

ERABI

EVIDENCE-BASED REVIEW
of moderate to severe
ACQUIRED BRAIN INJURY

15. Fatigue and Sleep Disorders Post Acquired Brain Injury

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Abbreviations

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

Key Points

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

Moderate exercise may reduce fatigue, and this reduction may persist 24-weeks after treatment in patients with TBI.

Programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce fatigue and sleepiness in patients with ABI, with treatment effects lasting longer for the latter.

Cognitive behavioural therapy may reduce fatigue and improve sleep in patients with TBI.

Problem solving therapy is not more effective than online health education at improving symptoms of fatigue and insomnia.

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 short-term in treating excessive daytime sleepiness, but may also cause insomnia post TBI.

Methylphenidate may not improve sleep-wake cycles post TBI, but may not have an adverse effect on this outcome when administered in commonly accepted dosages.

15. Fatigue and Sleep Disorders Post Acquired Brain Injury

15.1 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 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., 2016). 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 (Mollayeva 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 (Mollayeva 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 (Mollayeva 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/traumatic brain injury (TBI), 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.

This module explores fatigue and sleep disorders post ABI first by reviewing studies identifying the incidence and prevalence of these symptoms, and subsequently by summarizing and evaluating studies investigating treatment interventions for each.

15.2 Sleep Disorders Post ABI

The relationship between sleep disorders and ABI has been well documented. Numerous studies have compared ABI populations with healthy controls to highlight the high relative occurrence of sleep disorders after an ABI (Duclos et al., 2014; Gardani et al., 2015; Imbach et al., 2016; Imbach et al., 2015; Sinclair et al., 2014; Sommerauer et al., 2013). In one prospective study, Imbach et al. (2015) compared patients with acute TBI with healthy controls. The TBI group had significantly higher total sleep time, higher average sleep needed per 24 hours, and more reports of excessive daytime sleepiness (EDS) as assessed by objective measures. Sommerauer et al. (2013) reported similar results: of the 36 study participants with TBI, 13 reported daytime sleepiness, and all participants with TBI had pleiosomnia (requiring at least 2 hours more sleep per day compared to pre-injury). In a study by Gardani et al. (2015), the investigators found high levels of sleep-wake cycle disturbances in patients with severe TBI undergoing rehabilitation. Sleep-wake cycle disturbances were also associated with fatigue, anxiety, and daytime sleepiness. Concerningly, a number of studies have reported that patients with ABI often underestimate their sleep disturbances based on subjective measures, suggesting that the problem may be even more pronounced than the literature currently presents (Imbach et al., 2016; Imbach et al., 2015).

While it is clear that individuals with ABI are disproportionately more affected by sleep disorders than the general population, the impact of sleep disorders on rehabilitation, recovery, and quality of life remains understudied in this population. 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). Few studies have investigated the impact of sleep disorders on ABI outcomes. In one study by Nakase-Richardson et al. (2013), sleep-wake cycle disturbances at 1 month post-injury predicted hospital length of stay and duration of posttraumatic amnesia. Sandsmark et al. (2016) reported that in the acute ABI setting, signs of sleep recorded by continuous electroencephalography are associated with good outcomes, such as likelihood to be discharged home, shorter intensive care unit and hospital length of stays, and decreased mortality.

It seems that sleep disorders may have a great impact on the success of ABI rehabilitation and patient outcomes, but there are few studies that have investigated sleep disorders and their effects on rehabilitation post ABI (Baumann et al., 2007; Clinchot et al., 1998). Moreover, evidence has suggested that more than half of the individuals who reported having sleep difficulties are not being treated for the condition (Ouellet et al., 2006). Interventional studies addressing sleep disorders in the ABI population are greatly needed.

15.3 Fatigue Post ABI

Even though fatigue has been recognized as a significant problem post ABI, few interventional studies attempting to alleviate fatigue in the ABI population have been identified. However, similar to sleep disorders, a number of studies have quantified the relative occurrence of fatigue in ABI populations compared to healthy controls (Ashman et al., 2008; Borgaro et al., 2005; Chiou et al., 2016; Ponsford et al., 2012; Ziino & Ponsford, 2006). In a study by Chiou et al. (2016), patients with TBI reported

significantly higher levels of fatigue versus healthy controls on the modified fatigue impact scale for both cognitive and physical components. Ponsford et al. (2012) reported that those with TBI had higher scores on the Fatigue severity scale and the causes of fatigue questionnaire, indicating that fatigue had a greater impact on their lifestyle compared to healthy controls. Ashman et al. (2008) administered a 30-minute computerized Cambridge neuropsychological test automated battery to measure fatigue in individuals with TBI versus healthy controls. Individuals with TBI had significantly higher day-to-day and situational fatigue in comparison to the controls. The TBI group also performed worse on the test with respect to task improvement and task accuracy. Between 33% and 64% of individuals reported fatigue post TBI (Englander et al., 2010; Ponsford et al., 2012).

