁴ one of the two methodologically strongest studies reviewed, specifically cited using GCS scores and CT findings based on the Marshall⁴⁸ criteria (I = no visible intracranial pathology, II–IV = midline shift, and V = mass lesion). It is necessary that there be consistency as to how to combine all of these factors together so that severity distinctions can be enabled when only some of the above features are present.

Measures. As per the comments of Orff and colleagues,⁷ there is also a significant discrepancy among the measures utilized. Of the 23 studies we evaluated under the epidemiology category, investigators used 19 different methods to evaluate sleep, of which four are objective (PSG, actigraphy, MSLT, Multiple Wake Test [MWT]). There is no

gold standard of standardized instruments that is accepted. Although locally developed measures and those that are clinically developed may be very useful, it is impossible to compare from one study to the next when different types of measures are being used to assess the outcomes. The issue is that sleep itself is very difficult to assess, as it is composed of many components. It would seem that among the validated instruments, the most commonly used and accepted are the Diagnostic Interview for Insomnia (DII), Insomnia Severity Index (ISI), PSQI, and the ESS. It has been proposed that the MWT may be more suitable for this population than the MSLT, as daytime sleepiness seems to be a hallmark of this condition. One study³⁰ utilized the 12-item Medical Outcome Scale for Sleep,⁴⁹ which has been found to have good psychometric properties and has been found to be useful for assessing sleep problems in adults. Each of these instruments contributes a unique component to the assessment of insomnia and sleep difficulties and as such should be used in combination, rather than in isolation.

The subjective or self-report measures ranged from the early work of Beetar, which relied on a

chart review, and concluded that “a sleep problem was judged as present if it was mentioned in the chart as reported by the patient,”^{35(p. 1299)} to the more robust PSQI used by Fichtenberg³² (and validated for use with TBI patients), the battery used by Ouellet and colleagues⁴⁴ that included the DII, ISI, Multidimensional Fatigue Inventory, in addition to other measures and nocturnal PSG, sleep diaries, and ESS used by Parcell and colleagues.^{26,29} The most commonly used measures included the PSQI, PSG, and some form of a sleep diary. It is positive to note that as the literature evolves, overall, the use of measures to evaluate sleep and wake disorders have become increasingly comprehensive, sensitive, and “robust” over time. This in and of itself, however, further emphasizes the weakness of recent studies that rely on limited and/or weak measures, such as the study by Watson and colleagues.³⁹ Although we recognize that this study was part of a larger study and had the strength of a follow-up in its design, the sole reliance on data obtained via four questions about sleep from the Sickness Impact Profile weakens the validity/generalizability of the overall findings.

TABLE 6

Practice Points	Research Agenda
1. Sleep and wake disorders are present across all levels of severity at all stages across the continuum of recovery following TBI.	1. A large scale multi-center collaborative trial involving all those with TBI (i.e., not limited to those who present with sleep problems) recruited in the acute stage, followed longitudinally into the community and evaluated at regular time points is warranted.
2. Sleep and wakefulness should be routinely and systematically assessed for the duration of medical and neuropsychological follow-up after TBI.	2. Functional measures should be used in addition to formal measures of cognition.
3. Risk factors for insomnia include mTBI, pain, anxiety, depression, fatigue, and older age.	
4. Risk factors for hypersomnia include more severe TBI.	
5. Increased BMI (>30) is a risk factor for OSA.	
6. The PSQI, followed by the ISI, are appropriate measures for initial screening and corroboration of the impact of the problem.	

2. Pathophysiology

We identified three papers, all of moderate quality, which look at varying aspects of pathophysiology of sleep/wake disturbances following TBI, including two Level III studies^{50,51} and one Level IVA study.⁵² In 2005, Baumann and colleagues⁵⁰ sought to test the hypothesis that deficiencies in hypocretin-orexin-1 (Orexin A) neurotransmission in acute TBI may play a role in the emergence of subsequent sleep/wake disorders. Orexin A is an excitatory hypothalamic neuropeptide involved in the regulation of the sleep/wake cycle, and its levels are typically reduced in persons with narcolepsy. Hypocretin-1 levels were measured in 44 patients by radioimmunoassay at 1–4 days following TBI (males, $n = 32$; 31 patients with sTBI, 8 with moderate TBI [modTBI], and 5 with mTBI), and compared with hypocretin-1 levels in healthy controls ($n = 20$). Their results indicated that in comparison with controls, hypocretin-1 levels were abnormally lower in 95% of patients with moderate-severe TBI, and in 95% of patients with posttraumatic brain CT findings. The authors postulated that hypocretin-1 deficiency following TBI may be reflective of hypothalamic damage (specifically to the posterolateral hypothalamus) and may be linked with the frequent development of posttraumatic sleep wake disorders. These findings are an important contribution to the determination of risk factors.

