

## 7. Fatigue and Sleep Disorders Post Acquired Brain Injury

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## Key Points

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

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

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

**Cognitive behavioural therapy may reduce fatigue and insomnia in patients with TBI.**

**Acupuncture therapy has may not improve insomnia in patients with TBI.**

**Blue light therapy may reduce fatigue and daytime sleepiness in patients with TBI, however this improvement may not persist beyond the treatment period.**

**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.**

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

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

**Melatonin treatment may improve sleep quality, sleep efficiency, and reduce fatigue in patients post TBI.**

**Melatonin treatment may not effect sleep onset latency or daytime sleepiness.**

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## Abbreviations

ABI	Acquired Brain Injury
CBT	Cognitive Behavioural Therapy
PSQI	Pittsburgh Sleep Quality Index
EDS	Excessive Daytime Sleepiness
FSS	Fatigue Severity Scale
GCS	Glasgow Coma Scale
RCT	Randomized Controlled Trial
TBI	Traumatic Brain Injury

# Fatigue and Sleep Disorders Post Acquired Brain Injury

## 7.0 Introduction

Fatigue is one of the more commonly reported symptoms associated with brain injury (Duclos et al., 2014; Elovic et al., 2005) and can exacerbate other co-morbidities. One of the greatest challenges is in properly defining fatigue; a clear definition is integral to determining how it should be measured and managed. It is believed that fatigue is a subjective experience and thus is not easily assessed by objective measures (Lewis & Wessely, 1992). Individuals experiencing fatigue report it as a feeling of tiredness, weakness, or exhaustion (Rao et al., 2006).

Fatigue has been defined as the *“unconscious decreased ability for physical and or mental activity due to an imbalance in availability, utilization or the retrieval of the physiological or psychological resources required to perform the activity”* p.2 (Aaronson et al., 1999). Those studying or reporting on fatigue have attempted to distinguish between physical and psychological fatigue (Aaronson et al., 1999). Physical fatigue has been defined as *“the result of excessive energy consumption, depleted hormones or neurotransmitters or diminished ability of muscle cells to contract”* p.2 (Jha et al., 2008). Psychological fatigue has been defined as *“a state of wariness related to reduced motivation, prolonged mental fatigue or boredom”* p.1 (Lee et al., 1991).

A meta-analysis conducted by Mathias and Alvaro (2012) found that 50% of people with traumatic brain injury (TBI) experience disturbed sleep. Common sleep complaints among individuals with moderate to severe brain injury are poor sleep quality, longer sleep-onset latency, increased nocturnal awakening, and insomnia (Duclos et al., 2014; Grima et al., 2016a). Unfortunately, there is large variability in the estimates of fatigue and sleep disorders within the ABI literature, much of which is due to variation in how data is collected. Both subjective and objective means of collecting this data are available. A systematic review found 16 measures of fatigue were commonly used in TBI studies (Mollaveya et al., 2013). Most common is the utilization of questionnaires, but polysomnography, actigraphy, multiple sleep latency tests, and maintenance of wakefulness tests are objective measures that may be used (Mollaveya et al., 2013).

Although it would seemingly make sense to link disorders of sleep with fatigue (Clinchot et al., 1998), this relationship remains inconclusive (Fellus & Elovic, 2007). Sleep disturbances can exacerbate fatigue, however fatigue may also manifest independent of sleep disorders (Ouellet et al., 2015). There are many plausible sources of fatigue including neuroanatomical, functional, psychological, biochemical, or endocrine causes (Mollaveya et al., 2013). A review by Duclos et al. (2014) suggests that sleep-wake disturbances may be due to altered circadian rhythms, damage to the cortical and subcortical structures involved, endocrine dysfunction (e.g., growth hormone or cortisol levels), pain, anxiety and depression, or the environment. This complex interplay between psychological, social, environmental, and pathophysiological factors interferes with our ability to determine the etiology of sleep disturbances (Ouellet et al., 2015). It is therefore important to investigate the medical and reversible causes of fatigue (e.g., anemia, hypothyroidism, medications that may be worsening fatigue, etc.) in patients with acquired brain injury (ABI). For those recovering from an ABI, fatigue and sleep disorders have the ability to interfere with an individual's ability to participate in rehabilitation programs designed to assist them in performing their activities of daily living. It also impacts one's physical, cognitive, and social abilities.

## 7.1 Sleep Disorders Post ABI

There are many different sleep disorders experienced by patients with brain injury including daytime sleepiness (El-Khatib et al., 2019; Imbach et al., 2016; Imbach et al., 2015; Kempf et al., 2010; Ponsford et al., 2013; Sinclair et al., 2014), poor sleep quality, insomnia (Cantor et al., 2012; Gardani et al., 2015; Kempf et al., 2010; Ponsford et al., 2013; Verma et al., 2007), sleep disorganization (Nakase-Richardson et al., 2013), sleep wake disturbance, and hypersomnia (Gardani et al., 2015; Kempf et al., 2010). Sleep disorders tend to be classified as insomnia, excessive sleep, or excessive daytime sleepiness (EDS) (Elovic et al., 2005; Ouellet et al., 2015).

