Study Protocol

1. Protocol Title

Sleep Management And Recovery after Trauma in Kids (SMART-Kids): Melatonin Pilot Trial
NCT04932096
IND reference number 157247

PI: Cydni N. Williams, MD, MCR
707 SW Gaines St, CDRC-P
Oregon Health & Science University
Department of Pediatrics, Division of Pediatric Critical Care
Portland, OR 97239
(503) 494-5522

2. Objectives

This is a randomized controlled phase II intervention trial evaluating early melatonin and a sleep educational intervention versus placebo following pediatric traumatic brain injury (TBI). No changes to typical TBI care will be made. This single center trial will focus on feasibility and acceptability outcomes of a real world pragmatic sleep intervention frequently utilized in the outpatient setting among pediatric TBI patients when employed earlier in the recovery process during hospitalization. We will also obtain data on effectiveness to reduce sleep disturbances at 30-day outcomes assessment to help inform a larger trial that would be powered to evaluate effectiveness among a heterogeneous population.

3. Background

Sleep wake disturbances (SWD) affect over 50% of the 50,000 children surviving critical care hospitalization for traumatic brain injury (TBI) each year in the United States.[1-5] SWD are known to significantly impair quality of life and persist for years after TBI of all severities and in children of all ages.[6-13] SWD place these children at risk for long-term adverse health outcomes as recognized in Healthy People 2020.[14-16] However, interventions for SWD after pediatric TBI are poorly studied and clinicians are left with little evidence base to guide care for this debilitating morbidity after TBI.[17-19] Despite known benefits of healthy sleep on brain development and healing,[20-25] it remains unknown how SWD impact recovery in other physical, cognitive, and psychosocial outcomes after pediatric TBI, especially among children hospitalized with complicated mild, moderate, and severe injuries. Our research shows 52% of these TBI patients have SWD and 84% with SWD have phenotypes consistent with insomnia and circadian disturbance, though multiple SWD phenotypes often coexist.[5] SWD may be particularly important in recovery of executive functions after TBI that are linked to poor academic and functional outcomes.[11, 26-29] Therefore, we will conduct a pilot randomized controlled trial of an early sleep management intervention (melatonin and a sleep education handout) to determine acceptability and feasibility of an intervention directly applicable to the pediatric TBI population. We will also explore clinical effectiveness outcomes of this real-world intervention to provide preliminary data for a larger trial with the long-term goal of improving quality of life and multimodal outcomes through sleep interventions.

Early sleep intervention may be particularly important for children suffering TBI as sleep promotes neuronal healing and reduces inflammation that could maximize functional recovery.[30-35] However, two recent systematic reviews show no studies evaluating interventions to improve sleep after TBI hospitalization in children.[17, 36] Melatonin and behavioral/educational interventions are safe, first line therapies for multiple SWD phenotypes in pediatric primary care and sleep clinics.[37-46] In our multidisciplinary Pediatric Critical Care and Neurotrauma Recovery Program at OHSU, standard clinical care for SWD after TBI in the outpatient setting includes melatonin and sleep educational interventions used together as first line treatments for difficulty initiating and maintaining sleep starting at the first outpatient visit typically 4-6 weeks after hospital discharge (see uploaded example of actual clinical recommendations in supporting documents). Our research shows children with TBI have high rates of difficulty with onset and maintenance of sleep.[5] Our recently accepted publication showed that SWD occurred in 2/3 of pediatric TBI patients and were associated with significantly worse objective and subjective measures of cognitive function 1-3months after pediatric TBI hospitalization; interestingly in this cohort of 131 children, 12% of patients had already started melatonin after hospital discharge prior to the appointment without a clinical prescription, and we prescribed melatonin together with sleep education targeting behavioral modifications to address sleep newly in 43% at the clinical visit.[47] This is also in line with research showing up to 1 in 17 school aged children from the general population have used melatonin more than once a week within the last 6months.[48] Both melatonin and educational

