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 Ministry of Health, 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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Dr. Shawn Marshall is a physician specializing in Physical Medicine and Rehabilitation (Physiatrist). He is the Division Head of Physical Medicine and Rehabilitation at the University of Ottawa and The Ottawa Hospital where he manages both in-patients and out-patient clinics for patients with concussion to severe traumatic brain injury. Dr. Marshall has a Master's degree in Clinical Epidemiology and is a Full Professor at the University of Ottawa in the Department of Medicine.

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 alterations in the level of consciousness experienced by the patient following injury (Table 2). Alterations in level of consciousness following ABI can range from transient disorientation to coma. Various measures of altered consciousness at the time of initial assessment are used in practice to determine injury severity. Of these, the most widely used is the Glasgow Coma Scale, which assess level of consciousness using a composite of eye opening, verbal, and

motor responses; its ease and widespread use makes it the most common outcome to understand the severity of a brain injury (Teasdale et al., 2014). Together with the Glasgow Coma Scale (GCS), the duration of loss of consciousness (LOC) and the duration of post-traumatic amnesia (PTA) are frequently used to define the severity of injury (Table 2). Another factor used to distinguish moderate and severe brain injury from concussion or mild brain injury is evidence of intracranial injury on conventional brain imaging techniques.

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–July 2021 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, additional databases and the gray literature 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.

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, Herbert, Sherrington, & Maher, 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.

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. 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 best evidence. Ultimately, healthcare professionals 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

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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 individuals with TBI *There is level 2 evidence that a home-based walking program may reduce fatigue for up to 24 weeks following treatment compared to a nutritional counselling program in individuals with TBI.* *There is level 2 evidence that yoga-based physical therapy is feasible and safe in a mixed population with TBI; however, it may not reduce fatigue and is not more effective than conventional physical therapy or seated rest for reducing fatigue*
Cognitive Behavioural Therapy	Cognitive behavioural therapy may reduce fatigue in individuals with TBI. *There is level 1b evidence that cognitive behavioural therapy may be effective in reducing fatigue in individuals with TBI.*
Light Therapy	Blue light therapy may reduce fatigue and daytime sleepiness in individuals with TBI. Yellow light therapy and bright white light therapy may not be effective in reducing fatigue and sleep, respectively post TBI. *There is level 1a that blue light therapy may be effective in reducing fatigue and daytime sleepiness compared to no treatment in individuals with TBI.* *There is level 1b evidence that yellow light therapy may not be effective in reducing fatigue and daytime sleepiness compared to control.* *There is level 1b evidence that bright white therapy during acute rehabilitation may not impact sleep.* *There is level 1b evidence that an in-home dynamic light intervention may not improve fatigue; however, participants' subjective reports on sleep quality and insomnia symptoms were positive.*
Lifestyle Management Strategies	Programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce fatigue and sleepiness in individuals with ABI.

	Group therapy sessions focused on fatigue may not be effective; feedback was that individuals wanted an opportunity to address personal queries on a one-to-one basis. *There is level 4 evidence 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 individuals with ABI.* *There is level 1b evidence that discussion-based, group therapy sessions may not improve fatigue, when compared to usual care, in individuals with ABI.*
Pacing	More research is necessary to determine the efficacy of pacing interventions for individuals with ABI. *No studies to date have examined the benefits of pacing within a population with ABI.*
Pharmacological Interventions	
Melatonin	Melatonin may reduce fatigue in individuals with TBI. *There is level 1b evidence that melatonin treatment may be effective in reducing fatigue compared to a placebo group in individuals post TBI.*
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 that modafinil may not be effective for treating fatigue compared to placebo in individuals 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 that (-)-OSU6162 may not be effective for treating fatigue compared to placebo in individuals with 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 individuals with TBI.

	There is level 1b evidence 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 individuals with TBI.
Cognitive Behavioural Therapy	Cognitive behavioural therapy may improve sleep quality and reduce insomnia in individuals with TBI. *There is level 1b evidence that cognitive behavioural therapy may improve sleep quality and reduce insomnia compared to usual care in individuals with TBI.*
Acupuncture	Acupuncture therapy may not improve insomnia in individuals with TBI. *There is level 2 evidence that acupuncture may not improve insomnia compared to instructions on good sleep habits in individuals with TBI.*
Sleep Hygiene	More research is necessary to determine the efficacy of sleep hygiene interventions for individuals with ABI. *There is level 2 evidence that a sleep hygiene intervention is feasible in a population with moderate to severe TBI; however, it did not improve total sleep time, sleep efficiency, or wakefulness after sleep more than standard care.*
Lifestyle Management	Programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce sleepiness, but may not improve insomnia in individuals with ABI. *There is level 4 evidence that programming focusing on lifestyle factors, adaptive coping, and goal management training may not reduce insomnia severity but may reduce daytime sleepiness up to 9 months post intervention in individuals with ABI.*
Pharmacological Interventions	
Melatonin	Melatonin may improve sleep quality and sleep efficiency in individuals post TBI; however, it may not improve sleep onset latency or daytime sleepiness. *There is level 1b evidence that melatonin treatment may be effective in improving sleep quality and sleep efficiency compared to a placebo group in individuals post TBI; however, it may not be effective in improving sleep onset latency or daytime sleepiness.*

Modafinil	Modafinil has been shown to be effective in the short-term for treating excessive daytime sleepiness but may also cause insomnia in individuals with TBI. *There is level 1a evidence that modafinil may be effective short-term in treating excessive daytime sleepiness but may also cause insomnia post TBI.*
Methylphenidate	Methylphenidate may not have an adverse effect on the sleep-wake cycle post TBI. *There is level 3 evidence that methylphenidate may not have adverse effects on the sleep-wake cycle in individuals with TBI, when compared to those not receiving medication.*
Lorazepam & Zopiclone	More research is necessary to determine the safety and efficacy of benzodiazepines and non-benzodiazepine hypnotics for individuals with ABI. *No studies to date have examined the effects of benzodiazepines and non-benzodiazepine sleep aids in individuals with ABI.*

Introduction

Fatigue and disordered sleep are some of the most commonly reported symptoms associated with brain injury (Cronin & O'Loughlin, 2018; Duclos et al., 2014; Elovic, Dobrovic, & Fellus, 2005). When present, fatigue and disordered sleep can exacerbate other co-morbid symptoms and negatively affect quality of life. Therefore, it is important for clinicians to develop an approach to the assessment and management of fatigue and sleep disorders to optimize recovery post ABI. Although it seems intuitive to link disorders of sleep with fatigue (Clinchot et al., 1998), this relationship is complex (Fellus & Elovic, 2007). While disordered sleep can exacerbate fatigue, fatigue may also present independent of sleep disorders and not all sleep disorders produce fatigue (M.-C. Ouellet, Beaulieu-Bonneau, & Morin, 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, Bushnik, Oggins, & Katznelson, 2010; M.C. Ouellet, Beaulieu-Bonneau, & Morin, 2019; J. L. 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, Colantonio, Mollayeva, & Shapiro, 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 (M.C. Ouellet et al., 2019; Rao, Neubauer, & Vaishnavi, 2015; Silver, McAllister, & Arciniegas, 2019).

