7. Fatigue and Sleep Disorders Post ABI

On behalf of the ERABI Research Group

7.1 Fatigue Post ABI

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).

Q. How is fatigue defined?

Answer

- 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.46, Aaronson et al. 1999).

Physiological versus Psychological Fatigue

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.53, Jha et al. 2008). Psychological fatigue has been defined as *"a state of wariness related to reduced motivation, prolonged mental fatigue or boredom"* (p.291, Lee et al. 1991).

Clinical Features of Fatigue

Q. What symptoms of fatigue are most commonly reported by those who sustain an ABI?

Answer

- Commonly reported symptoms include tiring easily, increased headaches and irritability.

In the Ziino and Ponsford (2006b) study of 46 individuals with and without a traumatic brain injury (TBI), those without a TBI scored higher on the vigilance task test than those with a TBI. The number of misses recorded on the vigilance task was significantly higher for those with a TBI ($p<0.001$). Decision-making times on the vigilance task became faster for controls ($p<0.006$) indicating that control participants learnt how to improve performance at a greater rate than participants with TBI (Time on Task Effect). Movement time was slower for those with a TBI than for controls ($p<0.001$). Mean movement times

indicated there were no significant differences between the two groups on movement time when Time on Task Effect (p=0.08) or Group x Time on Task Interaction (p=0.86) were measured. Results from the fatigue subscale indicate that both groups had increased fatigue levels following the completion of vigilance tasks. In TBI subjects, higher VAS-F fatigue ratings were associated with more missed targets over the entire vigilance task (p<0.03). Additionally, lower vigilance was linked to a greater number of missed targets in the TBI group (Ziino & Ponsford 2006b).

Toda et al. (2006) 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 (p=0.0092). It was hypothesized that perhaps rehabilitation itself played a role in the feeling of fatigue and once removed from these demands along with the individuals' greater understanding of their deficits, the feelings of fatigue lessened. However, the literature shows that fatigue can persist for many years post injury (Bay & de-Leon 2011; Olver et al. 1996; Ouellet & Morin 2004; Rao et al. 2006).

A meta-analysis conducted by Mathias and Alvaro (2012) found that 50% of people with TBI experience disturbed sleep. Duclos et al. (2014) report the following as common sleep complaints among individuals with moderate to severe brain injury: poor sleep quality, longer sleep-onset latency, increased nocturnal awakening, and insomnia. 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.

Reports of Fatigue Post ABI

To gain information on 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 (FSS), the Fatigue Impact Scale, the Visual Analogue Scale-F (VAS-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).

Q. What does the evidence tell us about the levels of fatigue felt by those who have sustained an ABI?

Answer

- There is Level 3 evidence that those who sustain a TBI report greater levels of fatigue post injury.

When comparing individuals with TBI to healthy controls, it is apparent that those who sustained a brain injury report greater levels of fatigue (Ashman et al. 2008; Borgaro et al. 2005; LaChapelle & Finlayson 1998; Ponsford et al. 2012; Ziino & Ponsford 2006a). Between 33% and 64% of individuals reported fatigue post TBI (Englander et al. 2010; Ponsford et al. 2012). Englander et al. (2010) found that over two-thirds of participants (n=119) had abnormal sleep based on the Pittsburg Sleep Quality Index. The overwhelming conclusion is that fatigue has a greater impact on the lifestyles of those with brain injuries.

Bushnik et al. (2008) found improvements on self-reported fatigue during the first year post injury, although no further changes were seen up to two years post TBI. Unfortunately, when fatigue worsened over the course of two years, it was accompanied by poorer cognitive and motor outcomes as well as reduced levels of general functioning (Bushnik et al. 2008). The former conclusions are unfortunate as the literature suggests that pain, depression and motor deficits are significant predictors of fatigue post TBI (Englander et al. 2010), which could perpetuate a cycle of disability if fatigue is not appropriately managed. The studies have also shown pain, depression and anxiety to be associated with fatigue (Englander et al. 2010; Ponsford et al. 2012; Ziino & Ponsford 2006a). Disability has also been correlated with fatigue (Juengst et al. 2013). Again, fatigue proves to be a complex and multifaceted concept.

Impact on Participation and Quality of Life

There are many challenges to studying fatigue post TBI. One of the challenges is in separating fatigue from pain, depression and many other health related issues. Several assessments, including the DSM-IV (American Psychiatric Association) and the Beck Depression Inventory (Beck et al. 1996), assess fatigue as a symptom of depression. Few scales assess fatigue alone. To do so, one must reduce the overlap that exists between the various scales or tools that are used post TBI (Cantor et al. 2008).

Q. How do higher levels of fatigue impact on quality of life?

Answer

- There is Level 3 evidence to suggest that higher levels of fatigue may lead to a poorer quality of life.

Unfortunately Individuals with TBI were shown to not only use more sleep medications but also have longer sleep latency, lower sleep quality and more daytime dysfunction compared to healthy controls (Fogelberg et al. 2012). Further, those in the TBI group showed greater levels of fatigue, depression, and pain and reported poorer health related quality of life (Cantor et al. 2008). Even when compared to a group of patients with TBI, Schnieders et al. (2012) found that those with fatigue had more anxiety and depression as well as lower quality of life. Huang et al. (2013) found those with persistent sleep complaints had higher scores on the beck depression inventory and the impact event scale.

