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Effective Pharmacological and Non-pharmacological Treatments for Sleep Disturbances and Fatigue in Patients Who Have Experienced a Mild to Severe Traumatic Brain Injury

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Effective Pharmacological and Non-pharmacological Treatments for Sleep Disturbances and
Fatigue in Patients Who Have Experienced a Mild to Severe Traumatic Brain Injury

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Abstract

Background: In the United States alone, an estimated 1.5 million people sustain a head injury every year.¹ With improved recognition of traumatic brain injuries by healthcare providers, the number of patients diagnosed with a traumatic brain injury (TBI) is only increasing.

Unfortunately, many patients who sustain a TBI, regardless of the severity, experience sleep

disturbances, insomnia, fatigue, and daytime sleepiness. **Purpose:** For the purposes of this systematic review, the focus will be primarily on the comparison of nonpharmacological treatments of sleep disturbances or fatigue secondary to a TBI. In addition, the focus will include

recent studies on pharmacological treatments of post-TBI fatigue and insomnia. **Methods:** A

literature review was conducted to critique current evidence on nonpharmacological and pharmacological interventions for the treatment of sleep disturbances, insomnia, and fatigue in adults following a traumatic brain injury. Searches were performed for articles published

between 2015-2022, using PubMed, UpToDate, Academic Search Ultimate, APA Psycinfo, and

Google Scholar. **Conclusions:** As a result of the nuanced pathophysiological processes behind TBIs and subsequent insomnia, a multifaceted, holistic approach to care is the most effective.

Many of the included studies are pilot trials or preliminary studies— further research with larger participant quantity is warranted to determine or elaborate specific treatment efficacy. Given the

most recent research, providers should consider cognitive behavioral therapy, bright light

therapy, sleep hygiene, and melatonin as first-line treatments for sleep disturbances, insomnia, and fatigue after a traumatic brain injury.

Introduction

Each year, an estimated 1.5 million people in the US sustain a mild to severe traumatic brain injury (TBI).¹ In 2013 alone, there were approximately 2.8 million emergency department visits, hospitalizations, or deaths resulting from TBIs in the USA.² After sustaining traumatic brain injuries, many patients experience new onset or exacerbated sleep disturbances and daytime fatigue. In fact, a 2017 meta-analysis by J.L. Mathias and P.K. Alvaro found that 50% of the patients suffered from some sort of sleep disturbance after the TBI and 25-29% had a diagnosed sleep disorder thereafter.³ For providers who treat sleep disturbances, it is essential to evaluate each patient who sustains a traumatic brain injury for subsequent sleep disturbances, insomnia, and fatigue.

Pertaining to the treatment of fatigue and sleep disturbances in a healthy adult with no traumatic brain injury, there are a variety of treatment modalities recommended such as benzodiazepines, nonbenzodiazepines, melatonin, ramelteon, low-dose doxepin, sedating antidepressants, CBT, bright light therapy, etc.⁴ For patients who have experienced a TBI and insomnia, recent research is limited. However, recent studies on non-pharmacological options for insomnia, sleep disturbances, and fatigue after a TBI are extensive. In this essay, the non-pharmacological treatments for sleep disturbances after a TBI will be compared to one another, and the most recent pharmacological treatments will be assessed. The interventions will be evaluated to inform optimal provider practice, and the discussion will elaborate on the efficacy of non-pharmacological vs. pharmacological treatments.

Methods

A comprehensive literature review was conducted using The National Library of Medicine, Google Scholar, Academic Search Ultimate, APA Psycinfo, and UpToDate applying the search terms traumatic brain injury, TBI, brain injuries, acquired brain injury, concussions, insomnia, fatigue, sleepiness, sleep disturbances, pharmacological treatments, non-pharmacological treatments. For the most part, the included studies are on TBI patient populations, but multiple research articles incorporated participants who had strokes as well. Criteria for inclusion: All but one research study included only adult participants. Since 2015, the pharmacological studies on patients with sleep disturbances after a TBI are sparse. This discrepancy may be partially due to the COVID-19 pandemic. Patients in the collected original studies were diagnosed with mild to severe TBI or stroke, and struggled with insomnia, sleep disturbances, daytime fatigue. The participants in the studies had newly acquired sleep disorders or exacerbated sleep disorders which were attributable to the TBI.

Review of Literature: Background & Pathophysiology

In order to understand the treatments of sleep disturbances, fatigue, and insomnia after a traumatic brain injury, it is essential to first recognize the pathophysiological changes that occur in the brain. A traumatic brain injury is defined by the Department of Veteran Affairs⁵ as, “a traumatically induced structural injury and/or physiologic disruption of brain function as a result of an external force.” New onset or exacerbation of one of the following clinical manifestations must be present after the insult: loss of consciousness, loss of memory, change in mental status, neurological deficits, or cranial lesions. In order to assess TBI severity, the Glasgow Coma scale is often utilized. Patients are assessed for their capacity to complete eye opening responses, verbal responses, and motor responses.⁶ Each of the criteria are delegated points, and the higher the patient scores, the more severe the TBI.