There are many 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 (M.-C. 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 individuals with ABI. When individuals are recovering from an ABI, fatigue and disordered sleep may interfere with their ability to participate in rehabilitation programs and reach optimal recovery.

Fatigue

Fatigue is a subjective experience that is not easily defined, 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, Rollings, & Spiro, 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 fatigue often 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 (K. A. Lee, Hicks, & Nino-Murcia, 1991).

Although fatigue has been recognized as a significant problem post ABI, characterizing the prevalence and severity is challenging. Between 32% and 73% of individuals report experiencing fatigue post TBI, higher than in the general population (Silver et al., 2019). The presence and severity of fatigue may fluctuate and evolve over the course of a person's recovery. For instance, 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. Other studies have shown that fatigue can persist for years post injury (Bay & de-Leon, 2011; Olver, Ponsford, & Curran, 1996; M. C. Ouellet & Morin, 2004; Rao et al., 2006). Compared to healthy controls, individuals who have had a brain injury report greater severity of fatigue (Ashman et al., 2008; Borgaro, Baker, Wethe, Prigatano, & Kwasnica, 2005; Chiou, Chiaravalloti, Wylie, DeLuca, & Genova, 2016; LaChapelle & Finlayson, 1998; J. L. Ponsford et al., 2012; Ziino & Ponsford, 2006). The multidimensional nature of fatigue makes it difficult to measure in a quantitative way. To better understand the severity of the problem, data is often collected through surveys, interviews, and/or questionnaires. Comparison groups in many of studies are individuals without an ABI. Measurement tools frequently used to assess subjective fatigue severity 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 and, aside from the Fatigue Severity Scale, most have not been validated in ABI (Dittner, Wessely, & Brown, 2004; Ziino & Ponsford, 2005).

Fatigue can arise as a result of the primary brain injury, from secondary neuropathological cascades, or can stem from the patient's hospital or home environment, mood dysfunction, pain, medications, and other intrinsic and extrinsic factors (M.-C. Ouellet et al., 2015; Schönberger et al., 2017). Risk factors for fatigue post ABI include pre-injury factors, injury factors, acute and post-acute factors. Pre-injury risk factors include older age, genetics, female sex, and personal history of pre-injury sleep dysfunction (Lichstein, Means, Noe, & Aguillard, 1997; Wang, Yin, Miller, & Xiao, 2017; Westerlund et al., 2010).

Features of the brain injury which increase risk of post ABI fatigue include damage to sleep-wake structures within the brain, acceleration, deceleration and rotational forces, secondary injury, and the psychological trauma of injury (Kumar, Gao, Juengst, Wagner, & Fabio, 2018; M.-C. Ouellet et al., 2015; Schönberger et al., 2017). In the acute phase, the hospital environment, presence of pain, and medications contribute to the risk of post ABI fatigue (Duclos et al., 2014; Mollayeva et al., 2014; M.-C. Ouellet et al., 2015). In the post-acute phase, altered neurologic function, environmental stressors, sleep behaviours, pain, medications, and substance use also contribute to post ABI fatigue (Mollayeva et al., 2014; M.C. Ouellet et al., 2019).

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). Ponsford et al. (J. Ponsford, Schonberger, & Rajaratnam, 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. While there is a strong association between fatigue, anxiety, and depression following ABI, most studies do not provide a method to determine which of these symptoms is the most significant contributor to a patient's presentation (Bruijel et al., 2020).

As part of the wide-ranging impact of fatigue, it can have a significant negative effect on an individual's ability to reintegrate in their community post ABI. 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, Skoglund, & Sunnerhagen, 2013). Fatigue can also negatively impact relationships, as there is a tendency to react 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 non-pharmacological and/or 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 unknown, and patients may require a combination 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
Krese et al. (2020) USA RCT Crossover PEDro=4 $N_{initial}$=13 N_{final}=11	**Population:** TBI=13; Mean Age= 45.31±14.23yr; Gender: Male=8 (62%), Female=5; Median Time Post Injury=15d; Severity: Mean GCS=10.43±3.91. **Intervention:** Each individual participated in yoga-based physical therapy (YPT), conventional physical therapy (CPT), and seated rest (SR) on different days in a crossover design. Each condition lasted one hour for a total of three hours. 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. No significant differences were observed for fatigue (GFI, p>.05). 2. Actigraphy sleep metrics (incidence rate ratio of WASO) for SR were significantly improved compared with CPT (p=.0218) and YPT (p=.0089), but not significantly different between CPT and YPT (p>.05). 3. Changes in WASO from pre- to post treatment differed between treatments, as the overall interaction effect was significant (p=0.0203). 4. Individuals with TBI showed reduced WASO after 1 hour of seated rest in a relaxing environment. 5. No significant differences were found between treatment groups for anxiety (STAI, p>.05) or HRV (SDNN, p>.05).
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 (56%), 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 coaching calls on a tapering schedule. Participants were encouraged to increase their	1. Participants had significantly less fatigue (GFI) at the end of the walking intervention (p<0.001). 2. According to the BNI Overall Score, 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

	steps by 5% each week until an overall step increase of 40% above baseline was achieved. A 12wk nutritional counselling program with 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).	walking intervention ($p<0.001$) and after 36wk ($p<0.001$). 4. The nutrition intervention did not have a significant effect on BNI Overall Scores at 12 or 24 weeks, but BNI Overall Scores were reduced at 36 weeks. 5. 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, compared to immediately after the walking intervention, MFI scores significantly increased by 36 weeks ($p<0.05$).

Discussion

The impact of exercise on fatigue was evaluated in two crossover RCTs. The first, by Kolakowsky-Hayner et al. (2017), assessed the impact of a 12-week walking program on fatigue, which was measured with three different fatigue outcome measures, the Global Fatigue Index (GFI), Barrow Neurological Institute Fatigue Scale Overall Severity Score, and the Multidimensional Fatigue Inventory. The study found the walking intervention reduced fatigue significantly. The positive improvements in fatigue lasted 12 to 24 weeks after the intervention was completed, but appeared to taper off by 36 weeks, suggesting the benefit of a short-duration walking program may not be sustained long-term. It appears a progressive walking program is an effective and low-cost intervention for fatigue. The second, by Krese et al. (2020), examined the impact of a yoga-based intervention compared to conventional physical therapy and seated rest on fatigue. Numerous outcome measures were assessed before and immediately after the activities; fatigue was assessed using the GFI. While the yoga-based intervention was feasible, it did not improve fatigue. Moreover, the yoga-based intervention was not found to be superior to the other treatments and none of the three interventions significantly impacted fatigue (Krese et al. 2020). Seated rest in a relaxing environment was beneficial for some measures of sleep, including instances of wake after sleep onset. The authors concluded that dedicated seated rest may be a beneficial addition to rehabilitation.

