

A Review of Assessment of Sleep Disruption in Adults Following Traumatic Brain Injury

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Abstract

Sleep disruptions are prevalent following head injury, but are presently poorly understood. The current paper examines literature that pertains to assessment of sleep function during acute, intermediate and chronic periods following Traumatic Brain Injury (TBI). Review of the literature indicates that initial assessment was focused on primarily self-report measures, which may have psychometric limitations. Many of the findings from previous studies are not directly comparable, as there is significant heterogeneity between sample populations. However, more recent focus on objective measures such as overnight Polysomnography (PSG), Multiple Sleep Latency Test (MSLT) and ambulatory measurements such as actigraphy during multiple time periods post-injury has the potential for further identification and classification of patients with significant sleep disruption following TBI and holds promise in assisting with the treatment of identifiable sleep disorders. The development of state of the art assessment techniques should ultimately assist with evolution of the identification and management of sleep disorders that are related to TBI.

Keywords: Trauma; Brain injury; Sleep disruption; Adults; Head injuries

Introduction

Sleep disruptions are prevalent following head injuries [1-3], although frequency estimates remain broad and range from 30% to 70% [4]. Of these, dysomnias are the most common, with insomnia being the most widely reported among nearly 30-60% of individuals with a TBI [5]. Some research has suggested a greater rate of development of insomnia among individuals with mild Traumatic Brain Injury (mTBI) compared to those with severe TBI [6], which may be associated with their ability to recognize and report their own symptoms of poor sleep [7]. While there is an overall dearth of primary research on the subject, a number of reviews have covered the empirical findings in some detail [4,8]. This article, therefore, was undertaken to review the completeness of variable coverage in the primary research and to highlight those areas requiring additional investigation. Additionally, specific emphasis is placed on the assessment techniques used by the researchers and the major variables involved in sleep disturbances. In order to cover the information in a manageable way and not suggest moment occurrences of sequelae instead of continuous development, studies were grouped into three major categories representing different time periods post-injury, with up to three months representing acute disturbance, from three months to one year being intermediate length of sleep sequelae and findings longer than one year representing chronic disruptions.

The pathophysiology of sleep disturbances includes many etiological pathways and these multiple pathways reflect the complexity of the underlying physiological processes. Seyone and Kara [9] outlined ten major pathways that may either mediate or moderate the relationship between brain trauma and resultant sleep sequelae and account for significant levels of variance in sleep disruptions in Traumatic Brain Injury (TBI) clinical populations. These pathways include direct focal lesions, neurotransmitter (NT) imbalances, neuroendocrine imbalances, increased nocturnal seizures, psychiatric disorders, substance use/abuse, pain, mobility limitations, psychotropic medications, and psychosocial stressors. It is paramount for researchers to account for these variables when investigating the course and presentation of sleep sequelae in order to determine the pathways involved for development of appropriate treatment. Research linking sleep-related problems to the damage of specific regions has been limited [3]; however, damage to the central nervous system is postulated to be the largest contributor

to acute sleep disruptions and is thought to involve the physiological alterations included in structural damage (direct focal lesions, axonal shearing), neurochemistry changes (NT, neuroendocrine imbalances), and reduced seizure thresholds (increased nocturnal seizures) [10-12]. The remaining six pathways represent additional sources of sleep disturbance, either as a consequence of the TBI, or as a comorbid condition that influences the expression of sleep in the post-TBI sample [9]. Many of these six pathways contain multiple specific types of disturbances within the large sections (Psychiatric Disorders, Psychosocial Stressors, Psychotropic Medications, and Substance Use/Abuse). Given each pathway showing effects on sleep disruptions, it is imperative that researchers attempt to account for these variables in order to make definitive conclusions regarding the link between the Direct Pathways and sleep disturbances following the TBI.

Currently, the status of research on sleep disturbance and TBI is fraught with heterogeneity within and across studies, from lack of a standard method for determining TBI severity, particularly that of mTBI, mixed samples regarding severity, unclear or diverse times of assessment post-injury, use of a wide variety of assessment techniques or instruments, and a lack of information regarding specific disruptions of dimensions of sleep (onset latency, efficiency, etc.). This has occurred even though there are fairly well established standards for obtaining objective sleep information through polysomnographic studies, structured clinical interviews, standards for taking sleep history information [13], and standards for differentiating mTBI from moderate to severe cases [14]. Evaluation of current studies remains difficult because of this heterogeneity of method and prevents true synthesis of findings. Increasing the use of standardized assessment methods and operational definitions, plus ensuring a complete coverage

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of sleep related symptoms, will aid in allowing future studies to reduce the current disparate nature of TBI sleep investigations.

Assessment Instruments

Initial assessment of injury severity is commonly done through use of the Glasgow Coma Scale (GCS), which is a fifteen point scale based on three gross measures of nervous system functioning to provide a swift, general level of depth of coma [15]. The GCS quickly distinguished brain injury severity as “mild”, “moderate” or “severe”, utilizing three tests, which measure eye, verbal, and motor responses. Common dividing points separate mild in the 13-15 range, moderate in the 9-12 range, and severe at 8 or below. This scale sees widespread use in both clinical and research environments, although it is not without its limitations. Recent evaluations of the scale note that timing is inconstant, components are underutilized, and that components are not assessed and reported in any standardized sequence [16,17]. Further, it has been suggested that differences related to teaching and experience may influence the reliability of the scale [18]. Some author's note that alternative instruments with more robust clinimetrics have emerged and should be considered as a replacement in both research and practice [15], while others suggest that a consensus statement outlines a uniform usage and assessment scheme be utilized to improve the use of the scale between studies [17].