To better understand the severity of the problem, data is often collected through surveys, interviews, 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). This variability in performance may be the result of fatigue (Cohen, 1993). 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. In a study by Esbjornsson et al. (2013), eighteen TBI participants 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). More studies are needed to better understand the relationship between fatigue and rehabilitation. Finding efficient rehabilitation interventions that limit the exacerbation of fatigue, and addressing the underlying causes of fatigue in individuals with ABI looks promising for improving outcomes and quality of life in patients with ABI.

15.4 Non-pharmacological Management Strategies

Fatigue 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.

15.4.3 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. This of course does not invalidate any findings, however, the appropriate approach to incorporating lifestyle changes will be based on individual cases.

Table 15.1 Lifestyle Management Program for the Treatment of Fatigue and Sleep Disorders Post ABI

Author/ Year Country/ Study Design/ N	Methods	Outcome
Chiu et al. (2017) Taiwan RCT Crossover PEDro=8 N=24	<p>Population: TBI; Mean Age=35.9 yr; Gender: Male=9 Female=15; Mean Time Post Injury=27.6 mo.</p> <p>Intervention: Using a crossover design, TBI patients received a 30 min, 41°C warm footbath each day for 3 days then usual care for 3 days (or vice versa), separated by a 3 day washout period.</p> <p>Outcome Measure: Sleep Efficiency (SE), Sleep Onset Latency (SOL), Total Sleep Time (TST), Wake After Sleep Onset (WASO).</p>	<ol style="list-style-type: none"> 1. Warm footbaths showed non-significant improvement in SE compared to control (p=0.09). 2. SOL was significantly reduced during the warm footbath phase as compared with control (p<0.001). 3. TST was not significantly increased during the warm footbath phase compared with control. 4. WASO was significantly reduced during the warm footbath phase as compared with control (p=0.006).
Kolakowsky-Hayner et al. (2017) USA RCT Crossover PEDro=4 N _{initial} =128 N _{final} =62	<p>Population: TBI; Mean Age=42.7 yr; Gender: Male=72 Female=56; Mean Time Post Injury=97.6 mo.</p> <p>Intervention: The treatment group received a 12 wk 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 wk until an overall step increase 40% above baseline was achieved. A 12 wk nutritional counselling program and the same frequency of tapered coaching calls served as the control. Measurements were taken at baseline and wk 12, 24, and 36.</p> <p>Outcome Measure: Global Fatigue Index (GFI), Barrow Neurological Institute (BNI) Fatigue Scale Overall Severity Score, Multidimensional Fatigue Inventory (MFI).</p>	<ol style="list-style-type: none"> 1. Participants had significantly less fatigue at the end of the walking intervention (p<0.001) on GFI scale. 2. According to the BNI Fatigue Scale Total, participants had significantly less fatigue at the end of the walking intervention (p<0.003). 3. According to the BNI Overall Score, participants had significantly less fatigue at the end of the walking intervention (p<0.001) and after 36 wk (p<0.001). The walking intervention in the nutritional first group did not have a significant effect on BNI Overall Score but had significantly reduced BNI Overall Scores by wk 36. 4. According to the MFI, participants had significantly less fatigue at the end of the walking intervention (p<0.001) and after 36wk (p<0.05). However, MFI scores significantly increased following the end of the walking intervention. (p<0.05).

Author/ Year Country/ Study Design/ N	Methods	Outcome
		5. No significant improvements in BMI or blood pressure were observed.
Stubberud et al. (2017) Norway Pre-Post N=8	<p>Population: ABI; Mean Age=41.6 yr; Gender: Male=3, Female=5; Mean Time Post Injury=40.1 mo; Injury Etiology: TBI=3, Cerebrovascular Insults=5.</p> <p>Intervention: Participants underwent 36 hr of programming over 1 mo. 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>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).</p>	<ol style="list-style-type: none"> 1. FSS scores were significantly improved at posttest (p=0.035) and at 3 mo follow-up (p=0.018), but not at 9 mo follow-up. 2. At posttest, FQ total (p=0.018) and physical (p=0.042) scores were significantly improved, but not FQ mental scores. These improvements were not sustained to follow-up. 3. HAD total (p=0.041) and anxiety scores were significantly improved only at 9mo follow-up. 4. ESS scores were significantly improved at 3 mo (p=0.042) and 9 mo (p=0.024) follow-up. 5. No significant changes in ISI, GPSS, or CPT-II scores were reported.

PEdro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

Using a crossover randomized controlled trial (RCT) design, 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.

In another study, the impact of exercise on sleep and fatigue was evaluated in a crossover RCT by Kolakowsky-Hayner et al. (2017). Participants were randomly assigned to receive a 12-week home-based walking program with coaching calls where they were encouraged to increase their weekly step count or were placed on a wait-list. Results indicated that fatigue was significantly improved in the exercise group at posttest according to multiple fatigue scales and these results persisted at 24-week follow-up.

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 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 2 evidence that a home-based walking program may reduce fatigue up to 24 weeks following treatment compared to a nutritional control program 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.

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

Moderate exercise may reduce fatigue, and this reduction may persist 24-weeks after treatment in patients with TBI.

Programming focusing on lifestyle factors, adaptive coping, and goal management training may reduce fatigue and sleepiness in patients with ABI, with treatment effects lasting longer for the latter.