Conclusions

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

There is level 2 evidence that yoga-based physical therapy is feasible and safe in a mixed population with TBI; however, it may not reduce fatigue and is not more effective than conventional physical therapy or seated rest for reducing fatigue (Krese et al., 2020).

KEY POINTS

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

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 (Joshua B. Cantor et al., 2014); however, limited research exists regarding the effect on fatigue after ABI (M. C. Ouellet & Morin, 2004).

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=45.5yr; Gender: Male=9 (69%), Female=4; Mean Time Post Injury=795d. *Control Group (n=11):* Mean Age=41.9yr; Gender: Male=7 (64%), Female=4; Mean Time Post Injury=2093d. **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 fatigue as measured by 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 (47%), Female=9; Mean Time Post Injury=9.9 mo. *Control Group (n=21):* Mean Age=48.1yr; Gender: Male=13 (62%), Female=8; Mean Time Post Injury=11.1 mo. Dropouts=3. **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; however, this was a pilot feasibility study not powered for this purpose.

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 (55%), Female=5; Mean Time Since Injury=25.6mo. **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 Measures:** Total Wake Time, Sleep Efficiency, Sleep Time, Insomnia Severity Index (ISI), Multidimensional Fatigue Inventory (MFI), Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS).	1. The CBT group had significant reductions in fatigue as measured by MFI scores after treatment ($p<0.012$).

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 BFI). 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. 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.

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 intervention to teach individuals with TBI to manage their fatigue.

Conclusions

There is level 1b evidence that cognitive behavioural therapy may be effective in reducing fatigue in individuals with TBI (Nguyen et al., 2017; M. C. Ouellet & Morin, 2007).

KEY POINTS

- Cognitive behavioural therapy may reduce fatigue in individuals 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, Vanuk, Smith, Dailey, & Killgore, 2017). However, light therapy has not been well studied in a population with moderate to severe ABI.

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

Author Year Country Study Design Sample Size	Methods	Outcome
Bell et al. (2021) USA RCT PEDro=9 N=131	**Population:** Moderate-Severe TBI=131*; Bright White Light Therapy (BWL) group (n=65):* Mean Age=39.7yr; Gender: Male=45 (69%), Female=20; Mean Time Post Injury=33.2days. Sham Red *Light Therapy group (n=66):* Mean Age=42.1yr; Gender: Male=44 (67%), Female=20; Mean Time Post Injury=33.2days. **Intervention:** Participants were randomized into two groups: BWL (active treatment) or Red Light (control) for 30 minutes each morning between 7:30 and 9:30am for up to 10 days. Both interventions were delivered using a Litebook, which was placed 12-24 inches from the face within 45° of the visual field. BWL used peak wavelengths between 440 and 480 nm, while the red light (sham) emitted no light between 440 and 480 nm. **Outcome Measure:** Positive and Negative Affect Scale (PANAS), Karolinska Sleepiness Scale (KSS), Barrow Neurological Institute Fatigue Scale (BNI-FS), Symbol Digit Modalities Test (SDMT), Participation.	1. No significant differences were reported between groups for PANAS, KSS, BNI-FS, therapy participation, and SDMT, post-treatment (p=0.722, p=0.351, p=0.807, p=0.345, p=0.252, respectively). 2. BWL treatment did not appear to impact sleep or outcome measures commonly associated with sleep. 3. Cooperation with therapy was high at the start of the intervention at 86.5%. 4. Pre-treatment scores indicated that participants self-reported feeling "rather alert" on the KSS despite meeting study inclusion criteria.
Connolly et al. (2021) Australia RCT Crossover PEDro=8 $N_{initial}$=28 N_{final}=24	**Population:** Mild-Severe TBI=19, Stroke=5. *Dynamic Light Intervention-Placebo (n=16):* Mean Age=49.1yr; Gender: Male=9, Female=7; Mean Time Post Injury >3mo. *Placebo-Dynamic Light Intervention (n=8):* Mean Age=46.7yr; Gender: Male=5, Female=3; Mean Time Post Injury >3mo. **Intervention:** Participants were randomized into either Dynamic Light Intervention (treatment) followed by Usual Lighting (placebo) or vice versa. The active lighting intervention consisted of short wavelength enriched high-intensity white light with correlated colour temperature varying >5000 K depending on the time of day. In the placebo condition, lamps were changed as per treatment condition but did not change in colour temperature or intensity from participants' normal lighting (typically ~3000-4000 K). Participants completed each condition for 2 months in counter-	1. No statistically significant changes were reported in the treatment condition relative to placebo for BFI (p=0.33), FSS (p=0.20), and ESS (p=0.41). 2. Treatment was associated with a significant improvement in measures of subjective sleep; with significant reductions in sleep disturbance (PSQI) by 1.50 points, and insomnia symptoms (ISI) by 2.13 points, relative to baseline. 3. There was a statistically significant increase in daily reported productive activity (p=0.005), increasing by an average of 5.40% from baseline to post-treatment. 4. There were no significant differences in subjectively rated levels of POPS or HADS. 5. On average, treatment lighting had significantly greater melanopic illuminance

Author Year Country Study Design Sample Size	Methods	Outcome
	balanced order, without a washout period and with a 1-month follow-up. **Outcome Measure:** Brief Fatigue Inventory (BFI), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Psychomotor Vigilance Task (PVT), Hospital Anxiety and Depression Scale (HADS), Participation Objective Participation Subjective (POPS).	during daytime, and significantly less melanopic illuminance during evenings, compared to control lighting (p=0.009). 6. Treatment sequence was insignificant across all outcome measures.
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=34.2±10.7yr; Gender: Male=7, Female=3; Mean Time Post Injury=7.9±9.9yr; Initial GCS=5.88. *Control Group (No light therapy, N-BWL; n=10):* Mean Age=39±9.8yr; Gender: Male=4, Female=6; Mean Time Post Injury=10±10.7yr; Initial GCS=6.00. **Intervention:** Participants were randomly allocated to receive light therapy (BWL) 30min upon waking everyday 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 (HDS-17, 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 (80%), Female=6; Mean Time Post Injury=1106d; Severity: Mild=7, Moderate=8 (27%), Severe=15 (50%). **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

Two randomized controlled trials have evaluated blue light therapy and two have evaluated white light therapy. 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 (2 weeks after light therapy discontinuation). Consistent with the study by Sinclair et al. (2014), Quera Salva et al. (2020) found that blue-enriched white light therapy significantly improved measures of fatigue severity when compared to a control group that did not receive light therapy; similarly, improvements in fatigue were not maintained over time once the light therapy was discontinued. Quera Salva et al. (2020) also observed improvements measures of depression during blue light treatment that were maintained two weeks after discontinuation of treatment. This finding is consistent with the literature on the use of light therapy to treat depression, particularly seasonal affective disorder (Mårtensson, Pettersson, Berglund, & Ekselius, 2015). No improvements were reported for daytime sleepiness, sleep quality, or quality of life. The yellow light therapy did not improve measures of fatigue compared to the control group.