According to the medical database, UpToDate, all TBI severities have the propensity for acute or chronic sleep disturbances, insomnia, pleiosomnia, daytime fatigue, sleep fragmentation, and other circadian disorders.⁴ Even though there are a variety of possible TBI sleep sequelae, the participants included in this paper were experiencing sleep disturbances, insomnia, daytime sleepiness, or generalized fatigue; for clarification, the researchers studied participants who had ample opportunity to sleep, but couldn't easily fall asleep during the desired hours. For those studies in which the participants met criteria for a DSM-5 diagnosis of insomnia, multiple of the following criteria were present: the patient must be dissatisfied with sleep quality or quantity;⁷ patients may wake early, have difficulty falling asleep, or struggle to stay asleep. Finally, insomnia can be distinguished from circadian rhythm disorders by assessing if a patient can sleep

or feel rested when they don't have work, school, or other commitments. When it is insomnia, the patient will struggle to sleep regardless of their preferred hours of sleep and wake.

Even though the prevalence of sleep disturbances is high after TBI, the pathophysiological causes of these TBI sequelae are not entirely clear. However, there are multiple theories about why TBIs induce residual sleep disturbances. For some patients, headaches resulting from the injury cause symptoms of insomnia. Some studies have focused on structural changes in the brain. Baumann et al.⁸ have recognized abnormal hypothalamic insufficiency in “a neuropeptide involved in sleep-wake regulation.” In fact, decreased hypocretin has also been linked to narcolepsy type-1; similarly to people with narcolepsy, TBI victims may experience REM abnormalities throughout the day.^[8,9] Multiple theories regarding structural abnormalities exist, but none of the theories have been confirmed prospectively. A study conducted in 2018 by Clark et al. found an association between reduced thalamic volume and fatigue following traumatic brain injury.^[8,10] Researchers postulate that the vulnerability of the thalamus is perhaps due to its central anatomical location.¹¹

The pathophysiological mechanisms are likely multifaceted— a study by Parcell¹² et al. suggests that damage to sleep-wake regulation centers, neurotransmitter systems, and circadian rhythm centers in the hypothalamic suprachiasmatic nuclei could induce sleep pathologies. As a part of the endocrine system, the pineal gland responds to feedback from the hypothalamus; the suprachiasmatic nuclei decides the time of sleep and resulting melatonin release based on retinal light exposure— for the studies on light therapy, this physiology explains why the intervention is theoretically effective.¹³ It also explains the reason providers may recommend melatonin to TBI patients who are experiencing sleep disturbances. Two recent studies measured the evening or

overnight production of melatonin in patients with traumatic brain injuries and found decreased melatonin synthesis; therefore, patients may experience symptoms of insomnia during these hours.^{14,15} Supplementation with melatonin or a melatonin agonist, such as ramelteon, could be beneficial for patients who have a TBI and subsequent sleep disturbances.

Non-Pharmacological Options

The non-pharmacological research on insomnia, sleep disturbances, and daytime fatigue after a traumatic brain injury are numerous and diverse. The most recent non-pharmacological studies provide data on bright light therapy, blue-light pulses, cognitive behavioral therapy, sleep hygiene education, and acupuncture. The efficacy of these treatment modalities will be discussed and compared to one another.

Bright Light Therapy

Bright light therapy involves using pulses of bright light, often around 10,000 lux, illuminated from a light box, and it is often used to treat seasonal affective depression and sleep disturbances.¹⁶ An open-label, single-arm trial studied the efficacy of bright light therapy for improvement of sleep, mental health, and plasma biomarkers of inflammation in United States Veterans who had sustained a TBI.¹⁶ The inclusion of plasma biomarkers and mental health was based on the possible association between higher-quality sleep and improvement of symptoms of PTSD and pain. Elliott et al.¹⁶ excluded participants from participating in the study if they did not meet criteria for a mild TBI (mTBI), or if they had bipolar disorder, macular degeneration, dementia, and depression. None of the 33 remaining participants were taking melatonin, and no one was excluded if they used medications to aid in sleep.

A baseline period of seven days was established wherein the participants did not alter their sleep-wake rituals.¹⁶ This controlled week was then followed by 28 days of 60-minute, 10,000 lux light therapy in the morning. The participants completed a diary in which they noted sleep time, wake time, naps, and prolonged wake time. Sleep assessments were completed before and after the course of light therapy intervention: Insomnia Severity Index (ISI) and the Sleep Hygiene Index (SHI). For objective data, Elliott et al.¹⁶ had the participants wear an actiwatch over 35 days. The watch actigraphy specifically measured “bedtime, sleep onset, wake time, mid-sleep time, total sleep time (TST), time in bed (TIB), sleep onset latency (SOL), sleep efficiency (SE), wake after sleep onset (WASO), total activity, average activity/epoch, and number of nocturnal awakenings.” The watch also measured light exposure and, subsequently, adherence to the regimen.

