ERABI
EVIDENCE-BASED REVIEW
of moderate to severe
ACQUIRED BRAIN INJURY

FATIGUE & SLEEP DISORDERS

POST ACQUIRED BRAIN INJURY

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Disclaimer

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Conflict of Interest

In the context of ERABI development, the term "conflict of interest" (COI) refers to situations in which an author or ERABI staff member's financial, professional, intellectual, personal, organizational or other relationships may compromise their ability to independently conduct this evidence-based review. No limiting conflicts were identified.

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Greetings from Dr. Robert Teasell,

Professor and Chair-Chief of Physical Medicine and Rehabilitation

The Collaboration of Rehabilitation Research Evidence (CORRE) team is delighted to present the Evidence-Based Review of moderate to severe Acquired Brain Injury (ERABI) *Fatigue and Sleep Disorders post Acquired Brain Injury.* Through collaboration of researchers, clinicians, administrators, and funding agencies, ERABI provides an up-to-date review of the current evidence in brain injury rehabilitation. ERABI synthesizes the research literature into a utilizable format, laying the foundation for effective knowledge transfer to improve healthcare programs and services.

We offer our heartfelt thanks to the many stakeholders who are able to make our vision a reality. Firstly, we would like to thank the Ontario Neurotrauma Foundation, which recognizes ERABI's capacity to lead in the field of brain injury evidence-based reviews and is committed to funding it. We would also like to thank the co-chairs of ERABI, Dr. Mark Bayley (University of Toronto) and Dr. Shawn Marshall (University of Ottawa) for their invaluable expertise and stewardship of this review. Special thanks to the authors for generously providing their time, knowledge and perspectives to deliver a rigorous and robust review that will guide research, education and practice for a variety of healthcare professionals. We couldn't have done it without you! Together, we are building a culture of evidence-based practice that benefits everyone.

We invite you to share this evidence-based review with your colleagues, patient advisors that are partnering within organizations, and with the government agencies with which you work. We have much to learn from one another. Together, we must ensure that patients with brain injuries receive the best possible care every time they require rehabilitative care – making them the real winners of this great effort!

Robert Teasell, MD FRCPC

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PREFACE

About the Authors

ERABI is internationally recognized and led by a team of clinicians and researchers with the goal of improving patient outcomes through research evidence. Each ERABI module is developed through the collaboration of many healthcare professionals and researchers.

Amber Harnett, MSc, BScN (candidate), CNF scholar, completed her MSc in pathology at Western University and is currently a first-year nursing student in the accelerated BScN program at Western University. Passionate about supporting and advocating for those with brain injuries, she also works as a research coordinator to improve the rehabilitation system through research synthesis, guideline development, knowledge translation, education and outreach, in the CORRE lab at Parkwood Institute.

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Shannon Janzen, MSc, is a research associate and the project coordinator for the Evidence-Based Review of Acquired Brain Injury (ERABI). Her research interests focus on the integration of best evidence into clinical practice to optimize patient outcomes, with an emphasis on knowledge translation initiatives.

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Dr. Robert Teasell is Professor of Physical Medicine and Rehabilitation, Schulich School of Medicine and Dentistry, Western University and a Clinical Researcher at Lawson Research Institute in London, Ontario. He is a clinician at Parkwood Institute, St. Joseph's Health Care London.

Purpose

The Evidence-Based Review of Acquired Brain Injury (ERABI) is a systematic review of the rehabilitation literature of moderate to severe acquired brain injuries (ABI). It is an annually updated, freely accessible online resource that provides level of evidence statements regarding the strength of various rehabilitation interventions based on research studies. The ERABI is a collaboration of researchers in London, Toronto and Ottawa. Our mission is to improve outcomes and efficiencies of the rehabilitation system through research synthesis, as well as from providing the foundational research evidence for guideline development, knowledge translation, and education initiatives to maximize the real-world applications of rehabilitation research evidence.

Key Concepts

Acquired Brain Injury

For the purposes of this evidence-based review, we used the definition of ABI employed by the Toronto Acquired Brain Injury Network (2005). ABI is defined as damage to the brain that occurs after birth and is not related to congenital disorders, developmental disabilities, or processes that progressively damage the brain. ABI is an umbrella term that encompasses traumatic and non-traumatic etiologies.

TABLE 1 | Defining Acquired Brain Injury

Included in ABI definition	Excluded from ABI definition
Traumatic Causes • Motor vehicle accidents • Falls • Assaults • Gunshot wounds • Sport Injuries **Non-traumatic Causes** • Tumours (benign/meningioma only) • Anoxia • Subarachnoid hemorrhage (non-focal) • Meningitis • Encephalitis/encephalopathy (viral, bacterial, drug, hepatic) • Subdural Hematoma	**Vascular and Pathological Incidents** • Intracerebral hemorrhage (focal) • Cerebrovascular accident (i.e., stroke) • Vascular accidents • Malignant/metastatic tumours **Congenital and Developmental Problems** • Cerebral Palsy • Autism • Developmental delay • Down's syndrome • Spina bifida with hydrocephalus **Progressive Processes** • Alzheimer's disease • Pick's disease • Dementia • Amyotrophic Lateral Sclerosis • Multiple Sclerosis • Parkinson's disease • Huntington's disease

Given that 'ABI' can have multiple definitions, studies with an 'ABI' population can be equally heterogeneous in terms of the sample composition. Such studies may include any combination of persons with TBI, diffuse cerebrovascular events (i.e., subarachnoid hemorrhage) or diffuse infectious disorders (i.e., encephalitis or meningitis). The vast majority of individuals with ABI have a traumatic etiology; therefore, much of the brain injury literature is specific to TBI. The terms ABI and TBI have been used intentionally throughout ERABI to provide more information about populations where relevant.

Moderate to Severe Brain Injury

ABI severity is usually classified according to the level of altered consciousness experienced by the patient following injury (Table 2). The use of level of consciousness as a measurement arose because the primary outcome to understand the severity of an injury is the Glasgow Coma Scale. Consciousness levels following ABI can range from transient disorientation to deep coma. Patients are classified as having a mild, moderate or severe ABI according to their level of consciousness at the time of initial assessment.

Various measures of altered consciousness are used in practice to determine injury severity. Common measures include the Glasgow Coma Scale (GCS), the duration of loss of consciousness (LOC), and the duration of post-traumatic amnesia (PTA). Another factor used to distinguish moderate and severe brain injury is evidence of intracranial injury on conventional brain imaging techniques which distinguish severity of injury from a mild or concussion related brain injury.

TABLE 2 | Defining Severity of Traumatic Brain Injury, adapted from Veterans Affairs Taskforce (2008) and Campbell (2000)

Criteria	Mild	Moderate	Severe	Very Severe
Initial GCS	13-15	9-12	3-8	Not defined
Duration LOC	< 15minutes*	<6 hours	6-48 hours	>48 hours
Duration PTA	< 1hour*	1-24 hours	1-7 days	>7 days
	*This is the upper limit for mild traumatic brain injury; the lower limit is any alteration in mental status (dazed, confused, etc.).			

Methods

An extensive literature search using multiple databases (CINAHL, PubMed/MEDLINE, Scopus, EMBASE, and PsycINFO) was conducted for articles published in the English language between 1980–March 2020 that evaluate the effectiveness of any intervention/treatment related to ABI. The references from key review articles, meta-analyses, and systematic reviews were reviewed to ensure no articles had been overlooked. For certain modules that lacked research evidence the gray literature, as well as additional databases, were searched in order to ensure the topic was covered as comprehensively as possible.

Specific subject headings related to ABI were used as the search terms for each database. The search was broadened by using each specific database's subject headings, this allowed for all other terms in the database's subject heading hierarchy related to ABI to also be included. The consistent search terms used were "head injur*", "brain injur*", and "traumatic brain injur*". Additional keywords were used specific to each module. A medical staff librarian was consulted to ensure the searches were as comprehensive as possible.

Every effort was made to identify all relevant articles that evaluated rehabilitation interventions/ treatments, with no restrictions as to the stage of recovery or the outcome assessed. For each module, the individual database searches were pooled, and all duplicate references were removed. Each article title/abstract was then reviewed; titles that appeared to involve ABI and a treatment/intervention were selected. The remaining articles were reviewed in full.

Studies meeting the following criteria were included: (1) published in the English language, (2) at least 50% of the study population included participants with ABI (as defined in Table 1) or the study independently reported on a subset of participants with ABI, (3) at least three participants, (4) ≥50% participants had a moderate to severe brain injury (as defined in Table 2), and (5) involved the evaluation

of a treatment/intervention with a measurable outcome. Both prospective and retrospective studies were considered. Articles that did not meet our definition of ABI were excluded.

Interpretation of the Evidence

The levels of evidence (Table 3) used to summarize the findings are based on the levels of evidence developed by Sackett et al. (2000). The levels proposed by Sackett et al. (2000) have been modified; specifically, the original ten categories have been reduced to five levels. Level 1 evidence pertains to high quality randomized controlled trials (RCTs) (PEDro ≥6) and has been divided into two subcategories, level 1a and level 1b, based on whether there was one, or more than one, RCT supporting the evidence statement.

The evidence statements made in evidence-based reviews are based on the treatment of groups rather than individuals. There are times when the evidence will not apply to a specific case; however, the majority of patients should be managed according to the evidence. Ultimately, the healthcare professional providing care should determine whether an intervention is appropriate and the intensity with which it should be provided, based on their individual patient's needs. Furthermore, readers are asked to interpret the findings of studies with caution as evidence can be misinterpreted. The most common scenario occurs when results of a trial are generalized to a wider group than the evidence allows. Evidence is a tool, and as such, the interpretation and implementation of it must always be done with the known limitations in mind.

TABLE 3 | Levels of Evidence

Level	Research Design	Description
1A	Randomized Controlled Trial (RCT)	More than one RCT with PEDro score ≥6. Includes within subject comparisons, with randomized conditions and crossover designs
1B	RCT	One RCT with PEDro ≥6
2	RCT	One RCT with PEDro <6
	Prospective Controlled Trial (PCT)	Prospective controlled trial (not randomized)
	Cohort	Prospective longitudinal study using at least two similar groups with one exposed to a particular condition
3	Case Control	A retrospective study comparing conditions including historical controls
4	Pre-Post Trial	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects
	Post-test	A prospective intervention study using a post intervention measure only (no pre-test or baseline measurement) with one or more groups
	Case Series	A retrospective study usually collecting variables from a chart review
5	Observational study	Using cross sectional analysis to interpret relations
	Clinical Consensus	Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or "first principles"
	Case Reports	Pre-post or case series involving one subject

Strength of the Evidence

The methodological quality of each randomized controlled trial (RCT) was assessed using the Physiotherapy Evidence Database (PEDro) rating scale developed by the Centre for Evidence-Based Physiotherapy in Australia (Moseley et al., 2002). The PEDro is an 11-item scale; a point is awarded for ten satisfied criterion yielding a score out of ten. The first criterion relates to external validity, with the remaining ten items relating to the internal validity of the clinical trial. The first criterion, eligibility criteria, is not included in the final score. A higher score is representative of a study with higher methodological quality.