Ayalon and colleagues⁵¹ conducted a study to diagnose and describe the physical and behavioral characteristics of circadian rhythm sleep disorders (CRSDs) in patients with mTBI. Forty-two patients with mTBI and complaints of insomnia were screened, and those who were suspected of having CRSDs underwent further diagnostic evaluation. In total, 15 of the 42 patients (36%) were formally diagnosed with CRSDs, eight patients displayed a delayed sleep phase syndrome (DSPS), and seven patients displayed an irregular sleep-wake pattern (ISWP). All patients exhibited a 24-hour period of melatonin rhythm, and those with DSPS exhibited a 24-hour periodicity oral-temperature rhythm. However, three of the seven patients with ISWP lacked such a daily rhythm. Furthermore, the patients with ISWP exhibited smaller amplitudes of temperature rhythm. Given that the authors found that as many as 36% of their particular sample had

been diagnosed with insomnia when in fact they had a CRSD, they concluded that CRSDs may be a relatively frequent sleep disorder among these patients, and that misdiagnosis of patients with CRSDs as insomniacs may lead to inappropriate prescription of hypnotic medications.

Quinto and colleagues⁵² described the case of posttraumatic DSPS in a 48-year-old male, 4 years following TBI. (Note: the authors use the term cerebral concussion; however, as the patient was in coma for “several days,” we will consider this to be a severe TBI [sTBI]). Although the patient was 4 years postinjury, the emergence of his sleep onset insomnia was during the acute phase of recovery. Since his injury, it took him 1 to 2 hours to fall asleep. He reported through a sleep diary that he would go to bed between 3:00 and 5:00 a.m., awaken after 1 to 1-and-a-half hours, return to sleep, and awaken between 11:00 a.m. and 12:00 p.m. These findings were confirmed by actigraphy. The patient did not have any other medical or psychiatric disorders. Circadian rhythms are quite strict and are in fact slightly less than 24 hours in humans. The “circadian clock” located in the suprachiasmatic nucleus (SCN) of the hypothalamus serves to keep physiologic functions in synchrony with each other and with the environmental light/dark cycle, thus making a small daily phase advance to entrain to the 24-hour day. A decreased ability to make this phase advance in response to environmental cues is thought to be the underlying pathophysiology behind DSPS, and the authors of this study postulate that damage to the SCN sustained during trauma may result in circadian cycle disorder.

3. Pediatrics

We identified six studies, five of which were of moderate quality, which reported sleep complaints in children and adolescents. Five of these studies focused specifically on mTBI. In a 2001 study of 19 adolescents 3 years following minor head injury (mHI), Kaufman and colleagues⁵³ reported that in comparison with healthy controls, head-injured teens had significantly reduced periods of sleep time, total sleep time, and sleep efficiency, as well as an increased number and length of awakenings, objectively measured by PSG and

TABLE 7

Practice Points

1. It may be of benefit to measure hypocretin-1 in patients with moderate-severe TBI (who are being monitored for Intracranial Pressure [ICP]) during the acute stage as a potential marker/risk factor for the emergence of sleep and wake disorders.
2. Lesions/damage to the hypothalamus are a risk factor for sleep/wake disorders following TBI.
3. Awareness of DSPS as a possible consequence of TBI is important as its symptoms may be overlooked and attributed to the “typical” postconcussion syndrome complex.
4. Proper diagnosis of CRSDs is important as a misdiagnosis of insomnia may lead to inappropriate prescription of hypnotic medication, which “may help patients fall asleep, but would not be efficacious in normalization of the sleep-wake cycle.” ^{51(p. 1139)}
5. Treatments with melatonin or bright light may be more appropriate with CRSDs.