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

It is believed that, in individuals with ABI, sleep complaints correlate with 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 (Thaxton & Patel, 2007). Furthermore, 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). Individuals with sleep disturbances have longer length of stay in hospital (Duclos et al., 2014; Nakase-Richardson et al., 2013; Sandsmark et al., 2016). Further, Nakase-Richardson et al. (2013) discovered that the duration of post-traumatic amnesia was longer when moderate to severe sleep disorders were present. Sandsmark et al. (2016) reported that in the acute ABI setting, sleep was associated with good outcomes, such as likelihood to be discharged home, shorter intensive care unit and hospital length of stays, and decreased mortality.

Brain injury rehabilitation is often intense and requires the patient to be alert and focused to achieve the greatest extent of rehabilitation possible; however, sleep disorders are often associated with fatigue, difficulty focusing and maintaining attention, anxiety, depression, and other neurological disorders (Cohen, 1993; Gardani et al., 2015; Ziino & Ponsford, 2006). Gardani et al. (2015) report that in severe brain injuries, insomnia and sleep quality are associated with anxiety during subacute-chronic rehabilitation. Moreover, Cantor et al. (2012) found that at one-year, insomnia was associated with the presence of anxiety, major depression, and poor sleep quality. Whereas, at two years, the presence of anxiety, higher discharge cognitive Functional Independence Measure scores and poorer sleep quality were predictors of insomnia (Cantor et al., 2012). Fichtenberg et al. (2000) also noted the association between insomnia, pain disturbance, and depression. A study by Wiseman-Hakes et al. (2013) supported the concept that sleep disturbances associated with TBI exacerbate cognitive, communication and mood deficits that are trauma-related. Total sleep time, determined by observation, during inpatient rehabilitation is negatively associated with neurobehavioural impairment among individuals with TBI (Maneyapanda et al., 2018). Dealing with sleep disturbances is necessary for optimal recovery.

## 7.2 Fatigue Post ABI

Even though fatigue has been recognized as a significant problem post ABI, few interventional studies have been researched in this population. When comparing individuals with TBI to healthy controls, those who have had a brain injury experience greater levels of fatigue (Ashman et al., 2008; Borgaro et al., 2005; Chiou et al., 2016; LaChapelle & Finlayson, 1998; Ponsford et al., 2012; Ziino & Ponsford, 2006). Between 33% and 64% of individuals reported fatigue post TBI (Englander et al., 2010; Ponsford et al., 2012).

Sleep disturbances were shown to negatively impact ones' satisfaction with life, and scores on the Functional Independence Measure and Disability Rating Scale (Fogelberg et al., 2012). Moreover, fatigue has been associated with subjective determination of cognitive problems, difficulties with decision-making, working slowly to ensure accuracy and challenges in getting things done on time (Esbjornsson et al., 2013). Fatigue can also negatively impact relationships, as there is a tendency towards reacting too quickly in response to others among individuals suffering from fatigue (Esbjornsson et al., 2013). Further, one's ability to work is often compromised when sleep disturbances are present. Schnieders et al. (2012) found those with fatigue, compared to those without, had lower level jobs and more nonpaying jobs. Evidently, managing fatigue is imperative in helping individuals live a productive life post injury.

To better understand the severity of the problem, data is often collected through surveys, interviews, and/or questionnaires. Comparison groups in many of the studies are those without an ABI. Scales frequently used in these surveys include the Fatigue Severity Scale, the Fatigue Impact Scale, the Visual Analogue Scale-F, the Global Fatigue Index, the Barroso Fatigue Scale, and the Epworth Sleepiness Scale; however, none of these scales were designed specifically for use in patients with brain injury, but rather they were developed for patients with Human Immunodeficiency Virus or Multiple Sclerosis (Armutlu et al., 2007; Fish et al., 2007).

Fatigue is highly associated with psychological and cognitive comorbidities frequently found in the ABI population such as vigilance, attention, depression, anxiety, and cognitive problems. It has been noted that those who sustain a TBI have a lower cognitive reserve and often are not able to maintain the same levels of vigilance or sustained attention as they did before the injury (Ziino & Ponsford, 2006). Mental fatigue has also been explored by Jonasson et al. (2018) who found after cognitive activity, those dealing with mental fatigue had impaired cognitive performance. Ponsford et al. (2015) reported on the relationship between fatigue, depression, and anxiety post TBI. Fatigue strongly predicted depression and anxiety according to the Hospital Anxiety and Depression Scale. A review by Kumar et al. (2018) also found numerous studies reported a positive correlation between post-traumatic depression and self-reported fatigue. In a study by Esbjornsson et al. (2013), eighteen participants with TBI completed questionnaires 1 year post injury. They found fatigue to be significantly associated with cognitive problems, difficulties in decision making, difficulty getting things done on time, and working slowly for accuracy. Bay & de-Leon (2011) surveyed individuals with TBI from an outpatient clinic and reported significant correlation between fatigue and perceived stress.

Similar to sleeping disorders, fatigue can have a significant effect on an individual's ability to fully participate in rehabilitation post ABI. Additionally, the often intense rehabilitation programs themselves may exacerbate fatigue. In a study by Toda et al. (2006), the investigators found that individuals who had sustained a TBI reported significantly higher levels of fatigue during their time in rehabilitation than they did at 6 or 12 months post injury. Once the patient is removed from these demands and has achieved a greater understanding of their deficits, the feelings of fatigue may lessen; however, literature shows that

fatigue can persist for many years post injury regardless (Bay & de-Leon, 2011; Olver et al., 1996; Ouellet & Morin, 2004; Rao et al., 2006).