Other common brief measures include length of Post Traumatic Amnesia (PTA) and the length of Loss of Consciousness (LOC) following the TBI. Common usage of length of PTA to assess TBI severity places PTA less than one hour as mild TBI, from one to twenty four hours as moderate, and greater than one day as severe (although some also extend into very severe range at greater than 7 day PTA) [19]. It has been argued, however, that this system was developed utilizing clinical observations and retrospective self-report, rather than statistical analysis of patient outcomes [20]. LOC is utilized in some situations, but primary usage is in combination with PTA into a PTA-LOC measure. The GCS, PTA, and PTA-LOC show only modest correlations with each other, calling the clinical utility of each into question [21]. However, due to the common use of the GCS, PTA and LOC in diagnosing TBI, both the World Health Organization (WHO) and the American Congress of Rehabilitation Medicine (ACRM) use these measures in recommendations for diagnosing TBI and mTBI in particular [14].

Assessment of concomitant psychiatric disorders and substance use/abuse disorders commonly occur through intake questionnaires or brief phone interviews, instead of the more comprehensive and structured clinical interviews [22]. The current recommendations regarding gathering information regarding patient complaints of sleep disturbance, contributing factors and assessment of specific information regarding the history and changes in sleep characteristics is the combination of the structured clinical interview combined with specific sleep history information recommended by Kales et al. [13], Seyone and Kara [9]. The comprehensiveness of this history will aid in assessing the changes in sleep behavior and will not be restricted to a single snapshot of current functioning inherent in questionnaires or PSG sleep studies.

However, the creation and refinement of intake questionnaires specific to gathering information regarding sleep behaviors and specific dimensions of sleep disruption has increased the usefulness of using these measures in research studies. Although there are many self-report measures of sleep quality, the Pittsburgh Sleep Quality Index (PSQI) is one of the most widely used instruments to define sleep quality in

current sleep literature [23]. The PSQI is swift to administer (18-items; 4-point likert scale) and covers these dimensions of disruption in some detail, but remains a brief snapshot covering only sleep behaviors within one month of administration. The index does cover sleep quality in some detail with 7 component scores that include sleep-onset latency, sleep duration, sleep efficiency, medications, daytime sleep dysfunctions, specific sleep disruptions, and subjective sleep quality and a global score from the sum of the components. The scale has shown good sensitivity and specificity for sleep disturbance and good test-retest reliability [24]. This instrument has also shown to be valid and useful as a screening instrument for a TBI sample, including the items that select for mood disturbance, pain involvement, and daytime sleepiness, and use of the global score shows sensitivity above 90% and specificity of 100% for insomnia in TBI samples [25].

Another group of scales used to gather self-report information are the Rivermead questionnaires. The Rivermead Post-Concussion Symptom Questionnaire (RPQ) is a brief (16 questions; 5 point likert scale) self-report questionnaire that quickly evaluates a wide range of symptoms common to TBI patients and includes one item regarding sleep disturbances. The reliability of the scale differs depending upon when it is administered post-injury and the symptom being assessed, with the sleep item in the acute phase ($R_s=0.80$) being higher than at 6 months post-injury ($R_s=0.68$). However, this instrument remains in use because of the brevity of the scale and because it may be either self or clinician administered [26]. However, studies identified that the RPQ does not have robust enough psychometric properties in its originally designed form for clinical use. The scale was shown to tap into more than one construct and that splitting the original 16 items into two separate scales (RPQ-13 and RPQ-3) removes the multidimensionality of the scale and increases reliability to 0.89 for the RPQ-13, which includes the item pertaining to sleep disruption [27]. However, this split use of the RPQ is recent and previous studies utilizing the scale have not used the split forms. Other researchers choose to include batteries of questionnaires that include many different scales to evaluate many of the pathways to sleep disruption, trading increased information regarding specific pathways to sleep disruption for increased respondent burden [28].

One of the most comprehensively covered area of TBI sleep disruption is the relationship between mood disturbances and sleep disruption in clinical samples [11,29], however, variability issues have resulted from the choice of assessment instruments [30]. A few authors suggest utilizing structured psychiatric interviews to assess diagnosable mood disruptions and use this information to assess relationships between mood disturbances and insomnia in TBI populations to increase sensitivity and specificity [31]. However, subsyndromal levels of mood symptoms have been shown to induce sleep disruptions, and scales that capture greater information on relative levels would be of high utility in addressing subsyndromal impact [30]. The most common scales used for assessing mood and psychological functioning are the Beck Depression Inventory (BDI) [32], Profile of Mood States (POMS) [33], the Hamilton Rating Scale for Depression (HRSD) [34,35], Minnesota Multiphasic Personality Inventory (MMPI) [36,37] and the Zung Self Rating Depression Scale [38]. Use of each of these scales that differ on dichotomous or continuous nature of responses, respondent burden and lack of validation within TBI populations results in widely variable prevalence estimates between studies [30].

This lack of consistency in diagnostic criteria, assessment methodology, and TBI group disparities prompted authors to suggest adoption of instruments specifically designed for assessing the DSM-

IV-TR guidelines and normed on TBI populations [30]. One such instrument is the Neurobehavioral Functioning Inventory (NFI) which was developed for and validated using large TBI samples [39,40]. This instrument is longer than previously described scales (105 items, 4 point likert scale), giving six principle components including depression, memory/attention, communication, aggression, motor impairment, and somatic complaints. Unlike the other two general screening questionnaires, the NFI contains two items regarding sleep onset latency and difficulty awakening, as well as the coverage of depression and motor impairment. The reliability for the subscales are higher than the RPQ at between 0.86 and 0.95, and the more comprehensive coverage lends itself as a general screening instrument for a variety of TBI related symptoms, although the specific coverage of sleep is not as detailed as with the PSQI [39].