Studies of white light therapy in ABI yielded fewer promising results. Connolly et al. (2021) examined the efficacy of a novel in-home white light therapy and did not report any significant differences in measures of fatigue or daytime sleepiness compared to control, although there was improvement in fatigue outcomes over time (medium effect size). The authors advocate for future researchers to include larger samples to detect an effect. A similar study conducted by Bell et al. (2021) examined the impact of bright white light exposure on sleep quality, compared to a red-light control. No differences were reported between the two groups on measures of fatigue, sleep duration, and other sleep outcome measures. The authors identified several confounding variables that were not accounted for which should be considered in future research, including medication, socioeconomic factors, and existing medical conditions (Bell et al., 2021).

Conclusions

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

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

There is level 1b evidence that bright white light therapy during acute rehabilitation may not impact sleep (Bell et al., 2021).

There is level 1b evidence that an in-home dynamic light intervention may not improve fatigue; however, participants' subjective reports on sleep quality and insomnia symptoms were positive (Connolly et al., 2021).

KEY POINTS

- Blue light therapy may reduce fatigue and daytime sleepiness in individuals with TBI.
- Yellow light therapy and bright white light therapy may not be effective in reducing fatigue and sleep, respectively post TBI.

Lifestyle Management Strategies

Lifestyle management interventions involve making changes to one's habits as part of a 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
Killington et al. (2021) Australia RCT PEDro=6 N=78	**Population:** Moderate-Severe TBI=78. *Fatigue Management (n=38):* Gender: Male=23 (29%), Female=15. *Usual Care (n=40):* Gender: Male=22 (55%), Female=18. **Intervention:** The participants were randomized into two groups: fatigue management (intervention) or usual care (control). Those allocated to fatigue management group attended group sessions 2x/wk for 2wk and received insightful education about the common effects of fatigue after brain injury. Those allocated to the usual care group received one 60-min therapy session, one-to-one with an occupational therapist. Therapy sessions included open discussions on fatigue and rehabilitation goal attainment training. Both groups were assessed for outcome measures at baseline and 2wk. Qualitative interviews were conducted between 2 and 12mos post-intervention. **Outcome Measure:** Quality of Life After Brain Injury (QOLIBRI), Barrow Neurological Institute Fatigue Scale (BNI-FS), self-evaluation of perceptions of fatigue and fatigue management principles.	1. No significant differences between the groups for BNI-FS, QOLIBRI, or acquisition of knowledge; however, knowledge improved over time irrespective of treatment condition ($p<0.01$). 2. Participants were able to explain how therapy supported their recognition of fatigue, as well as providing strategies to manage it. 3. Some participants required extra support and assistance with strategies to deal with their fatigue, such as keeping a fatigue log. 4. Participants agreed that receiving support in one-to-one sessions appeared to be superior to group sessions.
Stubberud et al. (2019) 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.	1. FSS scores were significantly improved after the intervention ($p=0.035$) and at 3mo follow-up ($p=0.018$), but not at 9mo follow-up. 2. ESS scores were significantly improved at 3mo ($p=0.042$) and 9mo ($p=0.024$) follow-up. 3. FQ total ($p=0.018$) and physical ($p=0.042$) scores were significantly improved after the intervention, but not FQ mental scores.

Author Year Country Study Design Sample Size	Methods	Outcome
	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).	These improvements were not sustained at 3 and 9mos. 4. HAD total (p=0.041) and HAD anxiety scores (p=0.27) were significantly improved at 9mo follow-up.

Discussion

In a small (n=8) pre-post study by Stubberud et al. (2019), participants with ABI or cerebrovascular insults underwent 36 hours of programming focusing on lifestyle factors, adaptive coping, and goal management training. The intervention significantly reduced fatigue post-intervention and at 3-month follow-up, but not at 9-month follow-up. Sleepiness was significantly reduced post-intervention, at 3-month follow-up, and at 9-month follow-up. The authors also reported a significant improvement on anxiety scores on the Hospital Anxiety and Depression Scale at 9-month follow-up.

Killington et al. (2021) conducted a RCT and a concurrent qualitative investigation of a fatigue management education intervention. When compared to a control group that received usual care, the fatigue management protocol did not significantly improve measures of fatigue, quality of life, or acquisition of knowledge. However, knowledge acquisition improved over time, irrespective of treatment condition. Participants recognized the importance of therapy and reported that one-to-one support sessions were more beneficial for the management of their fatigue than group sessions.

Conclusions

There is level 4 evidence 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 individuals with ABI (Stubberud et al., 2019).

There is level 1b evidence that discussion-based, group therapy sessions may not improve fatigue, when compared to usual care, in individuals with moderate to severe TBI (Killington et al., 2021).

KEY POINTS

- Programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce fatigue and sleepiness in individuals with ABI.
- Group therapy sessions focused on fatigue may not be effective; feedback was that individuals wanted an opportunity to address personal queries on a one-to-one basis.

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 their 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, to recognize their abilities and limitations, and plan for when to do activities in order to pace themselves (Fellus & Elovic, 2007). For some this may come easily, but for others it may require more education or other interventional programs. Although pacing is a concept that has been accepted with health care professionals and encouraged within the ABI population, pacing has 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 individuals 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 evaluated to help address these issues in brain injury specifically. Some authors propose using over-the-counter treatments for fatigue including sleep aids and sedating medications such as melatonin and diphenhydramine (e.g., Sleep-Eze, Nytol), etc.) (Thaxton & Patel, 2007). However, only melatonin has been studied in persons with ABI. Although some authors discuss the possible therapeutic benefits of prescription medications for fatigue post TBI, such as dextroamphetamine, levodopa-carbidopa, and amantadine (Rao et al., 2006), but few have been studied in 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. Individuals with TBI showed 42% less melatonin production, and melatonin secretion was delayed by 1.5 hours on average compared to controls (N. A. Grima et al., 2016). Because melatonin has minimal side effects, it may be useful for treating sleep disorders (N. A. Grima et al., 2018). However, only one RCT has examined the impact of melatonin on fatigue post ABI.