Research Questions

1. “Future research specifically designed to explore the role of neurophysiologic and psychological factors in the emergence of CRSDs following mTBI may improve our understanding of the nature of this association.” ^{51(p.1139)}

actigraphy over 5 days. Subjectively, those with mHI reported significantly more difficulties falling asleep, difficulty waking in the morning, restless sleep and parasomnias, fearful awakenings from sleep, and increased daytime sleepiness than did healthy controls. Further investigations by this group of authors⁵⁴ found that in comparison with healthy controls, nearly one third (27/98) of the subjects aged 8–18 years, with 0.5–6 years following mHI, had subjective complaints of sleep disturbance and shorter weekend sleep time than did healthy controls. The authors identified that those with mHI and complaints of sleep disturbance were also more likely to complain of bruxism and manifested a significantly greater BMI. Furthermore, these subjects came from families with a lower level of parental education. Although no information was available regarding preinjury BMI or any patterns of weight gain postinjury, the authors concluded that risk factors for sleep disturbance in mHI include heavier body mass and lower levels of parental education.

In 2004, Korinthenberg and colleagues⁵⁵ examined predictive factors of posttraumatic syndrome in children (range, 3–13 years) with mHI.

The authors used data from EEG, in addition to a published neurological examination protocol and a structured validated interview at two time points (T1: within 24 hours of the injury, and T2: 4–6 weeks postinjury) to identify that at follow-up, 23 of 98 patients continued to present with psychiatric complaints, including sleep disturbance and fatigue. These findings did not correlate with the severity of the injury, or somatic, neurologic, or EEG findings immediately postinjury. In their discussion, the authors stated that the “lack of a correlation with the acute concussional symptoms, acute neurological findings and the acute EEG abnormalities suggests that post traumatic complaints in our patients are not primarily caused by organic structural or functional changes.”^{55(p.116)} They noted that parental and patient anxiety is a frequent problem even after mHI, and it correlates with persistent symptoms.

In contrast, however, Necajauskaite and colleagues⁵⁶ studied 102 matched pairs of children aged 4–16 years, including a case group with mTBI and comparison group with mild bodily injury but no mTBI. They found that although 16.7% of the parents in the case group reported

sleep disturbances in their children shortly after the trauma (exact time not defined), they did not find any significant differences in subjective reports of sleep disturbance between the two groups in the month prior to follow-up (1–5 years postinjury; mean, 27 months).

In the most recent study to examine sleep in children with mTBI, Milroy and colleagues⁵⁷ compared 18 children aged 7–12 years with mTBI with 30 children with orthopaedic injuries (average time postinjury, 24 months). These authors used both subjective and objective measures (parental and self-report sleep questionnaires and actigraphy), and while parents reported greater sleep disturbances in the mTBI group, there were no significant differences between the groups with respect to daytime sleepiness, children’s self-report of sleep disturbance, and actigraphy results.

We found only one study that examined sleep in children with moderate-severe TBI. Beebe and colleagues⁵⁸ compared parental reports of sleep behaviors in approximately 100 children (aged 6–12 years), 50 with modTBI and 50 with sTBI, with a comparison group of 80 children with orthopaedic

injuries. The children were followed longitudinally over three time points at approximately 6, 12, and 48 months postinjury. The authors reported that for both groups, daytime sleepiness and nocturnal sleep duration were increased following TBI. The modTBI group reported higher baseline sleep problems than the sTBI group and the orthopaedic group; however, this declined over the follow-up period (the specific time course was not specified) to a level consistent with the general population (6–9%). However, the authors reported that the sTBI group displayed an injury-associated increase in sleep problems, with the prevalence nearly doubling from 16% at baseline to 31% postinjury (again, specific timelines were not specified). The authors cautioned that these results should be considered as preliminary given the limitations of the outcome measure; however, they concluded that sleep problems emerge after severe pediatric TBI (and are present in the postacute stage in modTBI).

In conclusion, there is emerging conclusive evidence to support the incidence and prevalence of sleep disturbances in children and adolescents following TBI, across all levels of severity. There

TABLE 8

Practice Points

1. Children and adolescents with mTBI/mHI need to be systematically and routinely assessed for subjective complaints of sleep disturbances and followed-up over time.
2. Children with moderate-severe TBIs should be followed and assessed for emergence of sleep problems, with provisions of appropriate sleep interventions.
3. Adolescents with mHI, higher BMI, and lower levels of parental education are at increased risk for sleep disturbances. Educating adolescents and parents about healthy eating and regular activity may be of benefit.
4. Providing parents with education and information during the acute stage post mHI may help to alleviate anxiety and improve outcome.