15.4.4 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 (Fellus & Elovic, 2007). Although pacing is a concept that has been accepted with health care professionals and encouraged within the ABI/TBI population, its benefits have not yet been studied with this group and as a result the treatment effects of pacing strategies are not known.

15.4.5 Cognitive and Behavioural Therapies

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). Three studies to date have evaluated the effectiveness of CBT on fatigue and sleep disorders.

Table 15.2 Cognitive Behavioural Therapy for the Treatment of Fatigue and Sleep Disorders Post ABI

Author/ Year Country/ Study Design/ N	Methods	Outcome
<p>Nguyen et al. (2017) Australia RCT PEDro=8 N=24</p>	<p>Population: TBI; <i>CBT Group (n=13)</i>: Mean Age=45.53 yr; Gender: Male=9, Female=4; Mean Time Post Injury=795.15 days. <i>Control Group (n=11)</i>: Mean Age=41.90 yr; Gender: Male=7, Female=4; Mean Time Post Injury=2093.36 days.</p> <p>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 4 mo.</p> <p>Outcome Measure: Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Brief Fatigue Inventory (BFI), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale (HADS),</p>	<ol style="list-style-type: none"> 1. The CBT group had significantly improved PSQI scores posttreatment and at follow-up compared to control ($p<0.001$). There was also a significant improvement in PSQI scores over time for the CBT group ($p=0.032$), but not the control group. 2. The CBT group had significantly improved ISI scores posttreatment ($p<0.01$) and at follow-up ($p<0.001$) compared to control. There was also a significant improvement in ISI scores over time for the CBT group ($p=0.010$), but not the control group. 3. The CBT group had significantly improved BFI scores posttreatment ($p<0.05$) 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. 4. The FSS and ESS yielded no significant between group differences or time effects for either group. 5. The CBT group had significantly improved HADS anxiety scores compared with control only at follow-up ($p<0.05$). There was also a significant improvement in HADS anxiety scores over time for the CBT group ($p=0.050$), but not the control group. 6. The CBT group had significantly improved HADS depression scores compared with control posttreatment ($p<0.05$) and at follow-up ($p<0.001$). There was also a significant improvement in HADS anxiety scores over time for the CBT group ($p<0.001$), but not the control group.
<p>Raina et al. (2016) USA RCT PEDro=4 N_{Initial}=41 N_{Final}=38</p>	<p>Population: TBI; <i>MAX Group (n=17)</i>: Mean Age=43.8 yr; Gender: Male=8, Female=5; Mean Time Post Injury=9.9 mo. <i>Control Group (n=21)</i>: Mean Age=48.1 yr; Gender: Male=13, Female=8; Mean Time Post Injury=11.1 mo.</p> <p>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 sessions per wk for 8 wk, delivered via webcam by 2 occupational therapists.</p> <p>Outcome Measure: Modified Fatigue Impact Scale (MFIS), Patient-Reported Outcomes Measurement Information System Fatigue Scale (PROMIS), Fatigue Severity Scale (FSS).</p>	<ol style="list-style-type: none"> 1. No significant differences between groups were found for all measures.

Author/ Year Country/ Study Design/ N	Methods	Outcome
<p>Ouellet & Morin (2007) Canada Pre-Post N=11</p>	<p>Population: TBI=11; Mean age=27.3 yr; Male=6, Female=5; Mean Time Since Injury=25.64 mo. Intervention: Patients received cognitive behavioural therapy (CBT) for insomnia (8 wk, 1 hr/wk). Specifically, CBT focused on stimulus control, sleep restriction, cognitive restructuring, sleep hygiene education, and fatigue management. Outcome Measure: Total Wake Time, Sleep Efficiency, Sleep Time, Insomnia Severity Index (ISI), Multidimensional Fatigue Inventory (MFI), Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS).</p>	<ol style="list-style-type: none"> Following CBT, significant improvements were seen in total wake time ($p<0.001$) and sleep efficiency ($p=0.01$). 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 ($p=0.24$). 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 ($p<0.015$). Significant reductions in scores were seen after treatment on the DBAS, ISI (both $p<0.01$), and the MFI ($p<0.012$).

PE德罗=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

One RCT has investigated the effect of CBT on fatigue and sleep in the TBI population. Nguyen et al. (2017) randomized patients to receive 8 sessions of CBT or treatment as usual. The CBT group showed significant improvements in sleep quality, insomnia, anxiety, and depression, but not in sleepiness. Results conflicted for fatigue, with the Brief Fatigue Inventory reporting significant between-group differences, as opposed to the Fatigue Severity Scale, which did not report significant differences. In another RCT, participants received either maximum energy (MAX) training or online health education which served as a control (Raina et al., 2016). MAX training consisted of 2 online, webcam-delivered 30-minute 1:1 sessions with an occupational therapist who discussed health education and energy conservation strategies with the patient. No significant between-group differences were reported for any of the 3 fatigue scale outcome measures.

In a pre-post study, Ouellet and Morin (2007) found that CBT was effective for insomnia post TBI. Patients received eight to ten weeks of CBT, totaling eight sessions. 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 ($p<0.001$), sleep efficacy ($p=0.01$), fatigue ($p<0.012$), and insomnia ($p<0.01$), but not for total sleep time (Ouellet & Morin, 2007). No additional 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.

