TREATING FATIGUE AND SLEEP DISTURBANCE FOLLOWING BRAIN INJURY

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Fatigue and/or sleep disturbance are reported by up to 80% of patients with TBI and stroke. They impact negatively on functional outcomes, productivity and quality of life.

(Baumann et al., 2007; Borgaro et al., 2005; Bushnik et al., 2007; 2008; Cantor et al., 2008; Cohen et al., 1992; Clinochot et al., 1998; Duncan et al., 2012, 2014; Haboubi et al. 2001; Kempf et al., 2010; Ormstad & Eilertsen, 2015; Ouellet & Morin, 2006; Parsons & Ver Beek, 1982; Ponchel et al., 2015; Ponsford et al., 2000, 2012, 2013; Olver et al., 1996; Terzoudi et al., 2007; Wallace et al., 2012; Wu et al., 2015; ).
Neurological symptoms in 141 indivs with mod-severe TBI at 2, 5 and 10 years post-injury (Ponsford et al., 2014)
POST-CONCUSSIVE SYMPTOMS AT 1 WEEK POST-INJURY (PONSFORD ET AL., J NEUROTRAUMA, 2011)

- Slowed
- Fatigue
- Headache
- Drowsiness
- Concentration
- Falling Asleep
- Foggy
- Sleeping More
- Irritability
- Emotional
- Balance
- Dizziness
- Tingling
- Remembering
- Sleeping Less
- Pain
- Noise
- Nervousness
- Nausea
- Visual
- Light
- Vomiting

Percentage with symptoms

Mild TBI
Controls

* p<.05
POST-CONCUSSIVE SYMPTOMS AT 3 MONTHS POST-INJURY (PONSFORD ET AL., J NEUROTRAUMA, 2011)

Percentage with symptoms

- Fatigue
- Headache
- Drowsiness
- Slowed
- Irritability
- Falling Asleep
- Sleeping Less
- Emotional
- Nervousness
- Rembering
- Concentrating
- Foggy
- Tingling
- Pain
- Dizziness
- Sleeping More
- Visual
- Balance
- Light
- Nausea
- Noise
- Vomiting

Mild TBI
Controls
STROKE (Wu et al., 2014)

- Five longitudinal studies found that more than one third of patients had fatigue 3 months post-stroke.
- Of these approx. two-thirds had fatigue at a later stage (usually > 1 year).
- Of those not reporting fatigue early post-stroke fatigue developed later in 12-58% of cases.
WHAT IS FATIGUE?

• A universal, subjective and multi-dimensional construct
DEFINING FATIGUE

• “The awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity” (Aaronson et al., 1999, p. 46).

• Distinction between:
  - Physiological fatigue – excess energy consumption, or depletion of hormones, neurotransmitters, muscles
    Central (CNS) vs peripheral (PNS) fatigue
  - Psychological fatigue - decreased motivation, boredom associated with chronic stress, anxiety, depression
    ▪ Fatigue experience interpreted within a social and cultural framework
Fatigue Classifications

Fatigue

Physiological
- Central malfunction of CNS
- Peripheral neuro-muscular transmission

Psychological
- Exacerbation due to additional conditions
  - Primary
  - Secondary
  - Proposed subdivision DeLuca (2005)
WHAT IS FATIGUE?

The experience of fatigue generally represents a combination of all these influences
FATIGUE MEASURES

• Visual Analogue Scale for Fatigue (VAS-F) (Lee et al., 1991)
• Fatigue Severity Scale (FSS) (Krupp et al., 1989)
• Barrow Neurological Institute Fatigue Scale (Borgaro et al., 2004)
• Global Fatigue Index (GFI) derived from the Multidimensional Assessment of Fatigue (Cantor et al, 2008; Ashman et al, 2008)
• Modified Fatigue Impact Scale (Fisk et al, 1994)
• Brief Fatigue Inventory (Mendoza et al., 1999)
• Fatigue Assessment Scale (Lynch et al., 2007)
• Structured clinical interview
  - Variability in content and focus (physical, cognitive, emotional symptoms vs impact)
TIME COURSE OF FATIGUE

TBI

• Variability in trajectory, with some showing recovery, some showing persisting fatigue and others showing late onset fatigue (Mollayeva et al., 2014)

• Studies in mild TBI show improvement over time (Beaulieu-Bonneau et al., 2016)

• Studies in mod to severe TBI studies show fatigue remains stable or worsens slightly over time (Beaulieu-Bonneau et al., 2017; Ziino et al., 2006)

STROKE

• Variability in trajectory, with some showing recovery, some showing persisting fatigue and others showing late onset fatigue (Duncan et al., 2014; Wu et al., 2015)
FATIGUE PREDICTORS: DEMOGRAPHIC & OTHER PRE-INJURY FACTORS

TBI
• No sig association of fatigue with age, education, marital status
• Weak association with female gender (Ziino et al., 2006)

STROKE
• No sig association of fatigue with age, education, marital status or social support
• Association with gender in 12/46 studies (Ponchel et al., 2015)
**BIOLOGICAL FACTORS ASSOCIATED WITH FATIGUE**

**TBI**

- No sig association with injury severity (PTA or GCS) (Borgaro et al., 2005, Ziino & Ponsford, 2005; Ponsford et al., 2012)

- Lesions postulated in ARAS, anterior cingulate, middle frontal and basal ganglia areas (Chaudhuri and Behan, 2004; Kohl et al., 2009; Pardini et al., 2010), BUT no evidence of association lesion site with MRI with self-reported fatigue (Schönberger et al., 2016)

- No support for association with neuroendocrine abnormalities (England et al., 2010; Bushnik et al., 2007)

- Decreased CSF hypocretin causing excessive daytime sleepiness (Baumann et al., 2009)

**STROKE**

- No sig association with stroke type, severity, etiology, infarct volume (Ponchel et al., 2015)

- Limited evidence of association lesion side and site on MRI with PSF (Ponchel et al., 2015); some evidence of association with brain stem or basal ganglia lesions early post-stroke (Kutlabaev et al., 2012; Wu et al., 2015)

- No support for association with neuroendocrine abnormalities (Ponchel et al., 2015)

- Preliminary evidence of association with inflammatory markers (one study showing elevated C reactive protein) but more studies needed (Ponchel et al., 2015)
FATIGUE PREDICTORS: COGNITIVE FACTORS

TBI

• Sig association of subjective fatigue with performance on tests of attention and information processing speed, vigilance performance and psychophysiological costs (Ashman et al., 2008; Ziino & Ponsford, 2006a,b)

• No sig association of fatigue with other cognitive performances

STROKE

• Sig association of PSF with concentration difficulty and performance on tests of attention and information processing speed < 1 year post-stroke (Ponchel et al, 2015)

• No sig association of fatigue with other cognitive functions
POST-INJURY FACTORS ASSOCIATED WITH FATIGUE

**TBI**
- Depression
- Anxiety
- Sleep disturbance
- Pain
- Analgesic use
- Unemployment

(Bushnik et al., 2008; Cantor et al., 2008; Ponsford et al., 2012)

**STROKE**
- Depression
- Anxiety
- Sleep disturbance
- Pain
- Analgesic use
- Unemployment
- Disability and HR QOL
- Emotion-focused and/or passive coping; locus of control; self-efficacy

(Ponchel et al., 2015; Wu et al., 2015)
SEM MODEL: RELATIONSHIPS OF FATIGUE WITH ATTENTION, DAYTIME SLEEPINESS, ANXIETY AND DEPRESSION

\[ X^2 = 1.3, \ p = 0.54, \ df=2 \]
\[ \text{RMSEA}=0.0, \ \text{PCLOSE}=.59, \ \text{NNFI}=1.0, \ \text{CFI}=1.0, \ \text{AGFI}=.95, \ \text{Stand. RMR}=.02 \]
Cross-lagged path analysis: fatigue was predictive of depression (b=.20, p<.05) and sleepiness (b=.25, p<.05), but depression and sleepiness did not predict fatigue (p>.05).
FATIGUE AND DEPRESSION IN STROKE

• Less is known of this relationship of fatigue and depression in stroke.