Research Questions

1. Sleep (and wake) problems in children and adolescents with both mild and moderate-severe TBIs should be evaluated longitudinally by both objective and subjective measures beginning at the onset of injury, to determine any patterns in the developmental course of sleep disturbance.

is both subjective and objective evidence documenting the prevalence of sleep disturbance in adolescents with mTBI several years postinjury. There is emerging subjective evidence to suggest that sleep disturbances become more prevalent over time in children with sTBI, yet decline over time postinjury in children with modTBI. There is evidence to suggest that sleep problems in children with mTBI do not correlate with initial neurological findings. Clearly, the research on sleep disturbances in children with TBI is in the early stage and warrants further scientific investigation to more clearly identify the nature and patterns of the disturbance, any functional implications, and appropriate interventions.

4. Neuropsychological Implications

Sleep disturbances following TBI have been reported to exacerbate cognitive and behavioral sequelae. We identified four studies of moderate quality: three evaluated neuropsychological (and cognitive-communication) function in relation to sleep disorders following TBI, and one documented both sleep and neuropsychological sequelae following nonimpact brain injury. In 2000, Henry and colleagues⁵⁹ retrospectively investigated the neuropsychological and behavioral functioning of 32 adults (aged 18–66 years) with “non-impact brain injury” (i.e., whiplash) up to 65 months postinjury. The authors used a comprehensive battery of standardized neuropsychological and psychological tests to assess cognition, motor skills, and mood functioning. As the study was retrospective, some subjects had had structural neuroimaging, and three had undergone overnight sleep studies, in addition to neurological examination and interview. Results indicated that patients with whiplash injury demonstrated persistent cognitive, behavioral, and emotional dysfunction years postinjury. Fifty-three percent had problems with sleep (not defined) in addition to difficulties with attention, concentration, executive functions, reduced information processing, word finding, sexuality, anxiety, and depression. Of the three subjects who underwent a nocturnal sleep study, sleep maintenance insomnia was identified with altered sleep stage percentages and altered REM

rhythms. Although the authors cite methodological limitations as precluding any conclusions regarding causation, finding sleep disturbance following whiplash is not surprising given the shearing injury and potential involvement of the hypothalamus.

In 2004, Mahmood and colleagues⁶⁰ conducted an investigation of the relationship between sleep disturbance and neurocognitive ability in 87 adults with TBI across all levels of severity who had been admitted to a comprehensive outpatient rehabilitation program. The authors conducted a cross-sectional examination of scores on patients’ neuropsychological examinations, the BDI-II and the PSQI. They reported that: “as would be expected, PSQI scores and BDI-II scores were significantly correlated because of the partial overlap of depression symptoms and insomnia.”^{60(p.382)} The authors also reported that measures sensitive to higher-order executive functioning and speed of information processing showed a positive relationship with PSQI scores. Their findings supported a hypothesis of a predictive relationship between performance on neuropsychological tests and reports of sleep disturbance in adults with TBI.

In 2007, Wilde and colleagues⁶¹ examined the impact of comorbid OSA (diagnosed after the TBI) on the cognitive functioning of 19 patients with TBI, in comparison with 16 patients with TBI but without OSA. The subjects were otherwise comparable in terms of age, education, injury severity, time postinjury, and GCS score (where available). The patients with TBI and OSA performed significantly worse on verbal and visual delayed recall measures, and had more attention lapses than the patients with TBI without OSA. Interestingly, they did not differ on other measures of visual construction and motor and attention tests. The authors concluded that patients with TBI and OSA had greater impairments in sustained attention and memory than did those patients with TBI without OSA.