Participants were asked to complete multiple questionnaires that measured mood, PTSD, pain, and quality of life. The results demonstrated a benefit to the ISI score by 3.4 points on average, which correlates to a change from moderate to mild insomnia— there were no significant changes in the sleep hygiene index. Total Sleep Time (TST) was on average improved by 47 minutes. The subject’s bedtime was on average 77 minutes earlier, their wake-time was on average 30 minutes earlier, and their circadian phase shift was 37 minutes. Overall, this study draws preliminary associations between light therapy, improvement of sleep, and the “downstream effects” of sleep disturbances.¹⁶

There are multiple shortcomings of this study— because this study was conducted to obtain feasibility and preliminary efficacy, the study size was not large enough to generalize to all patients with insomnia secondary to TBIs. In addition, the veteran sample population had

higher rates of mental illness and PTSD which can affect sleep quality; however, their baseline sleep was examined prior to the initiation of the light therapy for control. Lastly, if participants were taking medication for sleep, they were allowed to continue taking that medication for the duration of the study. The study may have been improved if any medication used for the treatment of sleep had been discontinued; if future study designers allow for use of nightly sleep medications, perhaps they could discontinue PRN medications during the study.

Even though parts of this study are not generalizable to all patients with TBIs, there are components of the results that can inform treatment and future studies. The authors contend that in many previous studies on bright light therapy, the researchers do not report an estimated retinal light exposure, which makes the findings difficult to generalize. In this study, the researchers quantified the light using a spectrophotometer, which estimates a “dose” in units of lux; therefore, their results will be more easily compared to future studies that use spectrophotometry to verify dosing. Finally, Elliot et al.¹⁶ only allowed participation of patients with mild TBIs. Many studies on treatments of sleep disorders secondary to a TBIs observe multiple diagnostic TBI severities, which leads to less experimental specificity. Since their study only included one diagnostic severity, the research is more specific to people who have sustained a mTBI.

Blue Light Therapy

Blue light therapy is similar to bright light therapy, but has a color temperature > 5000 Kelvin (K)— in the following study, blue-enriched light is compared to blue depleted light (< 3000 K) to determine if there is a difference in efficacy.¹⁷ In a generalized population of participants who had sustained a mTBI or stroke with subsequent fatigue or sleep disturbances,

in-home blue light-specific therapy was compared to blue-depleted light.¹⁷ Most light therapy studies, like the prior study conducted on veterans,¹⁶ have participants complete light therapy in the morning— these researchers instructed their 24 participants to do light therapy three hours before sleep. Unlike in the other studies on bright light therapy, which tend to be conducted in acute stages of TBI recovery, the participants in this study experienced their TBI or stroke anywhere between 1-26 years prior to the commencement of this study.¹⁷ Furthermore, the positive results of their work are less likely to be due to healing.

The primary outcome evaluated in this study was fatigue, but daytime sleepiness, sleep disturbance, insomnia symptoms, psychomotor vigilance, mood, and activity levels were also measured.¹⁷ A two week baseline period for control was established, whereafter participants completed 2 months of nightly light therapy followed by two months of control light exposure or vice versa. Fatigue was measured using a Brief Fatigue Inventory, and the secondary outcomes were measured using the Fatigue Severity Scale, Epworth Sleepiness Scale, Pittsburgh SQI, ISI, Activity Diary, Light therapy questionnaire, sleep diary, and actiwatch for actigraphy. The results showed no statistically significant change in The Brief Fatigue Inventory and watch actigraphy. However, multiple secondary measures of sleep quality were improved as stated, “reductions in sleep disturbance (PSQI) by 1.50 points on average and insomnia symptoms (ISI) by 2.13 points, relative to baseline.”¹⁷

In comparison to the study by Elliot et al.,¹⁶ the average ISI score was improved by 1.27 points less in the blue light therapy study by Connolly et al..¹⁷ No improvement to actigraphy was noted in the latter case, but significant circadian shifts were noted with the former. Additionally, given the slightly higher quantity of participants in the bright light therapy study,

the results are not only more effective, but they are more credible. Regardless, the purpose of the Connolly et al. research was to provide preliminary support for in-home light therapy, and it achieved that goal.¹⁷

In the next article, instead of using PSQI and ISI for subjective measures, the researchers studied the effects of blue wavelength light on sleep and brain recovery with the Epworth Sleepiness Scale (ESS). This randomized, double-blind, placebo-controlled trial had 32 participants with a mTBI in the last 18 months.¹⁸ Some of the participants underwent 30 minutes of blue light pulses per morning for 6 weeks, while the placebo group was exposed to amber light at 578 nanometers. In order to be included in this study, the participants, who were 18-50 years of age, needed to have reported “significant sleep-related problems” that began or worsened after the injury.¹⁸ In the lab, participants answered questions regarding sleep history, completed the Epworth Sleepiness Scale for day time fatigue, and the Stanford Sleepiness Scale. Along with the use of an actiwatch for actigraphy, the participants wrote in a sleep and light diary every morning after the light therapy.