• Ormstad & Eilertsen (2015) acknowledge the common co-existence of fatigue and depression, that PSF may precede depression and encourage intervention for fatigue to prevent development of depression.
SLEEP DISTURBANCE AFTER TBI & STROKE
PROCESS C & PROCESS S
CIRCADIAN RHYTHMICITY AND HOMEOSTASIS

Zigmond et al. (1999), p 1216
SLEEP DISTURBANCES AFTER TBI AND STROKE:

TBI

• Documented in individuals with mild, moderate and severe TBI (30-84% of cases)

• In the early stages of recovery, during PTA (Makley et al., 2008; Sherer et al., 2009) and in acute rehabilitation (Rao et al., 2008)

• Some sleep disturbances resolve with emergence from PTA, chronic sleep dist is reported 6 months (Baumann et al., 2007) and several years post-injury (Ouellet et al., 2006; Kempf et al, 2010; Parcell et al, 2006; Ponsford et al., 2013)

STROKE

• Reported by 32-69% of patients

• High rates of obstructive sleep apnea (72%)
SLEEP DISTURBANCES INCLUDE

- Insomnia
- Hypersomnia – abnormal need for long-lasting sleep
- Obstructive Sleep Apnea - present in up to 72% of stroke patients (Johnson & Johnson, 2010)
- Snoring
- Excessive daytime sleepiness – increased napping
- Poor sleep quality
- Poor sleep efficiency
- Delayed sleep onset
- Early awakenings
- Nightmares
- Periodic Limb Movement/restless leg syndrome
- Narcolepsy

Mathias & Alvaro, 2012; Ormstad & Eilertsen, 2015; Ponchel et al., 2015
SLEEP DISTURBANCES IN POLYSOMNOGRAPHY

STUDIES

TBI

- Documented in 50% of cases
- Difficulties initiating sleep
- Increased nocturnal arousals
- Reduced total sleep duration
- Reduced sleep efficiency
- Reductions in REM sleep
- Changes in slow wave sleep
- Individuals with TBI experienced increased daytime sleepiness and reported reduction in sleep quality.

(Grima, Ponsford et al., 2015, meta-analysis)

STROKE

- Sleep disordered breathing present in 58%
- Sleep disturbance present regardless of sleep-disordered breathing (SDB)
- Patients without SDB had reduced total sleep duration
- Increased sleep latency
- Increased wakefulness during sleep
- Reduced sleep efficiency
- Reduced Stage II and Slow Wave Sleep
- Rapid Eye Movement (REM) sleep reduced when SDB present
- Sleep stages I and REM negatively associated with stroke severity and latency to REM sleep assoc with good outcome

(Terzoudi et al., 2007)
COMPARE THE PAIR-ACTIGRAPHY
BIOLOGICAL FACTORS ASSOCIATED WITH SLEEP DISTURBANCES

- Cardio-respiratory insufficiency - Obstructive sleep apnea
- Daytime sleepiness/increased napping
- Reduced hypocretin secretion
- Disruption to homoestatic sleep mechanism
- Circadian Rhythm disorder
- Hypopituitarism

Castriotta & Murphy, 2011; Orff et al., 2009; Zgaljardic et al., 2014
Mean (SE) salivary melatonin levels calculated every half hour during sampling period (18:00 to 00:30 hours).
Control group had higher melatonin output than the TBI group \((p = 0.031)\).
Melatonin level (AUC) not associated with sleep efficiency or WASO, or anxiety or depression scores \((p > .05)\).
Melatonin level was associated with REM sleep \((r = .35, n = 45, p = .017)\). REM sleep is regulated by the circadian system and is temporally associated with high circulating levels of endogenous melatonin.
MECHANISMS OF SLEEP DISTURBANCE IN TBI

Overnight Salivary Melatonin Profiles in Patients with TBI and Controls

- **Control**
- **TBI**

Melatonin concentration (pM/ml)

Clock time (hr)

- **SynOn**
- **SynOff**
SECONDARY CAUSES

- Sleep
- Chronic Pain
- Depression /anxiety
- Fatigue
- Cognitive Deficits

Strong correlations between fatigue, sleep disorders, depression, anxiety, chronic pain and cognitive deficits (Bushnik et al., 2008; Ponsford et al., 2012; Ponchel et al., 2015)

Need to concurrently address sleep, fatigue, depression, anxiety and cognitive inefficiencies to alleviate symptoms??

Ouellet & Morin, 2006; Parcell et al., 2006; Ponsford et al., 2013; Orff et al., 2009
Treatment

Findings provide some basis for the development of interventions for fatigue and sleep disturbance following traumatic brain injury.
TREATMENT

• Clearly need to assess many potential contributors to fatigue and sleep disturbance

• Treatments will vary accordingly

• For example, where attentional problems and mental slowness are contributing to fatigue, may need to adapt tasks to reduce time pressure

• Or where a person has increased daytime sleepiness and excessive napping, disrupting nighttime sleep there may be a focus on sleep

• ...etc, etc
TREATING FATIGUE AND SLEEP DISTURBANCE

• **CPAP** for sleep apnea; **dopamine agonists** for restless leg syndrome

• **Hypnotics** (e.g., Zolpidem, Zopiclone) not effective in long-term; may cause adverse effects on cognition, daytime sleepiness, sleepwalking, hallucinations *(Grunstein, 2002)*

• **Modafinil** – wake-promoting drug approved for narcolepsy
  
  o RCT by Jha et al *(JHTR, 2008, 23(1) 52-63)* showed no evidence of impact on fatigue following TBI in general TBI sample.
  
  o RCT by Kaiser et al. *(Neurology, 2010, 75)* showed reduction in daytime sleepiness on ESS but no impact on fatigue (FSS) in 20 people with fatigue/sleepiness problems.

• **Methylphenidate** – stimulant – Johannson et al (2014, 2015, 1016) found reduced mental fatigue and increased processing speed following mild to moderate TBI but significant side-effects, including insomnia.