One possible limitation associated with analyzing cognitive and behavioural interventions for fatigue and sleep disorders is that the interventions have important differences that make them difficult to compare. For example, studies can focus on any area of cognition or behavior, and choose for a variety of outcomes to measure the resultant effects. This makes it illogical to equate all cognitive and behavioural studies, in the future standardized protocols for the implementation of specific cognitive strategies should be developed in order to create more robust conclusions.

Conclusions

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

There is level 2 evidence that problem solving therapy compared to online health education is no more effective in improving symptoms of fatigue or insomnia in individuals post-ABI.

<p>Cognitive behavioural therapy may reduce fatigue and improve sleep in patients with TBI.</p> <p>Problem solving therapy is not more effective than online health education at improving symptoms of fatigue and insomnia.</p>
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15.4.6 Acupuncture

A number of RCTs have demonstrated the effectiveness of acupuncture in treating insomnia within healthy individuals and various other patient populations; however, many of these studies are methodologically limited (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 15.3 Acupuncture for the Treatment of Sleep Disorders Post ABI

Author/ Year Country/ Study Design/ N	Methods	Outcome
<p>Zollman et al. (2012) USA RCT PEDro=5 N_{Initial}=24, N_{Final}=20</p>	<p>Population: TBI=20; Gender: Male=9, Female=11. <i>Treatment Group (n=12):</i> Mean age=44.5 yr; Mean Time Since Injury=2.17 yr. <i>Control Group (n=8):</i> Mean age=43.5 yr; Mean Time Since Injury= 3yr.</p> <p>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 72 hr before and after treatment.</p> <p>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).</p>	<ol style="list-style-type: none"> 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). 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. Depression was positively associated with ISI scores at baseline (p<0.01), but not post treatment (p=0.45). PASAT scores were positively associated with ISI at baseline (p=0.02) and follow-up (p=0.03). RBANS scores were not associated with sleep variables.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

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.

15.4.7 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 15.4 Light Therapy for the Treatment of Insomnia Post ABI

Author/ Year Country/ Study Design/ N	Methods	Outcome
Sinclair et al. (2014) Australia RCT PEDro=6 N=30	<p>Population: TBI=30; Mean Age= 42 yr; Male=24, Female=6; Mean Time Post Injury=1106 days; Severity: Mild=7, Moderate=8, Severe=15.</p> <p>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 45 min each morning, within 2 hr of waking up, over the course of the 4 wk treatment phase.</p> <p>Outcome Measure: Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI).</p>	<ol style="list-style-type: none"> 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; $p<0.01$). However, these improvements were not observed in the yellow light therapy group when compared to controls. 2. There was no significant change in PSQI score in any treatment condition ($p>0.05$).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

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.

15.5 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).

15.5.1 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 (Fry, 1998; Group, 2000). Modafinil was found to enhance the 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). Studies exploring the effectiveness of modafinil within the ABI population are limited.

Table 15.5 Modafinil for the Treatment of Fatigue and Excessive Daytime Sleepiness Post ABI

Author/ Year Country/ Study Design/ N	Methods	Outcome
Kaiser et al. (2010) Switzerland RCT PEDro=9 N=20	Population: TBI=20; Gender: Male=17, Female=3. <i>Treatment Group (n=10):</i> Mean age=37 yr; Mean GCS=7. <i>Control Group (n=10):</i> Mean age=43 yr; Mean GCS=8. Intervention: Patients received either 100-200 mg modafinil or placebo every morning for 6 wk. Outcome Measure: Excessive Daytime Sleepiness (EDS), Fatigue Severity Scale (FSS), Maintenance of Wakefulness Test (MWT).	<ol style="list-style-type: none"> At 6 weeks, the decrease in FSS scores was greater in the modafinil group (-0.8 ± 1.0 versus 0.0 ± 0.6), but this was not significant ($p=0.07$). The modafinil group had greater decreases in EDS scores versus placebo ($p<0.005$). On the MWT, a significant increase was shown for the modafinil group when compared to placebo (8.4 ± 9.6 versus 0.4 ± 6.2 min, $p=0.04$). Of those patients with fatigue at baseline ($FSS \geq 4$), decreases in FSS scores were not greater in the treatment group.
Jha et al. (2008) USA	Population: TBI=51; Mean age=38.25 yr; Gender: Male=35, Female=16; Mean Time Post Injury=5.77 yr.	<ol style="list-style-type: none"> No significant between-group differences were found at week 4 or week 10 on the