TABLE 8 | 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. The melatonin formula was a prolonged release formula (2mg). Outcomes 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 functioning (PF); Role Physical (RP); Role-emotional (RE); Vitality (VT); Mental Health (MH); Social functioning (SF); Bodily Pain (BP); General Health (GH).	1. Fatigue, as measured by FSS, was significantly improved in the melatonin arm compared to the placebo arm (p=0.03). 2. Sleepiness, as measured by ESS, was not significantly different between treatments (p=0.15). 3. HADS anxiety scores were significantly lower in the melatonin arm compared to the placebo arm (p=0.0006). 4. HADS depression scores were not significantly different between treatments (p=0.68). 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). 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 33 individuals with TBI. Participants showed significant improvements in fatigue, sleep quality, and sleep efficiency scores after the four weeks of melatonin treatment compared to placebo. Participants did not show a significant difference in daytime sleepiness scores when comparing melatonin to placebo. Based on this study, melatonin treatment may improve fatigue, sleep quality, and sleep latency in individuals post TBI, but may not significantly affect daytime sleepiness (N. A. Grima et al., 2018).

Conclusions

There is level 1b evidence that melatonin treatment may be effective in reducing fatigue compared to a placebo group in individuals post TBI (N. A. Grima et al., 2018).

KEY POINTS

- Melatonin may reduce fatigue in individuals with TBI.

Modafinil

Modafinil is a central nervous system stimulant and wakefulness promoting agent. 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). Two RCTs for TBI specific populations are summarized below.

TABLE 9 | 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 (85%), 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. The modafinil group had greater decreases in EDS scores versus placebo ($p<0.005$). 2. Of those patients with fatigue at baseline (FSS≥4), decreases in FSS scores were not greater in the modafinil group. 3. 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 ($p=0.07$). 4. 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=38.3yr; Gender: Male=35 (69%), Female=16; Mean Time Post Injury=5.8yr. **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 Measures:** Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFI), Epworth Sleepiness Scale (ESS).	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 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%). 4. 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 excessive daytime sleepiness (EDS) for individuals with TBI (Jha et al., 2008; Kaiser et al., 2010). Neither study found modafinil produced a significant difference in fatigue, as measured by the FSS, compared to placebo control. Further, when Kaiser et al. (2010) compared those with significant fatigue at baseline (FSS ≥4),

the decrease in FSS scores remained non-significant between groups. In one study, modafinil was associated with a significantly greater decrease in Epworth Sleepiness Scale and EDS scores when compared with controls (Jha et al., 2008). However, this improvement was significant at week four (p=0.02) but not at the end of modafinil treatment at week ten (p=0.56), highlighting that the benefit may not be sustained. In addition, 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 that modafinil may not be effective for treating fatigue compared to placebo in individuals with TBI but may be effective short-term in treating excessive daytime sleepiness post TBI (Jha et al., 2008; Kaiser et al., 2010).

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, Nordstrom, Schuit, & Nordstrom, 2017; Khemiri et al., 2015; Kloberg et al., 2014; Nilsson et al., 2017). (-)-OSU6162 works on both the dopamine and serotonin systems; however, it 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. This medication is not available in Canada.

TABLE 10 | (-)-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=41.4yr; Gender: Male=17 (52%), Female=16; Mean Time Post Injury=8.6yr. *Control Group (n=31):* Mean Age=42.6yr; Gender: Male=20 (65%), Female=11; Mean Time Post Injury=8.1yr. **Intervention:** (-)-OSU6162 was compared with placebo	1. No significant between group differences were observed for fatigue, as measured by the FSS and MFS. 2. No significant between group differences were observed for the RPCSQ.

Author Year Country Study Design Sample Size	Methods	Outcome
	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), Hospital Anxiety and Depression Scale (HADS).	3. Both groups showed significant improvement in fatigue as measured by FSS and MFS (all p<0.01) after the trial but not at 2- or 6mo follow-up. 4. Both groups had significantly lower scores on the RPCSQ (p<0.01) after the trial but not at 2- or 6mo follow-up. 5. Compared to placebo, the treatment group had significantly lower scores on the HADS after treatment but not at 2- or 6mo follow-up. 6. 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 participants with TBI (GCS>5). On the Fatigue Severity Scale and Mental Fatigue Scale, both groups showed significant reductions in fatigue after the trial; however, no significant between-group differences were observed. It is worth noting that the mean plasma concentration was lower than expected (0.14µM) at the end of the trial, which may indicate poor compliance and/or tolerability. However, signficantly larger changes in folic acid, prolactin, and heart rate were recorded for the experimental group, suggesting that the plasma levels of (-)-OSU6162 may have been sufficient to elicit a physiological effect. Based on this study, (-)-OSU6162 may not be effective in reducing fatigue in individuals with TBI.

Conclusions

There is level 1b evidence that (-)-OSU6162 may not be effective for treating fatigue compared to placebo in individuals with TBI (Berginstrom et al., 2017)

KEY POINTS

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

Sleep Disorders

One of the most common outcomes of TBI is sleep impairment. A meta-analysis conducted by Mathias and Alvaro (2012) found that 50% of persons with a 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, Ponsford, Rajaratnam, Mansfield, & Pase, 2016). Sleep disorders tend to be classified in broad categories of insomnia, sleep disordered breathing, excessive sleep (hypersomnia), or excessive daytime sleepiness (Elovic et al., 2005; J. Ponsford et al., 2015). Sleep dysfunction experienced by individuals with brain injury may include insomnia (J. B. Cantor et al., 2012; Gardani, Morfiri, Thomson, O'Neill, & McMillan, 2015; Kempf, Werth, Kaiser, Bassetti, & Baumann, 2010; J. L. Ponsford, Parcell, Sinclair, Roper, & Rajaratnam, 2013; Verma, Anand, & Verma, 2007), sleep apnea or sleep disordered breathing (Viola-Saltzman & Musleh, 2016), sleep disorganization (Nakase-Richardson et al., 2013), sleep-wake disturbance or circadian rhythm disorders (Aaronson et al., 1999; M.-C. Ouellet et al., 2015; M.C. Ouellet et al., 2019; Rao et al., 2015), hypersomnia (Gardani et al., 2015; Kempf et al., 2010), and excessive daytime sleepiness (EDS) (El-Khatib et al., 2019; L. L. Imbach et al., 2016; Lukas L. Imbach et al., 2015; Kempf et al., 2010; J. L. Ponsford et al., 2013; Sinclair et al., 2014).