• **Graded Exercise Therapy** – Limited benefits for TBI-related fatigue *(Cantor et al., 2014)*; Some evidence in stroke for physical fatigue *(Zedlitz et al., 2012)*

• **Melatonin for sleep** – RCT in TBI *(Grima, Rajaratnam, Mansfield, Sletten, Spitz, & Ponsford)*

• **Light therapy** – RCT in TBI *(Sinclair, Ponsford, Lockley, & Rajaratnam, JNNR, 2014)*

• **Cognitive Behavioural Therapy** : RCTs in TBI and stroke *(Nguyen, McKay, Wong, Spitz, Mansfield, Williams, Rajaratnam & Ponsford, APMR, 2017; Nguyen, McKay, Wong, Spitz, Mansfield, Williams, Rajaratnam & Ponsford, Neuropsych Rehab 2017;)*
Efficacy of Melatonin for Sleep Disturbance Following TBI: A RCT

Natalie Grima 1, 2, 3, 4, 5, Shantha M.W. Rajaratnam 5, 6, 7, Darren Mansfield 2, 7, 8, Tracey L Sletten 5, Gershon Spitz 1, 2, 5 & Jennie Ponsford

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What is melatonin?

Endogenous Melatonin
- Secreted by the pineal gland only at night
- Plays a role in circadian rhythmicity
- Provides body with internal representation of night
- Correlated with sleep propensity
What is melatonin?

Exogenous Melatonin
- Phase-shifting effects
- Closely associated with sleep propensity, referred to as the ‘soporific effect’
Mechanisms of sleep disturbance in TBI patients: Reduced melatonin

Sample characteristics:
- Moderate to severe n = TBI
- Healthy Controls n = 23

Figure adapted from Shekleton... Ponsford, Rajaratnam. 2010, *Neurology*
Mechanisms of sleep disturbance in TBI

Overnight Salivary Melatonin Profiles in Patients with TBI and Controls

- Control
- TBI

Melatonin concentration (pM/ml)

Clock time (hr)

18:00 20:00 22:00 24:00 02:00 04:00 06:00 08:00 10:00 12:00
Melatonin supplementation RCT protocol

Aims:
• To examine the impact of melatonin supplementation on sleep quality and sleep onset latency in individuals with sleep disturbance following TBI

Design
• 10 week, randomized, double-bind, placebo-controlled, 2-treatment (melatonin & placebo) crossover study (2 x 4-week treatment phases).

Participants
• Community dwelling mild-to-severe TBI patients recruited from hospitals in Melbourne, Australia
• Newly developed sleep disturbance (PSQI>7) post TBI
• No pre-injury sleep disorder; sleep apnea; use of hypnotics; benzodiazepines or illicit drugs; recent transmeridien travel or shift work.
• Permitted to continue other rehabilitative or pharmacologic therapy provided it remained stable throughout intervention.
Melatonin supplementation RCT protocol

Treatment

- Circadin 2mg (prolonged release melatonin)
- Placebo identical in color and appearance
- Treatments consumed 2 hours before bed time

In insomnia in older adults, Circadin (2mg) has been shown to:

- Improve sleep quality, sleep efficiency and sleep onset latency  
  (Garfinkel et al., 1995; Haimov et al., 1995; Lemoine et al., 2007; Wake et al., 2011; Wake et al., 2010; Wade et al., 2007)
## Outcomes

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sleep quality (Pittsburgh Sleep Quality Index; PSQI)</td>
<td>• Wrist actigraphy sleep efficiency</td>
</tr>
<tr>
<td>• Wrist actigraphy sleep onset latency corroborated with sleep diary</td>
<td>• Daytime sleepiness (Epworth Sleepiness Scale; ESS)</td>
</tr>
<tr>
<td></td>
<td>• Fatigue Severity Scale (FSS)</td>
</tr>
<tr>
<td></td>
<td>• Anxiety and depression (Hospital Anxiety and Depression Scale; HADS)</td>
</tr>
<tr>
<td></td>
<td>• Quality of life (SF-36 Health Survey)</td>
</tr>
</tbody>
</table>
107 referred to the study

35 randomized to treatment

Melatonin 1st
(n = 18)

Placebo 2nd
(n = 18)

Placebo 1st
(n = 17)

Melatonin 2nd
(n = 14)

33 TBI patients included in ITT analysis
<table>
<thead>
<tr>
<th>TBI characteristics</th>
<th>Melatonin then placebo ( n = 18 )</th>
<th>Placebo then Melatonin ( n = 15 )</th>
<th>Overall ( n = 33 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (range)</td>
<td>35 (19-54)</td>
<td>38 (20-58)</td>
<td>37 (19-58)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>11 (61)</td>
<td>11 (73)</td>
<td>22 (67)</td>
</tr>
<tr>
<td>Months post injury, mean (range)</td>
<td>72 (5 – 245)</td>
<td>60 (6 - 251)</td>
<td>66 (5-251)</td>
</tr>
<tr>
<td>Mild TBI, No. (%)</td>
<td>-</td>
<td>2 (13)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Moderate TBI, No. (%)</td>
<td>2 (11)</td>
<td>1 (7)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Severe TBI, No. (%)</td>
<td>16 (89)</td>
<td>12 (80)</td>
<td>28 (85)</td>
</tr>
<tr>
<td>Prescribed Meds, No. (%)</td>
<td>(Analgesics; Antacid; Antidepressants; Antiepileptic's; Multivitamins; NSAID)</td>
<td>13 (72)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>PSQI sleep quality, m (SD)</td>
<td>10 (5)</td>
<td>11 (4)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>ESS daytime sleepiness, m (SD)</td>
<td>6 (5)</td>
<td>9 (6)</td>
<td>8 (6)</td>
</tr>
</tbody>
</table>
Statistical analysis

- Random-effects mixed-model analysis to model each of the outcome variables as linear functions:
  - **Treatment** (i.e., melatonin or placebo)
  - **Period** (i.e., pre-treatment versus post-treatment)
  - **Sequence** (i.e., whether they received melatonin 1\textsuperscript{st} or 2\textsuperscript{nd}).

- Results considered significant if p value <0.05
**Did melatonin improve sleep?**

<table>
<thead>
<tr>
<th></th>
<th>Melatonin Treatment Mean (95%CI)</th>
<th>Placebo Treatment Mean (95%CI)</th>
<th>Effect size (d)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSQI, global score</strong></td>
<td>7.7 (6.3 to 9.0)</td>
<td>9.5 (8.1 to 10.8)</td>
<td>0.46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Sleep latency, min</strong></td>
<td>1.37 (1.26 to 1.48)</td>
<td>1.42 (1.31 to 1.53)</td>
<td>0.18</td>
<td>0.23</td>
</tr>
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</table>