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SUMMARY OF THE EVIDENCE

Intervention	Key Point Level of Evidence
MANAGEMENT OF FATIGUE	
Non-pharmacological Interventions	
Exercise	A progressive walking program may reduce fatigue in patients with TBI *There is level 2 evidence (from one randomized controlled trial; Kolakowsky-Hayner et al., 2017) that a home-based walking program may reduce fatigue up to 24 weeks following treatment compared to a nutritional counselling program in patients with TBI.*
Pacing	More research is necessary to determine the efficacy of pacing interventions for patients with ABI. *No studies to date have examined the benefits of pacing within a population with ABI.*
Cognitive Behavioural Therapy	Cognitive behavioural therapy may reduce fatigue in patients with TBI. *There is level 1b evidence (from one randomized controlled trial; Ngyuen et al., 2017) and level 4 evidence (from one pre-post test; Ouellet and Morin, 2007) that cognitive behavioural therapy may reduce fatigue compared to usual care in patients with TBI.*
Light Therapy	Blue light therapy may reduce fatigue and daytime sleepiness in patients with TBI. *There is level 1a evidence (from two randomized controlled trials; Quera Salva et al., 2020, Sinclair et al., 2014) that blue light therapy may be effective in reducing fatigue and daytime sleepiness compared to no treatment in patients with TBI.* *There is level 1b evidence (from one randomized controlled trial; Sinclair et al., 2014) that yellow light therapy may not be effective in reducing fatigue and daytime sleepiness compared to control.*
Lifestyle Management Strategies	Programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce fatigue and sleepiness in patients with ABI. *There is level 4 evidence (from one pre-post trial; Stubberud et al., 2017) that programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce fatigue up to 3 months and sleepiness up to 9 months post intervention in patients with ABI.*

Pharmacological Interventions	
Modafinil	Modafinil has not been shown to be effective in treating fatigue post TBI.
	Modafinil has been shown to be effective in the short-term for treating excessive daytime sleepiness, but may also cause insomnia post TBI. *There is level 1a evidence (from two randomized controlled trials; Kaiser et al., 2010, Jha et al., 2008) that modafinil may not be effective for treating fatigue compared to placebo in patients with TBI, but may be effective short-term in treating excessive daytime sleepiness post TBI.*
(-)-OSU6162	(-)-OSU6162 treatment may not be effective for reducing fatigue post TBI. *There is level 1b evidence (from one randomized controlled trial; Berginstrom et al., 2017) that (-)-OSU6162 may not be effective for treating fatigue compared to placebo in patients with TBI.*
Melatonin	Melatonin may reduce fatigue in patients post TBI. *There is level 1b evidence (from one randomized controlled trial; Grima et al., 2018) that melatonin treatment may be effective in reducing fatigue compared to a placebo group in patients post TBI.*
MANAGEMENT OF SLEEP DISORDERS	
Non-Pharmacological Interventions	
Relaxation Strategies	A warm footbath in the evening may improve waking after sleep onset and sleep onset latency in patients with TBI. *There is level 1b evidence (from one randomized controlled trial; Chiu et al., 2017) that a warm footbath in the evening may improve wake after sleep onset and sleep onset latency but not sleep efficiency or sleep time compared to usual care in patients with TBI.*
Lifestyle Management	Programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce sleepiness, but may not improve insomnia in patients with ABI. *There is level 4 evidence (from one pre-post trial; Stubberud et al., 2017) that programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce sleepiness up to 9 months post intervention, but may not improve insomnia in patients with ABI.*
Cognitive Behavioural Therapy	Cognitive behavioural therapy may improve sleep quality and reduce insomnia in patients with TBI. *There is level 1b evidence (from one randomized controlled trial; Ngyuen et al., 2017) and level 4 evidence (from one pre-post trial; Ouellet and Morin, 2007) that cognitive behavioural therapy may reduce insomnia compared to usual care in patients with TBI.*
Acupuncture	Acupuncture therapy may not improve insomnia in patients with TBI.

	There is level 2 evidence (from one randomized controlled trial; Zollman et al., 2012) that acupuncture may not improve insomnia compared to instructions on good sleep habits in patients with TBI.
Sleep Hygiene	More research is necessary to determine the efficacy of sleep hygiene interventions for patients with ABI. *There is level 2 evidence (from one randomized controlled, unblinded trial; Markley et al., 2020) that a sleep hygiene intervention is feasible in a population with moderate to severe TBI; however, more research is needed to determine its efficacy.*
Pharmacological Interventions	
Modafinil	Modafinil has been shown to be effective in the short-term for treating excessive daytime sleepiness, but may also cause insomnia post TBI. *There is level 1a evidence (from two randomized controlled trials; Kaiser et al., 2010, Jha et al., 2008) that modafinil may be effective short-term in treating excessive daytime sleepiness but may also cause insomnia in patients post TBI.*
Methylphenidate	Methylphenidate may not have an adverse effect on the sleep-wake cycle of patients post TBI. *There is level 3 evidence (from one case-control; Al-Adawi et al., 2006) that methylphenidate may not have adverse effects on the sleep-wake cycle compared to those not receiving medication post TBI.*
Lorazepam & Zopiclone	More research is necessary to determine the safety and efficacy of benzodiazepines and non-benzodiazepine hypnotics for patients with ABI. *No studies to date have examined the effects of benzodiazepines and non-benzodiazepine sleep aids within a population with ABI.*
Melatonin	Melatonin may improve sleep quality and sleep efficiency in patients post TBI. *There is level 1b evidence (from one randomized controlled trial; Grima et al., 2018) that melatonin treatment may be effective in improving sleep quality and sleep efficiency compared to a placebo group in patients post TBI.*
	Melatonin may not improve sleep onset latency or daytime sleepiness. *There is level 1b evidence (from one randomized controlled trial; Grima et al., 2018) that melatonin treatment may not affect sleep onset latency or daytime sleepiness in patients post TBI.*

INTRODUCTION

Fatigue and sleep disorders are among the more commonly reported symptoms associated with brain injury (Cronin & O'Loughlin, 2018; Duclos et al., 2014; Elovic et al., 2005) and can exacerbate other co-morbid symptoms and negatively affect quality of life. Understanding fatigue and sleep disorders and how to manage them is therefore important for addressing the needs of persons with ABI and can be a crucial complement to other efforts to optimize recovery post ABI. Although it would seemingly make sense to link disorders of sleep with fatigue (Clinchot et al., 1998), this relationship remains inconclusive (Fellus & Elovic, 2007). Sleep disturbances can exacerbate fatigue; however, fatigue may also manifest independent of sleep disorders and not all sleep disorders may produce fatigue (Ouellet et al., 2015).

One of the major challenges in this area is the large variability in the prevalence estimates of fatigue and sleep disorders within the ABI literature, which may affect 30-73% of persons post ABI (Englander et al., 2010; Ouellet et al., 2019; Ponsford et al., 2012). Much of this variability is due to variation in how data is collected: both subjective and objective means of collecting fatigue and sleep data are available. A systematic review found 16 measures of fatigue and sleep were commonly used in TBI studies (Mollayeva et al., 2013). Subjective questionnaires are the most commonly used, but polysomnography, actigraphy, multiple sleep latency tests, and maintenance of wakefulness tests are objective measures that may also be used (Mollayeva et al., 2013). Most of these measures have not been validated in persons with ABI. Despite the significant methodologic variability, epidemiologic estimates indicate that persons with ABI more often experience disorders of fatigue and/or sleep than the general population (Ouellet et al., 2019; Rao et al., 2015; Silver et al., 2018).

There are many putative sources of fatigue and sleep dysfunction, including neuroanatomical, psychological, biochemical, endocrine, or environmental causes (Mollayeva et al., 2013). A review by Duclos et al. (2014) suggests that fatigue and sleep disturbances may be due to altered circadian rhythms, damage to the cortical and subcortical structures involved in sleep and wakefulness, endocrine dysfunction (e.g., growth hormone or cortisol levels), pain, anxiety and depression, environmental factors, or may be multifactorial, encompassing elements in each of these categories. This complex interplay between pathophysiological, psychological, social, and environmental factors complicates our ability to determine the precise etiology of fatigue or sleep dysfunction (Ouellet et al., 2015). It is therefore important to investigate potentially treatable or reversible causes of fatigue or sleep dysfunction (e.g., anemia, hypothyroidism, obstructive sleep apnea, medications that may cause insomnia or worsen fatigue, etc.) in patients with ABI. When recovering from an ABI, fatigue and sleep disorders have the ability to interfere with their ability to participate in rehabilitation programs designed to assist them in performing their activities of daily living. It also impacts their physical, cognitive, and social abilities, emphasizing the importance of addressing fatigue and sleep dysfunction.

FATIGUE

One of the greatest challenges is in properly defining fatigue, which is a subjective experience and thus is not easily assessed by objective measures (Lewis & Wessely, 1992). Individuals experiencing fatigue report it as a feeling of tiredness, weakness, or exhaustion (Rao et al., 2006). Others define fatigue as the "*unconscious decreased ability for physical and or mental activity due to an imbalance in availability, utilization or the retrieval of the physiological or psychological resources required to perform the activity*" p.2 (Aaronson et al., 1999). Those studying or reporting on fatigue have attempted to distinguish between physical and psychological fatigue (Aaronson et al., 1999). Physical fatigue has been defined as "*the result of excessive energy consumption, depleted hormones or neurotransmitters or diminished ability of muscle cells to contract*" p.2 (Jha et al., 2008). Psychological fatigue has been defined as *"a state of weariness related to reduced motivation, prolonged mental fatigue or boredom"* p.1 (Lee et al., 1991).

Although fatigue has been recognized as a significant problem post ABI, there are few interventional studies addressing fatigue in this population. When comparing individuals with TBI to healthy controls, those who have had a brain injury experience greater levels of fatigue (Ashman et al., 2008; Borgaro et al., 2005; Chiou et al., 2016; LaChapelle & Finlayson, 1998; Ponsford et al., 2012; Ziino & Ponsford, 2006). Between 32% and 73% of individuals reported fatigue post TBI (Englander et al., 2010; Ponsford et al., 2012; Silver et al., 2018). To better understand the severity of the problem, data is often collected through surveys, interviews, and/or questionnaires. Comparison groups in many of the studies are those without an ABI. Scales frequently used in these surveys include the Fatigue Severity Scale, the Fatigue Impact Scale, the Visual Analogue Scale-F, the Global Fatigue Index, the Barroso Fatigue Scale, and the Epworth Sleepiness Scale; however, none of these scales were designed specifically for use in patients with brain injury, but rather they were developed for patients with Human Immunodeficiency Virus or Multiple Sclerosis (Armutlu et al., 2007; Fish et al., 2007). Because fatigue is a subjective experience, there are no objective measures of fatigue severity.