sleep interventions targeting improvements in sleep hygiene, which are most often used in combination to provide the greatest benefit, are shown to improve SWD in multiple other pediatric populations, including improvements in sleep latency, efficiency, and duration directly applicable to our TBI cohort.[37, 38, 40, 42, 44, 46, 49-54] In most instances, melatonin is utilized in the 1-2 hours before bedtime for soporific effects in pediatric patients in conjunction with education about the importance of a good sleep routine, environmental changes to promote sleep, and recommendations for behavioral modifications to promote sleep.[51, 55] Melatonin levels and circadian rhythms are known to be altered in hospitalized patients and TBI patients, and could contribute to ongoing circadian disturbance, which may be another way melatonin could be helpful.[56-61] Additionally, melatonin has analgesic, anti-oxidant, anti-inflammatory, and anti-apoptotic effects relevant to TBI outcomes.[33, 34, 36, 44, 62-69] Inflammation in particular is chronic after TBI, is linked to SWD including insomnia, and targeting inflammation may improve SWD.[31, 34, 70-73] A randomized trial in 33 adults with TBI and SWD approximately 46 months after injury showed melatonin improved subjective sleep quality, fatigue, and sleep efficiency on actigraphy compared to placebo.[74] A retrospective study of adolescent concussion showed 67% reported improved sleep subjectively with melatonin prescribed in clinic.[75] A recent randomized controlled trial in outpatient pediatric concussion in children aged 8-18years found no evidence of improvement in overall post-concussive symptoms, but did improve sleep efficiency on actigraphy, and there were no serious adverse events.[76, 77] Improved sleep latency and duration with melatonin after non-traumatic pediatric acquired brain injuries are also reported.[44, 46, 78] A recent randomized trial of pediatric cancer survivors, including those with brain tumors, showed 3mg of melatonin improved aspects of sleep and cognition, and also noted that the addition of interventions targeting behavioral changes based in cognitive behavioral therapy for insomnia (CBT-I) could have improved gains further based on results in prior trials.[79]

A 2022 systematic review that included analyses of recent randomized controlled trials in pediatric neurodevelopment populations reported no adverse events with short term <3month use and few mild side effects even with prolonged usage in pediatric patients.[80] While some healthy children may respond to behavioral interventions targeting sleep hygiene alone, those with neurodevelopmental and neurologic diagnoses are more likely to need additional interventions, with melatonin combination being the first line treatment to address sleep latency and maintenance.[42, 52, 54, 81] It should be noted that TBI patients have high rates of baseline neurodevelopmental disorders, which also increases the risk for post-traumatic SWD after hospital discharge.[47, 82] A recent literature review and expert consensus panel convened in 2019 additionally endorsed the safety of melatonin and recommended use in conjunction with educational and behavioral interventions (sleep hygiene, routines, family education, etc) in children; this review specifically highlighted the safety of melatonin in short and long-term use in pediatric patients and the fact that melatonin is used in conjunction with sleep education targeting improved sleep hygiene.[83] A recent study also showed a >200% increase in the use of melatonin among hospitalized children of all diagnoses in a large tertiary academic children's hospitals between 2016 and 2020, showing the increasingly ubiquitous use of melatonin in pediatrics; most of the doses were scheduled nightly during hospitalization, were used in ICU and non-ICU areas, ages ranged from 2months of age to >18years of age, doses ranged from <1mg to 30mg depending on age and indication targeted.[84] A dose finding trial in pediatric oncology showed melatonin was well tolerated at doses up to 0.3mg/kg (max 20mg).[85] Melatonin and sleep educational interventions are most often used in conjunction, though the combination has not been studied for SWD in hospitalized pediatric TBI populations. These interventions are promising given safety and pleiotropic effects with respect to sleep onset, maintenance, and anti-inflammatory properties, as well as potential for easy dissemination and implementation, directly applicable to the pediatric TBI population. This

study will primarily evaluate feasibility and acceptability of a real-world sleep intervention frequently employed in the pediatric TBI population within the outpatient setting. We will also explore whether earlier inpatient employment of standard SWD interventions (melatonin and sleep education) commonly administered in the outpatient setting can provide benefit when employed earlier in the disease course as an adjuvant to clinical TBI care.