**Global PSQI scores**

**AW Sleep Onset Latency**

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*MONASH University*
<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Melatonin Treatment Mean (95%CI)</th>
<th>Placebo Treatment Mean (95%CI)</th>
<th>Effect size (d)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep efficiency, %c</td>
<td>-3.2 (-3.6 to -2.8)</td>
<td>-3.5 (-3.9 to 3.1)</td>
<td>0.28</td>
<td>0.04</td>
</tr>
<tr>
<td>ESS, scored</td>
<td>2.4 (1.1 to 2.7)</td>
<td>2.5 (2.2 to 2.9)</td>
<td>0.17</td>
<td>0.15</td>
</tr>
<tr>
<td>HADS Anxiety, score</td>
<td>7.8 (6.2 to 9.5)</td>
<td>9.0 (7.4 to 10.6)</td>
<td>0.27</td>
<td>0.006</td>
</tr>
<tr>
<td>HADS Depression, score</td>
<td>8.5 (6.9 to 10.1)</td>
<td>8.3 (6.7 to 9.9)</td>
<td>0.04</td>
<td>0.68</td>
</tr>
<tr>
<td>Fatigue severity scale, scored</td>
<td>-4.2 (-4.7 to -3.6)</td>
<td>-3.7 (-4.3 to -3.2)</td>
<td>0.29</td>
<td>0.03</td>
</tr>
<tr>
<td>SF-36</td>
<td>Melatonin Treatment Mean (95%CI)</td>
<td>Placebo Treatment Mean (95%CI)</td>
<td>Effect size (d)</td>
<td>p Value</td>
</tr>
<tr>
<td>------------------------------</td>
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<tr>
<td>Physical functioning (PF), score</td>
<td>43.17 (39.1 to 47.2)</td>
<td>41.7 (37.7 to 45.7)</td>
<td>0.13</td>
<td>0.11</td>
</tr>
<tr>
<td>Role physical limitation (RP), score</td>
<td>37.7 (33.6 to 41.7)</td>
<td>38.1 (34.1 to 42.1)</td>
<td>0.03</td>
<td>0.77</td>
</tr>
<tr>
<td>Role-Emotional (RE), score</td>
<td>-3.4 (33.1 to 42.1)</td>
<td>36.9 (32.4 to 41.3)</td>
<td>0.05</td>
<td>0.73</td>
</tr>
<tr>
<td>Vitality (VT), score</td>
<td>42.4 (39.0 to 45.9)</td>
<td>38.8 (35.3 to 42.2)</td>
<td>0.35</td>
<td>0.03</td>
</tr>
<tr>
<td>Mental health (MH), score</td>
<td>43.6 (40.0 to 47.2)</td>
<td>41.1 (37.5 to 44.7)</td>
<td>0.23</td>
<td>0.01</td>
</tr>
<tr>
<td>Social functioning (SF), score</td>
<td>37.1 (33.1 to 41.1)</td>
<td>34.8 (30.8 to 38.9)</td>
<td>0.19</td>
<td>0.22</td>
</tr>
<tr>
<td>Bodily pain (BP), score</td>
<td>44.1 (39.8 to 48.3)</td>
<td>43.3 (39.1 to 47.5)</td>
<td>0.06</td>
<td>0.48</td>
</tr>
<tr>
<td>General health (GH), score</td>
<td>41.0 (36.9 to 45.0)</td>
<td>40.3 (36.3 to 44.3)</td>
<td>0.06</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Adverse effects

• We examined a range of adverse effects ranging from neurological to gastrointestinal

• Adverse effects were more commonly reported following placebo treatment than melatonin treatment
Summary of findings

Past research suggests that TBI is associated with sleep disturbances which may be underpinned by delayed and attenuated melatonin secretion

Supplementation with melatonin for 4 weeks improved:

• Subjective sleep quality
• Sleep efficiency (i.e., sleep duration relative to sleep opportunity)
• Fatigue
• Anxiety symptomatology
• Vitality and mental health

Melatonin was well tolerated and associated with no serious adverse events
Study limitations

- Small sample
- Participants did not have melatonin levels assessed
Conclusion

Melatonin is a safe and effective treatment for alleviating sleep disturbances in patients with TBI
Acknowledgement

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Publication:

Light therapy for treatment of fatigue & sleepiness following Traumatic Brain Injury

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\textsuperscript{b} Monash Epworth Rehabilitation Research Centre, Victoria, Australia
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Bright Light Therapy

- Light exerts non-visual effects on many biological functions
- Acute alerting effects distinct from its effects on circadian rhythms

In healthy and patient populations
- Reduced sleepiness
- Arousing effects on biological parameters
  - Body temperature *(increased)*
  - Heart rate *(increased rate)*
  - Melatonin levels *(suppressed)*
  - Sleep architecture *(shorted REM sleep duration)*
  - Increased vigilance performance
- Improved mood

- Light in the blue wavelength range shown to be most effective *(Cajochen et al, 2005; Lockley et al., 2006; Glickman et al., 2006)*
Circadian photoreception: spotlight on the brain,
What is Light Therapy?

- Involves exposure, through the eyes, to a bright light stimulus

- Effects are thought to occur through activation of novel photoreceptors that contain melanopsin (photopigment) → most sensitive to short-wavelength (blue) light
Fatigue following TBI

Epworth Sleepiness Scale

Fatigue Severity Scale

Vigilance Task (error rate)

HADS Depression

HADS Anxiety
Based on research demonstrating an alerting effect of short-wavelength (blue) light

Study aim: To investigate the efficacy of light therapy in the alleviation of **fatigue** and **sleepiness** following Traumatic Brain Injury

RCT comparing:
- short wavelength (blue) light, *active condition*
- yellow light therapy designed to be deficient in short wavelength (blue) light, *placebo condition*
- treatment as usual

4 week treatment phase, morning use (45 min per day within 2 hours of waking)
Participants

Inclusion Criteria
- Traumatic Brain Injury
- 18-65 years of age
- Current self reports of clinically significant fatigue, daytime sleepiness and/or poor sleep quality

Exclusion Criteria
- Pre-injury sleep disorders or chronic fatigue
- Medications for sleep
- Recent (last 6 weeks) transmeridian travel, shift work
- Epilepsy, photosensitive medications

Demographics

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>30</td>
</tr>
<tr>
<td>Age, years</td>
<td>42.0 (13.6)</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>24/6</td>
</tr>
<tr>
<td>Time since injury</td>
<td>3.0 yrs (2.7)</td>
</tr>
<tr>
<td>PTA (days)</td>
<td>20.0 (25.0)</td>
</tr>
<tr>
<td>Mild injury (%)</td>
<td>23%</td>
</tr>
<tr>
<td>Moderate injury (%)</td>
<td>27%</td>
</tr>
<tr>
<td>Severe injury (%)</td>
<td>50%</td>
</tr>
<tr>
<td>Cause of injury (%)</td>
<td></td>
</tr>
<tr>
<td>Motor vehicle accident</td>
<td>60%</td>
</tr>
<tr>
<td>Fall</td>
<td>23%</td>
</tr>
<tr>
<td>Pedestrian</td>
<td>17%</td>
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</table>
Method

Baseline (2 weeks)

Treatment Phase (4 weeks)

Follow-up Phase (4 weeks)

Randomisation

Blue Light

Yellow Light

Treatment as usual

Week 0 (Visit 1)

Week 2 (Visit 2)

Week 4 (Visit 3)

Week 6 (Visit 4)

Week 10 (Visit 5)
Study design

- **Subjective measures**
  - Fatigue (Fatigue Severity Scale)
  - Daytime sleepiness (Epworth Sleepiness Scale)
  - Sleep quality (Pittsburgh Sleep Quality Index)
  - Mood (Beck Depression Inventory)
  - Sleep diary

- **Objective measures**
  - Psychomotor Vigilance Task
  - Actiwatch (sleep timing)
Light Intervention