Fatigue is highly associated with psychological and cognitive comorbidities frequently found in the ABI population such as difficulties with vigilance, attention, depression, anxiety, and cognition. Those who sustain a TBI often have a lower cognitive reserve and may be unable to maintain the same levels of vigilance or sustained attention as they did before their injury (Ziino & Ponsford, 2006). This may be exacerbated by mental fatigue as reported by Jonasson et al. (2018) who found after cognitive activity, those dealing with mental fatigue had impaired cognitive performance. Ponsford et al. (2015) reported on the relationship between fatigue, depression, and anxiety post TBI: fatigue strongly predicted depression and anxiety according to the Hospital Anxiety and Depression Scale. A review by Kumar et al. (2018) also found numerous studies that reported a positive correlation between post-traumatic depression and self-reported fatigue. Bay & de-Leon (2011) surveyed individuals with TBI from an outpatient clinic and reported a significant correlation between fatigue and perceived stress.

Similar to sleep disorders, fatigue can have a significant negative effect on an individual's ability to fully participate in rehabilitation post ABI. Moreover, the often intense rehabilitation programs themselves may exacerbate fatigue. In a study by Toda et al. (2006), the investigators found that individuals who had sustained a TBI reported significantly higher levels of fatigue during their time in rehabilitation than they did at 6- or 12-months post injury. One putative explanation is that once the patient is removed from the demands of inpatient rehabilitation and has achieved a greater understanding of their deficits, the feelings of fatigue may lessen; alternatively, natural recovery may be associated with some improvements in fatigue. However, the literature shows that fatigue can persist for years post injury regardless (Bay & de-Leon, 2011; Olver et al., 1996; Ouellet & Morin, 2004; Rao et al., 2006). In addition to negatively affecting rehabilitation participation, fatigue has been associated with subjective reports of cognitive problems, difficulties with decision-making, needing to work slowly to ensure accuracy, and challenges in getting things done on time (Esbjornsson et al., 2013). Fatigue can also negatively impact relationships, as there is a tendency towards reacting too quickly in response to others among individuals suffering from fatigue (Esbjornsson et al., 2013). Additionally, one's ability to work is often compromised when fatigue is present. Schnieders et al. (2012) found those with fatigue, compared to those without, had lower-level jobs and more non-paying jobs. Therefore, managing fatigue is imperative in helping individuals live a productive life post injury.

MANAGEMENT OF FATIGUE

Fatigue post ABI can be managed using pharmacological or non-pharmacological techniques. Although fatigue is common post ABI and can have serious negative implications for recovery and quality of life, few interventions have been studied for these conditions. Moreover, the few studies available are often hampered by small sample sizes and short duration of follow-up. Thus, the optimal management of fatigue is likely elusive, and patients may require a constellation of interventions to meet their needs.

Non-Pharmacological Interventions

Non-pharmacological strategies for the management of fatigue include exercise, pacing, cognitive behavioural therapy, and light therapy. Diet and lifestyle may also play an important role in combating fatigue; thus, it is believed that eating a "balanced diet" and learning to balance exercise with rest may help to reduce fatigue (Elovic et al., 2005; Rao et al., 2006). In this section, we review the literature evaluating the effectiveness of each of these techniques in the ABI population.

Exercise

Exercise may improve fatigue and has significant benefits for cardiovascular health, general well-being, emotional and immune system functioning.

TABLE 4 | Exercise Interventions for the Management of Fatigue Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Kolakowsky-Hayner et al. (2017) USA RCT Crossover PEDro=4 $N_{initial}$=128 N_{final}=62	**Population:** TBI; Mean Age=42.7yr; Gender: Male=72 Female=56; Mean Time Post Injury=97.6mo. **Intervention:** The treatment group received a 12wk home-based walking program that included a pedometer to track daily number of steps and tapered coaching calls. Participants were encouraged to increase their steps by 5% each week until an overall step increase 40% above baseline was achieved. A 12wk nutritional counselling program and the same frequency of tapered coaching calls served as the control. Measurements were taken at baseline and week 12, 24, and 36. **Outcome Measures:** Global Fatigue Index (GFI), Barrow Neurological Institute (BNI) Fatigue Scale Overall Severity Score, Multidimensional Fatigue Inventory (MFI).	1. Participants had significantly less fatigue (GFI) at the end of the walking intervention ($p<0.001$). 2. According to the BNI Fatigue Scale Total, participants had significantly less fatigue at the end of the walking intervention ($p<0.003$). 3. According to the BNI Overall Score, participants had significantly less fatigue at the end of the walking intervention ($p<0.001$) and after 36wk ($p<0.001$). The walking intervention in the nutritional first group did not have a significant effect on BNI Overall Score but had significantly reduced BNI Overall Scores by week 36. 4. According to the MFI, participants had significantly less fatigue at the end of the walking intervention ($p<0.001$) and after 36wk ($p<0.05$). However, MFI scores significantly increased following the end of the walking intervention. ($p<0.05$).
Krese et al., (2020) USA Pre-Post $N_{Initial}$=13, N_{Final}=11	**Population:** TBI=13; Mean Age= 45.31±14.23yr; Gender: Male=8, Female=5; Median Time Post Injury=15.00yr (12.00, 20.00); Severity: Mean GCS=10.43±3.91. **Intervention:** Each subject participated in yoga-based physical therapy (YPT), conventional physical therapy (CPT), and seated rest (SR) on different days in a crossover design. Outcome measures were assessed immediately before and after each session. Sleep outcomes were measured at baseline and intervention days. **Outcome Measures:** Heart Rate Variability (HRV) standard deviation of the normal-to-normal interval (SDNN), Spielberger State-Trait Anxiety Inventory (STAI), Global Fatigue Index (GFI), Wake After Sleep Onset (WASO), nightly sleep duration, average duration of awakening	1. Significant improvements were observed in actigraphy sleep metrics in the SR group (WASO, $p=.006$) but not in YPT or CPT groups. 2. Significant improvements were observed in actigraphy sleep metrics (incidence rate ratio of WASO) for SR compared with CPT ($p=.0218$) and YPT ($p=.0089$), but not significantly different between CPT and YPT ($p>.05$). 3. No significant differences were found between treatment groups for anxiety (STAI, $p>.05$) or HRV (SDNN, $p>.05$). 4. No significant differences were observed for GFI ($p>.05$).

Discussion

The impact of exercise on fatigue was evaluated in a crossover randomized controlled trial (RCT) by Kolakowsky-Hayner et al. (2017). Assessing with three different outcome measures, the study found fatigue was positively influenced by exercise. The positive improvements in fatigue lasted 12 to 24 weeks after the intervention was completed. It appears a progressive walking program is an effective and low-cost intervention for fatigue. In contrast, Krese et al. (2020) found that while a yoga-based intervention

was feasible, no significant improvements in fatigue were observed. However, this may be attributed to the small sample size (n=13). Furthermore, this may indicate that different types of exercise are associated with differential effects on fatigue.

Conclusions

There is level 2 evidence (from one randomized controlled trial; Kolakowsky-Hayner et al., 2017) that a home-based walking program may reduce fatigue up to 24 weeks following treatment compared to a nutritional counselling program in patients with TBI.

There is level 4 evidence (from one pre-post trial; Krese et al., 2020) that yoga-based physical therapy is feasible and safe in a mixed population with TBI; however, more research is needed to determine its efficacy.

KEY POINTS

- A progressive walking program may reduce fatigue in patients with TBI.

Pacing

Those who are suffering from fatigue may benefit by performing important activities when they feel they are at their best (Lezak, 1978). Conserving energy and pacing are two ways an individual is encouraged to overcome or deal with his or her levels of fatigue following brain injury (Fellus & Elovic, 2007). Many patients find that simple tasks require more concentration and effort than they did previously and, as a result, they tire more easily (Lezak, 1978). As part of their rehabilitation, individuals may be taught or re-taught how to prioritize their commitments and are encouraged to recognize their abilities and limitations (Fellus & Elovic, 2007). For some this may come easily, but for others it may require more education or other interventional programs (2007). Although pacing is a concept that has been accepted with health care professionals and encouraged within the ABI population, its benefits have not yet been studied with this group and as a result the treatment effects of pacing strategies are not known.

KEY POINTS

- More research is necessary to determine the efficacy of pacing interventions for patients with ABI.

Cognitive Behavioural Therapy

Cognitive behavioural therapy (CBT) has been found to be effective at improving fatigue in disorders such as multiple sclerosis, chronic fatigue syndrome, and rheumatoid arthritis (Cantor et al., 2014); however, limited research exists regarding the effect on fatigue after ABI (Ouellet & Morin, 2004). Four studies to date have evaluated the effectiveness of CBT on fatigue post ABI.

TABLE 5 | Cognitive Behavioural Therapy for the Management of Fatigue Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Nguyen et al. (2017) Australia RCT PEDro=8 N=24	**Population:** TBI; *CBT Group (n=13)*: Mean Age=45.53yr; Gender: Male=9, Female=4; Mean Time Post Injury=795.15d. *Control Group (n=11):* Mean Age=41.90yr; Gender: Male=7, Female=4; Mean Time Post Injury=2093.36d. **Intervention:** Patients in the CBT group received 6 modules of CBT addressing sleep and fatigue over 8 sessions. Therapy content contained a framework that is relevant to TBI and facilitated the acceptance of increased sleep disturbance vulnerability and fatigue secondary to brain trauma. Controls received treatment as usual. Measurements were taken at baseline, 2, and 4mo. **Outcome Measures:** Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Brief Fatigue Inventory (BFI), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS).	1. The CBT group had significantly improved BFI scores post-treatment ($p<0.05$) and at follow-up ($p<0.01$) compared to control. There was also a significant improvement in BFI scores over time for the CBT group ($p=0.016$), but not the control group. 2. The FSS and ESS yielded no significant between group differences or time effects for either group.
Raina et al. (2016) USA RCT PEDro=4 N_{Intial}=41 N_{Final}=38	**Population:** TBI; *MAX Group (n=17)*: Mean Age=43.8yr; Gender: Male=8, Female=5; Mean Time Post Injury=9.9 mo. *Control Group (n=21):* Mean Age=48.1yr; Gender: Male=13, Female=8; Mean Time Post Injury=11.1 mo. **Intervention:** Participants received either Maximizing Energy (MAX) training (a cognitive behavioural intervention) or online health education which served as a control. MAX training consisted of 2 online 30min 1:1 session per week for 8 wk, delivered via webcam by 2 occupational therapists. **Outcome Measures:** Modified Fatigue Impact Scale (MFIS), Patient-Reported Outcomes Measurement Information System Fatigue Scale (PROMIS-F), Fatigue Severity Scale (FSS).	1. No significant differences between groups were found for MFIS, PROMIS-F or FSS.
Ouellet & Morin (2007) Canada Pre-Post N=11	**Population:** TBI=11; Mean age=27.3yr; Male=6, Female=5; Mean Time Since Injury=25.64mo. **Intervention:** Patients received cognitive behavioural therapy (CBT) for insomnia (8 wk, 1 hr/wk). Specifically, CBT focused on stimulus control, sleep restriction,	1. Significant reductions in scores were seen after treatment on the MFI ($p<0.012$).