The results demonstrated that blue light reduced daytime fatigue objectively and subjectively. In comparison to the placebo actigraphy, the blue light group displayed a circadian phase shift of 60.1 minutes earlier by the end of treatment— 73.3% of the blue light participants had some circadian phase advancement, meaning they went to bed earlier and woke up earlier.¹⁸ The ESS sleep measures found that daytime sleepiness was reduced on average by a 25% drop in score, whereas the amber light control experienced a 10% increase in their ESS score. Finally, Killgore et al. noted on MRI that posterior thalamus size after blue light pulses was increased in

comparison with placebo.¹⁸ In previous studies, an increase in thalamus size has been associated with decreased daytime fatigue.

The inclusion of MRI results is another objective measure which researchers can use to draw associations between variables and measured changes. In order to strengthen these associations, future studies could include watch actigraphy and MRI scans. The prior studies on blue and bright light did not include MRI scans, which could have been a valuable comparison. Regardless, valuable comparisons can be drawn between watch actigraphy. Both the bright light therapy study by Elliot et al.,¹⁶ and the previous study by Killgore et al.,¹⁸ noted circadian phase shifts of 37 minutes and 60.1 minutes, respectively. It is not clear whether a greater circadian phase shift demonstrates greater improvement in symptoms. Since both studies had similar participant quantities and different subjective measures, it is difficult to compare the results of their research beyond actigraphical data.

A more recent study published in 2021 by Raikes et al.,¹⁹ specifically focused on blue light therapy in 62 participants who had sustained a TBI and subsequent fatigue or daytime sleepiness. In this double blind, placebo controlled trial, participants experienced 6 weeks of morning blue light therapy or placebo amber light; before and after the study, they completed the Epworth Sleepiness Scale along with an MRI of their gray matter volume. The results demonstrated an increase in the size of gray matter volume between multiple brain regions in those who received blue light therapy. In addition, increased size of the thalamus, orbitofrontal, and prefrontal cortices was associated with reduced daytime sleepiness. Participants also experienced an increase in sleep time.^{18,19,20}

Although this research demonstrates promise for the treatment of fatigue after TBI, there are multiple limitations. For example, in this retrospective study, there was not a non-injured control group for comparison– would the cerebral changes be present in non-injured participants with sleep disturbances? Are the changes in their brain due to light therapy or healing? The researchers comment that mTBI patients were enrolled from 5-80 weeks post-injury, therefore, some of the changes on MRI and ESS scores may be due to recovery rather than light therapy. Regardless, this study by Raikes et al.,¹⁹ which showed significant improvements in fatigue severity, displays the positive effects of blue light therapy for fatigue and sleepiness. Another recent study by Quera Salva et al.,²¹ found similar efficacy of blue light on fatigue severity with an improvement in the FSS score ($P = .026$). These articles lay the groundwork for future research on blue-light therapy and its utility for patients who have sustained a TBI.

Cognitive Behavioral Therapy

Rather than using a light box in an at-home setting, the following studies worked to help participants restructure their thoughts and behaviors for better sleep. For those who have not sustained a TBI, cognitive behavioral therapy (CBT) is considered one of the first line interventions in helping people restructure their thoughts and behaviors.⁴ In a study by Ngyugen et al.,²² researchers sought to evaluate the efficacy of CBT for populations with a TBI.

This study was designed as an unblinded single-center, parallel 2-group trial– patients either received CBT or treatment as usual (TAU). Treatment as usual consisted of OT, physiotherapy, pharmacotherapy, and psychotherapy. The CBT included a combination of frameworks utilized for treating anxiety, depression, insomnia, and chronic fatigue. The researchers state, “Therapy content was adapted to include an explanatory framework that is

relevant to TBI and to facilitate acceptance of increased vulnerability to sleep disturbance and fatigue as a consequence of brain trauma.”²²

After the selection process was complete, 24 participants were delegated to either CBT or TAU. Each participant in the CBT cohort attended 8 sessions of CBT, and for the most part, they completed their suggested at-home tasks.²² The results of the study demonstrated that 55% of the participants in CBT had an improved sleep quality; 70% of the CBT group had reduced symptoms of insomnia by an average of 3.12 points on the insomnia severity index.²² On the PSQI, the follow up indicated that the CBT cohort had a 4.85 difference in score as compared to the TAU cohort, demonstrating greater subjective improvements of sleep quality for the CBT cohort.