In 2010, Wiseman-Hakes and colleagues⁶² assessed daily self- and clinician (rehabilitation worker) reports of changes in cognitive and communication functioning, including sustained auditory attention/vigilance, speed of language processing, verbal memory, and communication, in response to a course of pharmacological intervention phased in over 17 weeks for post-

traumatic hypersomnia. The self-report measure used in this study is the newly developed Daily Cognitive-Communication and Sleep Profile (D-CCASP), which is currently undergoing reliability and validity testing (Wiseman-Hakes, 2005, unpublished measure). This case-study participant was a young man in his late teens 11 months after sTBI when the study began. As treatment progressed, the authors found a clear positive relationship between improved quality of sleep and language processing (defined as the ability to follow and participate in conversation), sustained attention/vigilance (defined as the ability to pay attention and concentrate over time), and memory (defined as the ability to remember things that one has heard, done, or seen). This was seen across the different phases of the medication regime ($P < .01$). A follow-up conducted at 3 years and 8 months indicated that the gains in sleep, daytime wakefulness, and cognitive-communication function had been maintained. Although the data were limited to one subject, the findings suggest that appropriate, timely, and effective diagnosis, and management of sleep/wake disturbances following TBI, may facilitate improved cognitive-communication function. The authors concluded that their results need to be corroborated with a larger sample size and the addition of standardized neuropsychological and cognitive-communication assessment measures to clinically evaluate reported functional changes.⁶²

5. Intervention

The literature on the treatment of sleep disturbances following TBI is relatively limited at this time. This may be a reflection of the complexity of this disorder from a number of perspectives; that is, the lack of a clear etiology in many patients, mixed diagnoses, lack of consistency regarding the developmental course of the disorder, and interactions with secondary issues such as pain and depression. We identified six papers for review in total: four were of moderate quality and two of high quality. Four of the six articles focused upon pharmaceutical management; of these four, one was for the treatment of fatigue and excessive daytime sleepiness following TBI, one was for the treatment of narcolepsy, another was for the

treatment of insomnia following TBI and stroke, and only one addressed treatments for a number of different types of sleep disorders commonly associated with TBI. The remaining two articles focused on behavioral intervention specifically for insomnia.

These latter two moderate-quality articles by Ouellet and Morin^{63,64} assessed the efficacy of a protocol of CBT administered by a registered clinical psychologist over a period of 8 weeks. The first paper reports an individual case study and the second reports a single case series. The authors state that cognitive therapy for insomnia consists of “identifying, challenging and altering a set of dysfunctional beliefs and attitudes about sleep,” with the objective of “breaking the cycle of insomnia; dysfunctional thoughts and emotional distress that lead to further sleep disturbances.”^{63(p. 1299)} The authors do a thorough job of delineating the treatment protocol, which was adapted to take into account the deficits in memory, attention, and processing that can occur following TBI.

The results of the case study are promising; the participant experienced reduced sleep onset latencies and nocturnal awakenings, and an increase in sleep efficiency. These results were well maintained at follow-up at both 1 and 3 months. The authors built upon these initial results by expanding their assessment measures and number of subjects in a single-case series of 11 individuals (six males, five females) with mild to severe TBI. There are a number of relative strengths of this article, despite the small sample size. Subjects were recruited from a variety of locations using a variety of methods, including major rehabilitation centers across Quebec, Canada, as well as through advertisements to TBI associations and local support groups. Furthermore, all levels of injury severity were represented, indicating that although the sample size is small, their sample is likely fairly representative of the post-TBI population. Their results indicated a decline in total overnight wake time relative to baseline, as well as a reduction in overnight sleep variability in 8 of 11 participants. Treatment effects were seen 1–2 weeks after the beginning of therapy. All participants increased their sleep efficiency, and 5 of 11 achieved a sleep efficiency of greater than 90% at the 3-month follow-up. At posttreatment, 7 of 11 no longer fulfilled the diagnostic criteria

for insomnia. Based on their results, the authors suggest that insomnia associated with TBI can be successfully improved in a large proportion of cases with short-term cognitive behavioral intervention.