- Made to specifications
- Europe – circadian rhythm disorders
  - Shift work
  - Jet lag
- Australia – TGA approved for treatment of Seasonal Affective Disorder
### Baseline Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>% Clinically Significant Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime Sleepiness (ESS)</td>
<td>9.5 (4.1)</td>
<td>1-18</td>
<td>52</td>
</tr>
<tr>
<td>Fatigue (FSS)</td>
<td>5.9 (.6)</td>
<td>3.9-7</td>
<td>96</td>
</tr>
<tr>
<td>Sleep Quality (PSQI)</td>
<td>8.0 (4.3)</td>
<td>1-21</td>
<td>78</td>
</tr>
<tr>
<td>BDI-II</td>
<td>20.1 (9.0)</td>
<td>0-33</td>
<td>--</td>
</tr>
</tbody>
</table>

No group differences in these symptoms pre treatment phase
Baseline Symptom, per group

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>Blue Light Therapy (n=10)</th>
<th>Yellow Light Therapy (n=10)</th>
<th>No treatment control (n=10)</th>
<th>Total (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>FSS (Fatigue)</td>
<td>5.9</td>
<td>0.8</td>
<td>5.6</td>
<td>0.5</td>
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<tr>
<td>ESS (Daytime Sleepiness)</td>
<td>10.1</td>
<td>4.5</td>
<td>9.6</td>
<td>4.8</td>
</tr>
<tr>
<td>PSQI (Sleep Quality)</td>
<td>8.1</td>
<td>2.9</td>
<td>7.6</td>
<td>4.6</td>
</tr>
<tr>
<td>BDI-II (Depression)</td>
<td>20.3</td>
<td>10.0</td>
<td>20.3</td>
<td>8.1</td>
</tr>
<tr>
<td>PVT: mean RTa</td>
<td>427.1</td>
<td>267.4</td>
<td>348.6</td>
<td>90.7</td>
</tr>
<tr>
<td>PVT: lapsesa</td>
<td>31.5</td>
<td>33.9</td>
<td>17.0</td>
<td>18.4</td>
</tr>
</tbody>
</table>

There was no significant difference between participants on symptoms at baseline.
All but one participant had clinically significant fatigue (96%); more than half (52%) had excessive daytime sleepiness; and 78% had poor sleep quality.
# Light Intervention

<table>
<thead>
<tr>
<th>Therapeutic device/Distance from Meter</th>
<th>λ max</th>
<th>Illuminance (lux)</th>
<th>Irradiance (µW/cm²)</th>
<th>Photon Density (photons/cm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue goLITE®/50cm</td>
<td>465nm</td>
<td>39.5</td>
<td>84.81</td>
<td>1.89 x 10¹⁴</td>
</tr>
<tr>
<td>Yellow goLITE®/50cm</td>
<td>574nm</td>
<td>68</td>
<td>18.53</td>
<td>4.68 x 10¹³</td>
</tr>
</tbody>
</table>

Light Therapy following TBI
Analysis: Regression

Outcome variables were modelled via random effects regression as functions of treatment group, time, treatment by time interaction, age, female gender, baseline depression and, for the two PVT outcomes, mean time tested across the study protocol.

- The dependence on time (weeks since baseline: 0, 4, 6 or 10) was modelled as quadratic.
Fatigue severity reduced significantly by light intervention

Epworth Daytime Sleepiness scores improved by light intervention
Trend toward reduced depression on Beck Depression Inventory

[Graph showing trend in BDI-II change score over weeks]
No change in sleep quality on Pittsburgh Sleep Quality Index
Trend toward improvement in Psychomotor Vigilance

The graphs depict changes in Psychomotor Vigilance Task (PVT) measures over weeks. The left graph shows changes in mean reaction time (RT) with a trend toward improvement. The right graph illustrates changes in the number of lapses, also indicating a trend toward improvement.
## Regression Table; FSS, ESS & PSQI

<table>
<thead>
<tr>
<th></th>
<th>FSS</th>
<th></th>
<th>ESS</th>
<th></th>
<th>PSQI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>est coeff</td>
<td>95% CI</td>
<td>est coeff</td>
<td>95% CI</td>
<td>est coeff</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Treatment Group (reference: Blue Light Therapy)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow Light Therapy</td>
<td>-0.07</td>
<td>-0.9 to 0.7</td>
<td>-0.01</td>
<td>-3.6 to 3.6</td>
<td>0.73</td>
<td>-2.8 to 4.3</td>
</tr>
<tr>
<td>No Treatment Control</td>
<td>0.30</td>
<td>-0.5 to 1.1</td>
<td>-0.89</td>
<td>-4.3 to 2.6</td>
<td>0.64</td>
<td>-2.7 to 4.0</td>
</tr>
<tr>
<td><strong>Time (weeks)</strong></td>
<td>-0.48**</td>
<td>-0.7 to -0.3</td>
<td>-1.58**</td>
<td>-2.3 to -0.9</td>
<td>-0.46</td>
<td>-0.9 to 0.01</td>
</tr>
<tr>
<td><strong>Treatment Group x Time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow Light Therapy</td>
<td>0.41**</td>
<td>0.2 to 0.7</td>
<td>0.80</td>
<td>-0.2 to 1.8</td>
<td>0.41</td>
<td>-0.3 to 1.1</td>
</tr>
<tr>
<td>No Treatment Control</td>
<td>0.44**</td>
<td>0.2 to 0.7</td>
<td>1.46**</td>
<td>0.5 to 2.4</td>
<td>0.21</td>
<td>-0.4 to 0.9</td>
</tr>
<tr>
<td><strong>Time² (week²)</strong></td>
<td>0.04**</td>
<td>0.03 to 0.1</td>
<td>0.12**</td>
<td>0.1 to 0.2</td>
<td>0.04</td>
<td>-0.01 to 0.1</td>
</tr>
<tr>
<td><strong>Treatment Group x Time²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow Light Therapy</td>
<td>-0.04**</td>
<td>-0.1 to -0.01</td>
<td>-0.07</td>
<td>-0.2 to 0.03</td>
<td>-0.04</td>
<td>-0.1 to 0.02</td>
</tr>
<tr>
<td>No Treatment Control</td>
<td>-0.04**</td>
<td>-0.1 to -0.02</td>
<td>-0.11*</td>
<td>-0.2 to -0.02</td>
<td>-0.02</td>
<td>-0.1 to 0.04</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>0.02*</td>
<td>0.002 to 0.04</td>
<td>0.02</td>
<td>-0.1 to 0.1</td>
<td>0.10</td>
<td>-0.002 to 0.2</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>0.38</td>
<td>-0.2 to 1.0</td>
<td>0.33</td>
<td>-2.6 to 3.3</td>
<td>1.93</td>
<td>-1.3 to 5.1</td>
</tr>
<tr>
<td><strong>BDI at Week 0</strong></td>
<td>0.02</td>
<td>-0.01 to 0.1</td>
<td>0.06</td>
<td>-0.1 to 0.2</td>
<td>0.15*</td>
<td>0.01 to 0.3</td>
</tr>
<tr>
<td><strong>PVT mean time</strong></td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td><strong>tested</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Constant</strong></td>
<td>4.39**</td>
<td>3.2 to 5.6</td>
<td>7.49*</td>
<td>1.8 to 13.2</td>
<td>-0.01</td>
<td>-6.0 to 6.0</td>
</tr>
</tbody>
</table>