Even though this study displayed positive results, there were some limitations. Since this study was a pilot study, there was a reduced sample size. Thus, one cannot generalize the results of the study. Conducting a large-scale study in the future would be beneficial in researching the effectiveness of CBT. Next, results were not based on objective measures, so the data was at the liberty of each participant's subjectivity. The researchers could have included MRI scans or actiwatches for actigraphy in order to have objective measures. Finally, an exercise regimen was recommended to the CBT group; low compliance to this regimen was reported by the participants. It is difficult to determine whether increased compliance to the exercise regimen would have additionally affected sleep quality for the CBT cohort.²² A future study separating CBT and exercise could be beneficial to eliminate this added variable.

In another research trial by Nguyen et al. on fatigue and sleep disturbances after a stroke, 15 patients were allocated to two randomized groups.²³ The control group proceeded with TAU

while the other group attended 8 weekly sessions of CBT. Again, CBT demonstrated the most effective improvement for fatigue and sleep quality with a mean difference of 1.92 when compared to participants' prior Fatigue Severity score.²³ The previous study by Nguyen et al. for patients with TBIs showed no shift in FSS score after treatment.²² Therefore, larger studies on TBI and stroke patients should be conducted to elaborate on CBT efficacy— additionally, objective measures such as MRI scans or actigraphy would add to the validity of the data.

While the previous articles solely focused on CBT, the following article compared CBT with health education in order to control for effects not specific to therapy. The study conducted by Ymer, Mckay, and Wong,²⁴ was a parallel group, pilot randomized controlled trial that included 51 individuals who had either sustained a TBI or stroke. The participants had sleep or fatigue problems, and were either placed in cognitive behavioral therapy for sleep disturbance and fatigue (CBT-SF) or health education. After baseline assessment, the participants went through 8 weeks of their allocated treatment.

The measures included the Pittsburgh Sleep Quality Index (PSQI), ISI, ESS, measures of fatigue, sleepiness, and actigraphy sleep measures.²⁴ The results of the study indicated that CBT-SF leads to improvements in sleep quality and fatigue in comparison to health education, but there was no change from baseline in actigraphy. Whereas CBT-SF showed positive results within a couple of months, health education did not improve fatigue until 4 months after the intervention.²⁴ Regardless, changes in PSQI by the end of the study were similar between both groups at about -2.5 from abseline. Overall, this study provides evidence that suggests CBT-SF is an effective treatment for insomnia, sleep disturbances, and fatigue after a TBI or stroke. It also

demonstrates the need for more research comparing health education and CBT for more definitive results.

In an ever-digitizing world, health and therapy appointments alike have been moving to an online platform. In order to accommodate these changes, one pilot study collected data from 24 participants who were randomized to either receive online sleep hygiene education or online CBT.²⁵ The participants were diagnosed with either a mild or moderate TBI with subsequent sleep difficulties. The patients had to do 20-30 minutes of recommended intervention per week for 6 weeks. The main outcomes were measured using the PSQI and actigraphy. The results of the study revealed significantly improved sleep quality for the participants in CBT— the mean PSQI change was -4.00 compared to the control group of -1.50. Objective measures of watch actigraphy displayed little change. For future studies, more participants should be recruited— the researchers calculated that 128 people would be needed for there to be statistically significant results.²⁵

All of the articles on CBT demonstrated some improvement in subjective symptoms— the PSQI, if it was included as a measure, improved by between 2.5-4.85 points.^{22,25} However, the study with the most participants by Ymer et al. demonstrated no change in actigraphy. Thus, it is difficult to accurately gauge whether or not CBT improves sleep objectively. As stated before, future studies with consistent subjective and objective measures are needed to accurately compare studies on CBT to one another.

Sleep hygiene

Rather than comparing sleep hygiene and CBT, Dr. Michael J. Makley et al. compared sleep hygiene protocol (SHP) with the standard of care (SOC) in a hospital rehabilitation unit.²⁶

22 admitted patients were matriculated into one of the two groups, SHP or SOC. The researchers explain the conditions for SHP patients, “participants in the SHP received 30 minutes of blue-light therapy each morning, had restricted caffeine intake after noon, and were limited to 30-minute naps during the day.”²⁶ The SOC group did not have any changes to their routines and did not instate sleep protocol. For objective measures, all of the participants wore wrist actigraphs—in both groups, sleep metrics improved. The SHP cohort, however, exhibited significantly greater changes in total sleep time, sleep efficiency, and wakefulness after sleep onset.²⁶

The results of this study suggest positive effects of SHP, but one must also consider the limitations of the research. The cohort size was the main limitation of this study, but it was partially due to the exclusion criteria to maintain participant consistency. An additional limitation was the variability of treatments included in SHP. Perhaps some of the changes were due to one aspect versus another rather than the conjunction of all of the sleep hygiene protocol. For example, daily blue light therapy required by the SHP— it is difficult to assess whether the positive changes were due to blue light therapy or other SHP interventions. Regardless, this study’s objective was to study the practicality of an SHP on a hospital rehabilitation unit, and it completed that objective.²⁶