It is through these studies that it becomes apparent how many facets of life are impacted by sleep disturbances and fatigue. 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 (Esbjörnsson et al. 2013). Fatigue can also negatively impact upon relationships, as there is a tendency towards reacting too quickly in response to others among individuals suffering from fatigue (Esbjörnsson 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 and quality life post injury.

Vigilance and Fatigue

Vigilance has been defined as the ability to sustain a level of alertness over long periods of time (Parasuraman 1984). It has been noted that those who sustain a TBI do 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 2006b).

Q. What does the evidence tell us about the levels of fatigue felt by those who sustain an ABI and their ability to sustain levels of alertness?

Answer

- There is Level 3 evidence, based on one study, that individuals who sustain a TBI do experience greater levels of fatigue and a decrease in vigilance, compared to those without an injury.

In the study conducted by Ziino and Ponsford (2006b), individuals with TBI demonstrated slower decision-making on the vigilance task than those without TBI ($p<0.001$). Despite decision-making becoming faster for controls, this was not the case for the TBI group. The movement speed was also slower for those with TBI than for controls ($p<0.001$). Results from the fatigue subscale indicate that both groups had increased fatigue levels following the completion of the vigilance tasks. Therefore, although participants with TBI performed at a lower level on the task, the level at which they performed was consistent during the vigilance task. Those in the TBI group also had higher diastolic blood pressure readings afterwards, which were associated with subjective fatigue levels. Ziino and Ponsford (2006b) suggest that, in order to maintain a stable level of performance, individuals with TBI are forced to expend more energy (psychologically, physiologically, etc.) and this is associated with subjectively increased levels of fatigue.

7.2 Sleep Disorders Post ABI

Although it would seemingly make sense to link disorders of sleep with fatigue (Clinchot et al. 1998), this relationship remains inconclusive (Fellus & Elovic 2007). 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. It is therefore important to investigate for 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.

Sleep disorders tend to be classified as insomnia, excessive sleep, or excessive daytime sleepiness (EDS; Elovic et al. 2005). 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). There are few studies that have investigated sleep disorders and their effects on rehabilitation post ABI (Baumann et al. 2007; Clinchot et al. 1998). It has been suggested that those who sustain a more 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). Castriotta et al. (2007) found that 47% of individuals with TBI reported EDS. In a recent Canadian study, Ouellet et al. (2006) found, using subjective measures, that approximately 50% of their TBI sample (total n=452) reported symptoms of insomnia and those that did not report insomnia as a problem were sleeping more than before the injury. Individuals with insomnia reported having sleep difficulties 5.7 times per week (Ouellet et al. 2006). It was also noted that more than half of the individuals who reported having sleep difficulties were not being treated for the condition (Ouellet et al. 2006).

Q. In patients who sustain an ABI sleep disturbances are often reported. What do sleep complaints correlate with?

Answer

- Clinchot et al. (1998) revealed for individuals with ABI, sleep complaints correlate with:
  - GCS score >7 at presentation
  - Better immediate memory
  - Pre ABI presence of fatigue
  - A history of substance abuse
  - Age and gender (older and female)

7.3 Management of Fatigue and Sleep Disorders Post ABI

Fatigue post ABI can be treated using pharmacological or non-pharmacological techniques. Non-pharmacological strategies include educating both patients and their family members about the occurrence of fatigue post-TBI as well as the expectations with respect to fatigue following an injury. Diet and lifestyle may play a 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).

Non-Pharmacological Treatments

Pacing

Q. Pacing is a technique that has been suggested to patients by physicians to assist them in dealing with fatigue post ABI. What does the evidence say about the effectiveness of pacing post ABI?

Answer

- The effects of pacing strategies for those who have sustained an ABI are not known.

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.

Cognitive Behavioural Therapy

Cognitive behavioural therapy (CBT) is defined as a therapy that focuses on present cognitive and emotional feelings, and teaches behavioural techniques to aid these feelings through relaxation, promoting self-efficacy, challenging pessimism, graded exposure and activity scheduling (Waldron et al. 2013). CBT is based on the philosophy that the development and maintenance of behaviour and emotion is determined by cognitions held by the individual (Waldron et al. 2013).

Q. What does the evidence tell us about the effectiveness of using cognitive behavioural therapy to treat fatigue and insomnia that may develop post ABI?

Answer

- There is Level 4 evidence, based on one study, to suggest that cognitive behavioural therapy may assist in treating insomnia and help in the management of fatigue post TBI.

Although sleep disturbance is a frequently documented problem post ABI, there is little scientific research that has been conducted in this area (Ouellet & Morin 2004). Sleep disorders, such as insomnia, can affect a person's quality of life, family and social commitments, and their ability to return to work (Ouellet & Morin 2004). In a case study conducted by Ouellet and Morin (2004), sleep disturbances were alleviated through the implementation of CBT.