*P-values: *p < 0.05, **p < 0.01*
<table>
<thead>
<tr>
<th>Treatment Group (reference: Blue Light Therapy)</th>
<th>BDI-II</th>
<th>95% CI</th>
<th>PVT- RT</th>
<th>95% CI</th>
<th>PVT - Lapses</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Yellow Light Therapy</td>
<td>-0.19</td>
<td>-8.6 to 8.2</td>
<td>-0.24</td>
<td>-0.9 to 0.4</td>
<td>-0.47</td>
<td>-4.7 to 3.8</td>
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<tr>
<td>No Treatment Control</td>
<td>-0.26</td>
<td>-8.3 to 7.8</td>
<td>0.26</td>
<td>-0.3 to 0.9</td>
<td>-2.97</td>
<td>-7.1 to 1.1</td>
</tr>
<tr>
<td>Time (weeks)</td>
<td>-1.51*</td>
<td>-2.8 to -0.2</td>
<td>0.12</td>
<td>-0.01 to 0.3</td>
<td>-0.89</td>
<td>-1.8 to 0.1</td>
</tr>
<tr>
<td>Treatment Group x Time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow Light Therapy</td>
<td>0.83</td>
<td>-1.0 to 2.6</td>
<td>-0.05</td>
<td>-0.2 to 0.1</td>
<td>0.71</td>
<td>-0.7 to 2.1</td>
</tr>
<tr>
<td>No Treatment Control</td>
<td>1.50</td>
<td>-0.3 to 3.3</td>
<td>-0.16</td>
<td>-0.4 to 0.03</td>
<td>0.94</td>
<td>-0.4 to 2.3</td>
</tr>
<tr>
<td>Time² (week²)</td>
<td>0.10</td>
<td>-0.02 to 3.3</td>
<td>-0.01</td>
<td>-0.02 to 0.003</td>
<td>0.09</td>
<td>-0.003 to 0.2</td>
</tr>
<tr>
<td>Treatment Group x Time²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow Light Therapy</td>
<td>-0.01</td>
<td>-0.2 to 0.1</td>
<td>-0.01</td>
<td>-0.01 to 0.03</td>
<td>-0.08</td>
<td>-0.2 to 0.1</td>
</tr>
<tr>
<td>No Treatment Control</td>
<td>-0.07</td>
<td>-0.2 to 0.1</td>
<td>0.02</td>
<td>-0.002 to 0.03</td>
<td>-0.09</td>
<td>-0.2 to 0.04</td>
</tr>
<tr>
<td>Age</td>
<td>-0.02</td>
<td>-0.3 to 0.2</td>
<td>-0.03**</td>
<td>-0.1 to -0.02</td>
<td>0.16**</td>
<td>0.1 to 0.3</td>
</tr>
<tr>
<td>Female</td>
<td>-0.11</td>
<td>-7.7 to 7.5</td>
<td>0.07</td>
<td>-0.4 to 0.5</td>
<td>1.24</td>
<td>-1.8 to 4.2</td>
</tr>
<tr>
<td>BDI at Week 0</td>
<td>a</td>
<td>a</td>
<td>-0.03*</td>
<td>-0.1 to -0.002</td>
<td>0.11</td>
<td>-0.1 to 0.3</td>
</tr>
<tr>
<td>PVT mean time tested</td>
<td>a</td>
<td>a</td>
<td>0.13**</td>
<td>0.03 to 0.2</td>
<td>-0.49</td>
<td>-1.1 to 0.1</td>
</tr>
<tr>
<td>Constant</td>
<td>21.47**</td>
<td>8.8 to 24.1</td>
<td>3.58**</td>
<td>2.2 to 5.0</td>
<td>6.32</td>
<td>-2.8 to 15.5</td>
</tr>
</tbody>
</table>

28th February 2011   Presentation title
Participants did not differ significantly in their expectation of treatment efficacy.

No significant group differences in number of days light device turned on

No serious adverse events

No significant association between demographic factors, injury severity or cognitive function and response to treatment.

Magnitude of change in fatigue and daytime sleepiness was greater than that seen following 6 weeks of daily treatment with 100-200mg Modafinil in a comparable TBI sample.
Conclusion

- Preliminary findings support the use of light therapy in the alleviation of fatigue & sleepiness following TBI
- Anecdotally, several participants have reported benefits from use of the short wavelength light.
  - “more refreshed”
  - “less napping”

Mechanisms of Action?

- Melanopsin-containing short wavelength sensitive Retinal Ganglion Cells
- Mood enhancing
- Pathways for fatigue?
Acknowledgements

Supported by grants from:
  – The Jack Brockhoff Foundation
  – Centre for Integrated Research and Understanding Sleep (CIRUS, Woolcock Institute of Medical Research)
  – RACV Sir Edmund Herring Memorial Scholarship
  – Victorian Neurotrauma Initiative

goLITE® devices provided by Philips Lighting (Phillips goLITE blu)
Cognitive behaviour therapy to treat sleep disturbance and fatigue following acquired brain injury

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CBT in TBI & Stroke

ORIGINAL ARTICLE

Efficacy of Cognitive-Behavioral Therapy for Insomnia Associated With Traumatic Brain Injury: A Single-Case Experimental Design

Marie-Christine Ouellet, PhD, Charles M. Morin, PhD


Feasibility of a Cognitive Behavioral Intervention to Manage Fatigue in Individuals With Traumatic Brain Injury: A Pilot Study

Kotki D. Raina, PhD. OTR/L; Jennifer Q. Morse, PhD; Denise Chisholm, PhD. OTR/L; Mary Lou Leibold, PhD, OTR/L; Jennifer Shen, MD; Ellen Whyte, MD

No control group OR intervention did not include all CBT elements
Current Study

First study to evaluate efficacy of CBT for fatigue AND sleep compared with treatment as usual control.
Study Design

- **8 sessions of individual CBT** vs. TAU control in a ABI sample (n = 39)
- Participants were assessed at baseline, 2 months (post-intervention) and 4 months (follow-up)

**Hypotheses:**
1. Participants receiving CBT will report greater reductions in sleep difficulties and fatigue
2. Secondary improvements in mood and quality of life
3. Treatment gains will be maintained at follow-up
Participants

**Inclusion Criteria**
- Documented TBI (mild to severe) or stroke
- 16 – 70 years of age
- Clinically significant fatigue/sleep complaints
  - Fatigue Severity Scale [FSS] ≥ 4
  - Pittsburgh Sleep Quality Index [PSQI] > 5

**Exclusion Criteria**
- Co-morbid neurological disorders
- Acute psychiatric symptoms or substance
- Recent transmeridian travel or night shift work
- Sleep apnoea (clinically excluded)

Rehabilitative and pharmacological treatment permitted but must remain stable!
Data collection

WEEK -2

- 83 Screened for eligibility
- 24 declined
- 20 exclusion criteria

WEEK 0

- 39 Enrolled
- 2 withdrawn

Baseline + 2 weeks monitoring

WEEK 8

- Treatment (CBT) (n=22)
- Post-treatment (n=20)

WEEK 16

- Control (TAU) (n=17)
- Time point 2 (n=16)
- Time point 3 (n=17)

- 2 months follow-up (n=19)
- Post-treatment (n=20)
CBT Protocol

- Manualised protocol comprised of 6 modules delivered across 8 sessions

- Consulted previous CBT programs for insomnia, chronic fatigue syndrome and depression/anxiety (Ashworth et al., 2015; Hsieh et al., 2012, White et al., 2011)