### 7.3 Non-pharmacological Management Strategies

Fatigue and sleep disorders post ABI can be managed using pharmacological or non-pharmacological techniques. Non-pharmacological strategies include exercise, relaxation strategies, pacing, cognitive behavioural therapy, acupuncture, 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.

#### 7.3.1 Exercise

**Table 7.1 Exercise for the Treatment of Fatigue and Sleep Disorders Post ABI**

Author Year Country Study Design Sample Size	Methods	Outcome
<a href="#">Kolakowsky-Hayner et al.</a> (2017) USA RCT Crossover PEDro=4 N <sub>initial</sub> =128 N <sub>final</sub> =62	<p><b>Population:</b> TBI; Mean age=42.7yr; Gender: Male=72 Female=56; Mean Time Post Injury=97.6mo.</p> <p><b>Intervention:</b> The treatment group received a 12wk home-based walking program that included a pedometer to track daily number of steps and tapered coaching calls. Participants were encouraged to increase their steps by 5% each week until an overall step increase 40% above baseline was achieved. A 12wk nutritional counselling program and the same frequency of tapered coaching calls served as the control. Measurements were taken at baseline and week 12, 24, and 36.</p> <p><b>Outcome Measure:</b> Global Fatigue Index (GFI), Barrow Neurological Institute (BNI) Fatigue Scale Overall Severity Score, Multidimensional Fatigue Inventory (MFI).</p>	<ol style="list-style-type: none"> <li>1. Participants had significantly less fatigue (GFI) at the end of the walking intervention (<math>p&lt;0.001</math>).</li> <li>2. According to the BNI Fatigue Scale Total, participants had significantly less fatigue at the end of the walking intervention (<math>p&lt;0.003</math>).</li> <li>3. According to the BNI Overall Score, participants had significantly less fatigue at the end of the walking intervention (<math>p&lt;0.001</math>) and after 36wk (<math>p&lt;0.001</math>). The walking intervention in the nutritional first group did not have a significant effect on BNI Overall Score but had significantly reduced BNI Overall Scores by week 36.</li> <li>4. According to the MFI, participants had significantly less fatigue at the end of the walking intervention (<math>p&lt;0.001</math>) and after 36wk (<math>p&lt;0.05</math>). However, MFI scores significantly increased following the end of the walking intervention. (<math>p&lt;0.05</math>).</li> </ol>

#### Discussion

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



## Conclusions

*There is level 2 evidence that a home-based walking program may reduce fatigue up to 24 weeks following treatment compared to a nutritional counselling program in patients with TBI.*

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

## 7.3.2 Relaxation Strategies

**Table 7.2 Footbath for the Treatment of Fatigue and Sleep Disorders Post ABI**

Author Year Country Study Design Sample Size	Methods	Outcome
<a href="#">Chiu et al.</a> (2017) Taiwan RCT Crossover PEDro=8 N=24	<b>Population:</b> TBI; Mean age=35.9yr; Gender: Male=9 Female=15; Mean Time Post Injury=27.6mo. <b>Intervention:</b> Using a crossover design, TBI patients received a 30 min, 41°C warm footbath each day for 3d then usual care for 3 days (or vice versa), separated by a 3d washout period. <b>Outcome Measure:</b> Sleep Efficiency (SE), Sleep Onset Latency (SOL), Total Sleep Time (TST), Wake After Sleep Onset (WASO).	<ol style="list-style-type: none"><li>1. Warm footbaths showed non-significant improvement in SE compared to control (p=0.09).</li><li>2. SOL was significantly reduced during the warm footbath phase as compared with control (p&lt;0.001).</li><li>3. TST was not significantly increased during the warm footbath phase compared with control.</li><li>4. WASO was significantly reduced during the warm footbath phase as compared with control (p=0.006).</li></ol>

## Discussion

Using a crossover RCT, Chiu et al. (2017) evaluated the effect of a warm footbath each evening on sleep latency and efficiency in a TBI population. The results were unclear; while participants did not show significant improvements in total sleep time or sleep efficiency, both the number of times participants woke after sleep onset, and sleep onset latency, were significantly reduced in the warm footbath group compared to control. However, there were a few limitations in this study: firstly, the intervention only lasted for 3 nights, and secondly, the population size was small (n=24). Future long-term studies with a larger sample size are needed to determine the impact of relaxation strategies such as a warm footbath on sleep in individuals with ABI.

## Conclusions

*There is level 1b evidence that a warm footbath in the evening may improve wake after sleep onset and sleep onset latency but not sleep efficiency or sleep time compared to usual care in patients with TBI.*

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

### 7.3.3 Lifestyle Management Strategies

One category of interventions involves making a series of changes to one's lifestyle to take a more holistic approach to rehabilitation or remediation. These changes can be anything from diet to self-care to exercise. Lifestyle management strategies can 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 outcomes is significantly larger than in most areas of research.