Author Year Country Study Design Sample Size	Methods	Outcome
	cognitive restructuring, sleep hygiene education, and fatigue management. **Outcome Measures:** Total Wake Time, Sleep Efficiency, Sleep Time, Insomnia Severity Index (ISI), Multidimensional Fatigue Inventory (MFI), Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS).	

Discussion

In a pre-post study, Ouellet and Morin (2007) found that CBT was effective in reducing physical and general fatigue post TBI (as measured by the Brief Fatigue Inventory). No significant gains were made once the treatment had concluded, although gains were maintained at 3-month follow-up. This study suggests that a relatively short duration of CBT can lead to improvements in fatigue symptoms sustained for 3 months. Similarly, a RCT by Nguyen et al. (2017) showed that individuals who received CBT showed significant improvements in fatigue compared to those who received standard care. A secondary analysis of the previous study, and another involving stroke patients, found that participants who were younger, had better verbal memory, and with comorbid symptoms of depression were more likely to respond to CBT treatment (Nguyen et al., 2018).

Another study compared an education and problem-solving therapy program targeted to management of fatigue and health education and did not find any between group differences on three measures of fatigue (Raina et al., 2016). The results of this study should be interpreted with caution, as the purpose of the study was to determine the feasibility of conducting a larger trial using an internet-delivered manualized intervention.

Conclusions

There is level 1b evidence (from one randomized controlled trial; Ngyuen et al., 2017) and level 4 evidence (from one pre-post test; Ouellet and Morin, 2007) that cognitive behavioural therapy may reduce fatigue compared to usual care in patients with TBI.

KEY POINTS

- Cognitive behavioural therapy may reduce fatigue in patients with TBI.

Light Therapy

The goal of light therapy is to shift waking or bedtimes towards a more desirable sleep-wake schedule. Typically, light therapy involves a person being exposed to a short wavelength light (430-475 nm; blue wavelength light) upon awakening. The theoretical basis for light therapy is using light to alter melatonin production and secretion. Photosensitive retinal ganglion cells respond to blue light and transmit signals to hypothalamic nuclei to suppress the production of melatonin, leading to increased daytime alertness and earlier onset of evening sleep (Bajaj et al., 2017). However, light therapy has not been well studied in a population with ABI.

TABLE 6 | Light Therapy for the Management of Fatigue Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Quera Salva et al., (2020) France RCT PEDro=7 $N_{Initial}$=20, N_{Final}=20	**Population:** TBI=20; *Intervention Group (Blue-enriched white light therapy, BWL; n=10):* Mean Age=34.20±10.73yr; Sex Ratio=2.33; Mean Time Post Injury=7.93±9.99yr; Severity: Mean GCS=5.88±1.55. *Control Group (No light therapy, N-BWL; n=10):* Mean Age=39±9.81yr; Sex Ratio=1.22; Mean Time Post Injury=10.02±10.71yr; Severity: Mean GCS=6±1.83. **Intervention:** Participants were randomly allocated to receive light therapy (blue-enriched white light, 30min upon waking for 4wk) or no light therapy. Outcome measures were assessed at baseline, 2wk, 4wk and 6wk. **Outcome Measures:** Fatigue Severity Scale (FSS), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Hamilton Depression Scale (HDS-17), Short Form Health Survey (SF-12).	1. BWL significantly improved fatigue severity (FSS, p=.026) from baseline to 4wk. (p<.001); however, improvements disappeared at 6wk, 2wk following treatment cessation. 2. BWL significantly improved measures of depression from baseline to 4wk (HADS17, p=.04). Improvements were maintained at 6wk. 3. No significant differences in quality of life (SF-12, p>.05), sleep quality (PSQI, p>.05), or daytime sleepiness (ESS, p>.05) were observed between groups.
Sinclair et al. (2014) Australia RCT PEDro=6 N=30	**Population:** TBI=30; Mean Age= 42yr; Male=24, Female=6; Mean Time Post Injury=1106d; Severity: Mild=7, Moderate=8, Severe=15. **Intervention:** Participants were randomized to one of three home-based treatment groups: blue light therapy (n=10), yellow light therapy (n=10) or the no treatment control group (n=10). Participants were instructed to use the device for 45min each morning, within 2hr of waking up, for 4wk. Assessments were conducted at baseline, 4wk and 8wk. **Outcome Measures:** Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI).	1. Compared to the control group, the blue light therapy group showed a significantly greater reduction in fatigue (FSS; p<0.001) and a significant reduction in daytime sleepiness (ESS; p<0.01). 2. No significant differences were observed in the yellow light therapy group when compared to controls. 3. There was no significant change in PSQI score in any treatment condition (p>0.05).

Discussion

Sinclair et al. (2014) conducted a RCT examining the effectiveness of light therapy, both blue and yellow, compared to a control group. The blue light therapy significantly decreased fatigue ($p<0.001$) and daytime sleepiness ($p<0.01$) compared to the control group. The improvements measured during the treatment phase did not persist at follow-up (week 8, 2 weeks after light therapy discontinuation). The yellow light therapy did not show such improvements compared to the control group. Similarly, Quera Salva et al. (2020) found that blue light therapy significantly improved measures of fatigue severity when compared to a control group that did not receive light therapy; however, improvements were not maintained over time. In this study, no improvement in daytime sleepiness was observed, along with no improvements in sleep quality, or quality of life. However, this study observed an improvement in measures of depression that were maintained at two weeks following treatment.

Conclusions

There is level 1a evidence (from two randomized controlled trials; Quera Salva et al., 2020, Sinclair et al., 2014) that blue light therapy may be effective in reducing fatigue and daytime sleepiness compared to no treatment in patients with TBI.

There is level 1b evidence (from one randomized controlled trial; Sinclair et al., 2014) that yellow light therapy may not be effective in reducing fatigue and daytime sleepiness compared to control.

KEY POINTS

- Blue light therapy may reduce fatigue and daytime sleepiness in patients with TBI .

Lifestyle Management Strategies

This category of interventions involves making a series of changes to one's lifestyle to take a more holistic approach to rehabilitation, symptom management, or remediation. These changes can be wide-ranging, encompassing anything from diet to self-care to exercise. Lifestyle management strategies can also focus on emotional, physical, and/or mental health in an effort to improve a variety of symptoms. Although this approach intuitively makes sense, there are challenges when attempting to compare studies as the breadth of interventions and heterogeneity of outcomes are greater than in most areas of research.

TABLE 7 | Lifestyle Interventions for the Management of Fatigue Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Stubberud et al. (2017) Norway Pre-Post N=8	**Population:** ABI (Injury Etiology: TBI=3, Cerebrovascular Insults=5); Mean Age=41.6yr; Gender: Male=3, Female=5; Mean Time Post Injury=40.1mo. **Intervention:** Participants underwent 36hr of programming over 1mo. The program included 3 modules covering lifestyle factors and adaptive coping strategies, goal management training (GMT), and emotional regulation. Patients were assessed at baseline, posttest, and 3 and 6mo follow-up. **Outcome Measures:** Fatigue Severity Scale (FSS), Fatigue Questionnaire (FQ), Hospital Anxiety and Depression Scale (HADS), Epworth Sleepiness Scale (ESS), Insomnia Severity Scale (ISI), General Perceived Self-Efficacy Scale (GPSS), Conners Continuous Performance Test II (CPT-II).	1. FSS scores were significantly improved at posttest (p=0.035) and at 3mo follow-up (p=0.018), but not at 9mo follow-up. 2. At posttest, FQ total (p=0.018) and physical (p=0.042) scores were significantly improved, but not FQ mental scores. These improvements were not sustained at follow-up. 3. HAD total (p=0.041) and anxiety scores were significantly improved only at 9mo follow-up. 4. ESS scores were significantly improved at 3 mo (p=0.042) and 9 mo (p=0.024) follow-up.

Discussion

In a small (n=8) pre-post study by Stubberud et al. (2017), participants underwent 36 hours of programming focusing on lifestyle factors, adaptive coping, and goal management training. The intervention significantly reduced fatigue at post-test and 3-month follow-up, but not at 9-month follow-up. Sleepiness was significantly reduced at post-test, 3-month follow-up, and 9-month follow-up. The authors also reported a significant improvement on anxiety scores on the Hospital Anxiety and Depression Scale.

Conclusions

There is level 4 evidence (from one pre-post trial; Stubberud et al., 2017) that programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce fatigue up to 3 months and sleepiness up to 9 months post intervention in patients with ABI.

KEY POINTS

- Programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce fatigue and sleepiness in patients with ABI.

Pharmacological Interventions

Fatigue has been known to compound the neurocognitive difficulties experienced post ABI. Despite the knowledge that fatigue influences recovery post ABI, very few pharmacological interventions have been developed or evaluated to help address these issues. Many pharmacological interventions have been tested in other populations (narcolepsy, multiple sclerosis, Parkinson's, etc.) (Rao et al., 2006), but few have been tested within the ABI population specifically. Suggested treatments have included the administration of various over-the-counter medications (e.g., melatonin, diphenhydramine (e.g., Sleep-Eze, Nytol), etc.) (Thaxton & Patel, 2007), but of the over-the-counter treatments, only melatonin has been studied in persons with ABI. Although some clinicians have discussed the possible therapeutic benefits of prescription medications for fatigue dysfunction post TBI, such as dextroamphetamine, levodopa-carbidopa, and amantadine (Rao et al., 2006), the only prescription medications that have been studied in persons with ABI are modafinil, (-)-OSU6162, and methylphenidate, as reviewed here.

Modafinil

Modafinil is a central nervous system (CNS) stimulant and wakefulness promoting agent. Although modafinil was found to enhance quality of life for those with narcolepsy (Beusterien et al., 1999), studies exploring modafinil for fatigue and EDS among persons with Parkinson's disease, multiple sclerosis, TBI, and post-polio syndrome provide inconsistent results (Sheng et al., 2013).