Understanding how prevalent sleep disorders are post brain injury is challenging, as sleep disturbance may occur during the acute, subacute, and chronic stages of ABI recovery. Ascertaining the true prevalence of sleep dysfunction is further complicated by the subjective nature of reporting. Some studies have found that persons with severe TBI may underreport poor sleep, while those with mild TBI may be more likely to report sleep changes that have occurred as a result of their injury (Elovic et al., 2005). From limited available data, sleep dysfunction is highly prevalent. One study found that 47% of individuals with TBI reported EDS (Castriotta et al., 2007) and, based on subjective measures, approximately 50% of a TBI sample reported symptoms of insomnia; additionally, more than half of the individuals who reported having sleep difficulties were not being treated for the condition (M. C. Ouellet, Beaulieu-Bonneau, & Morin, 2006). In addition, studies have also found that self-report of symptoms such as EDS may be less severe on subjective measures compared to what is observed on objective measures (L. L. Imbach et al., 2016; Lukas L. Imbach et al., 2015).

Both subjective and objective measures can be used to screen for and/or diagnose sleep disorders. Commonly used self-reported, subjective questionnaires include: the Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI) to assess sleep quality (Bastien, Vallières, & Morin, 2001; Buysse, Reynolds Iii, Monk, Berman, & Kupfer, 1989); the Epworth Sleepiness Scale (ESS) and Stanford Sleepiness Scale (SSS) to assess daytime sleepiness (Johns, 1991; Shahid, Wilkinson, Marcu, & Shapiro, 2012); and the STOP-Bang questionnaire to assess for obstructive sleep apnea (Chung, Abdullah, & Liao, 2016). Commonly used objective measures of sleep dysfunction include sleep diaries (Aaronson et al., 1999), polysomnography (M.-C. Ouellet et al., 2015; Zasler, Katz, & Zafonte, 2012), actigraphy, multiple sleep

latency tests and maintenance of wakefulness tests (Zasler et al., 2012). Most of these subjective and objective measures have not been validated in persons with ABI, although these tests are commonly used and may be useful to clinicians as they work to screen, assess, and treat sleep disorders in persons with ABI.

Factors associated with higher rates of sleep dysfunction vary across studies. Causes of sleep disturbance are multifactorial and can include biological, hormonal, physical, psychological, and environmental factors (Amato & Anthony, 2020). Post ABI, trauma and/or injury to areas of the brain involved in sleep and wake cycle regulation may be a significant contributing factor (Fedele, McKenzie, Williams, Giles, & Olver, 2021). Other factors including 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 all been associated with higher frequency of sleep dysfunction by some researchers (Thaxton & Patel, 2007). In contrast, researchers 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).

According to Amato and Anthony (2020), among the many variables that may influence sleep dysfunction, the hospital environment may play a key role in contributing to irregular sleep patterns in patients recovering from illness or injury. Patient care activities—such as medication administration, checking vital signs, or repositioning—can disturb sleep, whereas exposure to light during times of sleep or insufficient exposure to light-dark contrast can disrupt the circadian rhythms (Amato & Anthony, 2020). These environmental effects can directly impact rehabilitation through reduced engagement or impaired learning and consolidation, as they may conflict with promoting adequate sleep and optimal recovery, it is important that clinicians consider and, whenever possible, minimize these stressors when providing care and implementing standard care practices (Amato & Anthony, 2020).

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, Hoffman, Dikmen, Temkin, & Bell, 2012). The presence of sleep dysfunction is associated with longer lengths of stay in hospital and longer durations of post-traumatic amnesia (Duclos et al., 2014; Nakase-Richardson et al., 2013; Sandsmark et al., 2016). Sandsmark et al. (2016)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 stay, and decreased mortality. In addition to influencing global outcomes, sleep dysfunction has a well-established relationship with mood dysfunction. For instance, Gardani et al. (2015) found that, in individuals with severe brain injuries, insomnia and poor sleep quality are associated with anxiety during subacute and chronic rehabilitation. Fichtenberg et al. (2000) found an association between insomnia and pain and depression. Moreover, insomnia was associated with the presence of anxiety, major depression, and poor sleep quality at one year post ABI; as well as an increase in anxiety, poorer sleep quality and higher discharge cognitive Functional Independence at 2 years post ABI (J. B. Cantor et

al., 2012). Whether sleep dysfunction leads to mood dysfunction or mood dysfunction contributes to sleep dysfunction is still unclear. However, these studies 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 maximize participation. The presence of sleep dysfunction may interfere with effective rehabilitation and recovery because sleep disorders are often associated with fatigue, difficulty focusing and maintaining attention, anxiety, depression, and other neurological symptoms (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 higher levels of neuro-behavioural impairment among individuals with TBI (Maneyapanda et al., 2018). Because sleep dysfunction can have significant impact on recovery and can continue long-term post ABI, identifying and treating sleep disturbances is important for persons with ABI.

Management of Sleep Disorders

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

Non-Pharmacological Interventions

Non-pharmacological strategies that have been studied for the management of sleep disorders post ABI 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	**Population:** TBI; Mean age=35.9yr; Gender: Male=9 (38%), Female=15; Mean Time Post Injury=27.6mo. **Intervention:** Using a crossover design, TBI patients	1. SOL was significantly reduced during the warm foot bath phase as compared with control ($p<0.001$).

Author Year Country Study Design Sample Size	Methods	Outcome
PEDro=8 N=24	received a 30 min, 41°C warm foot bath each day for 3d then usual care for 3 days (or vice versa), separated by a 3d washout period. The time of foot bath was 1 to 2 hours before bedtime. **Outcome Measure:** Sleep Efficiency (SE), Sleep Onset Latency (SOL), Total Sleep Time (TST), Wake After Sleep Onset (WASO).	2. WASO was significantly reduced during the warm foot bath phase as compared with control (p=0.006). 3. TST was not significantly different during the warm foot bath phase compared with control. 4. SE was not significantly different during the warm foot bath phase compared to control (p=0.09).

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 foot bath 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 foot bath group compared to control. Limitations of this study include that the intervention only lasted for three 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 a warm foot bath and/or other relaxation strategies on sleep in individuals with ABI.

Conclusions

There is level 1b evidence that a warm foot bath 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 individuals with TBI (Chiu et al., 2017).

KEY POINTS

- A warm foot bath in the evening may improve wake after sleep onset and sleep latency in individuals with TBI.

Cognitive Behavioural Therapy

Cognitive behavioural therapy (CBT), a widely used form of talk therapy or psychological therapy, has been found to be effective at improving a wide range of concerns, from anxiety to chronic pain to stress (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012). To date, two studies have evaluated the effectiveness of CBT on sleep dysfunction in persons with ABI.