Author/ Year Country/ Study Design/ N	Methods	Outcome
RCT PEDro=8 N _{Initial} =51, N _{Final} =46	<p>Intervention: The treatment group (n=27) received modafinil (100 mg/day for 3 days, then 200 mg/day for 11 days, then a maintenance dose of 400 mg/day for 8 wk thereafter). The control group (n=24) received placebo. At the end of phase 1 (8 wk) both groups crossed-over.</p> <p>Outcome Measure: Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFI), Epworth Sleepiness Scale (ESS).</p>	<p>FSS (p=0.80 and p=0.61, respectively) or the MFI (p=0.67 and p=0.73, respectively).</p> <ol style="list-style-type: none"> The change in ESS scores was significantly greater in the modafinil group versus placebo at week 4 (p=0.02) but not at week 10 (p=0.56). Adverse events for the treatment group included: headaches (29.5%), insomnia (19.6%), fatigue (9.8%), dizziness (7.8%), and tremors (5.9%). Adverse events reported for placebo: headaches.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Two RCTs have examined the effects of modafinil on fatigue and EDS for individuals with TBI (Jha et al., 2008; Kempf et al., 2010). The two studies followed similar protocols with the initial administration of modafinil 100mg daily, which was then titrated up to 100mg twice per day, and both studies also used a placebo control group. Both studies found no significant difference in terms of fatigue, as measured by the FSS, between the treatment and control groups. 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; Kempf et al., 2010). 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 short-term in treating excessive daytime sleepiness, but may also cause insomnia post TBI.

15.5.2 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. Logically, it follows that methylphenidate may have an adverse effect on sleep-wake cycles in those who it is administered to. We identified one study that examines the effect of methylphenidate on sleep-wake cycles in TBI.

Table 15.6 Methylphenidate for the Treatment of Sleep Disorders Post ABI

Author/ Year Country/ Study Design/ N	Methods	Outcome
<p>Al-Adawi et al. (2006) Oman Case Control N=30</p>	<p>Population: TBI=30; Mean age=51 yr; Gender: Male=23, Female=7. Intervention: Records of patients admitted to a dedicated brain injury unit in 1999 were retrospectively reviewed. Patients receiving methylphenidate (5-10 mg 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 Amigo Levels of Cognitive Functioning.</p>	<ol style="list-style-type: none"> The mean hours of sleep during a 24 hr period did not significantly differ between the treatment and control groups (8.3 versus 9.0 hr, p=0.096). Mean hours of sleep at night for the treatment and control groups were 6.4 and 6.9 hrs, respectively. 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). Rancho Scale scores were comparable between groups at baseline (p=0.479).

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 the sleep-wake cycle post ABI.

Conclusions

There is level 3 evidence that methylphenidate may not improve the sleep-wake cycle compared to no medication in patients with TBI.

Methylphenidate may not improve sleep-wake cycles post TBI, but may not have an adverse effect on this outcome when administered in commonly accepted dosages.

15.5.3 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 randomized, crossover, double blind trial conducted by Li Pi Shan and Ashworth (2004), the two medications were studied in a mixed population (i.e., stroke and TBI). Participants received either lorazepam (0 to 1mg) or zopiclone (3.75 to 7.5 mg), which were taken if needed orally in the evening on a daily basis. At the end of study, few differences pertaining to sleep

outcomes (e.g., length, depth, or quality of sleep) were found between groups. The authors reported that zopiclone was as equally 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.

15.5.4 (-)-OSU6162

(-)-OSU6162 is a dopamine stabilizer that has been investigated for the treatment of Huntington's disease, alcohol dependence, and fatigue (Berginstrom et al., 2017; Khemiri et al., 2015; Kloberg et al., 2014; Nilsson et al., 2017). In this section, we specifically examine the effect of (-)-OSU6162 on fatigue. Nilsson et al. (2017) found in an RCT that while well tolerated, (-)-OSU6162 did not differ from placebo in alleviating fatigue in patients with myalgic encephalomyelitis; however, it was superior to placebo in counteracting fatigue in a subset of patients who were also receiving treatment for depression. In another RCT, Berginstrom et al. (2017) compared (-)-OSU6162 with 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. Furthermore, the small sample size (n=10) limited the statistical power to detect small changes in outcomes. No studies were identified that evaluated the effectiveness of (-)-OSU6162 on alleviating fatigue in the moderate-severe TBI population.

15.6 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.

15.7 Summary

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 2 evidence that a home-based walking program may reduce fatigue up to 24 weeks following treatment compared to a nutritional control program 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 improve sleep and reduce fatigue compared to usual care in patients with TBI.

There is level 2 evidence that problem solving therapy compared to online health education is no more effective in improving symptoms of fatigue or insomnia in individuals post-ABI.

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 improve the sleep-wake cycle compared to no medication in patients with TBI.