**Table 7.3 Lifestyle Management Program for the Treatment of Fatigue and Sleep Disorders Post ABI**

Author Year Country Study Design Sample Size	Methods	Outcome
<a href="#">Stubberud et al.</a> (2017) Norway Pre-Post N=8	<p><b>Population:</b> ABI (Injury Etiology: TBI=3, Cerebrovascular Insults=5); Mean Age=41.6yr; Gender: Male=3, Female=5; Mean Time Post Injury=40.1mo.</p> <p><b>Intervention:</b> 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.</p> <p><b>Outcome Measure:</b> 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).</p>	<ol style="list-style-type: none"> <li>1. FSS scores were significantly improved at posttest (<math>p=0.035</math>) and at 3mo follow-up (<math>p=0.018</math>), but not at 9mo follow-up.</li> <li>2. At posttest, FQ total (<math>p=0.018</math>) and physical (<math>p=0.042</math>) scores were significantly improved, but not FQ mental scores. These improvements were not sustained at follow-up.</li> <li>3. HAD total (<math>p=0.041</math>) and anxiety scores were significantly improved only at 9mo follow-up.</li> <li>4. ESS scores were significantly improved at 3 mo (<math>p=0.042</math>) and 9 mo (<math>p=0.024</math>) follow-up.</li> <li>5. No significant changes in ISI, GPSS, or CPT-II scores were reported.</li> </ol>

### Discussion

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

### Conclusions

***There is level 4 evidence that programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce fatigue up to 3 months and sleepiness up to 9 months post intervention in patients with ABI.***

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

### 7.3.4 Pacing

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

### 7.3.5 Cognitive Behavioural Therapy

Cognitive behavioural therapy (CBT) has been found to be effective at improving fatigue in disorders such as multiple sclerosis, chronic fatigue syndrome, and rheumatoid arthritis (Cantor et al., 2014); however, limited research exists regarding the effect on fatigue and sleep disturbances after brain injury (Ouellet & Morin, 2004). Sleep disorders, such as insomnia, can affect a person's quality of life and family and social commitments, as well as their ability to return to work (Ouellet & Morin, 2004). Four studies to date have evaluated the effectiveness of CBT on fatigue and sleep disorders.

**Table 7.4 Cognitive Behavioural Therapy for the Treatment of Fatigue and Sleep Disorders Post ABI**

Author Year Country Study Design Sample Size	Methods	Outcome
<a href="#">Nguyen et al.</a> (2017) Australia RCT PEDro=8 N=24	<p><b>Population:</b> TBI; <i>CBT Group</i> (n=13): Mean Age=45.53yr; Gender: Male=9, Female=4; Mean Time Post Injury=795.15d. <i>Control Group</i> (n=11): Mean Age=41.90yr; Gender: Male=7, Female=4; Mean Time Post Injury=2093.36d.</p> <p><b>Intervention:</b> 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.</p> <p><b>Outcome Measure:</b> Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Brief Fatigue Inventory (BFI),</p>	<ol style="list-style-type: none"> <li>1. The CBT group had significantly improved PSQI scores post-treatment and at follow-up compared to control (p&lt;0.001).</li> <li>2. The CBT group had significantly improved ISI scores post-treatment (p&lt;0.01) and at follow-up (p&lt;0.001) compared to control. There was also a significant improvement in ISI scores over time for the CBT group (p=0.010), but not the control group.</li> <li>3. The CBT group had significantly improved BFI scores post-treatment (p&lt;0.05) and at follow-up (p&lt;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.</li> <li>4. The FSS and ESS yielded no significant between group differences or time effects for either group.</li> </ol>

Author Year Country Study Design Sample Size	Methods	Outcome
	Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS).	
<a href="#">Raina et al.</a> (2016) USA RCT PEDro=4 N <sub>Initial</sub> =41 N <sub>Final</sub> =38	<b>Population:</b> TBI; <i>MAX Group</i> (n=17): Mean Age=43.8yr; Gender: Male=8, Female=5; Mean Time Post Injury=9.9 mo. <i>Control Group</i> (n=21): Mean Age=48.1yr; Gender: Male=13, Female=8; Mean Time Post Injury=11.1 mo. <b>Intervention:</b> 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. <b>Outcome Measure:</b> Modified Fatigue Impact Scale (MFIS), Patient-Reported Outcomes Measurement Information System Fatigue Scale (PROMIS), Fatigue Severity Scale (FSS).	1. No significant differences between groups were found for MFIS, PROMIS or FSS.
<a href="#">Ouellet &amp; Morin</a> (2007) Canada Pre-Post N=11	<b>Population:</b> TBI=11; Mean age=27.3yr; Male=6, Female=5; Mean Time Since Injury=25.64mo. <b>Intervention:</b> 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. <b>Outcome Measure:</b> Total Wake Time, Sleep Efficiency, Sleep Time, Insomnia Severity Index (ISI), Multidimensional Fatigue Inventory (MFI), Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS).	1. Following CBT, significant improvements were seen in total wake time (p<0.001) and sleep efficiency (p=0.01). 2. Gains were maintained, but no significant changes occurred from the post treatment assessment and 3mo follow-up for total wake time (p=0.06) or sleep efficiency (p=0.24). 3. Sleep time from pre to post treatment did not change significantly (p=0.44); however, there was a significant improvement from baseline to the 3mo follow-up (p<0.015). 4. Significant reductions in scores were seen after treatment on the DBAS, ISI (both p<0.01), and the MFI (p<0.012).