4. Study Design

This is a pilot randomized controlled phase II intervention trial evaluating early melatonin and sleep education via handouts versus placebo following pediatric traumatic brain injury (TBI) in two parallel study arms. This single center trial will focus on feasibility and acceptability outcomes, but will also obtain data on clinical effectiveness to reduce sleep wake disturbances at 30-day outcomes assessment. Sleep disturbances (with questionnaires and actigraphy data from Fitbits), feasibility (with clinical data collection, participant survey), and acceptability (survey, medical chart review) outcomes will be collected.

The intervention of this study uses a dietary supplement (melatonin) and an educational intervention administered via handouts. This study is not designed to evaluate melatonin's therapeutic efficacy or potential to diagnose, cure, mitigate, or otherwise treat a specific medical disorder, only to evaluate potential benefits to the bodily function of sleep when used with sleep education. The combined intervention of melatonin and sleep education was designed to mirror real world clinical care employed in this population within the outpatient setting in order to be generalizable to a heterogeneous population that is representative of the pediatric TBI population; therefore, our trial is designed to be pragmatic and will be exploring effectiveness outcomes for SWD relevant to this population, rather than efficacy of any one part of the intervention. A primary focus will be feasibility and acceptability (including intervention usage) to inform a larger longitudinal trial that would be needed to account for unavoidable population heterogeneity in clinical characteristics and adherence to intervention recommendations within the clinical setting.

5. Study Population

a. Number of Subjects

We expect to enroll between 30-50 patients based on eligibility over 2.5 years of recruitment. This estimate is based on the most recent hospital admissions data since the start of the COVID-19 pandemic estimating approximately 100 patients will qualify for the study over 2.5 years. Participants will be randomized 1:1 to receive the intervention. Recruitment and retention will be assessed during the trial as outcomes.

b. Inclusion and Exclusion Criteria

Children ≥6 years and <19 years of age admitted with TBI (defined as injury to the head from external forces with severity mild, moderate, or severe classified by Glasgow Coma Scale) will be included.

Children under the age of 6 years will be excluded due to increased variability in baseline sleep patterns, daytime napping, and lack of standardized tools identifying sleep outcomes between children younger and older than 6 years. Patients over age 18 years will be excluded as they are primarily treated in adult care units and the study focus is pediatric. Patients unable to tolerate enteral medications within 72 hours of hospital admission, as defined by the clinical care Attending Physician, will be excluded from the study. Patients undergoing dialysis, requiring extracorporeal life support, or with significant liver dysfunction (defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 2 times the upper limit of normal for age) will be excluded. Patients about whom the Attending Physician has any safety

concerns regarding use of melatonin as per clinical judgement will be excluded from the study. Patients with abusive trauma will be excluded. Suspected or known prisoners are excluded. Pregnant patients are excluded. There will be no requirement for contraception during the trial in female patients of child-bearing age. Patients must have a parent or guardian with whom they reside in order to participate in the study given the parent-reported measures used for outcomes.

There is inherent heterogeneity in the pediatric TBI population, and this study is designed to be *inclusive of the representative clinical population*, including those with pre-existing conditions. Given the ubiquitous use of melatonin in pediatric clinical care and research studies in a variety of pediatric populations with medical, developmental, and psychiatric disorders, no patients will be excluded for underlying medical conditions or concomitant medication use outside of the above exclusion criteria unless clinical judgement by the Attending Physician on the clinical care team would preclude use of melatonin for safety concerns.