15.8 References

References

- Aaronson, L. S., Teel, C. S., Cassmeyer, V., Neuberger, G. B., Pallikkathayil, L., Pierce, J., Press, A. N., Williams, P. D., & Wingate, A. (1999). Defining and measuring fatigue. *Image J Nurs Sch*, 31(1), 45-50.
- Al-Adawi, S., Burke, D. T., & Dorvlo, A. S. (2006). The effect of methylphenidate on the sleep-wake cycle of brain-injured patients undergoing rehabilitation. *Sleep Med*, 7(3), 287-291.
- Armutlu, K., Korkmaz, N. C., Keser, I., Sumbuloglu, V., Akbiyik, D. I., Guney, Z., & Karabudak, R. (2007). The validity and reliability of the Fatigue Severity Scale in Turkish multiple sclerosis patients. *Int J Rehabil Res*, 30(1), 81-85.
- Ashman, T. A., Cantor, J. B., Gordon, W. A., Spielman, L., Egan, M., Ginsberg, A., Engmann, C., Dijkers, M., & Flanagan, S. (2008). Objective measurement of fatigue following traumatic brain injury. *J Head Trauma Rehabil*, 23(1), 33-40.
- Baumann, C. R., Werth, E., Stocker, R., Ludwig, S., & Bassetti, C. L. (2007). Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study. *Brain*, 130(Pt 7), 1873-1883.
- Bay, E., & de-Leon, M. B. (2011). Chronic stress and fatigue-related quality of life after mild to moderate traumatic brain injury. *J Head Trauma Rehabil*, 26(5), 355-363.
- Berginstrom, N., Nordstrom, P., Schuit, R., & Nordstrom, A. (2017). The Effects of (-)-OSU6162 on Chronic Fatigue in Patients With Traumatic Brain Injury: A Randomized Controlled Trial. *J Head Trauma Rehabil*, 32(2), E46-e54.
- Beusterien, K. M., Rogers, A. E., Walsleben, J. A., Emsellem, H. A., Reblando, J. A., Wang, L., Goswami, M., & Steinwald, B. (1999). Health-related quality of life effects of modafinil for treatment of narcolepsy. *Sleep*, 22(6), 757-765.
- Borgaro, S. R., Baker, J., Wethe, J. V., Prigatano, G. P., & Kwasnica, C. (2005). Subjective reports of fatigue during early recovery from traumatic brain injury. *J Head Trauma Rehabil*, 20(5), 416-425.
- Cantor, J. B., Ashman, T., Bushnik, T., Xinsheng, C., Farrell-Carnahan, L., Gumber, S., Hart, T., Rosenthal, J., & Dijkers, M. P. (2014). Systematic Review of Interventions for Fatigue After Traumatic Brain Injury: A NIDRR Traumatic Brain Injury Model Systems Study. *Journal of Head Trauma Rehabilitation*, 29(6), 490-497.
- Chiou, K. S., Chiaravalloti, N. D., Wylie, G. R., DeLuca, J., & Genova, H. M. (2016). Awareness of subjective fatigue after moderate to severe traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, 31(3), E60-E68.
- Chiu, H.-Y., Lin, E.-Y., Chiu, H.-T., & Chen, P.-Y. (2017). A feasibility randomized controlled crossover trial of home-based warm footbath to improve sleep in the chronic phase of traumatic brain injury. *Journal of Neuroscience Nursing*, 49(6), 380-385.
- Clinchot, D. M., Bogner, J., Mysiw, W. J., Fugate, L., & Corrigan, J. (1998). Defining sleep disturbance after brain injury. *Am J Phys Med Rehabil*, 77(4), 291-295.
- Cohen, R. A. S.-C., Y. A. . (1993). Response selection and the executive control of attention. In R.A.Cohen (Ed.), *The neuropsychology of attention* (pp. 49-73). New York, NY: Plenum Press.
- Duclos, C., Dumont, M., Wiseman-Hakes, C., Arbour, C., Mongrain, V., Gaudreault, P. O., Khoury, S., Lavigne, G., Desautels, A., & Gosselin, N. (2014). Sleep and wake disturbances following traumatic brain injury. *Pathol Biol (Paris)*, 62(5), 252-261.
- Elovic, E. P., Dobrovic, N. M., & Fellus, L. (2005). Fatigue after traumatic brain injury. In J. De Luca (Ed.), *Fatigue as a window to the brain*. (pp. 89-105). Massachusetts: Massachusetts Institute of Technology.