Acupuncture and Warm Foot Baths

The final two research studies on non-pharmacological treatments for insomnia following a TBI are on acupuncture and warm foot baths. In the study on acupuncture, all of the participants were veterans and had been diagnosed with a mTBI.²⁷ Additionally, it is mentioned that 66.7% of the veterans had been diagnosed with PTSD. The 60 participants were randomized into two groups based on PTSD status. All of the participants went to 10 acupuncture

appointments, but half of the group went to a sham needling procedure and acted as the placebo. Outcomes were measured with the PSQI and wrist actigraphy. On average, the PSQI improved by 4.4 points in the real acupuncture cohort and by 2.4 in the fake acupuncture.²⁷ Wrist watch actigraphy measured an improvement in sleep efficiency by 2.7% in the real acupuncture cohort, whereas the fake acupuncture group had reduced sleep efficiency. The veterans with PTSD had more severe sleep disturbances at baseline but experienced similar results to those without PTSD.

The final study, by Hsiao-Yen Chiu et al.,²⁸ was a randomized controlled crossover study with 23 adult participants who had sustained a TBI. All of the participants received both 30 minute 41°C/105.8 °F footbaths and TAU at different intervals during the study. Both groups of participants completed three days of the foot bath, three days of washout when no treatment was given, and three days of TAU. As an objective measure of sleep quality, participants wore an actigraphic watch. On average, results demonstrated reduced sleep onset latency by 5.11 minutes and wake after sleep onset change in 2.56 minutes.²⁸ There were no differences in sleep efficiency and total sleep time. Given the low participant quantity, more studies should be conducted before it can be generalized to all TBI patients. Additionally, subjective measures were not considered. Regardless, given its non-invasive nature, it could be an easy intervention to do in conjunction with other treatments.

Pharmacological Options

Perhaps due to the COVID-19 pandemic, studies on pharmacological treatments of sleep disturbances after a traumatic brain injury have been relatively scarce over the last several years, yielding only three pertinent studies during this time. These three studies explore the use of

melatonin and its hormone receptor agonist, ramelteon, to treat sleep disturbances in different age groups. Earlier studies from the early 2000s and a systematic review will be discussed to supplement the current literature.

Melatonin

A randomized, double-blind placebo-controlled trial in Australia that researched whether 2mg extended-release melatonin was effective vs. placebo for the improvement of sleep quality.²⁹ Thirty-three participants were included in the study, all of which were diagnosed with chronic insomnia secondary to a TBI. Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI), and sleep onset latency was measured by wrist actigraphy; the sequelae of low sleep quality were measured using the SF-36V1, Hospital Anxiety and Depression Scale, and Fatigue Severity scale.²⁹ In order to qualify for the sleep study, patients underwent numerous screening tests including pregnancy tests, an obstructive sleep apnea questionnaire, sleep testing, and urine drug screening. They were excluded from the study if they had traveled between time zones or worked night shifts in the past three months.

Melatonin was shown to improve subjective sleep quality by -1.79 points on the PSQI and actigraphic sleep efficiency $p\text{-value} \leq 0.05$. It also demonstrated reduction in symptoms of fatigue on the fatigue severity scale. The SF-36 V1, which measures self-perceived vitality and mental functioning, was improved as well with a $p\text{-value} \leq 0.05$. On the other hand, no difference was noted in daytime sleepiness or in depressive symptoms.²⁹ Overall, the results of the study demonstrate that melatonin supplementation is associated with reduction in symptoms of insomnia. The study size was smaller than the researchers intended, making it difficult to generalize the data collected. The researchers, Grima et al.,²⁹ report that future studies should be

performed using phenotyped circadian rhythms to observe underlying abnormalities for maximal benefit– in addition, short-acting and long-acting formulations of melatonin should be compared to one another in conjunction with CBT and light therapy.

The next pharmacological study on the treatment of sleep disturbance is specific to melatonin in the pediatric mTBI population. As in the previous studies, the children in this study were experiencing post-concussion symptoms and sleep disturbances.³⁰ All of the children were between 8-18 years old and were diagnosed with a mTBI. Three different doses were administered to separate groups: placebo, 3mg of melatonin, 10mg of melatonin. The placebo group consisted of 22 participants and the other two groups had 25 members each. The outcomes of the trial were measured with a post-concussion symptom inventory on sleep-related problems (SRPs). The results demonstrated an all-around decrease in SRPs, especially in the 3mg melatonin group.³⁰ The 3mg group reduced the SRP to 3.7, whereas the placebo and 10mg only reduced the SRP to 7.4 and 6.4 respectively. On average, sleep duration increased by 43 minutes in the 3mg cohort, and 55 minutes in the 10mg cohort.³⁰ The researchers conclude that melatonin is a safe option for short term treatment of post-concussive sleep disturbances in the pediatric population, especially at the 3mg dose.