TABLE 8 | Modafinil for the Management of Fatigue Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Kaiser et al. (2010) Switzerland RCT PEDro=9 N=20	**Population:** TBI=20; Gender: Male=17, Female=3. *Treatment Group (n=10):* Mean Age=37yr; Severity: Mean GCS=7. *Control Group (n=10):* Mean Age=43yr; Severity: Mean GCS=8. **Intervention:** Patients received either 100-200mg modafinil or placebo every morning for 6wk. **Outcome Measures:** Excessive Daytime Sleepiness (EDS), Fatigue Severity Scale (FSS), Maintenance of Wakefulness Test (MWT).	1. At 6 weeks, the decrease in FSS scores was greater in the modafinil group compared to the control group (-0.8± 1.0 versus 0.0± 0.6) but this was not significant (p=0.07). 2. The modafinil group had greater decreases in EDS scores versus placebo (p<0.005). 3. On the MWT, a significantly greater improvement was shown for the modafinil group when compared to placebo (8.4± 9.6 versus 0.4± 6.2 min, p=0.04). 4. Of those patients with fatigue at baseline (FSS≥4), decreases in FSS scores were not greater in the treatment group.
Jha et al. (2008) USA RCT PEDro=8 $N_{Initial}$=51, N_{Final}=46	**Population:** TBI=51; Mean Age=38.25yr; Gender: Male=35, Female=16; Mean Time Post Injury=5.77yr. **Intervention:** The treatment group (n=27) received modafinil (100 mg/d for 3d, then 200 mg/d for 11d, then a maintenance dose of 400 mg/d for 8wk). The	1. No significant between-group differences were found at week 4 or week 10 on the FSS (p=0.80 and p=0.61, respectively) or the MFI (p=0.67 and p=0.73, respectively). 2. The change in ESS scores was significantly greater in the modafinil group versus

Author Year Country Study Design Sample Size	Methods	Outcome
	control group (n=24) received a placebo. At the end of phase 1 (8wk) both groups crossed-over. **Outcome Measures:** Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFI), Epworth Sleepiness Scale (ESS).	placebo at 4wk (p=0.02) but not at 10wk (p=0.56). 3. Adverse events for the treatment group included: headaches (29.5%), insomnia (19.6%), fatigue (9.8%), dizziness (7.8%), and tremors (5.9%). Adverse events for placebo: headaches (19.6%) and nasopharyngitis (5.9%).

Discussion

Two RCTs have examined the effects of modafinil, compared to a placebo control, on fatigue and EDS for individuals with TBI (Jha et al., 2008; Kaiser et al., 2010). Neither study found a significant difference in terms of fatigue, as measured by the FSS, between the treatment and control group. Further, when Kaiser et al. (2010) compared those with fatigue at baseline (FSS ≥4) in both groups, the decrease in FSS scores remained non-significant between groups. In one study, the treatment group showed a significantly greater decrease in Epworth Sleepiness Scale scores when compared with controls, captured by a greater improvement in EDS (Jha et al., 2008). It should be noted, however, that Jha et al. (2008) found the improvement to be significant at week four (p=0.02) but not at the end of treatment at week ten (p=0.56), highlighting that the benefit may not be sustained. Of concern, those receiving modafinil reported more insomnia than controls (p=0.03) (Jha et al., 2008). These studies suggest that modafinil may be effective for improving daytime sleepiness, but not fatigue, and may increase the risk of insomnia.

Conclusions

There is level 1a evidence (from two randomized controlled trials; Kaiser et al., 2010, Jha et al., 2008) that modafinil may not be effective for treating fatigue compared to placebo in patients with TBI, but may be effective short-term in treating excessive daytime sleepiness post TBI.

KEY POINTS

- Modafinil has not been shown to be effective in treating fatigue post TBI.
- Modafinil has been shown to be effective in the short-term for treating excessive daytime sleepiness, but may also cause insomnia post TBI.

(-)-OSU6162

(-)-OSU6162 is a monoaminergic stabilizer that has been investigated for the treatment of Huntington's disease, alcohol dependence, and fatigue (Berginstrom et al., 2017; Khemiri et al., 2015; Kloberg et al., 2014; Nilsson et al., 2017). (-)-OSU6162 works on both the dopamine and serotonin systems, but is classified as a dopaminergic stabilizer due to its affinity for D2 and D3 receptors, meaning it can both inhibit and stimulate dopamine behavior (Berginstrom et al., 2017). In this section, we specifically examine the effect of (-)-OSU6162 on fatigue. Of note, this medication is not available in Canada.

TABLE 9 | (-)-OSU6162 for the Management of Fatigue Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Berginstrom et al. (2017) Sweden RCT PEDro=10 N=64	**Population:** TBI; *Treatment Group (n=33)*: Mean Age=41.42yr; Gender: Male=17, Female=16; Mean Time Post Injury=8.58yr. *Control Group (n=31):* Mean Age=42.58yr; Gender: Male=20, Female=11; Mean Time Post Injury=8.10yr. **Intervention:** (-)-OSU6162 was compared with placebo during a 4wk treatment period. 5mg of (-)-OSU6162 was given 2x/d in week 1, 10mg 2x/d in week 2, and 15mg 2x/d in weeks 3 and 4. Patients were evaluated at baseline, at days 7, 14, 22, and 28 during treatment, and for follow-up at 2 and 6mo. **Outcome Measures:** Fatigue Severity Scale (FSS), Mental Fatigue Scale (MFS), Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ).	1. No between group differences were observed. For the FSS, MFS, and RPCSQ, both groups showed significant improvement (all $p<0.01$) after the trial but not at 2- or 6mo follow-up. 2. During follow-up, the treatment group had significantly larger changes in folic acid ($p=0.02$), prolactin ($p=0.03$), and heart rate ($p=0.009$).

Discussion

In an RCT by Berginstrom et al. (2017), (-)-OSU6162 was compared to placebo in patients with TBI (GCS>5). On the Fatigue Severity Scale, Mental Fatigue Scale, and Rivermead Concussion Symptoms Questionnaire, both groups showed significant reductions in fatigue; however, no between-group differences were observed. It is worth noting that participants received a dose of 15mg twice per day, and at the end of the trial the mean plasma concentration was lower than expected (0.14µM), which may indicate poor compliance. However, signficantly larger changes in folic acid, prolactin, and heart rate were recorded for the experimental group, suggesting that these plasma levels may still have been high enough to elicit a physiological effect. Based on this study, (-)-OSU6162 may not be effective in reducing fatigue in patients with TBI.

Conclusions

There is level 1b evidence (from one randomized controlled trial; Berginstrom et al., 2017) that (-)-OSU6162 may not be effective for treating fatigue compared to placebo in patients with TBI.

KEY POINTS

- (-)-OSU6162 treatment may not be effective for reducing fatigue post TBI

Melatonin

Melatonin is an endogenous hormone that plays a role in the regulation of sleep-wake cycles (Driver & Stork, 2018). Individuals with TBI show lower levels of melatonin production in the evening, which may be a contributor to disruptions of the sleep-wake cycle (Shekleton et al., 2010). In an observational overnight study, Grima et al. (2016) compared melatonin production of individuals with TBI to healthy controls. TBI patients showed 42% less melatonin production, and melatonin secretion was delayed by 1.5 hours on average (N. A. Grima et al., 2016). Melatonin has minimal side effects, which may enhance the drug's usefulness in treating sleep disorders (Grima et al., 2018). One article met the inclusion criteria investigating melatonin as an intervention in individuals with severe TBI.

TABLE 10 | Melatonin for the Management of Fatigue Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Grima et al. (2018) Australia RCT Crossover PEDro=9 N=33	**Population:** *Melatonin-placebo group (N=18)*: Mean Age=35yr; Gender: Male=61%, Female=39%; Median Time Post Injury=61mo; Severity: Median GCS= 5. *Placebo-melatonin group (N=15)*: Mean Age=38yr; Gender: Male=73%, Female=27%; Median Time Post Injury= 25mo; Severity: Median GCS=8. **Intervention:** Participants with chronic insomnia were randomly allocated to a 4wk melatonin or placebo treatment before crossover. Melatonin formula was a prolonged release formula (2mg). Participants were measured at baseline and at the end of each treatment phase. **Outcomes:** Pittsburgh Sleep Quality Index (PSQI); Sleep onset latency (measured by wrist actigraphy); Epworth Sleepiness Scale (ESS); Hospital Anxiety Depression Scale (HADS); Fatigue Severity Scale (FSS);	1. ESS scores were not significantly different between treatments (p=0.15). 2. HADS anxiety scores were significantly lower in the melatonin arm compared to the placebo arm (p=0.0006). 3. HADS depression scores were not significantly different between treatments (p=0.68). 4. FSS scores were significantly better in the melatonin arm compared to the placebo arm (p=0.03). 5. VT and MH scores of the SF-36 were significantly higher in the melatonin arm compared to the placebo arm (p=0.03 and p=0.01 for VT and MH, respectively).

Author Year Country Study Design Sample Size	Methods	Outcome
	Short-form health survey (SF-36 v1) subscales: Physical functioning (PF); Role Physical (RP); Role-emotional (RE); Vitality (VT); Mental Health (MH); Social functioning (SF); Bodily Pain (BP); General Health (GH).	6. The other subscales of the SF-36 were not significantly different between treatments ($p>0.05$).

Discussion

Using a crossover RCT design, Grima et al. (2018) evaluated the effect of a 4-week melatonin treatment (2 mg prolonged release) on fatigue and areas of general and mental health in a TBI population. Participants showed significant improvements in sleep quality, sleep efficiency, and fatigue scores after the four weeks of the melatonin treatment phase compared to the placebo phase. Participants did not show a significant difference in daytime sleepiness scores when comparing the treatment phase to placebo. Based on this study, melatonin treatment may improve sleep quality, latency, and reduce fatigue in individuals post TBI, but not significantly affect daytime sleepiness (Grima et al., 2018).

Conclusions

There is level 1b evidence (from one randomized controlled trial; Grima et al., 2018) that melatonin treatment may be effective in reducing fatigue compared to a placebo group in patients post TBI.

KEY POINTS

- Melatonin may reduce fatigue in patients post TBI.

SLEEP DISORDERS

A meta-analysis conducted by Mathias and Alvaro (2012) found that 50% of people with TBI experience disturbed sleep. Common sleep complaints among individuals with moderate to severe brain injury include poor sleep quality, longer sleep-onset latency, increased nocturnal awakening, and insomnia (Duclos et al., 2014; N. Grima et al., 2016). Sleep disorders experienced by patients with brain injury include daytime sleepiness (El-Khatib et al., 2019; Imbach et al., 2016; Imbach et al., 2015; Kempf et al., 2010; Ponsford et al., 2013; Sinclair et al., 2014), insomnia (Cantor et al., 2012; Gardani et al., 2015; Kempf et al., 2010; Ponsford et al., 2013; Verma et al., 2007), sleep disorganization (Nakase-Richardson et al., 2013), sleep apnea or sleep disordered breathing (Viola-Saltzman & Musleh, 2016), sleep wake disturbance or circadian rhythm disorders(Ouellet et al., 2015, 2019; Rao et al., 2015), and hypersomnia (Gardani et al., 2015; Kempf et al., 2010). Sleep disorders tend to be classified as insomnia, sleep disordered breathing, excessive sleep (hypersomnia), or excessive daytime sleepiness (EDS) (Elovic et al., 2005; Ouellet et al., 2015).