Of note, the more recent release of the DSM-5 [41] provides additional attention to assessment and diagnosis of TBI. Within this framework, patients with TBI must meet criteria for either mild or major neurocognitive disorder, with the difference being primarily deficit severity and whether or not there is substantial deficit in independence with every day activities. In addition to the criteria for mild or major neurocognitive disorder, there must be evidence of TBI that includes at least one of various criteria including LOC, PTA, disorientation and confusion, and various neurological signs. The author of the DSM-5 also clarifies that the severity rating of the TBI (which is determined by various factors such as period of PTA and GCS score) does not necessarily correspond to the severity of the neurocognitive disorder. Specifically, the course of recovery is variable and dependent upon a wide range of factors.

Concomitant anxiety symptoms are another pathway shown to account for significant portions of variance in TBI samples with sleep disruptions [42]. In addition to the use of the clinical interviews to determine the presence of diagnostic levels of anxiety, the research literature shows use of three scales to specifically assess anxiety symptoms: the Beck Anxiety Inventory (BAI), the Hamilton Anxiety Rating Scale (HAMA), and the State-Trait Anxiety Inventory (STAI). The BAI is a short (21 items, 4 point likert scale) inventory used to assess a general level of anxiety and is one of the most widely used inventories to assess anxiety in research [43]. However, confirmatory factor analyses have revealed multiple possible factor structures including two, four, or five separate factors within the scale representing subjective, panic, autonomic, and neurophysiologic anxiety, and that each factor shows differing levels of construct validity [44]. Thus any use of the overall measure with the inventory will contain multiple sources of anxiety symptoms and not account for the shared symptoms with the depression scales. The HAMA is another short (14 item, 4 point likert scale) inventory with two subscales for both psychic and somatic anxiety, but with only moderate inter-rater reliability coefficients (total and subscales between 0.70 to 0.74), and somewhat higher concurrent validity (total 0.75, psychic 0.80, somatic 0.85) although a few of the individual items showed validity coefficients not significantly different from zero [45]. This coupled with the noted insensitivity to detect comorbid anxiety in depressed patients and limited usefulness as its total score represents a heterogeneous measure [45], calls its usefulness into question given the previously noted high levels of depression in TBI samples. The final measure, the STAI, is the most widely used of the three [43]. The STAI is somewhat longer (220 item scales, 4 point likert) and yields two different measures, the state measures showing expectantly low test-retest reliability 0.54 and the trait measure showing higher reliability 0.86 and concurrent validity with other trait anxiety measures between 0.80 and 0.52. Use of the STAI would allow for the

different effects of the state and trait measures have been shown to account for differences in sleep-onset latency and daytime sleepiness [46]. However, use of any of these scales of anxiety and depression have been called into question because of their lack of validation studies in TBI samples and the presence of TBI sequelae including sleep confounds the usefulness of even reliable inventories that have been validated on use in general TBI samples [47].

Finally, assessments of sleep problems themselves do not show a standardized algorithm. In addition to the mixed inventories noted earlier the RPQ and the PSQI, a number of scales are utilized to assess the quality of a number of specific sleep dimensions. The Insomnia Symptom Questionnaire designed around insomnia classification criteria, with high reliability at 0.89 and high sensitivity to insomnia (>90%), but with differing levels of specificity dependent on the validation technique used (sleep diary, polysomnography [PSG], PSQI), all while assessing the multidimensionality of insomnia in accordance with DSM-IV criteria [48]. The Pre-Sleep Arousal Scale is specific for assessing sleep-onset latency in a brief questionnaire (16 items) through both cognitive and somatic arousal and again shows good reliability and validity compared to the general questionnaires and is a good cost effective alternative to screen for sleep-onset latency disruptions [49]. The Sleep-Wake Activity Index (SWAI) contains two subscales assessing daytime sleepiness and nocturnal sleep onset, with the excessive daytime sleepiness scale (EDS) being a good predictor of the objective Multiple Sleep Latency Test (MSLT) [50]. The SWAI has been shown to retain its two factor structure and reliability above 0.70 in both community and clinical samples [51]. The Epworth Sleepiness Scale (ESS) is an 8-item instrument focusing on daytime somnolence exclusively and predicts performance on sleep-onset latency from the MSLT and overnight PSG [52]. This instrument possesses a more robust psychometric profile with test-retest reliability at 0.82, internal consistency at 0.88, and factor analytic techniques shows it is homogenous with only the single factor of daytime somnolence [53], suggesting use of the ESS as the primary instrument for brief screening of daytime somnolence.

Objective measures of sleep remain the standard for diagnosis and quantifying measures of sleep disturbance. These measures include the MSLT, PSG, use of sleep diaries, and ambulatory measurements such as actigraphy. Use of these techniques allows conformance to an already established standard in the long time standards of terminology, techniques, and scoring system [54], which are kept up to date by the American Academy of Sleep Medicine (AASM) and the American Sleep Disorder Association (ASDA) for PSG [55] and the MSLT [56]. This standardization increases the external validity of studies utilizing these techniques and will lead to better integration of results. Also, gathering objective information on sleep disturbance is important due to the implications of patient overestimation of sleep disturbance in subjective measures [57].

Acute Phase (0-3 Months)

Keshavan et al. [58] conducted much of the initial work on sequelae of psychiatric disorders on acute TBI patients. Although sleep disturbances were not the goal of the study, the authors found that 42 of 66 patients showed symptoms of sleeplessness, 35 showed symptoms of anxiety, and 18 irritability symptoms at a month and a half post injury, while the prevalence dropped to 22 with sleeplessness symptoms, 17 with anxiety symptoms, and 10 with irritability symptoms at three months post injury. The methods utilized ignored most of the indirect pathways, and semi-structured clinical interviews and diagnostic information from the ICD-9 were used to assess psychiatric sequelae.