- Therapy adapted for cognitive impairments
  - Greater structure, concrete concepts
  - Directive approach in cognitive restructuring
  - Repetition
  - Handouts with simplified information and pictorial cues
  - External aids (diaries, electronic reminders)
  - Close other to support practice of techniques at home
Therapy Modules

Module 1 (sess. 1)
- Psychoeducation
- Therapy goals for sleep/fatigue
- Physio assessment and exercise program set
- Treatment plan

Module 2 (sess. 2)
- Reorganize daily schedule
- Pacing tasks
- Incorporating rest breaks
- Sleep hygiene

Module 3 (sess. 3 + 4)
- Graded increase/decrease to activity
- Integrating activity goals
- Cognitive restructuring

Module 4 (sess. 5 + 6)
- Sleep education
- Behavioural interventions (stimulus control, bedtime restriction)
- Relaxation techniques

Module 5 (sess. 7)
- Strategies for physical fatigue
- Strategies for mental fatigue

Module 6 (sess. 8)
- Summary of therapeutic techniques
- Maintenance
- Relapse prevention
Integrity Monitoring

- 3 neuropsychologists with doctoral qualifications and CBT training
- Treatment fidelity assessed by 2 independent CBT experts
- Random sample of 10% of session audiotape recordings (19 sessions)
- CBT monitoring form used to rate
  1) Adherence to CBT approach
  2) Adherence to study-specific module
  3) Competency in delivering the session

<table>
<thead>
<tr>
<th>Rating</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT adherence</td>
<td>6.31</td>
<td>0.58</td>
<td>5 – 7</td>
</tr>
<tr>
<td>Module adherence</td>
<td>6.21</td>
<td>0.85</td>
<td>4 – 7</td>
</tr>
<tr>
<td>Delivery</td>
<td>6.26</td>
<td>0.81</td>
<td>5 – 7</td>
</tr>
</tbody>
</table>

0 = unacceptable  
7 = excellent
Assessments

RA conducting follow-ups blinded to group allocation

- **Primary Outcome**
  - Sleep Quality (PSQI)
  - Global Fatigue Impact (FSS)

- **Secondary Outcomes**
  - Insomnia (ISI)
  - Daily Fatigue Levels (BFI)
  - Daytime Sleepiness (ESS)
  - Mood (HADS)
  - Quality of Life (SF-36)

Baseline

Post-intervention

Follow-up

WEEK 0

WEEK 8

WEEK 16
## Sample Characteristics

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>CBT (n=22) M (SD)</th>
<th>TAU (n=17) M (SD)</th>
<th>P – value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI (TBI)</td>
<td>13 (59.09%)</td>
<td>11 (64.71%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Injury time (months)</td>
<td>24.32 (20.48)</td>
<td>57.41 (61.51)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>7 (31.82%)</td>
<td>5 (29.41%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Age</td>
<td>46.23 (14.10)</td>
<td>45.18 (12.17)</td>
<td>0.80</td>
</tr>
<tr>
<td>Years of Education</td>
<td>14.45 (1.71)</td>
<td>13.18 (2.10)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>112.67 (8.13)</td>
<td>108.76 (7.32)</td>
<td>0.13</td>
</tr>
<tr>
<td>CVLT-II t-score</td>
<td>48.55 (12.82)</td>
<td>51.12 (10.39)</td>
<td>0.51</td>
</tr>
<tr>
<td>Psychiatric history (yes)</td>
<td>15 (68.18%)</td>
<td>10 (58.82%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Pain at baseline (yes)</td>
<td>7 (31.82%)</td>
<td>10 (58.82%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Medication use (yes)</td>
<td>7 (31.82%)</td>
<td>8 (47.06%)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Sensitivity analyses indicated that injury time and years of education did not significantly predict response or alter significance of treatment effect.
Injury Variables

**Mechanism of Injury**
- 42% Motor vehicle accident
- 29% Falls
- 17% Pedestrian/cycling accident
- 13% Impact with moving or stationary object

**Injury Severity (PTA duration)**
- 21% Mild
- 46% Moderate
- 33% Severe

**Stroke Mechanism**
- 80% Ischemic
- 20% Hemorrhagic

**Hemisphere**
- 27% Left
- 60% Right
- 13% Bilateral

No significant group differences on injury variables
Sleep Scales (ABI)

**PSQI Score**

- **CBT**
  - Baseline: 9.2 (0.50)
  - 2 Mths: 7.0 (0.34)
  - 4 Mths: 4.8 (0.54)
  - Diff: 1.0

- **TAU**
  - Baseline: 10.2 (0.54)
  - 2 Mths: 9.5 (0.35)
  - 4 Mths: 8.8 (0.54)
  - Diff: 1.0

**p = 0.008***

*Post hoc analyses are bonferroni corrected

**ISI Score**

- **CBT**
  - Baseline: 14.2 (0.78)
  - 2 Mths: 10.4 (0.53)
  - 4 Mths: 6.6 (0.85)
  - Diff: 0.5

- **TAU**
  - Baseline: 14.7 (0.88)
  - 2 Mths: 13.6 (0.57)
  - 4 Mths: 12.6 (0.92)
  - Diff: 0.5

**p = 0.003***

*No group differences on ESS*
Fatigue Scales (TBI)

**Fatigue Scales (TBI)**

*Post hoc analyses are bonferroni corrected

**FSS Score**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline M (S.E)</th>
<th>2 Mths M (S.E)</th>
<th>4 Mths M (S.E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT</td>
<td>5.5 (0.17)</td>
<td>5.4 (0.13)</td>
<td>5.3 (0.15)</td>
</tr>
<tr>
<td>TAU</td>
<td>5.5 (0.20)</td>
<td>5.2 (0.15)</td>
<td>5.0 (0.20)</td>
</tr>
<tr>
<td>Diff</td>
<td>0.0</td>
<td>-0.2</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

**BFI Score**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline M (S.E)</th>
<th>2 Mths M (S.E)</th>
<th>4 Mths M (S.E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT</td>
<td>5.7 (0.30)</td>
<td>5.0 (0.22)</td>
<td>4.4 (0.31)</td>
</tr>
<tr>
<td>TAU</td>
<td>5.8 (0.31)</td>
<td>5.9 (0.23)</td>
<td>6.0 (0.32)</td>
</tr>
<tr>
<td>Diff</td>
<td>0.1</td>
<td>0.9*</td>
<td>1.6*</td>
</tr>
</tbody>
</table>
**Fatigue Scales (Stroke)**

### FSS Score

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline M (S.E)</th>
<th>2 Mths</th>
<th>4 Mths</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT</td>
<td>6.0 (0.17)</td>
<td>4.0 (0.30)</td>
<td>4.3 (0.49)</td>
</tr>
<tr>
<td>TAU</td>
<td>6.3 (0.25)</td>
<td>5.7 (0.37)</td>
<td>6.2 (0.57)</td>
</tr>
<tr>
<td>Diff</td>
<td>0.3</td>
<td>1.7*</td>
<td>1.9*</td>
</tr>
</tbody>
</table>