Understanding how prevalent sleep disorders are post brain injury is challenging. It has been shown that individuals with ABI self-report significantly less EDS on subjective measures compared to what is observed on objective measures (Imbach et al., 2016; Imbach et al., 2015). One study found that 47% of individuals with TBI reported EDS (Castriotta et al., 2007). Based on subjective measures, approximately 50% of a TBI sample reported symptoms of insomnia; however, more than half of the individuals who reported having sleep difficulties were not being treated for the condition (Ouellet et al., 2006). Ascertaining the true prevalence of sleep dysfunction is further complicated by reports that persons with severe TBI may underreport poor sleep, while those with mild TBI may be more aware of their sleep patterns and thus more likely to report sleep changes that have occurred as a result of their injury (Elovic et al., 2005).

Both subjective and objective measures can be used to screen for and/or diagnose sleep disorders. Commonly used self-reported questionnaires include: the Pittsburgh Sleep Quality Index and Insomnia Severity Index to assess sleep quality (Bastien et al., 2001; Buysse et al., 1989); the Epworth Sleepiness Scale and Stanford Sleepiness Scale to assess daytime sleepiness (Johns, 1991; Shahid et al., 2012); and, the STOP-Bang questionnaire to assess for obstructive sleep apnea (Chung et al., 2016). None of these measures have been validated in persons with ABI, although they may be used in this population for research and clinical purposes. Commonly used objective measures of sleep dysfunction include: sleep diaries (Aaronson et al., 1999), polysomnography (Ouellet et al., 2015; Zasler et al., 2012), actigraphy, multiple sleep latency tests (Zasler et al., 2012) and maintenance of wakefulness tests (Zasler et al., 2012). As with the subjective measures, most of these have not been validated in persons with ABI, aside from actigraphy (Kamper et al., 2016), although these tests are commonly used. These objective and subjective measures may be useful to clinicians as they work to screen, assess, and treat sleep disorders and/or fatigue in persons with ABI.

Factors associated with higher rates of sleep dysfunction vary across studies. Higher Glasgow Coma Scores (GCS >7) at time of injury, better immediate memory, pre-ABI presence of fatigue, a history of substance abuse, older age and female gender have been associated with higher frequency of sleep complaints by some researchers (Thaxton & Patel, 2007). In contrast, others report that increased injury severity is associated with more disturbances in sleep and wake cycles (Duclos et al., 2014), as well as fatigue and sleepiness (El-Khatib et al., 2019).

The presence of sleep disturbance has multiple negative implications for persons with ABI. Sleep disturbances may negatively impact satisfaction with life, and scores on the Functional Independence Measure and Disability Rating Scale (Fogelberg et al., 2012). Affected Individuals tend to have longer lengths of stay in hospital (Duclos et al., 2014; Nakase-Richardson et al., 2013; Sandsmark et al., 2016). Moreover, Nakase-Richardson et al. (2013) discovered that the moderate to severe sleep disorders were correlated with longer durations of post-traumatic amnesia, which has negative prognostic implications. The negative sequelae of sleep dysfunction are further underscored by Sandsmark et al. (2016) who reported that in the acute post ABI setting, sleep was associated with good outcomes, such as increased likelihood to be discharged home, shorter intensive care unit and hospital length of stays, and decreased mortality. Gardani et al. (2015) report that in severe brain injuries, insomnia and poor sleep quality are associated with anxiety during subacute and chronic rehabilitation. Moreover, Cantor et al. (2012) found that at one-year post ABI, insomnia was associated with the presence of anxiety, major depression, and poor sleep quality. At two years post ABI, the presence of anxiety, higher discharge cognitive Functional Independence Measure scores, and poorer sleep quality were predictors of insomnia (Cantor et al., 2012). Fichtenberg et al. (2000) found an association between insomnia and pain and depression. Although determination of causality is not possible for these studies, they highlight that sleep dysfunction can accompany multimorbidity that may interfere with recovery post ABI.

Many persons with moderate or severe TBI require multidisciplinary rehabilitation to address the sequelae of their injury. Brain injury rehabilitation is typically intense and requires the patient to be alert and attentive to achieve the greatest extent of recovery possible. The presence of sleep dysfunction may interfere with effective rehabilitation participation because sleep disorders are often associated with fatigue, difficulty focusing and maintaining attention, anxiety, depression, and other neurological disorders (Cohen, 1993; Gardani et al., 2015; Ziino & Ponsford, 2006). A study by Wiseman-Hakes et al. (2013) found that sleep disturbances associated with TBI exacerbate cognitive, communication, and mood deficits that are brain injury-related. Another study determined that greater total sleep time during inpatient rehabilitation, as measured by observation, is negatively associated with neurobehavioural impairment among individuals with TBI (Maneyapanda et al., 2018). Consequently, appropriately managing sleep disturbances is necessary for optimal recovery.

MANAGEMENT OF SLEEP DISORDERS

The management of sleep disorders varies based on the specific disorder and can be achieved through non-pharmacological and/or pharmacological approaches. To date, few studies have investigated effectiveness of treatment options for sleep disorders in the ABI population. In this following section, we present an overview of the literature examining pharmacological as well as nonpharmacological interventions for managing sleep disorders post ABI.

Non-Pharmacological Interventions

Non-pharmacological strategies for the management of sleep disorders include relaxation strategy training, lifestyle management, cognitive behavioural therapy, acupuncture, and sleep hygiene practices. In this section, we review the literature examining the effectiveness of these intervention strategies in the ABI population.

Relaxation Strategies

TABLE 11 | Relaxation Strategies for the Management of Fatigue and Sleep Disorders Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Chiu et al. (2017) Taiwan RCT Crossover PEDro=8 N=24	**Population:** TBI; Mean age=35.9yr; Gender: Male=9 Female=15; Mean Time Post Injury=27.6mo. **Intervention:** Using a crossover design, TBI patients received a 30 min, 41°C warm footbath each day for 3d then usual care for 3 days (or vice versa), separated by a 3d washout period. **Outcome Measure:** Sleep Efficiency (SE), Sleep Onset Latency (SOL), Total Sleep Time (TST), Wake After Sleep Onset (WASO).	1. Warm footbaths showed non-significant improvement in SE compared to control (p=0.09). 2. SOL was significantly reduced during the warm footbath phase as compared with control (p<0.001). 3. TST was not significantly different during the warm footbath phase compared with control. 4. WASO was significantly reduced during the warm footbath phase as compared with control (p=0.006).

Discussion

Very limited evidence exists examining the use of relaxation strategies for sleep disturbances following an ABI. Using a crossover RCT, Chiu et al. (2017) evaluated the effect of a warm footbath each evening on sleep latency and efficiency in a TBI population. The results were unclear; while participants did not show significant improvements in total sleep time or sleep efficiency, both the number of times participants woke after sleep onset and sleep onset latency were significantly reduced in the warm footbath group compared to control. However, limitations of this study include that the intervention only lasted for 3 nights and the sample size was small (n=24). Future long-term studies with a larger

sample size are needed to determine the impact of relaxation strategies such as a warm footbath on sleep in individuals with ABI.

Conclusions

There is level 1b evidence (from one randomized controlled trial; Chiu et al., 2017) that a warm footbath in the evening may improve wake after sleep onset and sleep onset latency but not sleep efficiency or sleep time compared to usual care in patients with TBI.

KEY POINTS

- A warm footbath in the evening may improve wake after sleep onset and sleep latency in patients with TBI.

Lifestyle Management Strategies

This category of interventions involves making a series of changes to one's lifestyle to take a more holistic approach to rehabilitation, symptom management, or remediation. These changes can be wide-ranging, encompassing anything from diet to self-care to exercise. Lifestyle management strategies can also focus on emotional, physical, and/or mental health in an effort to improve a variety of symptoms. Although this approach intuitively makes sense, there are challenges when attempting to compare studies as the breadth of interventions and heterogeneity of outcomes are greater than in most areas of research.

TABLE 12 | Lifestyle Interventions for the Management of Sleep Disorders Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Stubberud et al. (2017) Norway Pre-Post N=8	**Population:** ABI (Injury Etiology: TBI=3, Cerebrovascular Insults=5); Mean Age=41.6yr; Gender: Male=3, Female=5; Mean Time Post Injury=40.1mo. **Intervention:** Participants underwent 36hr of programming over 1mo. The program included 3 modules covering lifestyle factors and adaptive coping strategies, goal management training (GMT), and emotional regulation. Patients were assessed at baseline, posttest, and 3 and 6mo follow-up. **Outcome Measure:** Fatigue Severity Scale (FSS), Fatigue Questionnaire (FQ), Hospital Anxiety and Depression Scale (HAD), Epworth Sleepiness Scale (ESS), Insomnia Severity Scale (ISI), General Perceived Self-Efficacy Scale (GPSS), Conners Continuous Performance Test II (CPT-II).	1. ESS scores were significantly improved at 3 mo (p=0.042) and 9 mo (p=0.024) follow-up. 2. No significant changes in ISI, were reported.

Discussion

A pre-post study by Stubberud et al. (2017) examined the effects of a group-based intervention program with modules covering lifestyle factors, adaptive coping strategies, and goal management on sleep in patients with ABI. A significant reduction in sleepiness was observed at post-test, 3-month follow-up, and 9-month follow-up. However, the participants demonstrated no significant changes in insomnia severity after the intervention.

KEY POINTS

- Programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce sleepiness, but may not improve insomnia in patients with ABI.

Cognitive Behavioural Therapy

Sleep disorders, such as insomnia, can affect a person's quality of life and family and social commitments, as well as their ability to return to work (Ouellet & Morin, 2004). two studies to date have evaluated the effectiveness of CBT on sleep disorders.

TABLE 13 | Cognitive Behavioural Therapy for the Management of Fatigue and Sleep Disorders Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Nguyen et al. (2017) Australia RCT PEDro=8 N=24	**Population:** TBI; *CBT Group (n=13)*: Mean Age=45.53yr; Gender: Male=9, Female=4; Mean Time Post Injury=795.15d. *Control Group (n=11):* Mean Age=41.90yr; Gender: Male=7, Female=4; Mean Time Post Injury=2093.36d. **Intervention:** Patients in the CBT group received 6 modules of CBT addressing sleep and fatigue over 8 sessions. Therapy content contained a framework that is relevant to TBI and facilitated the acceptance of increased sleep disturbance vulnerability and fatigue secondary to brain trauma. Controls received treatment as usual. Measurements were taken at baseline, 2, and 4mo. **Outcome Measure:** Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Brief Fatigue Inventory (BFI), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS).	1. The CBT group had significantly improved PSQI scores post-treatment and at follow-up compared to control ($p<0.001$). 2. The CBT group had significantly improved ISI scores post-treatment ($p<0.01$) and at follow-up ($p<0.001$) compared to control. There was also a significant improvement in ISI scores over time for the CBT group ($p=0.010$), but not the control group. 3. The FSS and ESS yielded no significant between group differences or time effects for either group.