Medications, general medical conditions, pain and mobility limitations were not assessed relative to sleep disturbances. Also, psychosocial stressors were used as a dependent variable in assessing the outcome of TBI severity. However, this initial association of sleep, anxiety, mood, and TBI in the acute phase showed the possible presence of these indirect pathways as affecting sleep in the initial post-TBI period. However, neither the direction of associations nor attempts to determine symptom severity were investigated.

Parson and Van Beek [59] investigated sleep disturbance specifically for a mixed, but predominantly mild (81%) sample of mTBI patients aged 16-30. Level of injury severity was determined by GCS scores and LOC times at time of injury. The researchers used an adaptation of a general sleep habits questionnaire, and noted that the content validity of the originally designed instrument was established but no psychometric data reported for either the original or adaptation which included questions for current and pre-injury sleep patterns. Main results showed that sleep patterns did not change within the first 24 h post injury, but emerged within the first three months. Anatomical location was not found to affect sleep patterns, but GCS showed that lower scorers showed greater sleep pattern disruptions. However, all disruptions in this study were attributed to the head injury and no information regarding any involvement of the indirect pathways was gathered. Also, all information regarding sleep patterns was self-report and sleep history required direct patient recall of patterns.

Dikmen et al. [60] intended to study the effects of head injury and other orthopedic and soft tissue injuries on functioning at one month and one-year post injury. The authors focused on neuropsychological measures in addition to the inclusion of sleep and other general symptoms as psychosocial measures of disturbance. At one month post-injury, the head injured group showed wide range of psychosocial limitations including sleep disruption, with insomnia specifically significantly increased compared to uninjured controls. However, these differences in functioning were not present at a one year follow up. Interestingly, the presence of other limiting injuries during the acute phase were significantly increased the psychosocial disruptions compared to head injury only patients, but specific information regarding the interaction of the mobility limitations impact on sleep disruption between the two groups were not reported. Again, this study relied on self-report information and did not include objective sleep disruption measures. Additionally, psychosocial stressors, medication usage, pain, substance use/abuse, or presence of psychiatric disorders or subsyndromal anxiety or depression were not investigated. However, this study does implicate mobility limitations as contributing to psychosocial limitations, including sleep and insomnia, during the acute phase.

Bradshaw et al. [61] investigated the sleep disturbance within the first few weeks post injury (mean 7 days, SD 10 days) in 22 young active duty marines that suffered an mTBI. Severity was determined through GSC, LOC of less than 30 min and PTA of less than 24 h. Patients were given the ESS to measure daytime sleepiness and the PSQI to measure sleep disturbance within the month before testing (before the injury). The comparison group in the study was an uninjured military control matched for age, sex and military rank. The researchers found that both measures were more common in the TBI population and suggests that pre-injury sleep disturbances could be a risk factor for getting a TBI and not a consequence of the injury. However, both samples showed tendencies to high scores with excessive daytime sleepiness in 41 percent of the TBI sample and 31 percent of controls. PSQI global sleep scores showed that 72 percent of the TBI sample was qualified

as showing sleep disturbance, but 62 percent of controls also showed disturbance. Exclusion criteria included prior TBI, depression, alcohol/drug abuse and neurological disorders. The researchers did not account for psychiatric disorders, mobility limitations, psychosocial stressors, or medication usage, and all sleep disturbance measures relied on self-report data alone Mahmood et al. [62] investigated the link between sleep disturbances and neurocognitive deficits among a mixed severity sample within the first year post injury. However, since over 70 percent of the scores were gathered within the first three months, this study will be covered as an acute period study. In addition to the neuropsychological test battery, sleep disturbance was assessed using the PSQI alone, severity determined using the GCS and depression assessed using the BDI. The researchers found that 37 percent of the sample showed PSQI defined clinical sleep disturbance and differed by severity with the mTBI group reporting significantly higher sleep disturbance than the severe TBI group. Gender and severity combined accounted for 17 percent of the sleep disturbance variance and neuropsychological measures accounted for an additional 14 percent. In this sample, it was higher cognitive functioning and processing speed deficits that were most related to sleep disturbance. This study also relied on self-report, and did not attempt to account for medication usage, psychiatric disorders, mobility limitations, other psychosocial stressors or anxiety symptoms.

Lundin et al. [63] assessed mTBI patients at three time points in the first two weeks post-injury (1, 7 and 14 days) and again at three months post injury using the RPQ and the River mead Head Injury Follow-up Questionnaire and performed a factor analysis to determine a factor structure of symptom presentation in the acute period through changes in baseline symptoms taken at day 1. Sleep disturbance was one of the most common symptoms at each of the time points, but showed a slight decline from 1 day to 3 months; however, it persisted as the second highest loading symptom behind memory disturbance in the factor loadings. The researchers found a consistent four factor structure at each of the four time points with Somatic, Vision-Related, Affective, and Cognitive Symptoms. Within the affective symptom factor, feeling depressed showed the highest loading at day 1 ($r=0.48$) with sleep second ($r=0.42$), and sleep disturbances showed the highest loadings at all other time points. Again, the study was based on subjective self-report, and the presence of pain, psychosocial stressors other than disabilities, medication usage, substance use/abuse, presence of psychiatric disorders were not examined.