## Discussion

In a pre-post study, Ouellet and Morin (2007) found that CBT was effective for insomnia post TBI. For some, improvements in sleep were noted within the first 2 weeks of treatment; for others, improvement was more progressive. Pre to post treatment, significant improvements were found for total wake time, sleep efficacy, fatigue and insomnia, but not for total sleep time (Ouellet & Morin, 2007). No significant gains were made once the treatment had concluded, although gains were maintained at 3-month follow-up. This study suggests that a relatively short duration of CBT can lead to positive sleep improvements. Similarly, Nguyen et al. (2017) reported individuals in the CBT group showed significant improvements in sleep quality, insomnia, anxiety, and depression, but not in sleepiness. A secondary analysis of the previous study, and another involving stroke patients, found that participants who were younger, had better verbal memory and comorbid symptoms of depression were more likely to respond to CBT treatment (Nguyen et al., 2018).

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

## Conclusions

***There is level 1b evidence that cognitive behavioural therapy may reduce fatigue and insomnia compared to usual care in patients with TBI.***

**Cognitive behavioural therapy may reduce fatigue and insomnia in patients with TBI.**

## 7.3.6 Acupuncture

A number of studies have demonstrated the effectiveness of acupuncture in treating insomnia within healthy individuals and various other patient populations; however, many of these studies have methodological limitations (Zhao, 2013). Moreover, few studies have examined the benefits of acupuncture in the ABI population specifically. In this section, we review the available evidence.

**Table 7.5 Acupuncture for the Treatment of Insomnia Post ABI**

Author Year Country Study Design Sample Size	Methods	Outcome
<a href="#">Zollman et al.</a> (2012) USA RCT PEDro=5 N <sub>initial</sub> =24, N <sub>Final</sub> =20	<b>Population:</b> TBI=20; Gender: Male=9, Female=11. <i>Treatment Group (n=12):</i> Mean Age=44.5yr; Mean Time Since Injury=2.17 yr. <i>Control Group (n=8):</i> Mean age=43.5yr; Mean Time Since Injury= 3yr. <b>Intervention:</b> 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. <b>Outcome Measure:</b> Insomnia Severity Index (ISI), Hamilton Depression Rating Scale, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Paced Auditory Serial Addition Test (PASAT).	<ol style="list-style-type: none"> <li>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).</li> <li>The treatment group showed a decrease in ISI scores from baseline to post treatment (p&lt;0.01) and from baseline to 1mo follow-up (p&lt;0.01); no significant differences were found in the control group.</li> <li>Depression was positively associated with ISI scores at baseline (p&lt;0.01), but not post treatment (p=0.45).</li> <li>PASAT scores were positively associated with ISI at baseline (p=0.02) and follow-up (p=0.03).</li> <li>RBANS scores were not associated with sleep variables.</li> </ol>

## Discussion

Zollman et al. (2012) explored the use of acupuncture, compared to education, in addressing issues of insomnia within a TBI population. A between-group comparison showed no significant difference in the Insomnia Severity Index (ISI) scores at three time points (e.g., baseline, post treatment, and at one-month post treatment). The groups also did not differ significantly in terms of sleep time pre and post treatment.

When examining the within-group ISI scores, the treatment group showed a statistically significant decrease in the perception of insomnia severity between pre and post treatment. No such differences were seen in the control group. Those in the treatment group also showed significant improvement on overall cognitive functioning and divided attention. This treatment modality should be studied further within a brain injury population.

## Conclusions

***There is level 2 evidence that acupuncture may not improve insomnia compared to instructions on good sleep habits in patients with TBI.***

**Acupuncture therapy has may not improve insomnia in patients with TBI.**

### 7.3.7 Light Therapy

Light therapy has not been well studied in the ABI population; however, it has been suggested to be a potential treatment modality to address fatigue and daytime sleepiness. In healthy individuals and other patient populations, light exposure has led to improvements in sleepiness, mood and vigilance performance, as well as having an arousing effect on various biological mechanisms (Ponsford et al., 2012).

**Table 7.6 Light Therapy for the Treatment of Insomnia Post ABI**

Author Year Country Study Design Sample Size	Methods	Outcome
<a href="#">Sinclair et al.</a> (2014) Australia RCT PEDro=6 N=30	<p><b>Population:</b> TBI=30; Mean Age= 42yr; Male=24, Female=6; Mean Time Post Injury=1106d; Severity: Mild=7, Moderate=8, Severe=15.</p> <p><b>Intervention:</b> 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.</p> <p><b>Outcome Measure:</b> Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI).</p>	<ol style="list-style-type: none"> <li>1. Compared to the control group, the blue light therapy group showed a significantly greater reduction in fatigue (FSS; <math>p&lt;0.001</math>) and a significant reduction in daytime sleepiness (ESS; <math>p&lt;0.01</math>). However, no significant improvements were observed in the yellow light therapy group when compared to controls.</li> <li>2. There was no significant change in PSQI score in any treatment condition (<math>p&gt;0.05</math>).</li> </ol>

## Discussion

Sinclair et al. (2014) conducted a RCT examining the effectiveness of light therapy, both blue and yellow, compared to a control group. The blue light therapy significantly decreased fatigue ( $p<0.001$ ) and daytime sleepiness ( $p<0.01$ ) compared to the control group. The yellow light therapy did not show such improvements compared to the control group. The improvements measured during the treatment phase did not persist at follow-up (week 8).