Author Year Country Study Design Sample Size	Methods	Outcome
Ouellet & Morin (2007) Canada Pre-Post N=11	**Population:** TBI=11; Mean age=27.3yr; Male=6, Female=5; Mean Time Since Injury=25.64mo. **Intervention:** Patients received cognitive behavioural therapy (CBT) for insomnia (8 wk, 1 hr/wk). Specifically, CBT focused on stimulus control, sleep restriction, cognitive restructuring, sleep hygiene education, and fatigue management. **Outcome Measure:** Total Wake Time, Sleep Efficiency, Sleep Time, Insomnia Severity Index (ISI), Multidimensional Fatigue Inventory (MFI), Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS).	1. Following CBT, significant improvements were seen in total wake time ($p<0.001$) and sleep efficiency ($p=0.01$). 2. Gains were maintained, but no significant changes occurred from the post treatment assessment and 3mo follow-up for total wake time ($p=0.06$) or sleep efficiency ($p=0.24$). 3. Sleep time from pre to post treatment did not change significantly ($p=0.44$); however, there was a significant improvement from baseline to the 3mo follow-up ($p<0.015$). 4. Significant reductions in scores were seen after treatment on the DBAS, ISI (both $p<0.01$), and the MFI ($p<0.012$).

Discussion

In a pre-post study, Ouellet and Morin (2007) found that CBT was effective for post TBI insomnia (as measured by the Pittsburgh Sleep Quality Index and Insomnia Severity Index). There was no improvement in sleepiness (as measured by the Epworth Sleepiness Scale). For some, improvements in sleep were noted within the first 2 weeks of treatment; for others, improvement was more progressive. Pre to post treatment, significant improvements were found for total wake time, sleep efficacy, and insomnia, but not for total sleep time (Ouellet & Morin, 2007). No significant gains were made once the treatment had concluded, although gains were maintained at 3-month follow-up. This study suggests that a relatively short duration of CBT can lead to fatigue and sleep improvements sustained for 3 months.

Similarly, Nguyen et al. (2017) reported individuals who received CBT showed significant improvements in sleep quality, insomnia, anxiety, and depression, but not in sleepiness. A secondary analysis of the previous study, and another involving stroke patients, found that participants who were younger, had better verbal memory, and with comorbid symptoms of depression were more likely to respond to CBT treatment (Nguyen et al., 2018).

Conclusions

There is level 1b evidence (from one randomized controlled trial; Ngyuen et al., 2017) and level 4 evidence (from one pre-post test; Ouellet and Morin, 2007) that cognitive behavioural therapy may improve sleep quality and reduce insomnia compared to usual care in patients with TBI.

KEY POINTS

- Cognitive behavioural therapy may improve sleep quality and reduce insomnia in patients with TBI.

Acupuncture

A number of studies have demonstrated the effectiveness of acupuncture in treating insomnia within healthy individuals and various other patient populations; however, many of these studies have methodological limitations (Zhao, 2013), and only one has evaluated acupuncture for insomnia in the ABI population, reviewed here.

TABLE 14 | Acupuncture for the Management of Fatigue and Sleep Disorders Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Zollman et al. (2012) USA RCT PEDro=5 $N_{Initial}$=24, N_{Final}=20	**Population:** TBI=20; Gender: Male=9, Female=11. *Treatment Group (n=12)*: Mean Age=44.5yr; Mean Time Since Injury=2.17 yr. *Control Group (n=8)*: Mean age=43.5yr; Mean Time Since Injury= 3yr. **Intervention:** Patients in the treatment group received acupuncture (20 min sessions) and the control group received only instructions on good sleep habits. Participants wore an actigraph for 72hr before and after treatment. **Outcome Measure:** Insomnia Severity Index (ISI), Hamilton Depression Rating Scale, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Paced Auditory Serial Addition Test (PASAT).	1. ISI scores did not differ significantly between groups at baseline (p=0.47), post treatment (p=0.14), or at 1mo follow-up (p=0.08). 2. The treatment group showed a decrease in ISI scores from baseline to post treatment (p<0.01) and from baseline to 1mo follow-up (p<0.01); no significant differences were found in the control group. 3. Depression was positively associated with ISI scores at baseline (p<0.01), but not post treatment (p=0.45). 4. PASAT scores were positively associated with ISI at baseline (p=0.02) and follow-up (p=0.03). 5. RBANS scores were not associated with sleep variables.

Discussion

Zollman et al. (2012) explored the use of acupuncture, compared to education, in addressing issues of insomnia within a TBI population. A between-group comparison showed no significant difference in the Insomnia Severity Index (ISI) scores at three time points (e.g., baseline, post treatment, and at one-month post treatment). The groups also did not differ significantly in terms of sleep time pre and post treatment. When examining the within-group ISI scores, the treatment group showed a statistically significant decrease in the perception of insomnia severity between pre and post treatment. No such differences were seen in the control group. Those in the treatment group also showed significant improvement on overall cognitive functioning and divided attention. This

treatment modality needs to be studied further within a brain injury population to determine what benefit, if any, it may have.

Conclusions

There is level 2 evidence (from one randomized controlled trial; Zollman et al., 2012) that acupuncture may not improve insomnia compared to instructions on good sleep habits in patients with TBI.

KEY POINTS

- Acupuncture therapy may not improve insomnia in patients with TBI.

Sleep Hygiene

Sleep hygiene involves education about behavioural patterns and environmental factors that can impair sleep. Sleep hygiene strategies often include information about avoiding caffeine, reducing screen time before bed, having a consistent pre-sleep routine, and maintaining a daily sleep-wake schedule. Although sleep hygiene strategies are often used as part of management program for individuals experiencing sleep disturbances, little research exists regarding its efficacy in a population with ABI.

TABLE 15 | Sleep Hygiene Interventions for the Management of Fatigue and Sleep Disorders Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Makley et al., (2020) USA RCT PEDro=4 $N_{Initial}$=22, N_{Final}=18	**Population:** TBI=22; *Intervention Group (Sleep hygiene protocol, SHP; n=9):* Mean Age=26.0±9.7yr; Gender: male=7, female=2; Mean Time Post Injury=28.6±19.5d; severity: Mean GCS=6.9±3.5. *Control Group (Standard of care, SOC; n=9):* Mean Age=33.6±9.0yr; Gender: Male=7, Female=2; Mean Time Post Injury=25.9±13.8d; Severity: Mean GCS=8.6±4.1. **Intervention:** Participants were randomly allocated to receive a sleep hygiene protocol (SHP) or usual care (standard TBI rehabilitation). The sleep hygiene protocol involved 6 components: 1. Improved sleep environment 2. Increased daytime activation 3. Enhanced circadian stimuli 4. Consistent morning wake time and daily routine	1. No significant differences in actigraphy sleep metrics were observed between groups (TST, p>.05; SE, p>.05; WASO, p>.05) 2. Significant improvements in actigraphy sleep metrics from 1 wk to 3 wk were observed within the SHP group (TST, p=.028; SE, p=.008; WASO, p=.008); but not within the SOC group (TST, SE, WASO, p>.05). No significant differences in rehabilitation outcomes between groups (DRS, p>.05; LOS, p>.05).

Author Year Country Study Design Sample Size	Methods	Outcome
	5. 30 minutes of blue-light therapy 6. No caffeine intake after 12:00pm Outcome measures were assessed at baseline, 1wk, 2wk and 3wk. **Outcome Measures:** Total Sleep Time (TST), Sleep Efficiency (SE), Wakefulness After Sleep Onset (WASO), Disability Rating Scale (DRS), Length of Stay (LOS).	

Discussion

Makley et al. (2020) conducted a randomized controlled trial investigating the effects of a sleep hygiene protocol on sleep disturbances in a population of individuals with TBI. When compared to a control group that received standard rehabilitation, the sleep hygiene protocol did not significantly improve any outcome measures. Results trended towards significance, although lacked statistical power due to a small sample size (n=18). Sleep hygiene interventions may be a promising first line therapy, as they are a non-invasive, low-risk and low-cost option to address sleep disturbances following brain injury. Further research is warranted given that sleep hygiene interventions are effective in several other populations (Cohen, 2013; Engle-Friedman et al., 1992; Reid et al., 2010; Weiss et al., 2006).

Conclusions

There is level 2 evidence (from one randomized controlled, unblinded trial; Markley et al., 2020) that a sleep hygiene intervention is feasible in a population with moderate to severe TBI; however, more research is needed to determine its efficacy.

KEY POINTS

- More research is necessary to determine the efficacy of sleep hygiene interventions for patients with ABI.

Pharmacological Interventions

Only a few pharmacologic interventions have been developed or tested for sleep disorders post ABI. Suggested treatments have included the administration of various over-the-counter medications (e.g., melatonin, diphenhydramine (e.g., Sleep-Eze, Nytol), etc.) (Thaxton & Patel, 2007), but of the over-the-counter treatments, only melatonin has been studied in persons with ABI. Although some clinicians have discussed the possible therapeutic benefits of prescription medications for sleep and fatigue dysfunction

post TBI, such as dextroamphetamine, levodopa-carbidopa, and amantadine (Rao et al., 2006), the only prescription medications that have been studied in persons with ABI are modafinil, lorazepam, zopiclone, and methylphenidate, as reviewed here.

Modafinil

Modafinil has been approved to address EDS associated with narcolepsy, sleep disordered breathing, shift-work sleep disorder, some circadian rhythm disorders, multiple sclerosis, and other conditions not including ABI (Jha et al., 2008; US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000). Two studies have assessed the effectiveness of modafinil on EDS for individuals with TBI (Table 16).