Chaput et al. [64] conducted chart reviews of mTBI patients assessed at two time points (approx. 11 days and 6 weeks post injury) using self-report of symptoms and the RPQ. The authors found that presence of headaches showed a threefold increase in the probability of reporting concomitant sleep disturbances. The authors found that during this period, a two to three-fold increase in reported sleep and mood disturbances emerged between the two time points with 11.1% reporting sleep disruption at time point 1 and 34.7% at time point 2. However, no objective information regarding sleep disruption or the presence of indirect pathway information was completed. This study does show that sleep disruptions increase during the initial period post injury, but whether it is direct sequelae of the mTBI or due to other developing issues is not clear.

Rao et al. [42] looked specifically at the acute phase in order to determine prevalence and risk factors during this period on first time TBI patients with no previous brain related illness or injury. The assessment methods utilized covered many of the proposed pathways to sleep disturbance. The researchers initially classified TBI severity through use of the GCS, CT evidence of trauma or LOC. The

researchers also accounted for general medical conditions and use of medications using the General Medical Health Rating (GMHR), which was acknowledged by the authors as not normed on the TBI population and may not capture information on pain, specific medication usage or specific medical problems impacting sleep. The researchers relied on the structured clinical interviews for the DSM-IV axis I disorders (SCID-IV) to account for anxiety and depression disorders, but subsyndromal anxiety and depression scores were not collected. The presence of the anxiety disorder due to general medical condition (TBI) was the strongest predictor of correlate of sleep disturbances and the measures of sleep problems. Mood disorders due to general medical condition (TBI) were the secondary, but not as consistent a correlate. Additionally, the study was subjective in nature and use self-report measures to assess sleep disturbance, and did not use PSG, MSLT, or actigraphy to assess neither objective sleep disruption nor mobility limitations.

Some of the more recent studies have included more objective measurement of sleep disruption. Makley et al. found that length of stay in acute care increased risk of having sleep wake cycle disturbance and a total prevalence of 68 percent. Presence of sleep disruptions also predicted longer required stay in the rehabilitation center [65]. The second study utilized actigraphy measurements taken for seven consecutive days on a moderate to severe TBI sample, with measurements begun within the first 72 h after admission to a rehabilitation facility. The exclusion criteria removed those with previous history of sleep related disorder, BMI less than 30, lack of medications, psychiatric illnesses, and immobility issues. Use of the actigraphy produced a measure of sleep efficiency and the researchers discovered that initial disruption of sleep efficiency was correlated with duration of PTA, and that recovery of sleep efficiency occurred with return of memory disruptions. The presence of pain was accounted for using PSQI measurements, covering the breadth of indirect pathways (although most were exclusion criteria). These researchers also noted that use of actigraphy was indicated with this severity group due to commonly high agitation levels preventing compliance with PSG procedures [66].

Assessment of sleep disturbances during this period is problematic due to the presence of injury related complications that make the indirect pathways, and sleep disturbances in general as a secondary consideration, particularly with more severe injuries [9] and thus most sleep disruption studied is with mTBI patients. Subjective measures of sleep disruption, with very little information regarding the specific type of disturbances revealed with more thorough PSG and actigraphy sleep studies, are the most common method of assessing disruption during this period. Indeed, use of electroencephalography (EEG) during this period to predict sleep disorder or other affective disturbances shows mixed results at best. Korinthenberg et al. [67] used EEG and neurologic examinations on a pediatric mTBI sample within the first 24 h post-injury and at a 4-6 week follow-up, to determine if EEG abnormalities may be used to predict symptom complaints, including sleep disruption, during this acute period. The researchers found that somatic, neurologic and EEG techniques were not correlated with symptom complaints and could not detect disruptions.

While significant work has established the presence of sleep disruption during the acute period, most of the research has focused on mTBI and the time course of sleep disruption development. There is currently a lack of information regarding specific disruptions of sleep architecture during this period, through a lack of PSG or MSLT sleep information measured, but EEG disruptions common during the early acute period may confound PSG determinations of sleep stages and

architecture [22]. Also, although the emergence of sleep is shown to occur during this period, the concomitant emergence of depressive symptoms, anxiety symptoms and psychosocial disabilities has complicated the determination of sleep disturbance prevalence as direct sequelae of the TBI. Also, no studies have attempted to account for the full breadth of indirect sleep disruption pathways in mTBI samples, leaving the possible inclusion of each as an unaccounted for source of sleep variability in the studies.

As indicated above, prior studies have not utilized PSG with EEG, electrooculography (EOG) and chin electromyography (EMG) to examine sleep stages and architecture during the acute stage of severe TBI in non-sedated patients. There is one exception, however. A more recent study that utilized an adult population, and seems to have overcome some of the challenges of recording overnight PSG bedside during the acute phase found significant differences in 7 patients with severe TBI in comparison to patients with severe orthopedic or spinal cord injury (OSCI). For these patients, continuous intravenous sedation and analgesia were discontinued for a minimum of 48 h prior to study. Specifically, Wiseman-Hakes et al. [68] found that compared to OSCI, severe TBI patients showed significantly longer duration of nocturnal sleep and earlier nighttime onset. However, as with previous studies, these authors note and caution that PSG may not be usable for portions of this population due to the confusion and agitation.

Intermediate Phase (3 Months-1 Year Post Injury)

Cohen et al. [11] also used self-report questionnaires to assess prevalence of sleep disorder in a mixed TBI sample. This study crosses multiple phases as initial assessments were made near 3.5 months post injury, but long term follow-up completed two to three years post injury. The researchers found disorders of excessive sleepiness were associated with greater time post-injury while the reverse was also true and insomnia associated with less time since injury. Overall prevalence showed 73 percent of hospitalized patients and 52 percent of discharged patients evidenced sleep disturbances. Assessment instruments were not described completely in the study and questionnaire used had no associated psychometric properties reported. The researchers did account for a number of other indirect variables including motor deficits, medication usage, and psychiatric disturbances. Pain, psychosocial stressors, and substance use/abuse were either not assessed or not reported in the study. However, the lack of a validated measure of sleep makes the usefulness of this study very limited.