Potential participants will be screened on arrival through the OHSU Emergency Department (all traumas, suspected traumas, and trauma referrals from other institutions are evaluated by the Trauma Surgery team in the Emergency Department per OHSU policy prior to admission). Medical records will be reviewed by the study team to determine eligibility; a waiver of consent under "Activities Preparatory to Research" for participant eligibility determination by research coordinators will be obtained. Research coordinators with the Trauma Research Group are present in the Emergency Department and are available to screen all TBI admissions for inclusion into active research studies 24hours/day. Screening information regarding inclusion/exclusion criteria will be retained for further analysis of recruitment outcomes.

c. Vulnerable Populations

The aims of this study are entirely focused on children ≥6 years to <19 years old. Inclusion of children is appropriate given the proposal focus on sleep outcomes in pediatric traumatic brain injury. Traumatic brain injury is a significant problem for children, including the leading cause of death and disability over 1 year of age. Dr. Williams is a Pediatric Critical Care physician with significant expertise in caring for children of all ages with critical illnesses, including traumatic brain injury, during the acute hospitalization. Dr. Williams also has unique expertise in the longitudinal care of these children after discharge, directing the Pediatric Critical Care and Neurotrauma Recovery Program. Age will be evaluated as a covariate in the analysis of both aims. Pregnant patients and prisoners are excluded.

d. Setting

Patients will be recruited from OHSU and Doernbecher Children's Hospital

e. Recruitment Methods

Screening: Children with traumatic brain injury (TBI) will be screened for inclusion in the study by the Trauma Research Group (TRG) on admission to Oregon Health and Science University or Doernbecher Children's Hospital. Research coordinators with the TRG are available to screen all TBI admissions for inclusion into active research studies 24 hours per day. Screening activities will take place under a HIPAA waiver per the "Activities Preparatory to Research" policy at OHSU. Given the extensive experience and training of the TRG, we expect very few if any screen failures of TBI admissions, and this will be actively monitored throughout the study period.

Recruitment Procedures: Recruitment will be maximized by using consistent trained staff within the TRG that have extensive experience consenting subjects and surrogates for research, including critically injured children. The recruitment process will be overseen by Dr. Williams, a Pediatric Critical Care physician, with expertise in caring for critically injured children. TRG staff

are trained and mindful of the critical nature of traumatic brain injury and will ensure the appropriate time and conditions for obtaining informed consent. Individual staff are monitored to ensure adherence to TRG standard operating procedures and study protocols.

The appropriate time to approach patients will be determined by study staff and clinical care staff, and consent will be obtained within 72 hours of Pediatric Intensive Care Unit admission to ensure starting the intervention as early as possible. Delaying consent for critically ill patients will not adversely affect the study outcomes, but will allow for acute stabilization of patients prior to consideration of study inclusion, ensure ability to administer enteral medications, and to allow for determination by the primary clinical care team of a patient's likelihood of survival. Consent procedures will be reviewed at least quarterly during TRG coordinator meetings to ensure ongoing consistency. The minimum goal set for recruitment is 50% of eligible patients.

Retention: All patients consenting for inclusion will have phone, address, email contact information collected at time of consent. Outcomes will be obtained at 1-month follow-up as described.

Participants will be compensated $25 for time related to completion of study procedures at baseline and $50 for time to complete study procedures at 30-days (total $75 per participant). The FitBit account will be transferred to their participant preferred email account at study completion (cutting off research team access automatically) and can keep the FitBit device.