*p = 0.016*  
*Post hoc analyses are bonferroni corrected

### BFI Score

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline M (S.E)</th>
<th>2 Mths</th>
<th>4 Mths</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT</td>
<td>4.9 (0.39)</td>
<td>3.9 (0.68)</td>
<td>4.6 (0.68)</td>
</tr>
<tr>
<td>TAU</td>
<td>6.1 (0.74)</td>
<td>5.2 (0.85)</td>
<td>5.2 (0.79)</td>
</tr>
<tr>
<td>Diff</td>
<td>1.2</td>
<td>1.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*p = 0.728*
### Hospital Anxiety Depression Scale (ABI)

**Anxiety Scale**

- **CBT**
  - Baseline: 7.2 (0.54)
  - 2 Mths: 5.6 (0.40)
  - 4 Mths: 3.9 (0.57)
  - Diff: 0.2

- **TAU**
  - Baseline: 7.4 (0.61)
  - 2 Mths: 6.9 (0.45)
  - 4 Mths: 6.4 (0.61)
  - Diff: 0.1

**Depression Scale**

- **CBT**
  - Baseline: 7.8 (0.49)
  - 2 Mths: 5.7 (0.37)
  - 4 Mths: 3.6 (0.51)
  - Diff: 0.1

- **TAU**
  - Baseline: 7.9 (0.53)
  - 2 Mths: 8.0 (0.40)
  - 4 Mths: 8.2 (0.53)
  - Diff: 0.1

*Post hoc analyses are bonferroni corrected

\[ p = 0.048^* \]

\[ p = 0.000^* \]
### SF – 36 Quality of Life (ABI)

#### Physical Component

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline M (S.E)</th>
<th>2 Mths</th>
<th>4 Mths</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT</td>
<td>44.2 (1.41)</td>
<td>45.1 (1.01)</td>
<td>45.9 (1.49)</td>
</tr>
<tr>
<td>TAU</td>
<td>41.2 (1.71)</td>
<td>42.2 (1.21)</td>
<td>43.3 (1.71)</td>
</tr>
<tr>
<td>Diff</td>
<td>3.0</td>
<td>2.9</td>
<td>2.6</td>
</tr>
</tbody>
</table>

*Post hoc analyses are bonferroni corrected

#### Mental Component

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline M (S.E)</th>
<th>2 Mths</th>
<th>4 Mths</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT</td>
<td>37.4 (1.64)</td>
<td>42.4 (1.07)</td>
<td>47.4 (1.74)</td>
</tr>
<tr>
<td>TAU</td>
<td>37.3 (1.87)</td>
<td>39.1 (1.19)</td>
<td>41.0 (1.87)</td>
</tr>
<tr>
<td>Diff</td>
<td>0.1</td>
<td>3.3</td>
<td>6.4*</td>
</tr>
</tbody>
</table>
### Treatment Response (TBI vs Stroke)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Effect Size (g)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TBI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSQI</td>
<td>1.71</td>
<td>0.75 to 2.68</td>
</tr>
<tr>
<td>BFI</td>
<td>1.14</td>
<td>0.26 to 2.02</td>
</tr>
<tr>
<td>HADS – D</td>
<td>1.93</td>
<td>0.92 to 2.94</td>
</tr>
</tbody>
</table>

**STROKE**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Effect Size (g)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI</td>
<td>1.26</td>
<td>0.10 to 2.41</td>
</tr>
<tr>
<td>FSS</td>
<td>1.29</td>
<td>0.12 to 2.45</td>
</tr>
<tr>
<td>HADS – D</td>
<td>1.56</td>
<td>0.29 to 2.82</td>
</tr>
</tbody>
</table>

Large to very large effect sizes favouring CBT
Clinical Change (TBI vs Stroke)

**TBI**

<table>
<thead>
<tr>
<th>Measure</th>
<th>CBT Reliable Change</th>
<th>CBT Recovered</th>
<th>TAU Reliable Change</th>
<th>TAU Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI</td>
<td>70%</td>
<td>30%</td>
<td>27%</td>
<td>9%</td>
</tr>
<tr>
<td>BFI</td>
<td>55%</td>
<td>27%</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>HADS – D</td>
<td>60%</td>
<td>56%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**STROKE**

<table>
<thead>
<tr>
<th>Measure</th>
<th>CBT Reliable Change</th>
<th>CBT Recovered</th>
<th>TAU Reliable Change</th>
<th>TAU Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI</td>
<td>50%</td>
<td>38%</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>FSS</td>
<td>63%</td>
<td>38%</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>HADS – D</td>
<td>50%</td>
<td>50%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Summary

- CBT significantly **improved sleep** quality and reduced insomnia
  - Comparable effect sizes with CBT-I literature (Ashworth et al., 2015, Morin, 2011, Trauer et al, 2015)

- Significant **reduction in fatigue** but on different measures
  - TBI group improved on the Brief Fatigue Inventory
  - Stroke group improved on the Fatigue Severity Scale
  - FSS and BFI measures different facets of fatigue?

- Secondary **improvements in mood**
  - Significant reductions in depressive and anxiety symptoms
  - Expected to improve with reduced fatigue and insomnia (Moss-Morris et al., 2012; Zedlitz et al, 2012)
Factors associated with positive treatment response

- better memory
- younger age
- higher baseline depression
  - were associated with positive treatment response to CBT although individually these variables were not better than group alone in predicting outcomes
Clinical/Research Implications

- **Resolution of sleep** does not entirely **alleviate fatigue**
  - Fatigue exacerbated by insomnia but also independent construct (Ouellet et al., 2006)
  - *Fatigue precedes anxiety, depression and daytime sleepiness* (Ponsford, Rajaratnam et al., 2014)

- **Gains are maintained over time**
  - Cognitive impairment does not negate benefits from CBT

- **Lack of precision in fatigue measurement**
  - No reliable physiological correlates for fatigue
  - No gold standard of subjective measurement
Study Limitations

- **Methodological weaknesses**
  - Small sample size
  - Subjective measures
  - Poor adherence to exercise program, based on pedometer ratings

- **Group Design**
  - No control for therapeutic attention
  - Waitlist design precluded longer-term group comparisons

Larger scale RCTs required to replicate and extend results of this pilot study!
Q & A

Acknowledgements

**Therapists**
Dr Adam McKay
Dr Dana Wong
Dr Kate Frencham

**Clinical Consultants**
Dr Moira Junge
Dr Kerrie Haines

**Research Staff**
Dr Gershon Spitz
Jacqueline Owens
Olivia McConchie
Jade Murray

MOVING AHEAD
Centre of Research Excellence in Brain Recovery
Overall Conclusions

- Fatigue and Sleep disturbance are common following TBI and stroke and contribute to disability.
- Causes appear to be multi-faceted, relating to biological, cognitive and other injury-related factors, pain, and mood.
- Treatments need to assess and address all these factors, and will vary accordingly.
- Melatonin holds promise to improve sleep quality.
- Light therapy holds promise for alleviating fatigue and daytime sleepiness.
- Adapted CBT shows promise for reducing insomnia and improving certain aspects of fatigue.
Research Team

- Carlo Ziino
- Diane Parcell
- Shantha Rajaratnam
- Julia Shekleton
- Kelly Sinclair
- Natalie Grima
- Sylvia Ngyuyen
- Adam McKay
- Dana Wong
- Michael Schönberger
References