The remaining four papers for review addressed pharmacological intervention. Jha and colleagues⁶⁵ examined the efficacy of modafinil in treating fatigue and excessive daytime sleepiness in individuals with TBI. This high quality, comprehensive, and well-conceived study consisted of a double-blind placebo cross-over trial in which 53 patients with TBI were randomly assigned to receive up to 400 mg of modafinil, or an equal number of inactive placebo tablets. The participants were a minimum of 1 year postinjury, with a severity level such that they required inpatient rehabilitation (no other information regarding levels of severity was provided). For the modafinil regime, patients took 100 mg (one tablet) once per day at noon for 3 days, and then increased to 100 mg 2 times per day for the next 11 days, followed by the maintenance dose of 200 mg twice daily in the morning and at noon. Following the end of the randomized study, both groups were offered a 4-week open label period in which they could receive modafinil using individually clinically monitored titration and a maintenance dosage. However, results indicated that after adjusting for baseline scores and period effects, there were no statistically significant differences between improvements with modafinil versus placebo on any of the outcome measures (Fatigue Severity Scale, the Modified Fatigue Impact Scale, and the ESS). Thus, despite the scientific rigor of this study, there were no consistent and/or persistent clinical improvements.

The next study by Li Pi Shan and Ashworth⁶⁶ focused specifically on insomnia post-TBI and stroke, and aimed to compare the efficacy of lorazepam and zopiclone as treatment options. This study also followed a double-blind cross-over trial involving 18 patients with TBI or stroke (six patients with TBI, six with a right hemisphere stroke, and six with a left hemisphere stroke; no information about severity or time postinjury). Participants were prescribed 0.5–1.0 mg lorazepam at bedtime as needed for 7 days, followed by 3.75–7.5 mg zopiclone at bedtime also as needed. Participants were able to regulate their own dosage from 0 to 0.5 to 1 tablet per night,

to “empower them and to simulate what normally happens on our ward.”⁶⁶(p. 422) Results indicated no significant differences in total sleep time or in subjective measures of sleep. Furthermore, the authors evaluated cognition using the Mini-Mental State Exam (which in our view is an extremely weak and insensitive measure for this purpose, particularly for the TBI population), and found no changes with either medication. The authors concluded that zopiclone and lorazepam are equally effective in the treatment of insomnia for both populations. However, because the authors do not report any baseline information on sleep, the reader is not able to determine any actual level of improvement and any clinical application of their findings is thus negated, which is another weakness of this study.

The most recent study by Castriotta and colleagues⁶⁷ aimed to determine whether treatment of specific sleep disorders (which they diagnosed by means of PSG) would result in resolution of those disorders and improvement of symptoms and daytime function. The investigators conducted a thorough, high-quality prospective evaluation of 57 unselected patients with TBI, >3 months postinjury using PSG, MSLT, ESS, and neuropsychological testing, including the Psychomotor Vigilance Test (PVT), Profile of Mood States (POMS), and the Functional Outcome of Sleep Questionnaire (FOSQ), prior to and after treatment for OSA (23% of 22/57), posttraumatic hypersomnia (PTH) (3%), narcolepsy (5%), PLM (7%), and objective excessive daytime sleepiness (22%). In total, 22 of 57 subjects had abnormal polysomnograms (39%). Treatments included continuous positive airway pressure (CPAP) for OSA, modafinil (200 mg) for narcolepsy and PTH, or pramipexole (0.375 mg) for PLM. In terms of response to treatment, the investigators found that the apneas (and hypopneas, as well as snoring) were eliminated by CPAP; however, there was no significant change in MSLT scores. In addition, they found that PLMs were eliminated with pramipexole. One of three narcolepsy subjects and one of two subjects with PTH had resolutions of hypersomnia with modafinil. However, there were no significant changes in FOSQ, POMS, or PVT results after treatment. The authors concluded that treatment of various sleep disorders after TBI may result in polysomnographic resolution,

without change in sleepiness or neuropsychological function.

Overall, the results of these four studies on pharmacotherapy leave us with somewhat of a clinical conundrum. The results of Castriotta and colleagues⁶⁷ may provide guidance to those treating posttraumatic apnea (and hypopneas), PLMs, and hypersomnia, which makes intuitive sense from a clinical perspective because these disorders are relatively more “clear cut” in their etiology. However, insomnias can be more complex and multi-faceted in their etiology, potentially including a combination of underlying physiological and psychiatric issues, and thus are often harder to manage pharmacologically without a combination of medications. Furthermore, results of the Shan and Ashworth study⁶⁶ lead us to conclude that standardized dosages may not be effective, and that any medication regime needs to be fine tuned to the individual needs of the patient, an important protocol built into the final 4 weeks of the study by Jha and colleagues.⁶⁵ Thus, an ideal treatment regimen may include a trial of cognitive behavior therapy with the addition of pharmacotherapy as needed, specifically tailored to the individuals’ symptoms, body weight, and tolerance. In addition, Castriotta and colleagues⁶⁷ reported resolution of polysomnographic findings without associated improvements in daytime function, which suggests that a follow-up study may be of benefit, with an individual case-series design in which additional treatments and/or medications could be added that are specific to each participant. Based on the current findings to date, it is clear that intervention for sleep and wake disorders following TBI is an area of significant need with respect to future research directions.