TABLE 12 | 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=45.5yr; Gender: Male=9 (69%), Female=4; Mean Time Post Injury=795d. *Control Group (n=11):* Mean Age=41.9yr; Gender: Male=7 (64%), Female=4; Mean Time Post Injury=2093d. **Intervention:** Participants 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 sleep quality, as measured by PSQI scores, post-treatment and at follow-up compared to control ($p<0.001$). 2. The CBT group had significantly improved insomnia severity, as measured by ISI scores, post-treatment ($p<0.01$) and at follow-up ($p<0.001$) compared to control. 3. There was a significant improvement in insomnia severity, as measured by ISI scores, over time for the CBT group ($p=0.010$), but not the control group. 4. Fatigue and daytime sleepiness, as measured by the FSS and ESS, respectively, yielded no significant between group differences or time effects for either group.
Ouellet & Morin (2007) Canada Pre-Post N=11	**Population:** TBI=11; Mean age=27.3yr; Male=6 (55%), Female=5; Mean Time Since Injury=25.6mo. **Intervention:** Participants 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:** Sleep diary, Total Wake Time, Sleep Efficiency, Sleep Time, Insomnia Severity Index (ISI), Multidimensional Fatigue Inventory (MFI), Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI).	1. After CBT, insomnia severity, as measured by ISI, was significantly improved ($p<0.017$). 2. Following CBT, significant improvements were seen in total wake time ($p<0.001$) and sleep efficiency ($p=0.01$). 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 and the MFI (both $p<0.017$).

Discussion

In a pre-post study, Ouellet and Morin (2007) found that CBT was effective for insomnia associated with TBI, as measured by the ISI and the DBAS. The authors found no significant differences in the BDI and BAI scores. Pre to post treatment, significant improvements were found for total wake time, sleep efficacy, and insomnia, but not for total sleep time. For most participants, the benefits of this intervention appeared within 1 or 2 weeks of treatment, and were sustained over time, for at least 3 months (M. C. Ouellet & Morin, 2007).

Nguyen et al. (2017) reported individuals who received CBT showed significant improvements in sleep quality, fatigue levels and depression. The authors found minimal effect on daytime sleepiness (as measured by the Epworth Sleepiness Scale). Only the CBT group showed a clinically important improvement on the primary sleep measure (PSQI). While CBT participants reported a reduction in daily fatigue, perception of global fatigue, as measured by the FSS, did not shift after the intervention (Nguyen et al., 2017).

Conclusions

There is level 1b evidence that cognitive behavioural therapy may improve sleep quality and reduce insomnia compared to usual care in individuals with TBI (Nguyen et al., 2017; M. C. Ouellet & Morin, 2007).

KEY POINTS

- Cognitive behavioral therapy may improve sleep quality and reduce insomnia in individuals with TBI.

Acupuncture

Acupuncture involves piercing certain areas of the body with fine needles for therapeutic purposes, and it has been used to treat various illnesses, such as back pain, arthritis, headaches, asthma, as well as insomnia (Cheuk, Yeung, Chung, & Wong, 2012); however, only one study has evaluated acupuncture for insomnia in individuals with ABI.

TABLE 13 | 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 (45%), 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.	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).

Author Year Country Study Design Sample Size	Methods	Outcome
	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).	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) investigated the use of acupuncture, compared to education, in addressing insomnia in individuals with TBI. A between-group comparison showed no significant difference in the Insomnia Severity Index (ISI) scores at three time points (baseline, post treatment, and 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 after treatment. No such differences were seen in the control group. Participants in the treatment group also showed significant improvement on overall cognitive functioning and divided attention. The use of acupuncture needs to be studied further to determine its effects on sleep disorders such as insomnia in individuals with ABI.

Conclusions

There is level 2 evidence that acupuncture may not improve insomnia compared to instructions on good sleep habits in individuals with TBI (Zollman et al., 2012).

KEY POINTS

- Acupuncture therapy may not improve insomnia in individuals 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 consistent sleep-wake schedule (Mastin, Bryson, & Corwyn, 2006). Although sleep hygiene strategies are often used as part of a management program for individuals experiencing sleep disturbances, little research exists regarding its efficacy in a population with ABI.

TABLE 14 | 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; *Sleep Hygiene Protocol (n=9):* Mean Age=26.0yr; Gender: Male=7 (78%), Female=2; Mean Time Post Injury=28.6d; Mean GCS=6.9. Standard *Care (n=9):* Gender: Male=7 (78%), Female=2; Mean Time Post Injury=25.9d; Mean GCS=8.6. **Intervention:** The participants were allocated into two groups: Sleep Hygiene Protocol (SHP) or Standard of Care Protocol (SOC). The SHP employed concepts of both sleep restriction and stimulus control, including improved nighttime sleep environment, increased daytime activation, enhanced circadian stimuli, consistent activities of daily living, 30 minutes of blue-light therapy, and no caffeine intake after 12:00pm. Participants allocated to the SOC group underwent standard TBI rehabilitation. Both groups participated in physical and occupational therapy for a minimum of 3 hr per day, 5 days per week, for 4 weeks. Outcome measures were assessed at baseline, 1wk, 2wk, and 3wk. **Outcome Measure:** Orientation Log (O-Log), Confusion Assessment Protocol (CAP), Agitated Behaviour Score, Disability Rating Scale (DRS), Wakefulness After Sleep Onset (WASO), Total Sleep Time (TST), Sleep Efficiency (SE), Length of Stay (LOS).	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). 3. Both groups' overall sleep quantity and quality improved over the course of the study. However, the SOC group showed more extreme variability and did not significantly change (p=0.173), while the SHP group improved in a more statistically significant manner (p=0.008). 4. Improvements of TST, SE, and WASO were associated with DRS improvement, which reached significance for WASO (p=0.048). 5. No significant differences in rehabilitation outcomes between groups (DRS, p>.05; LOS, p>.05).

Discussion

Makley et al (2020) conducted a RCT investigating the effects of a sleep hygiene protocol on sleep disturbances in individuals with TBI. When compared to a control group that received standard rehabilitation, the sleep hygiene protocol did not significantly improve most outcome measures, aside from actigraphy. Results for other outcome measures trended towards significance, although lacked statistical power due to the small sample size (n=18). Notably, participants with better sleep metrics tended to have better rehabilitation outcomes. 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 (Makley et al., 2020). Further research is warranted to determine the effects of a sleep hygiene intervention on sleep time, efficiency and wakefulness in individual with moderate to severe TBI.

Conclusions

There is level 2 evidence that a sleep hygiene intervention is feasible in a population with moderate to severe TBI; however, it did not improve total sleep time, sleep efficiency, or wakefulness after sleep more than standard care (Makley et al., 2020).

KEY POINTS

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

Lifestyle Management Strategies

Lifestyle management interventions involve making changes to one's habits as part of a 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 15 | Lifestyle Interventions for the Management of Sleep Disorders Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Stubberud et al. (2019) 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. Insomnia, as measured by ISI, was not significantly improved after the intervention. 2. Daytime sleepiness, as measured by ESS scores, was significantly improved at 3mo (p=0.042) and 9mo (p=0.024) follow-up. 3. FSS scores were significantly improved after the intervention (p=0.035) and at 3mo follow-up (p=0.018), but not at 9mo follow-up. 4. FQ total (p=0.018) and physical (p=0.042) scores were significantly improved after the intervention, but not FQ mental scores. These improvements were not sustained at 3 and 9mos. 5. HAD total (p=0.041) and HAD anxiety scores (p=0.27) were significantly improved only at 9mo follow-up.