Ramelteon

With a similar mechanism of action to melatonin, ramelteon, a melatonin receptor agonist, has recently been studied in the TBI population. A pilot, double-blind, placebo-controlled study was conducted to trial the effectiveness of ramelteon on sleep and daytime functioning for those experiencing sleep disturbances after a traumatic brain injury.³¹ Thirteen individuals with traumatic brain injuries complaining of sleep disturbances were selected if they

scored >5 on the Pittsburgh Sleep Quality Index. The patients were given a dosage of 8mg ramelteon every night for three weeks. The outcomes measured, similarly to the previously described studies, had objective and subjective measures of sleep. A sleep log was kept in addition to watch actigraphy to measure sleep-wake patterns. In order to measure day time cognition, a neuropsychological examination was conducted. Subjective measures consisted of questionnaires on mood, fatigue, and daytime sleepiness.

The results demonstrated an average increase in total sleep time by around 30 minutes.³¹ Nine of the 13 participants fell asleep earlier after taking ramelteon. This study provides preliminary data in support of the efficacy and safety of ramelteon for short term use. However, future studies should be conducted with a larger sample size to further promote efficacy and generalizability. Lequerica et al. state that future studies could be improved by the recruitment of participants with more recent injuries or by recruiting participants who have not received previous treatment for their insomnia.³¹

Other Research

Before these three recent studies on treatments of sleep disturbances, there were multiple studies on pharmacological treatments for sleep disturbances or fatigue post-TBI. A systematic review published in 2018 by Sangeeta Driver and Ryan Stork explores pharmacological management of sleep after TBIs.³² Specifically, the following studies were on the use of nonbenzodiazepine GABA-A agonists, melatonin receptor agonists, antidepressants. In the first study on melatonin, Kemp et. al. found that supplementation helped with daytime alertness and corrected sleep-wake cycles.^{32, 33} The next research article compared melatonin and amitriptyline– the melatonin group experiencing improvements in day time alertness, but

otherwise there was no difference in sleep quality from baseline.^{32,34} Next, for treatment using nonbenzodiazepine GABA-A medications, research has shown equal efficacy for lorazepam vs. zolpidem, with improvements from baseline.³⁵

In a study out of 2015, hypnotics were the most commonly prescribed medication for TBI patients in acute rehabilitation. However, due to the intense adverse effects, including headaches, dizziness, nausea, and memory impairment, more research is warranted for these vulnerable populations. Driver argues that Benzo GABA-A medications, therefore, should be avoided.³² The final medications reviewed by Driver and Stork are in one of two categories: antidepressants or other agents. None of the research is on TBI specific populations, and Driver contends that more research is needed to decide if trazodone, mirtazapine, quetiapine, or gabapentin could be useful treatments for TBI patients.³² For this reason, practitioners should start at low dose and titrate accordingly if they choose medications with less research.

Discussion

The relationship between traumatic brain injuries and sleep disturbances or fatigue has long been established. In some patients, headaches and PTSD from the traumatic event prevent sleep. For those without nighttime headaches or PTSD, the cause of these sleep sequelae is less clear. Multiple studies have noted changes in gray matter volume and connectivity, neuropeptide levels, thalamic volume, or melatonin release.^{8,11,14,15,18} Despite the numerous and ambiguous pathophysiological associations noted on MRI after a TBI, there have not been definitive, unanimous findings. The causes of daytime sleepiness, fatigue, insomnia, and sleep disturbances after a TBI are likely multifactorial. Due to this multifaceted nature of sleep disturbances after a TBI and recent evidence of efficacy, a holistic approach to treatment should be initiated

including both non-pharmacological and pharmacological options. It is clear more detailed research is necessary to best treat this patient population.

For patients who are struggling with insomnia, sleep disturbances, and fatigue after a traumatic brain injury, there are a variety of non-pharmacological options available. The studies in this paper researched bright and blue light therapy, cognitive behavioral therapy, sleep hygiene education, acupuncture, and warm foot baths. The majority of the included research was pilot studies, meaning the amount of participants was often low. For example, three of the studies on light therapy had less than 35 participants, and only two had over 50 participants.¹⁶⁻²¹ All of the CBT trials had under 25 participants.²²⁻²⁵ Regardless, the growing volume of research on CBT and light therapy is promising, and is another option for providers to consider when treating these patients with TBIs who have issues related to sleep.

Whether for the treatment of insomnia or seasonal depression, light therapy has been at the forefront of current research.¹⁶ With a growing body of positive results in healthy patients without a TBI, scientists have started conducting trials on populations with TBIs. Three different types of bright light colors were included in this essay, blue light therapy, amber light therapy as a placebo, and broad spectrum bright light therapy. Both objectively and subjectively, bright light therapy and blue light therapy demonstrated large reductions in scores measuring fatigue and sleep disturbances.¹⁶⁻²¹ Subjective scores were measured either using the PSQI, Insomnia Severity Index, Epworth Sleepiness Scale, Fatigue Severity Scale, or Stanford Sleepiness Scale. Inconsistency in types of subjective measures, or the way the results were reported, made it difficult to compare the studies to one another. For example, some studies reported a percent increase or decrease in score and others only reported the average change. Most of the studies

also used actigraphy to measure objective sleep— improvements were seen in sleep time, sleep onset latency, and sleep wake disturbances.