f. Consent Process

This intervention study is considered more than minimal risk, but with potential to directly benefit the participant and uses a low-risk intervention frequently employed in the care of pediatric TBI patients in the outpatient setting. Therefore, written informed consent for study inclusion will be obtained from one parent or legal guardian able to provide consent for minors, and those <18 years meeting criteria under Oregon law to be considered adults and unable to provide consent themselves. As above, participants must have a parent or legal guardian with whom they reside in order to participate. Additionally, acute TBI is likely to affect participants' ability to provide informed consent. Therefore, minors will not be allowed to consent for themselves during this study, though we will require assent for those able to provide. Children who come of age or meet criteria under Oregon law to be considered adults during the study period will be re-consented for study inclusion. The logistics will be determined according to the convenience of the families considering enrollment. Every effort will be made to ensure that the consent discussion occurs in a private environment, when the subject/parent/guardian duress is minimized to the extent possible. Participants will be approached for the study within 72 hours of admission, after acute stabilization from the critical illness (defined by clinical care Attending Physicians assessment as likely to survive to hospital discharge and able to tolerate enteral medications), either while in the PICU or on the acute care ward prior to discharge. All consent forms, documentation, and discussion will be conducted in the parents' native language. We are aware that, under the circumstances, the study often needs extra-careful and repeated explanation. We routinely follow our explanation of the study protocol by a period for parents to ask questions, but in addition we also ask the parents questions to gauge their level of understanding. If it is our impression that parents remain unclear about aspects of the study, we spend extra time clarifying these specific issues. In this manner, all elements of the informed consent process will be discussed until the investigator is assured of the subject's or parent's (and, when appropriate the child's) full understanding.

Assent from children ≥7years of age for study inclusion will be obtained when possible:

- Children younger than 7 years: Assent is not required because the subjects are so young they cannot reasonably be consulted. However, a simple verbal explanation of the study procedures should be given if appropriate.

- Children ages 7 – 14 years: Researchers may obtain assent verbally and document this on the consent form or elsewhere in the research record, or researchers may ask the subject to sign an assent form after discussing the study with the subject at a level appropriate to the subject's understanding. Researchers will use the OHSU assent template.
- Children ages 15 – 17 years: The subject may sign the consent form along with his or her parent(s) or guardian as documentation of assent. A separate assent form is not needed.

For non-English speaking participants, we have 24/7 available translators over the phone that will assist with the consent process. We will submit short consent form(s) for IRB review and approval as appropriate. An interpreter will assist with the initial consent process and subsequent study visits for all non-English speaking subjects.

Other than screening procedures described above, no modifications to the written consent process will be used.

6. Procedures Involved

Data Collection: Patients meeting inclusion criteria (see Eligibility Criteria) will be approached within 72hours of hospital admission to provide written consent and assent where appropriate. Parents will be asked to complete "baseline" assessments retrospectively to reflect the patient's pre-injury status at the time of consent. Additional information will be collected by the study team from parents via survey and medical record review for demographic and clinical variables. Our goal recruitment and completion is for 30-50 patients.

Randomization: Patients will be randomized 1:1 to intervention and control arms using a covariate adaptive design through the randomize.net website. Given heterogeneity in age and TBI severity, we aim to balance these patient characteristics across the arms with a relatively small sample size. A covariate-adaptive design will achieve better balance than one based on block stratification, as such a scheme will increase a subject's probability of being assigned to the arm that improves overall balance in age and TBI severity (Glasgow Coma Scale Score groups: mild 13-15, moderate 9-12, severe ≤8). Initially, we will assign patients 1:1 to each arm by simple randomization, until six patients have been enrolled in each arm; this will allow us to collect sufficient information on covariates and determine the distribution of age and TBI severity in each arm. Once this criterion has been met, the Pocock-Simon minimization algorithm will be implemented and subsequent patients will be randomized with a probability of 0.85 to the arm that lowers overall imbalance in age and TBI severity. All patients will be randomized within 72 hours of hospital admission.

Intervention: All patients will receive standard clinical care for TBI regardless of study arm. Patients randomized to the intervention will receive a bundled sleep intervention consisting of melatonin and sleep education via a handout provided in discharge paperwork. Melatonin doses of 3mg and 5mg will be administered as part of the intervention arm in standard doses based on patient weight to target approximately 0.1mg/kg and not to exceed 0.2mg/kg. Melatonin will be administered on the first night following consent, 1 hour prior to habitual bedtime, and continued nightly for 30-days. Each participant will start the melatonin or placebo intervention within 96 hours of hospital admission, varying with time of admission and consent. Patients randomized to receive the intervention will be given a written sleep education handout developed with age-based recommendations from the American Academy of Sleep Medicine and access to web-based sleep educational resources developed from similar materials used in the care of pediatric brain injury patients within the outpatient setting.