Discussion

A pre-post study by Stubberud et al. (2019) examined the effects of a group-based intervention program with modules covering lifestyle factors, adaptive coping strategies, and goal management on sleep and fatigue in individuals with ABI. Participants demonstrated no significant changes in insomnia severity after the intervention; however, a significant reduction in daytime sleepiness, as measured by the ESS, was observed at post-test, 3-month follow-up, and 9-month follow-up.

There is level 4 evidence that programming focusing on lifestyle factors, adaptive coping, and goal management training may not reduce insomnia severity but may reduce daytime sleepiness up to 9 months post intervention in individuals with ABI (Stubberud et al., 2019).

KEY POINTS

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

Pharmacological Interventions

Only a few pharmacologic interventions have been developed or tested for sleep disorders post ABI. Some authors propose using over-the-counter treatments for sleep dysfunction including sleep aids and sedating medications such as melatonin and diphenhydramine (e.g., Sleep-Eze, Nytol), etc.) (Thaxton & Patel, 2007), but of these, only melatonin has been studied in persons with ABI. Few studies have evaluated the effectiveness of prescription sleep aids, such as lorazepam and zopiclone, in persons with ABI, although these and others are commonly used. Although some authors discuss the possible therapeutic benefits of prescription stimulant medications for sleep (Rao et al., 2006), few have been studied in ABI. Pharmacological stimulants, such as methylphenidate and modafinil, may be prescribed to promote alertness and awareness post ABI. These stimulants act via varying mechanisms upon subcortical dopaminergic neurons involved in arousal and cortical neurons that are responsible for attention (Barra et al., 2020). As a result, these medications promote recovery of consciousness and may alter a person's sleep-wake cycle or other sleep dysfunction.

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) examined characteristics of the circadian rhythm of melatonin in individuals with TBI. The authors compared melatonin production in individuals with TBI to a control group. Individuals with TBI showed 42% less melatonin production, and melatonin secretion was delayed by 1.5 hours on average compared to controls. The results of this study indicated that individuals with TBI present with a disruption of the circadian regulation of melatonin synthesis (N. A. Grima et al., 2016).

TABLE 16 | 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. A prolonged release formula of melatonin was utilized (2mg). Outcomes 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 Functioning (PF); Role Physical (RP); Role-emotional (RE); Vitality (VT); Mental Health (MH); Social Functioning (SF); Bodily Pain (BP); General Health (GH).	1. Sleep quality, as measured by PSQI scores, was significantly better in the melatonin arm compared to the placebo arm ($p<0.0001$). 2. Sleep efficiency scores were significantly higher in the melatonin arm compared to the placebo arm ($p=0.04$). 3. Sleep latency scores were not significantly different between treatments ($p=0.23$). 4. Daytime sleepiness, as measured by ESS scores, was not significantly different between treatments ($p=0.15$).

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 and the placebo phase was observed. Findings of this study suggest that melatonin treatment may be effective in improving sleep quality and efficiency, in individuals with TBI, but may not significantly affect sleep onset latency or daytime sleepiness (N. A. Grima et al., 2018).

Conclusions

There is level 1b evidence that melatonin treatment may be effective in improving sleep quality and sleep efficiency, compared to a placebo group in individuals post TBI; however, it may not be effective in improving sleep onset latency or daytime sleepiness (N. A. Grima et al., 2018).

KEY POINTS

- Melatonin may improve sleep quality and sleep efficiency in individuals post TBI; however, it may not improve sleep onset latency or daytime sleepiness.

Modafinil

Modafinil has been approved to address excessive daytime sleepiness (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 17 | 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 (85%), 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=38.2yr; Gender: Male=35 (69%), Female=16; Mean Time Post Injury=5.8yr. **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 daytime sleepiness, measured by 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%). 3. Adverse events for placebo group included: headaches (19.6%) and nasopharyngitis (5.9%).

Discussion

In an RCT, Kaiser et al. (2010), examined the effects of modafinil, compared to a placebo control, on EDS for individuals with TBI. Participants who received 100-200mg for six weeks had significantly greater decreases in EDS scores than those in the control group (Kaiser et al., 2010). In an RCT by Jha (2008), participants in the treatment group who received modafinil (100 mg/d for 3d, then 200 mg/d for 11d, then a maintenance dose of 400 mg/d for 8wk). Participants showed a significantly greater decrease in daytime sleepiness, as measured by the Epworth Sleepiness Scale scores, when compared with controls (Jha et al., 2008). It should be noted 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. Participants 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 individuals with TBI.

Conclusions

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

KEY POINTS

- Modafinil has been shown to be effective in the short-term for treating excessive daytime sleepiness but may also cause insomnia in individuals 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, Neumann, Kent, Stroud, & Bhakta, 2010). Lee et al. (2005) found that methylphenidate may be effective in reducing excessive daytime sleepiness in patients with mild to moderate TBI; however, this has not been investigated in individuals with moderate to severe TBI. One study that examines the effect of methylphenidate on sleep-wake cycles in individuals with TBI.

TABLE 18 | 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 (77%), 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. **Outcome Measure:** Sleep State, Functional Independence Measure (FIM), Rancho Los Amigos Levels of Cognitive Functioning (RLA).	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). 2. RLA scores were comparable between groups at baseline (p=0.479). 3. The mean hours of sleep during a 24hr period did not significantly differ between the treatment and control groups (8.3 versus 9.0hr, p=0.096). 4. 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), participants who received methylphenidate were compared to a control group. Sleep times between the two groups were not significantly different. Based on this study, methylphenidate does not seem to have adverse effects on sleep quantity post ABI. It should be noted that the participants selected to receive methylphenidate tended to have lower FIM scores, but no significant differences were observed in other areas, such as Ranchos Los Amigos Levels of Cognitive Functioning scores. This study did not assess whether methylphenidate improved EDS, fatigue, or rehabilitation participation.

Conclusions

There is level 3 evidence that methylphenidate may not have adverse effects on the sleep-wake cycle in individuals with TBI, when compared to those not receiving medication (Al-Adawi et al., 2006)

KEY POINTS

- Methylphenidate may not have an adverse effect on the sleep-wake cycle in individuals with 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, McCormack, & Curran, 2008; Thaxton & Patel, 2007). In an 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

KEY POINTS

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

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 despite their widespread use. Clinicians must therefore rely on their individual clinical experiences and expertise when addressing fatigue and sleep dysfunction. 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 dysfunction post ABI given the importance of these areas to the recovery, rehabilitation participation, community reintegration, and quality of life of individuals with a history of ABI.

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