Clinchot et al. [22] performed a one-year telephone follow up with a mixed severity sample regarding sleep disruptions. Prevalence in this sample was 50 percent for a sleep disturbance with the 64 percent of the patients having problems staying asleep while 45 percent showed difficulty falling asleep. The researchers again found a significant increase in sleep related disturbances in mTBI compared to more severe injuries. Measurements at one year only included a phone interview and questions regarding sleep medication usage and thus other indirect variables including pain, mobility limitations, current psychosocial stressors, depression and anxiety symptoms, and psychiatric disorders were not assessed and limit the generalizability of the study.

Fichtenberg et al. [25] investigated the impact of psychosocial variables on the presentation of insomnia in a mixed severity sample. The patients were assessed at a wide range of times post-injury; however the bulk of the patients were within this time period (mean 3.3 months) post-injury. Patients were given a clinical interview, PSQI, BDI and other information was gathered through medical record reviews including demographic and GCS, PTA and LOC at the time

of injury, also the financial status of the patient with regard to the presence of litigation or Worker's Compensation claims was recorded. The researchers found no association of demographic variables to insomnia, including age, education or gender. Also, the time post-injury was not associated with presence of insomnia, but GCS and CT findings were associated, with milder severity injuries and negative CT findings associated with increased presentation of insomnia, as were pain and depression. However, after logistical regression analysis, only depression and level of TBI severity contributed to prediction of insomnia. The researchers did not assess anxiety symptoms, mobility limitations, psychiatric disorders or medication usage.

Parcell et al. [69] assessed sleep disturbance in a mixed severity, community based sample with a large range of time post-injury (20-1194 days) with the mean of around 9 months (230 days). The researchers used sleep diaries, the ESS, the Hospital Anxiety and Depression Scale and a general sleep quality measure with no reported psychometric information. The exclusion criteria included previous sleep disorders, use of benzodiazepines or sleeping medication, previous head injury, neurological or psychiatric disorders. The researchers did not account for substance use/abuse or mobility limitations. The researchers found 80 percent of the sample reported sleep changes following TBI with more nighttime awakenings and longer sleep onset latency being the most frequent complaints, particularly from the mTBI group. The researchers also found a significant effect of both anxiety and depression symptoms with increased symptoms associated with increased subjective sleep changes. Main limitations include the self-report nature of the measures and the heterogeneity of the TBI sample post injury.

Ouellette and Morin [28] compared subjective and objective measures in a prospective study that included a mixed sample across a wide range of time post injury. A wide range of exclusion criteria included medical or psychiatric comorbid conditions, medication usage affecting sleep, previous sleep difficulties before injury, evidence of another sleep disorder through PSG or diagnostic interviews for insomnia or presence of pain. Clinical diagnostic interviews were conducted to evaluate the presence of insomnia, but also covered specific sleep quality measures, mood disturbances, fatigue, social discomfort and environmental factors. Subjective information was collected using sleep diaries, the insomnia severity index, the multidimensional fatigue inventory, the BDI and the BAL, while objective measures were taken using nocturnal PSG. The researchers found that there were no significant differences between groups on objective measures while subjective measures showed these differences. Limitations of the study included the very small sample size (14 patients/14 controls) and the lack of information regarding substance use/abuse and mobility limitations.

Baumann et al. [57] conducted the most thorough investigation of patient sleep disturbances at 6 months post injury, performing multiple subjective and objective measures to assess specific sleep disturbances, as well as concurrent neurotransmitter level measurements. The only exclusion criteria for this mixed severity sample included previous sleep disorder or psychiatric disorder diagnosed prior to this first TBI. The researchers used a variety of the more robust measures recommended for use, including direct clinical interviews, psychometrically sound questionnaires, and objective sleep studies, and they utilized international criteria standards for diagnoses. The researchers used the ESS for subjective excessive daytime sleepiness, but also the MSLT for a comparison objective measure of excessive daytime sleepiness. Baumann et al. used both the GCS and CT scans to determine the severity level of TBIs. The researchers assessed depression with the BDI, and utilized a general health questionnaire, the 36 item Short Form Health Survey,

(SF-36) to assess pain, physical and social functioning, mental health and general health. Substance use/abuse information was collected, as well as mobility restrictions were assessed for those evidencing sleep disturbances at the 6 month assessment. Sleep studies were also performed at 6 months post injury using combinations of instruments including sleep logs, actigraphy data, and full polysomnographic architecture analysis using the Rechtschaffen and Kales standards discussed previously. Outcomes showed 22 percent of patients diagnosed with hypersomnia and only 5% of this sample was diagnosed with insomnia. Excessive daytime sleepiness were reported in 28 percent of the sample on self-report and 25 percent discovered through objective MSLT, however, these were not correlated significantly due to only 9 patients showing both measures simultaneously, calling use of self-report measures of excessive daytime sleepiness into question in TBI patients, at least at this time post-injury. PSG only found significant differences on percentage of non-REM sleep in the second sleep cycle. Actigraphy revealed that 52 percent of patients showed significant hypersomnia and that this was not accounted for using fatigue, daytime sleepiness (subjective or objective), or depression, and identified that 28 of the 47 total patients with sleep disorders were only attributable to the TBI directly. Strength of this study is that subjects were able to be studied by localization of visible lesions on the CT scans, and there were no significant associations between location of lesions and sleep disturbances this long post-injury. The limitations of this investigation is in small sample size and a better outcome than expected when the sample is compared to average TBI outcome studies and could bias the results to underestimation of sleep disorder prevalence. The measures not conducted at the six-month assessment were complete psychiatric investigations and the authors note the possibility that those with sleep disturbance could have a high preponderance for psychiatric disorders. The main findings of this study concerning insomnia assessment is that accounting for depression accounted for 66 percent of the insomnia patients and that it appears that high levels of insomnia are not present, but instead the most common sleep disturbances during this intermediate period include hypersomnia and excessive daytime sleepiness.