TABLE 16 | Modafinil for the Management of Sleep Disorders Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Kaiser et al. (2010) Switzerland RCT PEDro=9 N=20	**Population:** TBI=20; Gender: Male=17, Female=3. *Treatment Group (n=10):* Mean Age=37yr; Severity: Mean GCS=7. *Control Group (n=10):* Mean Age=43yr; Severity: Mean GCS=8. **Intervention:** Patients received either 100-200mg modafinil or placebo every morning for 6wk. **Outcome Measure:** Excessive Daytime Sleepiness (EDS), Fatigue Severity Scale (FSS), Maintenance of Wakefulness Test (MWT).	1. The modafinil group had greater decreases in EDS scores versus placebo ($p<0.005$). 2. On the MWT, a significantly greater improvement was shown for the modafinil group when compared to placebo (8.4± 9.6 versus 0.4± 6.2 min, $p=0.04$).
Jha et al. (2008) USA RCT PEDro=8 $N_{Initial}=51$, $N_{Final}=46$	**Population:** TBI=51; Mean Age=38.25yr; Gender: Male=35, Female=16; Mean Time Post Injury=5.77yr. **Intervention:** The treatment group (n=27) received modafinil (100 mg/d for 3d, then 200 mg/d for 11d, then a maintenance dose of 400 mg/d for 8wk). The control group (n=24) received a placebo. At the end of phase 1 (8wk) both groups crossed-over. **Outcome Measure:** Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFI), Epworth Sleepiness Scale (ESS).	1. The change in ESS scores was significantly greater in the modafinil group versus placebo at 4wk ($p=0.02$) but not at 10wk ($p=0.56$). 2. Adverse events for the treatment group included: headaches (29.5%), insomnia (19.6%), fatigue (9.8%), dizziness (7.8%), and tremors (5.9%). Adverse events for placebo: headaches (19.6%) and nasoppharyngitis (5.9%).

Discussion

A RCT examined the effects of modafinil, compared to a placebo control, on EDS for individuals with TBI (Kaiser et al., 2010). It was found that participants who received 100-200mg for six weeks had significantly greater decreases in ESD scores than did the control group participants (Kaiser et al., 2010). Likewise, in another RCT, treatment group participants who received modafinil (100 mg/d for 3d, then 200 mg/d for 11d, then a maintenance dose of 400 mg/d for 8wk) showed a significantly greater decrease

in Epworth Sleepiness Scale scores when compared with controls, captured by a greater improvement in EDS (Jha et al., 2008). It should be noted, however, that Jha et al. (2008) found the improvement to be significant at week four (p=0.02) but not at the end of treatment at week ten (p=0.56), highlighting that the benefit may not be sustained. Of concern, those receiving modafinil reported more insomnia than controls (p=0.03) (Jha et al., 2008). These studies suggest that modafinil may be effective for improving daytime sleepiness but may increase the risk of insomnia in patients with TBI.

Conclusions

There is level 1a evidence (from two randomized controlled trials; Kaiser et al., 2010, Jha et al., 2008) that modafinil may be effective short-term in treating excessive daytime sleepiness but may also cause insomnia in patients post TBI.

KEY POINTS

- Modafinil has been shown to be effective in the short-term for treating excessive daytime sleepiness, but may also cause insomnia post TBI.

Methylphenidate

Methylphenidate is a CNS stimulant commonly used to treat narcolepsy and attention deficit hyperactivity disorder (Weber & Lutschg, 2002). Methylphenidate increases dopamine and norepinephrine within the brain. Conflicting evidence exists on the effectiveness of methylphenidate for improving attention and other cognitive functions in patients with TBI (Sivan et al., 2010). A study by Lee et al. (2005) reported that methylphenidate may be effective in reducing excessive daytime sleepiness in patients with mild to moderate TBI; however, this has not been investigated in moderate to severe TBI. We identified one study that examines the effect of methylphenidate on sleep-wake cycles in TBI.

TABLE 17 | Methylphenidate the Management of Sleep Disorders Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Al-Adawi et al. (2006) Oman Case Control N=30	**Population:** TBI=30; Mean Age=51yr; Gender: Male=23, Female=7. **Intervention:** Records of patients admitted to a dedicated brain injury unit in 1999 were retrospectively reviewed. Patients receiving methylphenidate (5-10mg at 8am and 2pm) made up the treatment group (n=17). The control group (n=13) were patients that received no medication.	1. Mean total FIM score at baseline was lower for those in the methylphenidate group than for controls (30.0 versus 34.9, p=0.4). RLA scores were comparable between groups at baseline (p=0.479). 2. The mean hours of sleep during a 24hr period did not significantly differ between

Author Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measure: Sleep State, Functional Independence Measure (FIM), Rancho Los Amigo: Levels of Cognitive Functioning (RLA).	the treatment and control groups (8.3 versus 9.0hr, p=0.096). 3. Mean hours of sleep at night for the treatment and control groups were 6.4 and 6.9hr, respectively.

Discussion

In a study by Al-Adawi et al. (2006) in which patients were selected to receive methylphenidate on clinical grounds, sleep times between the two groups were not significantly different. Based on this study, methylphenidate does not seem to have adverse effects on sleep-wake quantity post ABI. Of note, the patients selected to receive methylphenidate tended to have lower FIM scores, but no significant differences in other areas such as Ranchos Los Amigos Scale scores. This study did not assess whether methylphenidate improved EDS, fatigue, or rehabilitation participation.

Conclusions

There is level 3 evidence (from one case-control; Al-Adawi et al., 2006) that methylphenidate may not have adverse effects on the sleep-wake cycle compared to those not receiving medication post TBI.

KEY POINTS

- Methylphenidate may not have an adverse effect on the sleep-wake cycle of patients post TBI.

Lorazepam & Zopiclone

Lorazepam, a benzodiazepine also known as Ativan or Temesta, is primarily an anti-anxiety medication that, due to its sedating side effect, has been used for the treatment of sleep disorders (Thaxton & Patel, 2007). Zopiclone is a non-benzodiazepine sedative hypnotic that works at the same receptor sites as benzodiazepines. Zopiclone has been used in the treatment of insomnia for individuals experiencing problems with delayed sleep onset, difficulties maintaining sleep, and/or early waking (Hair et al., 2008; Thaxton & Patel, 2007). In a RCT-crossover trial conducted by Li Pi Shan and Ashworth (2004), the two medications were studied in a mixed stroke and TBI population. Participants received either lorazepam (0 to 1 mg) or zopiclone (3.75 to 7.5 mg), which were taken orally in the evening on an as-needed basis. At the end of study, the two groups did not differ significantly in terms of average sleep time, quality of sleep, depth of sleep, feelings of being refreshed, or feelings of alertness or tiredness during the day.

The authors reported that zopiclone was as effective as lorazepam in treating insomnia (Li Pi Shan & Ashworth, 2004). Due to less than 50% of the study population sustaining a brain injury, no level of evidence will be drawn from this study. Additional studies focusing on a brain injury population are needed before determining the effectiveness and safety of lorazepam and zopiclone for insomnia post TBI.

KEY POINTS

- More research is necessary to determine the efficacy of benzodiazepines and non-benzodiazepine sedative hypnotics for patients with ABI.

Melatonin

Melatonin is an endogenous hormone that plays a role in the regulation of sleep-wake cycles (Driver & Stork, 2018). Individuals with TBI show lower levels of melatonin production in the evening, which may be a contributor to disruptions of the sleep-wake cycle (Shekleton et al., 2010). In an observational overnight study, Grima et al. (2016) compared melatonin production of individuals with TBI to healthy controls. TBI patients showed 42% less melatonin production, and melatonin secretion was delayed by 1.5 hours on average (N. A. Grima et al., 2016). Melatonin has minimal side effects, which may enhance the drug's usefulness in treating sleep disorders (Grima et al., 2018). One article met the inclusion criteria investigating a melatonin intervention in individuals with severe TBI.

TABLE 18 | Melatonin for the Management of Sleep Disorders Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Grima et al. (2018) Australia RCT Crossover PEDro=9 N=33	**Population:** *Melatonin-placebo group (N=18)*: Mean Age=35yr; Gender: Male=61%, Female=39%; Median Time Post Injury=61mo; Severity: Median GCS= 5. *Placebo-melatonin group (N=15)*: Mean Age=38yr; Gender: Male=73%, Female=27%; Median Time Post Injury= 25mo; Severity: Median GCS=8. **Intervention:** Participants with chronic insomnia were randomly allocated to a 4wk melatonin or placebo treatment before crossover. Melatonin formula was a prolonged release formula (2mg). Participants were measured at baseline and at the end of each treatment phase. **Outcomes:** Pittsburgh Sleep Quality Index (PSQI); Sleep onset latency (measured by wrist actigraphy); Epworth Sleepiness Scale (ESS); Hospital Anxiety Depression Scale (HADS); Fatigue Severity Scale (FSS); Short-form health survey (SF-36 v1) subscales: Physical	1. PSQI scores were significantly better in the melatonin arm compared to the placebo arm ($p<0.0001$). 2. Sleep latency scores were not significantly different between treatments ($p=0.23$). 3. Sleep efficiency scores were significantly higher in the melatonin arm compared to the placebo arm ($p=0.04$). 4. ESS scores were not significantly different between treatments ($p=0.15$).

Author Year Country Study Design Sample Size	Methods	Outcome
	Functioning (PF); Role Physical (RP); Role-emotional (RE); Vitality (VT); Mental Health (MH); Social Functioning (SF); Bodily Pain (BP); General Health (GH).	

Discussion

Grima et al. (2018) examined the effectiveness of a 4-week melatonin treatment (2mg prolonged release) on sleep quality, as well as sleep latency and efficiency in patients with TBI. Significant improvements in sleep quality and sleep efficiency were observed in participants after the intervention phase compared to the placebo phase. No significant difference in sleep onset latency or daytime sleepiness scores between the treatment phase to the placebo phase was observed. Findings of this study suggest that melatonin treatment may be effective in improving sleep quality and latency, in individuals post TBI, but may not significantly affect sleep onset or daytime sleepiness (Grima et al., 2018).

Conclusions

There is level 1b evidence (from one randomized controlled trial; Grima et al., 2018) that melatonin treatment may be effective in improving sleep quality and sleep efficiency compared to a placebo group in patients post TBI.

There is level 1b evidence (from one randomized controlled trial; Grima et al., 2018) that melatonin treatment may not affect sleep onset latency or daytime sleepiness in patients post TBI.

KEY POINTS

- Melatonin may improve sleep quality and sleep efficiency in patients post TBI.
- Melatonin may not improve sleep onset latency or daytime sleepiness.

CONCLUSION

Current research has focused on exploring and identifying sleep and fatigue related issues post ABI but minimal research has focused on treatment interventions. Consequently, the results of this review provide limited guidance to clinicians in the management of fatigue and sleep disorders post ABI. Lifestyle interventions, including sleep hygiene, energy conservation, and pacing, which are commonly

encouraged by health professionals have little published research evidence supporting their use. Pharmacological interventions for management of fatigue are also understudied. Clinicians must rely on their individual clinical experiences and expertise when addressing such issues. Adapting research evidence from other patient populations may be useful given the paucity of research in persons with ABI. Future research should focus on the management of fatigue and sleep disorder symptoms post ABI given the importance of these areas to the recovery, rehabilitation participation, community reintegration, and quality of life post ABI.

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