## Conclusions

*There is level 1b evidence that blue light therapy, but not yellow light therapy, may be effective in reducing fatigue and daytime sleepiness compared to no treatment in patients with TBI.*

Blue light therapy may reduce fatigue and daytime sleepiness in patients with TBI, however this improvement may not persist beyond the treatment period.

## 7.4 Pharmacological Management Strategies

Individuals who have sustained a brain injury often have cognitive disabilities as a result. Insomnia and sleep disorders have been known to compound the neurocognitive difficulties experienced post injury. Despite the knowledge that fatigue and sleep disorders play a role in the recovery from an ABI, very few interventions have been developed to help manage these issues. Many pharmacological interventions have been tested in other populations (narcolepsy, multiple sclerosis, Parkinson's, etc.) (Rao et al., 2006), but few have been tested within the ABI population specifically. Treatments have included the administration of various over-the-counter medications (e.g., Sleep-Eze, Nytol, etc.) (Thaxton & Patel, 2007). There has been some discussion about the possible therapeutic benefits of using medications such as methylphenidate, dextroamphetamine, carbidopa, amantadine, and modafinil to treat fatigue post TBI (Rao et al., 2006).

### 7.4.1 Modafinil

Modafinil, a wakefulness promoting agent, has been approved to address EDS (Jha et al., 2008). Additionally, the drug was approved for use to address narcolepsy and sleeping difficulties associated with shift work (US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000). Modafinil was found to enhance quality of life for those with narcolepsy (Beusterien et al., 1999). Studies exploring modafinil for fatigue and EDS among Parkinson's disease, multiple sclerosis, TBI, and post-polio syndrome populations provide inconsistent results (Sheng et al., 2013).

**Table 7.7 Modafinil for the Treatment of Fatigue and Excessive Daytime Sleepiness Post ABI**

Author Year Country Study Design Sample Size	Methods	Outcome
<a href="#">Kaiser et al.</a> (2010) Switzerland RCT PEDro=9 N=20	<b>Population:</b> TBI=20; Gender: Male=17, Female=3. <i>Treatment Group (n=10):</i> Mean Age=37yr; Mean GCS=7. <i>Control Group (n=10):</i> Mean Age=43yr; Mean GCS=8. <b>Intervention:</b> Patients received either 100-200mg modafinil or placebo every morning for 6wk. <b>Outcome Measure:</b> Excessive Daytime Sleepiness (EDS), Fatigue Severity Scale (FSS), Maintenance of Wakefulness Test (MWT).	<ol style="list-style-type: none"><li>1. At 6 weeks, the decrease in FSS scores was greater in the modafinil group compared to the control group (-0.8± 1.0 versus 0.0± 0.6) but this was not significant (p=0.07).</li><li>2. The modafinil group had greater decreases in EDS scores versus placebo (p&lt;0.005).</li><li>3. On the MWT, a significantly greater improvement was shown for the modafinil group when compared to placebo (8.4± 9.6 versus 0.4± 6.2 min, p=0.04).</li></ol>



Author Year Country Study Design Sample Size	Methods	Outcome
		4. Of those patients with fatigue at baseline (FSS $\geq$ 4), decreases in FSS scores were not greater in the treatment group.
<a href="#">Jha et al. (2008)</a> USA RCT PEDro=8 N <sub>Initial</sub> =51, N <sub>Final</sub> =46	<b>Population:</b> TBI=51; Mean Age=38.25yr; Gender: Male=35, Female=16; Mean Time Post Injury=5.77yr. <b>Intervention:</b> 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. <b>Outcome Measure:</b> 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 EDS for individuals with TBI (Jha et al., 2008; Kaiser et al., 2010). Neither study found a significant difference in terms of fatigue, as measured by the FSS, between the treatment and control group. Further, when Kaiser et al. (2010) compared those with fatigue at baseline (FSS  $\geq$ 4) in both groups, the decrease in FSS scores remained non-significant between groups. In one study the treatment group showed a significantly greater decrease in Epworth Sleepiness Scale scores when compared with controls, representing a greater improvement in EDS (Jha et al., 2008). It should be noted, however, that Jha et al. (2008) found the improvement to be significant at week four (p=0.02) but not at week ten (p=0.56), highlighting that there was no clear temporal pattern of benefit. Of concern, those receiving modafinil reported more insomnia than controls (p=0.03) (Jha et al., 2008). These studies suggest that modafinil may be effective for improving daytime sleepiness, but not fatigue.