IV. DISCUSSION

This systematic review was conducted to summarize the current literature on the topic of sleep and wake disorders following TBI and to critically appraise the research directions. In summary, our findings concur with previous reviews: sleep and wake disorders are a prevalent and complex sequelae of TBI, occurring at all stages across the continuum of recovery from acute, to postacute, to rehabilitation, in both

children and adults, and for a number of patients, continuing for many years postinjury, long into the community. These disorders are complex and multi-factorial, and have an impact on neuropsychological functioning and participation in rehabilitation and quality of life. They may evolve from a neurophysiological disruption in brain function to a secondary disorder associated with depression, anxiety, weight gain, and other factors. As such, intervention is equally complex and much more work needs to be done to fully understand the underlying etiologies and to find appropriate treatments. With regard to methodological quality and scientific rigor of the literature, there is a readily observable trend toward higher-quality, more methodologically sound studies as the literature evolves over time. To date, however, most studies have been limited by small sample sizes, large ranges in time postinjury of participants, loss to, or lack of, follow-up, and sample bias due to timing and methods of recruitment. Thus, it is still unclear exactly which members of the TBI population are affected and how the disorder evolves over time. Furthermore, it is unclear why those with mTBI are more likely to present with insomnia or symptoms of insomnia, and whether this is a true manifestation of the disorder or a reflection of other issues such as self-awareness or the challenges of returning to work, school, and/or the community. We recognize, however, that the current state of the literature also reflects the inherent complexities of conducting clinical research with this highly diverse, heterogeneous population.

A. Limitations

Although the current review utilized a systematic approach for the critical appraisal and determination of methodological quality of the literature, we recognize a number of limitations in this methodology. All of the articles included have been peer-reviewed and, as such, there is publication bias. Furthermore, while we have attempted to fully capture all of the recent relevant articles with our search criteria, it is possible that we may have missed articles; thus, this review may not be fully representative of the current literature.

Given constraints of time, we did not contact any of the study authors directly to clarify any points of confusion; our quality rating system is based upon our understanding of the reporting of the methodology and results, and thus may not be truly representative of the actual study design and quality.

B. What This Review Adds

Despite its limitations, this review adds to the body of knowledge regarding sleep and wake disorders following TBI. To date, it is the most comprehensive review, with the inclusion of literature specific to the pediatric population, and is also the first to attempt to delineate the prevalence and nature of sleep disorders by timing of recruitment and levels of severity across the continuum of recovery. It is also the first review to systematically appraise the methodological quality of the current literature.

C. Conclusions and Future Research Directions

Sleep and wake disorders following TBI have received increasingly considerable attention among the clinical and scientific community. Researchers have attempted to quantify the incidence and prevalence of these disorders, as well as to define and describe the nature of the disorder with both subjective and objective measures. Furthermore, attempts have been made to understand the underlying pathophysiological mechanisms and other contributing factors, as well as the functional implications and treatment options. However, additional research is needed to fully understand this complex disorder and to identify appropriate and timely interventions. A large, multi-center study is needed that follows all of those with TBI from the acute stage with regular follow-up into the community, such that results can be reliable, valid, and stratified by nature and severity of injury, age, sex, imaging results, and development of the disorder over time. In addition, we recommend that outcomes for either epidemiological or intervention studies should also capture functional outcomes in addition to sleep measures and cognitive measures to fully assess

the impact of the intervention. Finally, we concur with statements by Dr. Richard Castriotta in his recent editorial that “careful study will require much effort and many resources,” which can best be brought to fruition “through collaborative efforts across multiple centers,” with an aim to “elucidate the causes, foster early diagnosis, and develop optimal treatment for these problems.”^{68(p. 177)} These continuing efforts will further inform clinical practice and ultimately contribute to the development of practice guidelines for the systematic evaluation and treatment of sleep and wake disorders following TBI.

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