The handouts delivered with discharge paperwork will be incorporated into the discharge instructions section within the electronic medical record by a research assistant. Handouts contain resources outlined below educating patients and families on the importance of sleep, sleep hygiene, sleep

routines, environmental changes to facilitate sleep, and relaxation techniques; the handouts were adapted from standard care provided in our outpatient program for TBI management (see details below). Further, a study in a pediatric ICU cohort designed to directly compare modes of educational intervention delivery, and included parents of pediatric TBI patients, recently showed an educational handout was just as effective as a scripted conversation or a short video when attempting to educate families about morbidities after hospital discharge, but the handout was the most sustainable and supported by hospital staff.[86]

Participants randomized to the control arm will receive placebo (microcrystalline cellulose) and the sleep education handout delivered with discharge paperwork as above. All patients will receive clinical care as usual for management of TBI. All traumatic brain injury patients at OHSU receive referrals for clinical follow up with the Pediatric Critical Care and Neurotrauma Recovery Program (PCCNRP); other referrals made to outpatient programs are made on an as needed basis depending on type of TBI and other concurrent injuries or morbidities identified during hospitalization. While in the hospital, current standard of care treats morbidities after TBI as needed and varies by clinical provider; there is no standard for treating sleep problems in the hospital. As outpatients, all hospitalized pediatric trauma patients at OHSU are referred to the PCCNRP clinic 4-6weeks after discharge. At this outpatient visit, a comprehensive assessment in physical function and morbidity is made by Dr. Cydni Williams (Pediatric Intensivist), which includes assessment of sleep; a brief neuropsychological assessment of cognitive function and a comprehensive psychological assessment are made by Dr. Trevor Hall (Pediatric Neuropsychologist). Given this study's intervention is designed for 30days and we plan to make no changes to clinical care, all patients in the trial will still have access to these evaluations at clinic appointments 4-6weeks after discharge.

As noted above, we see high rates of SWD with regard to initiation and maintenance of sleep and our first line recommendations at these outpatient appointments for pediatric TBI patients are a combination of melatonin supplementation (at doses of 1mg to 10mg targeting soporific effects depending on child age and size) and sleep education targeting improvements in sleep hygiene, routines, relaxation, and environment to facilitate sleep delivered in conjunction with each other. The sleep education recommendations are included in a paper report of the entire visit that includes education about the importance of sleep, sleep hygiene, environmental changes to promote sleep, and relaxation techniques. This report also includes links to videos developed by Dr. Cydni Williams, Dr. Trevor Hall, and Dr. Andrew Riley utilizing the CBT-I principles (links to videos found in supplemental documents). Both the written information and video links provided in clinic were used to develop the proposed sleep education handout portion of this study's intervention delivered at hospital discharge in this trial; the videos for the study were placed in Qualtrics to aid in tracking usage for the study and generating links and QR codes for easy access, and the written information was formatted for the study to provide concise information across a broad population and visual appeal for children or teens.

Participants and study staff assessing outcomes will be blinded to intervention status. Research assistants on the study staff will add the sleep education handouts with video links to discharge instructions to be delivered by the bedside nurse in concurrence with clinical care. The intervention was designed this way to increase feasibility and generalizability for the future by providing a means of information dissemination that could be easily and widely adopted if effective within different health systems in conjunction with clinical care. This research assistant will be notified by REDCap when a participant is enrolled, and will place instructions in the discharge section of the electronic health record that is automatically printed at discharge, without interaction with other study team members or families. Additionally, this portion of the intervention will be delivered at hospital discharge concurrent with clinical care to improve generalizability in future work by limiting change to institutional care practices. The sleep handout will be delivered in conjunction with standard discharge instructions provided to all TBI patients and other care will remain per our institutional TBI standards directed by the

patient's care team (an example of these standard TBI discharge instructions are uploaded in supporting documentation).