## Conclusions

***There is level 1a evidence that modafinil may not be effective for treating fatigue compared to placebo in patients with TBI, but may be effective short-term in treating excessive daytime sleepiness post TBI.***

**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.**



## 7.4.2 Methylphenidate

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

**Table 7.8 Methylphenidate for the Treatment of Sleep Disorders Post ABI**

Author Year Country Study Design Sample Size	Methods	Outcome
<a href="#">Al-Adawi et al.</a> (2006) Oman Case Control N=30	<b>Population:</b> TBI=30; Mean Age=51yr; Gender: Male=23, Female=7. <b>Intervention:</b> 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. <b>Outcome Measure:</b> Sleep State, Functional Independence Measure (FIM), Rancho Los Amigo: Levels of Cognitive Functioning (RLA).	<ol style="list-style-type: none"><li>1. 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).</li><li>2. Mean hours of sleep at night for the treatment and control groups were 6.4 and 6.9hr, respectively.</li><li>3. 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).</li><li>4. RLA scores were comparable between groups at baseline (p=0.479).</li></ol>

## Discussion

In a study by Al-Adawi et al. (2006), no significant differences were found between those who received methylphenidate and those who did not when looking at the scores of various assessment scales (e.g., activities of daily living, mobility, and cognition). Further, sleep times between the two groups were not significantly different. Based on this study, methylphenidate does not seem to have adverse effects on sleep-wake quantity post ABI.

## Conclusions

***There is level 3 evidence that methylphenidate may not have adverse effects on the sleep-wake cycle compared to those not receiving medication post TBI.***

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

## 7.4.3 Lorazepam and Zopiclone

Lorazepam, a benzodiazepine also known as Ativan or Temesta, is primarily an anti-anxiety medication that, due to its side effects, has been used for the treatment of sleep disorders (Thaxton & Patel, 2007).

Zopiclone is a non-benzodiazepine medication, however it works at the same receptor sites as benzodiazepines. Zopiclone has been used in the treatment of insomnia for individuals experiencing problems with delayed sleep onset, difficulties maintaining sleep, and/or early waking (Hair et al., 2008; Thaxton & Patel, 2007). In a RCT-crossover trial conducted by Li Pi Shan and Ashworth (2004), the two medications were studied in a mixed stroke and TBI population. Participants received either lorazepam (0 to 1 mg) or zopiclone (3.75 to 7.5 mg), which were taken orally in the evening on an as-needed basis. At the end of study, the two groups did not differ significantly in terms of average sleep time, quality of sleep, depth of sleep, feelings of being refreshed, or feelings of alertness or tiredness during the day. The authors reported that zopiclone was as effective as lorazepam in treating insomnia (Li Pi Shan & Ashworth, 2004). Due to less than 50% of the study population sustaining a brain injury, no level of evidence will be drawn from this study. Additional studies, focusing on a brain injury population, are needed before determining the effectiveness of lorazepam and zopiclone for insomnia post TBI.

#### 7.4.4 (-)-OSU6162

(-)-OSU6162 is a monoaminergic stabilizer that has been investigated for the treatment of Huntington's disease, alcohol dependence, and fatigue (Berginstrom et al., 2017; Khemiri et al., 2015; Kloborg et al., 2014; Nilsson et al., 2017). (-)-OSU6162 works on both the dopamine and serotonin systems, but is classified as a dopaminergic stabilizer due to its affinity for D2 and D3 receptors, meaning it can both inhibit and stimulate dopamine behavior (Berginstrom et al., 2017). In this section, we specifically examine the effect of (-)-OSU6162 on fatigue.

**Table 7.9 (-)-OSU6162 for the Treatment of Fatigue Post ABI**

Author Year Country Study Design Sample Size	Methods	Outcomes
<a href="#">Berginstrom et al.</a> (2017) Sweden RCT PEDro=10 N=64	<p><b>Population:</b> TBI; <i>Treatment Group</i> (n=33): Mean Age=41.42yr; Gender: Male=17, Female=16; Mean Time Post Injury=8.58yr. <i>Control Group</i> (n=31): Mean Age=42.58yr; Gender: Male=20, Female=11; Mean Time Post Injury=8.10yr.</p> <p><b>Intervention:</b> (-)-OSU6162 was compared with placebo during a 4wk treatment period. 5mg of (-)-OSU6162 was given 2x/d in week 1, 10mg 2x/d in week 2, and 15mg 2x/d in weeks 3 and 4. Patients were evaluated at baseline, at days 7, 14, 22, and 28 during treatment, and for follow-up at 2 and 6mo.</p> <p><b>Outcome Measure:</b> Fatigue Severity Scale (FSS), Mental Fatigue Scale (MFS), Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ).</p>	<ol style="list-style-type: none"> <li>1. For the FSS, MFS, RPCSQ, and both groups showed significant improvement (all p&lt;0.01) after the trial but not during follow-up. No between group differences were observed.</li> <li>2. During follow-up, the treatment group had significantly larger changes in folic acid (p=0.02), prolactin (p=0.03), and heart rate (p=0.009).</li> </ol>

#### Discussion

In an RCT by Berginstrom et al. (2017) (-)-OSU6162 was compared to placebo in patients with TBI (GCS>5). On both the Fatigue Severity Scale and the Mental Fatigue Scale, both groups showed significant reductions in fatigue; however, no between-group differences were observed. It is worth noting that

participants received a dose of 15mg twice per day, and at the end of the trial the mean plasma concentration was lower than expected (0.14µM). However, significantly larger changes in folic acid, prolactin, and heart rate were recorded for the experimental group, suggesting that these plasma levels may still have been high enough to elicit a physiological effect. Based on this study, (-)-OSU6162 may not be effective in reducing fatigue in patients with TBI.