Cognitive behavioral therapy demonstrated similar efficacy to light therapy improving PSQI, ISI, and fatigue severity scores. PSQI score changes, if they were included, changed between 4.00 and 4.85, but participant quantity ranged from 15-51 with only one study having above 30 participants.²²⁻²⁵ In all but one of the studies, objective measures of sleep quality improved in addition to subjective measures. Subjective sleep measures were more consistently PSQI, ISI, and FSS, but there was still variation— the studies would be more easily compared if they had the same tests of measure.

Given the volume of research rather than data from one single study, CBT and light therapy are the most effective non-pharmacological treatments of insomnia, sleep disturbances, and fatigue after a TBI. Sleep hygiene was effective, but was shown to be more beneficial when done in conjunction with CBT. The research on acupuncture indicated positive PSQI and watch actigraphy results, but the research should be repeated to confirm efficacy before it is a recommended treatment due to the small sample size.²⁷ Warm foot baths and sleep hygiene both had positive results, but again, due to having low participant numbers, more research needs to be done before it is considered an effective treatment.^{26,28} However, given its non-invasive nature and ease in implementation, it may be worth trying for some patients.

Recent research on pharmacological treatments of this patient population has been relatively scarce. A recent systematic review entitled *Pharmacological Management of Sleep after Traumatic Brain Injury* by Sangeeta Driver and Ryan Stork comments on this discrepancy, “It is important to acknowledge that most research regarding the side effects of sleep medications

has focused on neurologically intact populations and little evidence is available regarding the tolerance of side effects in a TBI population.”³² For healthcare providers who treat patients with sleep disturbances after a TBI, it is important to know efficacy and side effect profiles specific to this population. Regardless, the current research from pediatric and adult studies suggests that melatonin is the most effective pharmacological treatment for insomnia and sleep disturbances after a TBI.^{29,30} The study that included ramelteon did not have enough participants to direct treatment. Other medications have not been studied in detail in recent years, so if providers decided to use other medications, they should start at a low dose and titrate slowly monitoring for changes in cognition, memory loss, or headaches.³²

For the treatment of daytime fatigue or sleepiness, there is no recent pharmacological research of armodafinil and methylphenidate in TBI populations. Nevertheless, a study published in 2010 did demonstrate the efficacy of modafinil for excessive daytime sleepiness.³⁷ Furthermore, provider recommendations and prescriptions for daytime sleepiness should focus on non-pharmacological options, melatonin, and possibly modafinil.

Future Pharmacological Research: Fatigue and Sleep Disturbances

As informed by the current recommendations for treatment of primary insomnia in an adult without a TBI, the efficacy of melatonin, ramelteon, benzodiazepines, trazodone, gabapentin, amitriptyline, histamine receptor antagonists (low-dose doxepin), and dual orexin receptor antagonists could be further investigated for TBI populations.⁴ For daytime fatigue, armodafinil and methylphenidate could be assessed in patients with TBI, if it is not otherwise contraindicated. In a study published in 2010, modafinil has been endorsed as an effective treatment for excessive daytime sleepiness but not for fatigue.³⁷ Excessive daytime sleepiness is

differentiated from fatigue by the Casper Editorial Team: “EDS can be a symptom of hypersomnia, which is a condition that makes a person feel very tired during the day, even if they get what should be enough sleep. Fatigue, on the other hand, has to do with a lack of energy and sometimes feeling unable to fall asleep despite being tired.”³⁸ Updated studies should be conducted to confirm safety and efficacy of modafinil. Finally, studies on the treatment of headaches that cause sleep disturbances after a TBI would also be beneficial.

Conclusions

Traumatic brain injuries and the sleep disturbances or fatigue that follow, can have a life altering impact on a patient. Considering the complex pathophysiological changes after a TBI, it is most helpful for providers to offer diverse resources for their patients. Whether it be sleep hygiene patient education, a referral for CBT, light therapy prescriptions, or melatonin, providers are in a position to help alleviate their patient’s suffering. Reflecting on the most recent research, providers should consider CBT and bright light therapy as first-line treatments.¹⁶⁻²⁵ Due to the limited recent research for pharmacological approaches, non-pharmacological treatments for TBIs should be used more readily. If a patient continues to have sleep disturbances, insomnia, and fatigue after non-pharmacological interventions, pharmacological treatments such as melatonin or ramelteon, may be used to promote further improvement of the symptoms. It is clear that more research is required on pharmacological and non-pharmacological treatments for sleep sequelae after a TBI before further conclusions can be drawn.

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