Ouellet and Morin (2007) found that CBT was effective in dealing with insomnia. 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. Evidently, psychological interventions for insomnia may have therapeutic benefits for individuals post TBI.

Pharmacological Treatments

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).

Methylphenidate

Of the neurostimulants used in the post-acute care of TBI, methylphenidate is common, assisting with memory, attention, verbal fluency, and improving processing speed. While its use is heavily focused on the improvement of functional and cognitive deficits, methylphenidate has been reported to have unfavourable effects on sleep patterns of individuals with brain injuries. However, little has been written focusing directly on the effects of methylphenidate on the sleep-wake cycles of those with ABI (Al-Adawi et al. 2006).

Q. What does the evidence tell us about the effects that methylphenidate has on the sleep-wake cycle?

Answer

- There is Level 2 evidence, based on a single study, that methylphenidate does not have an adverse effect on the sleep-wake cycle of those who have sustained a TBI.

In a double-blind, placebo-controlled study looking at the effects of methylphenidate, sertraline or placebo on individuals with a mild or moderate TBI, Lee et al. (2005) noted that those on methylphenidate, along with those in the placebo group, reported significantly less daytime sleepiness than those in the sertraline group. In this study, all medications were given during the day for a total of four weeks, which may have impacted on the effectiveness of sertraline (Lee et al. 2005). In the 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). More importantly, 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.

Lorazepam and Zopiclone

Lorazepam, a benzodiazepine also known has Ativan or Temesta, is primarily an anti-anxiety medication; however, due to its side effects it has been used for the treatment of sleep disorders (Thaxton & Patel 2007). Zopiclone is a non-benzodiazepine medication, although it works at the same receptor sites as benzodiazepines, that has also 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).

Q. What is the evidence for using either Lorazepam or Zopiclone to treat insomnia in patients who have sustained an ABI?

Answer

- Lorezapam and Zopiclone work equally well in assisting with insomnia, however no level of evidence can be given as a result of the study's less than 50% ABI population.

In a randomized, crossover, double blind trial conducted by Li Pi Shan and Ashworth (2004) the two medications were studied in a mixed population (e.g., 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, little differences pertaining to sleep outcomes (e.g., length, depth or quality of sleep) were found between groups. The authors reported that zopiclone was 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, with a brain injury population, are needed before determining the effectiveness of lorazepam and zopiclone for insomnia post TBI.

Modafinil

Modafinil, a wakefulness promoting agent, was 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 2000; US Modafinil in Narcolepsy Multicenter Study Group 1998). Modafinil was found to enhance the quality of life for those with narcolepsy (Beusterien et al. 1999).

Q. When treating fatigue post ABI what does the evidence say about the administration of modafinil?

Answer

- There is Level 1a evidence that Modafinil is not effective in treating fatigue but has been shown to be effective in the short-term in treatment of excessive daytime sleepiness post ABI.

Two RCTs 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 compared with a placebo control group. Both studies found no significant difference in 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 ≥4) in both groups, the decreases shown in FSS scores remained non-significant between groups (Kempf et al. 2010). The two studies also examined EDS using the Epworth Sleepiness Scale. The treatment groups both showed a significantly greater decrease in ESS scores when compared with controls, representing a greater improvement in EDS (Jha et al. 2008; Kempf et al. 2010).

Study Snapshot

A Randomized Trial of Modafinil for the Treatment of Fatigue and Excessive Daytime Sleepiness in Individuals with Chronic Traumatic Brain Injury (Jha et al. 2008).

- 51 patients with a TBI were randomly assigned to one of two groups (modafinil 100mg n=27 or placebo n=24).
- Those in the modafinil group remained on the medication for 8 weeks and then, following a 4-week wash out period, were given the placebo, while the placebo group simultaneously began taking modafinil.
- No significant differences were noted between the two groups at the 4 week assessment period or at the 10 week assessment period when looking at Fatigue Severity Scale scores
- The modafinil group scored significantly higher on the Epworth Sleepiness Scale at week four ($p=0.02$) than the placebo group; however scores at week ten showed no significant differences between the two groups ($p=0.56$).
- The lack of statistically significant differences on the various subjective and objective measures of fatigue used in this study suggest modafinil was not effective in treating fatigue in post ABI patients.
- These results appear to be similar to those found when using modafinil to treat fatigue in other populations such as Parkinson disease or multiple sclerosis.

7.4 Summary

Current research has focused on exploring and identifying sleep related issues post ABI and has not of yet significantly addressed treatment interventions. The results of this review provide little guidance to clinicians in the management of the common problems of fatigue and sleep disorder post ABI. The significance of the symptom of fatigue remains important since the high prevalence can influence not only the rehabilitation process early on in the course of recovery, but can also affect quality of life in the long run where many survivors have persisting symptoms. Cognitive behavioural strategies such as energy conservation and pacing that are commonly encouraged by health professionals have little published research evidence to support their effectiveness. Pharmacological interventions for management of fatigue also appear to be under studied leading clinicians to rely on their individual clinical experiences or research conducted in patients with other medical conditions. Clearly, there is a need for further research into the management of fatigue and sleep disorder symptoms post ABI.

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