The work of Ouellette and Morin [28] highlighted the large differences between subjective and objective measures of insomnia and highlight that previous studies relying exclusively on these self-report questionnaires remain as overestimations of prevalence. Baumann et al. [57] were much more comprehensive in use of recommended breadth of indirect dimensions assessed and use of objective sleep measures. This study shows a much lower incidence of insomnia (5%) than previous estimates with samples showing higher levels of hypersomnia. This suggests that TBI samples, particularly those of lower severity to overestimate disturbances. The completeness of coverage leaves a more thorough investigation of concomitant psychiatric disorders during this period and their interaction with sleep variables, and larger sample sizes taken from samples that replicate the demographic stratification of the TBI population and not just those in rehabilitative or clinic based care.

More recently, although not an adult population, Tham et al. [70] examined sleep in 50 adolescents with mTBI (3-12 month post injury) compared to 50 healthy controls adolescents using subjective and objective measures. Measures assessing sleep quality, depression, and pain symptoms were completed, as well as 10 day actigraphic assessment. Poorer self-reported sleep quality was predicted by greater depressive symptoms for both groups. Poorer sleep efficiency (measures via actigraphy) was predicted by membership for mTBI after controlling relevant demographic factors as well as depression and pain.

Chronic Phase (Greater than 1 Year Post Injury)

Perlis et al. [71] investigated the differences between an mTBI sample and an orthopedic traumatic injury control 2 years post injury. mTBI was diagnosed through LOC of less than 2 h, PTA of less than 24 h and no positive imaging findings. Subjects completed an undisclosed questionnaire with no reported psychometric data. Main findings were that the TBI patients complained of more problems with sleep initiation, maintenance of sleep and excessive daytime sleepiness than physical trauma patients. The researchers controlled for pain and mobility limitations. However, no information regarding psychiatric disorders, medication usage, psychosocial stressors, or substance use/abuse was collected, and all sleep disturbances measured through self-report on an instrument with no psychometric data or established validity.

Masel et al. [61] investigated hypersomnolence in a mixed severity sample. Severity level was difficult to determine with only GCS or LOC information for 56-59 percent of the subjects. Also, the sample was not restricted to TBI and other injury types included anoxia, gunshot wounds, cerebral infarct, and non-traumatic subarachnoid hemorrhage. Patients were given the ESS and PSQI as well as full sleep studies including PSG, MSLT, and actigraphy information, and then separated into hypersomnolence group and non-hypersomnolence group. The researchers also performed medical history reviews and current physical examinations. There were no exclusion criteria for the study and all patients in the brain injury rehabilitation facility were invited to participate. Results showed that no differences across groups on ESS or PSQI scores, actigraph tracings, or PSG measures. Only the MSLT confirmed the hypersomnolence, even with a lack of self-report complaints of excessive daytime sleepiness. The examiners utilized the current recommended objective measures of sleep disturbance and the most psychometrically robust self-report measures of sleep disturbance. The researchers did not control for psychosocial stressors and measured but did not directly integrate information on observed differences in anxiety and affective disorders between groups. Other limitations of the study include the presence of a mixed source of brain injury sources and very mixed use of medications within the patients.

Ouellette et al. [28] investigated insomnia specifically in a largely severe TBI sample (59.9%), but overall a mixed sample. This study was exclusively self-report and significant other measures after an average time of 7.85 years post injury. Measures used include the Insomnia Severity Index, the multidimensional fatigue inventory and a French adaptation of the Psychiatric Symptom Index. Dimensions assessed included pre-injury sleep difficulties, depression symptoms, anxiety symptoms, pain, fatigue and psychiatric disorders. Those not assessed include general psychosocial stressors, mobility limitations and substance use/abuse. The researchers found that over half the sample presented with insomnia symptoms and 29.4% showing full diagnostic criteria, with a higher prevalence in the milder severity groups. Additional predictors of insomnia included higher severity of depression symptoms, pain, and fatigue.

Castriotta et al. [33] used a wide variety of measures with a mixed severity sample with patients assessed at least three months post injury. The researchers assessed excessive daytime sleepiness using both the self-report ESS and the objective MSLT, sleep architecture assessed using PSG, and affective disturbance using the profile of mood states questionnaire. The authors identified an issue where there was not a significant correlation between the subjective and objective excessive daytime sleepiness measures ($r=0.10$), but 25 percent of the sample showed excessive daytime sleepiness on MSLT. Sleep disruptions were seen in 46 percent of the sample, but unlike other studies, obstructive

sleep apnea (OSA) was the most prevalent (23%) followed by hypersomnia (11%) and no insomnia evident.

Verma et al. [72] conducted an investigation of chronic presentation of sleep disorders on a mixed severity sample, but time course was restricted to between 3 months and two years post-injury. Detailed histories were taken, along with neurological examinations and a physical examination of physical factors related to sleep disorders. The researchers used a mixture of self-report questionnaires in the ESS, BDI, GAF scores and the Hamilton Anxiety Index, coupled with objective measures of sleep disruption in MSLT and PSG sleep studies. Exclusion criteria included prior sleep dysfunction symptoms prior to TBI. The researchers found that 50% of the sample presented with excessive daytime sleepiness as the most common symptom, with insomnia second at 25% of the sample, and a wide variety of parasomnias making up the remaining 25%. GAF scores were correlated with specific differences in sleep architecture including increased stage 1 percentage, lower sleep efficiency, and increased awakenings during sleep. The researchers did not account for the effects of medications, pain, mobility limitations, full assessment of psychiatric disorders or substance use/abuse.