- Englander, J., Bushnik, T., Oggins, J., & Katznelson, L. (2010). Fatigue after traumatic brain injury: Association with neuroendocrine, sleep, depression and other factors. *Brain Inj*, 24(12), 1379-1388.
- Esbjornsson, E., Skoglund, T., & Sunnerhagen, K. S. (2013). Fatigue, psychosocial adaptation and quality of life one year after traumatic brain injury and suspected traumatic axonal injury; evaluations of patients and relatives: a pilot study. *J Rehabil Med*, 45(8), 771-777.
- Fellus, J., & Elovic, E. (2007). Fatigue: assessment and treatment. *Brain injury medicine. Zasler ND, Katz DI, Zafonte R, editors. New York: Demos Medical Publishing.*
- Fish, J., Evans, J. J., Nimmo, M., Martin, E., Kersel, D., Bateman, A., Wilson, B. A., & Manly, T. (2007). Rehabilitation of executive dysfunction following brain injury: "content-free" cueing improves everyday prospective memory performance. *Neuropsychologia*, 45(6), 1318-1330.
- Fry. (1998). Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. *Ann Neurol*, 43(1), 88-97.
- Gardani, M., Morfiri, E., Thomson, A., O'Neill, B., & McMillan, T. M. (2015). Evaluation of Sleep Disorders in Patients With Severe Traumatic Brain Injury During Rehabilitation. *Arch Phys Med Rehabil*, 96(9), 1691-1697.e1693.
- Grima, N., Ponsford, J., Rajaratnam, S. M., Mansfield, D., & Pase, M. P. (2016). Sleep disturbances in traumatic brain injury: A meta-analysis. *Journal of Clinical Sleep Medicine*, 12(3), 419-428.
- Group, U. M. i. N. M. S. (2000). Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy: US Modafinil in Narcolepsy Multicenter Study Group. *Neurology*, 54(5), 1166-1175.
- Hair, P. I., McCormack, P. L., & Curran, M. P. (2008). Eszopiclone: a review of its use in the treatment of insomnia. *Drugs*, 68(10), 1415-1434.
- Imbach, L. L., Buchele, F., Valko, P. O., Li, T., Maric, A., Stover, J. F., Bassetti, C. L., Mica, L., Werth, E., & Baumann, C. R. (2016). Sleep-wake disorders persist 18 months after traumatic brain injury but remain underrecognized. *Neurology*, 86(21), 1945-1949.
- Imbach, L. L., Valko, P. O., Li, T., Maric, A., Symeonidou, E.-R., Stover, J. F., Bassetti, C. L., Mica, L., Werth, E., & Baumann, C. R. (2015). Increased sleep need and daytime sleepiness 6 months after traumatic brain injury: A prospective controlled clinical trial. *Brain: A Journal of Neurology*, 138(3), 726-735.
- Jha, A., Weintraub, A., Allshouse, A., Morey, C., Cusick, C., Kittelson, J., Harrison-Felix, C., Whiteneck, G., & Gerber, D. (2008). A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury. *J Head Trauma Rehabil*, 23(1), 52-63.
- Kempf, J., Werth, E., Kaiser, P. R., Bassetti, C. L., & Baumann, C. R. (2010). Sleep-wake disturbances 3 years after traumatic brain injury. *J Neurol Neurosurg Psychiatry*, 81(12), 1402-1405.
- Khemiri, L., Steensland, P., Guterstam, J., Beck, O., Carlsson, A., Franck, J., & Jayaram-Lindstrom, N. (2015). The effects of the monoamine stabilizer (-)-OSU6162 on craving in alcohol dependent individuals: A human laboratory study. *Eur Neuropsychopharmacol*, 25(12), 2240-2251.
- Kloberg, A., Constantinescu, R., Nilsson, M. K., Carlsson, M. L., Carlsson, A., Wahlstrom, J., & Haghghi, S. (2014). Tolerability and efficacy of the monoaminergic stabilizer (-)-OSU6162 (PNU-96391A) in Huntington's disease: a double-blind cross-over study. *Acta Neuropsychiatr*, 26(5), 298-306.
- Kolakowsky-Hayner, S. A., Bellon, K., Toda, K., Bushnik, T., Wright, J., Isaac, L., & Englander, J. (2017). A randomised control trial of walking to ameliorate brain injury fatigue: A NIDRR TBI model system centre-based study. *Neuropsychological Rehabilitation*, 27(7), 1002-1018.

- Lee, H., Kim, S. W., Kim, J. M., Shin, I. S., Yang, S. J., & Yoon, J. S. (2005). Comparing effects of methylphenidate, sertraline and placebo on neuropsychiatric sequelae in patients with traumatic brain injury. *Hum Psychopharmacol*, *20*(2), 97-104.
- Lee, K. A., Hicks, G., & Nino-Murcia, G. (1991). Validity and reliability of a scale to assess fatigue. *Psychiatry Res*, *36*(3), 291-298.
- Lewis, G., & Wessely, S. (1992). The epidemiology of fatigue: more questions than answers. *J Epidemiol Community Health*, *46*(2), 92-97.
- Lezak, M. D. (1978). Subtle sequelae of brain damage. Perplexity, distractibility, and fatigue. *Am J Phys Med*, *57*(1), 9-15.
- Li Pi Shan, R. S., & Ashworth, N. L. (2004). Comparison of lorazepam and zopiclone for insomnia in patients with stroke and brain injury: a randomized, crossover, double-blinded trial. *Am J Phys Med Rehabil*, *83*(6), 421-427.
- Mathias, J. L., & Alvaro, P. K. (2012). Prevalence of sleep disturbances, disorders, and problems following traumatic brain injury: A meta-analysis. *Sleep Medicine*, *13*(7), 898-905.
- Mollayeva, T., Colantonio, A., Mollayeva, S., & Shapiro, C. M. (2013). Screening for sleep dysfunction after traumatic brain injury. *Sleep Medicine*, *14*(12), 1235-1246.
- Moseley, A. M., Herbert, R. D., Sherrington, C., & Maher, C. G. (2002). Evidence for physiotherapy practice: a survey of the Physiotherapy Evidence Database (PEDro). *Aust J Physiother*, *48*(1), 43-49.
- Nakase-Richardson, R., Sherer, M., Barnett, S. D., Yablon, S. A., Evans, C. C., Kretzmer, T., Schwartz, D. J., & Modarres, M. (2013). Prospective evaluation of the nature, course, and impact of acute sleep abnormality after traumatic brain injury. *Arch Phys Med Rehabil*, *94*(5), 875-882.
- Nguyen, S., McKay, A., Wong, D., Rajaratnam, S. M., Spitz, G., Williams, G., Mansfield, D., & Ponsford, J. L. (2017). Cognitive Behavior Therapy to Treat Sleep Disturbance and Fatigue After Traumatic Brain Injury: A Pilot Randomized Controlled Trial. *Arch Phys Med Rehabil*, *98*(8), 1508-1517.e1502.
- Nilsson, M. K. L., Zachrisson, O., Gottfries, C. G., Matousek, M., Peilot, B., Forsmark, S., Schuit, R. C., Carlsson, M. L., Kloberg, A., & Carlsson, A. (2017). A randomised controlled trial of the monoaminergic stabiliser (-)-OSU6162 in treatment of myalgic encephalomyelitis/chronic fatigue syndrome. *Acta Neuropsychiatr*, 1-10.
- Olver, J. H., Ponsford, J. L., & Curran, C. A. (1996). Outcome following traumatic brain injury: a comparison between 2 and 5 years after injury. *Brain Inj*, *10*(11), 841-848.
- Ouellet, M.-C., Beaulieu-Bonneau, S., & Morin, C. M. (2015). Sleep-wake disturbances after traumatic brain injury. *The Lancet Neurology*, *14*(7), 746-757.
- Ouellet, M. C., Beaulieu-Bonneau, S., & Morin, C. M. (2006). Insomnia in patients with traumatic brain injury: frequency, characteristics, and risk factors. *J Head Trauma Rehabil*, *21*(3), 199-212.
- Ouellet, M. C., & Morin, C. M. (2004). Cognitive behavioral therapy for insomnia associated with traumatic brain injury: a single-case study. *Arch Phys Med Rehabil*, *85*(8), 1298-1302.
- Ouellet, M. C., & Morin, C. M. (2007). Efficacy of cognitive-behavioral therapy for insomnia associated with traumatic brain injury: a single-case experimental design. *Arch Phys Med Rehabil*, *88*(12), 1581-1592.
- Ponsford, J., Schonberger, M., & Rajaratnam, S. M. (2015). A Model of Fatigue Following Traumatic Brain Injury. *J Head Trauma Rehabil*, *30*(4), 277-282.
- Ponsford, J. L., Ziino, C., Parcell, D. L., Shekleton, J. A., Roper, M., Redman, J. R., Phipps-Nelson, J., & Rajaratnam, S. M. W. (2012). Fatigue and sleep disturbance following traumatic brain injury—their nature, causes, and potential treatments. *Journal of Head Trauma Rehabilitation*, *27*(3), 224-233.