## Conclusions

***There is level 1b evidence that (-)-OSU6162 may not be effective for treating fatigue compared to placebo in patients with TBI.***

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

## 7.4.5 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 cause disruptions to the sleep-wake cycle (Shekleton et al., 2010). In an observational overnight study, Grima et al. (2016b) compared melatonin production of individuals with TBI to healthy controls. TBI patients showed 42% less melatonin production, and was delayed by 1.5 hours on average (Grima et al., 2016b). Melatonin offers very minimal side effects, enhancing the drugs usefulness in aiding treatment of sleep disorders (Grima et al., 2018). One article met the inclusion criteria investigating a melatonin intervention in individuals with severe TBI.

**Table 7.10 Melatonin for the Treatment of Fatigue and Sleep Disorders Post ABI**

Author Year Country Study Design Sample Size	Methods	Outcome
<a href="#">Grima et al. (2018)</a> Australia RCT Crossover PEDro=9 N=33	<p><b>Population:</b> Melatonin-placebo group (N=18): Mean Age=35yr; Gender: Male=61%, Female=39%; Median Time Post Injury=61mo; Median GCS= 5. Placebo-melatonin group (N=15): Mean Age=38yr; Gender: Male=73%, Female=27%; Median Time Post Injury= 25mo; Median GCS=8.</p> <p><b>Intervention:</b> Participants with chronic insomnia were randomly allocated to a 4wk melatonin or placebo treatment before crossover. Melatonin formula was a prolonged release formula (2mg). Participants were measured at baseline and at the end of each treatment phase.</p> <p><b>Outcomes:</b> 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); vRole Physical (RP);</p>	<ol style="list-style-type: none"> <li>1. PSQI scores were significantly different between melatonin and placebo treatments (p&lt;0.0001) showing the melatonin treatment group had lower scores.</li> <li>2. Sleep latency scores were not significantly different between treatments (p=0.23).</li> <li>3. Sleep efficiency scores were significantly different between treatments (p=0.04) showing the melatonin treatment had higher scores.</li> <li>4. ESS scores were not significantly different between treatments (p=0.15).</li> <li>5. HADS anxiety scores were significantly different between treatments (p=0.0006) showing the melatonin treatment had lower scores.</li> <li>6. HADS depression scores were not significantly different between treatments (p=0.68).</li> </ol>

	Role-emotional (RE); Vitality (VT); Mental Health (MH); Social functioning (SF); bodily pain (BP); general health (GH).	<p>7. FSS scores were significantly different between treatments (<math>p=0.03</math>) showing the melatonin treatment had lower scores.</p> <p>8. VT and MH scores of the SF-36 were significantly different between treatments (<math>p=0.03</math> and <math>p=0.01</math>, respectively) showing the melatonin treatment had higher scores.</p> <p>9. The other subscales of the SF-36 were not significantly different between treatments (<math>p&gt;0.05</math>).</p>
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## Discussion

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

## Conclusions

***There is level 1b evidence that melatonin treatment may be effective in improving sleep quality, sleep efficiency, and fatigue compared to a placebo group in patients post TBI.***

***There is level 1b evidence that melatonin treatment may not effect sleep onset latency or daytime sleepiness in patients post TBI.***

**Melatonin treatment may improve sleep quality, sleep efficiency, and reduce fatigue in patients post TBI.**

**Melatonin treatment may not effect sleep onset latency or daytime sleepiness.**

## 7.5 Conclusions

Current research has focused on exploring and identifying sleep and fatigue related issues post ABI but minimal research has focused on treatment interventions. Therefore, the results of this review provide little guidance to clinicians in the management of fatigue and sleep disorders post ABI. Cognitive behavioural strategies, such as energy conservation and pacing, that are commonly encouraged by health professionals have little published research evidence supporting their use. Pharmacological interventions for management of fatigue also appear to be understudied. Clinicians must rely on their individual clinical experiences/expertise when treating such issues. Utilizing research conducted on other patient populations may also be useful. Future research should focus on the management of fatigue and sleep disorder symptoms post ABI.

## 7.6 Summary

*There is level 2 evidence that a home-based walking program may reduce fatigue up to 24 weeks following treatment compared to a nutritional counselling program in patients with TBI.*

*There is level 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 patients with TBI.*

*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 patients with ABI.*

*There is level 1b evidence that cognitive behavioural therapy may reduce fatigue and insomnia compared to usual care in patients with TBI.*

*There is level 2 evidence that acupuncture may not improve insomnia compared to instructions on good sleep habits in patients with TBI.*

*There is level 1b evidence that blue light therapy, but not yellow light therapy, may be effective in reducing fatigue and daytime sleepiness compared to no treatment in patients with TBI.*

*There is level 1a evidence that modafinil may not be effective for treating fatigue compared to placebo in patients with TBI, but may be effective short-term in treating excessive daytime sleepiness post TBI.*

*There is level 3 evidence that methylphenidate may not have adverse effects on the sleep-wake cycle compared to those not receiving medication post TBI.*

*There is level 1b evidence that (-)-OSU6162 may not be effective for treating fatigue compared to placebo in patients with TBI.*

*There is level 1b evidence that melatonin treatment may be effective in improving sleep quality, sleep efficiency, and fatigue compared to a placebo group in patients post TBI.*

*There is level 1b evidence that melatonin treatment may not effect sleep onset latency or daytime sleepiness in patients post TBI.*

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