Schreiber et al. [73] investigated the patterns of sleep disturbance in long term chronic mTBI. Inclusion criteria included non-recent mTBI (1 year or more post injury), with no abnormal CT, MRI or EEG studies. Exclusions included any CNS pathology, psychiatric diagnosis or other sleep disorder. The subjects were given PSG and MSLT tests, with no subjective sleep measures other than patient complaints. The researchers found differences from the mTBI group with controls on sleep latency or REM latency. There was a significant reduction in REM sleep in the mTBI group and the second period of non-REM was higher in the mTBI group. Also, the mTBI group showed a lower total sleep time, but a higher number of awakenings in controls, however, the mTBI group showed lower sleep efficiency. Finally, mTBI patients showed a significant increase in daytime sleepiness from MSLT information. This study did not attempt to account for subsyndromal depression or anxiety, psychosocial stressors, pain, mobility limitations, medication, or substance use/abuse.

A more recent study of a small sample of patients (N=13) who had moderate to severe TBI (or mTBI with persistent symptoms) with a mean of 4.5 years post-injury found increased N1, reductions in REM sleep ($p=0.017$) and total sleep time, and poor sleep efficiency. A treatable sleep disorder was diagnosed in all of the patients and 92% of the patients had abnormal sleep architecture [74]. A larger sample of 140 patients comprised of predominately individuals with mild TBI found noteworthy differences in total sleep time records via overnight PSG and actigraphy, as well as differences recorded on the MSLT [75].

The results of the chronic period show a continuation of the intermediate findings that use of objective measures shows that hypersomnolence and excessive daytime sleepiness are the most common disruption of sleep patterns, while subjective measures show increased reporting of insomnia in mTBI groups, possibly due to a tendency for patients to overestimate sleep disturbance.

Discussion

Findings in the acute period support that the disruptions in this initial period include sleep dysfunction. Most of these studies focus on mTBI and very little objective sleep information has been collected. This lack of PSG or MSLT information may include confounds resultant from EEG disruptions common during the early acute period [67], however actigraphy during this initial period has been used to some success in

measuring objective disturbances [66]. The concomitant emergence of depressive and anxiety symptoms and psychosocial disabilities has complicated the determination of sleep disturbance prevalence as direct sequelae of the TBI. Also, no studies have attempted to account for the full breadth of indirect sleep disruption pathways in TBI samples, leaving the possible inclusion of each as an unaccounted for source of sleep variability in the studies.

The intermediate period shows an increase in the completeness of coverage of indirect effects and use of recommended assessment methods. This period highlights the large differences between subjective and objective measures of insomnia and shows that excessive daytime sleepiness and hypersomnolence are the most prevalent sleep dysfunction. Baumann et al. [57], as the most comprehensive study to date, shows a much lower incidence of insomnia (5%) than previous estimates with hypersomnia the most common disturbance. This suggests that TBI samples, particularly those of lower severity tend to overestimate disturbances.

The chronic period continues the hypersomnolence and excessive daytime sleepiness as the most common chronic sequelae of TBI. This period does show considerable measurement using objective sleep studies, however, there is a paucity of indirect pathway coverage and samples are contaminated with possible variance due to these possible confounds. Of note, there is now increasing focus on the chronic period and associated sleep dysfunction, particularly with regard to objective measures; this increased focus may indicate that sleep disruption is currently under-identified within this population.

The research findings regarding sleep disturbance and TBI show high variability in findings and little complimentary assessment methods, so much so that at present a comprehensive integration of findings is not possible. Early studies focused heavily on self-report methods with some only scoring patient complaints directly from medical records [76], or using questionnaires with questionable or unreported psychometric data [59]. Later studies focused on utilizing more robust questionnaires including the PSQI and the ESS, but studies continued reliance on self-report measures and utilized very little objective sleep studies [4]. The findings of these studies that rely solely on self-report measures may be called into question by the more recent findings that TBI samples do not show correlations between subjective and objective measures of sleep disturbance [7,57,61]. Use of objective measures has increased within the past ten years, but variability in prevalence rates and main findings continues to show high variability [8]. However, some of the variability is likely due to variables known to impact sleep patterns, but not excluded or assessed in these studies [9]. However, some recent studies have included more comprehensive coverage of these variables coupled with use of robust self-report measures and recommended objective sleep studies [7,57,72]. Continued investigations using these measures as a standard procedure across the time course sequelae will aid future integration of findings and make comprehensive meta-analytical summaries a possibility. Indeed, more recent studies that utilize the objective measures of PSG, actigraphy and MSLT appear as a promising approach to identification of sleep disruption in TBI [75].

In conclusion, Baumann [1] notes that at present there is no official classification of post-traumatic sleep-wake disturbances. However, the ICSD-3 [76] does provide some framework and guidelines that are similar to the DSM-5 [41] in that there are classifications available for chronic insomnia caused by a medical condition, hypersomnia caused by a medical condition, and circadian-rhythm sleep disorders not otherwise specified. Likewise, the DSM-5 provides the opportunity to code sleep disorders “with other medical comorbidity” or “with medical

condition.” Future research with a combination of the aforementioned self-report and objective measures may also focus on classification of severity of disrupted sleep as it pertains to TBI, which will aid in the evolution of state of the art assessment techniques in this population.

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