- Raina, K. D., Morse, J. Q., Chisholm, D., Leibold, M. L., Shen, J., & Whyte, E. (2016). Feasibility of a cognitive behavioral intervention to manage fatigue in individuals with traumatic brain injury: A pilot study. *The Journal of Head Trauma Rehabilitation, 31*(5), E41-E49.
- Rao, V., Rollings, P., & Spiro, J. (2006). Fatigue and sleep problems. In T. W. M. J.M.Silver, & S. C. Yudofsky (Ed.), *Textbook of Traumatic Brain Injury First Edition ed.* (pp. 369-384). Washington, DC.: American Psychiatric Publishing, Inc.
- Sandsmark, D. K., Kumar, M. A., Woodward, C. S., Schmitt, S. E., Soojin, P., & Lim, M. M. (2016). Sleep Features on Continuous Electroencephalography Predict Rehabilitation Outcomes After Severe Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation, 31*(2), 101-107.
- Sinclair, K. L., Ponsford, J., & Rajaratnam, S. M. W. (2014). Actigraphic Assessment of Sleep Disturbances following Traumatic Brain Injury. *Behav Sleep Med, 12*(1), 13-27.
- Sommerauer, M., Valko, P. O., Werth, E., & Baumann, C. R. (2013). Excessive sleep need following traumatic brain injury: a case-control study of 36 patients. *J Sleep Res, 22*(6), 634-639.
- Stubberud, J., Edvardsen, E., Schanke, A. K., Lerdal, A., Kjeverud, A., Schillinger, A., & Lovstad, M. (2017). Description of a multifaceted intervention programme for fatigue after acquired brain injury: a pilot study. *Neuropsychol Rehabil, 1*-23.
- Thaxton, L., & Patel, A. (2007). Sleep disturbances: Epidemiology, assessment, and treatment. In N. D. Zasler, D. I. Katz, & R. D. Zafonte (Eds.), *Brain injury medicine* (pp. 557-575). New York: Demos.
- Toda, K., Wright, J., & Bushnik, T. . (2006). Fatigue in the first year after traumatic brain injury. *Journal of Head Trauma Rehabilitation, 26*, 421.
- Weber, P., & Lutschg, J. (2002). Methylphenidate treatment. *Pediatr Neurol, 26*(4), 261-266.
- Zhao, K. (2013). Acupuncture for the treatment of insomnia. *Int Rev Neurobiol, 111*, 217-234.
- Ziino, C., & Ponsford, J. (2006). Vigilance and fatigue following traumatic brain injury. *J Int Neuropsychol Soc, 12*(1), 100-110.
- Zollman, F. S., Larson, E. B., Wasek-Throm, L. K., Cyborski, C. M., & Bode, R. K. (2012). Acupuncture for treatment of insomnia in patients with traumatic brain injury: a pilot intervention study. *J Head Trauma Rehabil, 27*(2), 135-142.