Outcomes: We will include measures of feasibility, acceptability, and effectiveness. See **Table 1** for summary of outcomes and schedule of collection. Outcomes will be assessed at hospital discharge, and a study visit at 30 days ±17 days. 30-day outcomes assessments will be defined from the time of study intervention initiation. The primary outcomes will be measures of feasibility and acceptability, with exploration of effectiveness in this pilot trial. Quantitative measures of recruitment and retention (feasibility), adverse events and utilization (acceptability), and total score of the Sleep Disturbances Scale for Children (SDSC) at 30-days (clinical effectiveness) will be used. Outcomes will be collected by the study team over the phone, via chart review, or via electronic survey administered through REDCap. Secondary and other outcome measures will be collected by activity monitor, chart review, survey, sleep questionnaire, and actigraphy devices. Fitbits will be worn continuously during the 30 day study period except when removed for charging the device.

Text messaging will be used for system generated reminder prompts such as "Please sync your device"; or if battery is low, "Please charge your battery" during the 1-month study period while participants wear the Fitbit. Text messaging functions require sharing of participant phone numbers with the Fitabase platform and Twilio, Inc.

Feasibility benchmarks will be assessed every 6 months during the trial. If feasibility benchmarks are not met, study procedures and the protocol will be reviewed using input from stakeholders and preliminary data to determine if changes are warranted.

Table 1. Outcomes Evaluation and Analysis for Melatonin Trial

Outcome (**time collected**)	Measurement or Assessment Tool	Analysis
Feasibility Outcomes		
*Recruitment (**6-monthly feasibility reviews**)	Number subjects consented/approached; goal >50%	Descriptive percent
*Retention (**6-monthly feasibility reviews**)	Quantitative Number completed/consented; Goal >90%	Descriptive percent
Screen failure (**6-monthly feasibility reviews**)	Number approached/eligible patients; expect <<5%; eligible patients will be derived from the OHSU Trauma Registry and compared to study logs	Descriptive percent
Reasons for Participation/ Non-participation (**time of approach/consent**)	Qualitative response to survey: "Please describe reasons you chose [not to or to] participate in this research study"; "Could the study team do something different in the future to increase chances you would participate in future studies?"	Thematic analysis
Reasons for drop-out (**30-day**)	Qualitative response to survey: "We would like to know how we can improve our study in the future. Please tell us your reasons for leaving the trial"; "How could the study team have assisted you better in completing the trial?"	Thematic analysis
Adherence (**30-day**)	Pill counts: adherent if ≥75% prescribed pills are taken at the follow-up study visit; will be counted as unknown if pill count not available Sleep tracking usage: actigraphy data and sleep diaries will be compared to age based recommendations; actigraphy counted as	Descriptive percent; Chi-square to compare intervention arms Descriptive percent; Chi-square to compare intervention arms

	adherent if device worn for ≥5 nights consecutively; we will assess sleep routines through actigraphy; will be counted as unknown if did not participate in the actigraphy portion Quantitative survey: "How many nights each week did you take the study medication since discharge?" None, 1-3, 3-4, 5-7, All Quantitative survey response: "Did you receive sleep education with your hospital discharge paperwork?"; choices of a) did not receive discharge paperwork; b) I did not receive any sleep education at discharge; c) I received it, but did not use it; d) I received it, but did not find it helpful; e) I received it, and found it helpful; responses to this question will also be compared with the discharge instructions within the electronic health record to determine if the resource was provided as intended.	Descriptive percent; Chi-square to compare intervention arms
Acceptability Outcomes		
*Adverse Events (**discharge, 30-day**)	Qualitative response to survey: "Did you have any new medical problems since the last study visit?" Quantitative yes/no response: "Did you have any of the following symptoms since the last visit" a. Nausea b. Vomiting c. Diarrhea d. Drowsiness e. Fatigue f. Headache g. Behavioral changes h. Vivid dreams i. Nightmares j. Waking up at night k. Itchy skin l. Rash m. Appetite changes n. Bodily pain or aches o. Chest pain p. Enuresis or bedwetting q. Dizziness r. Tinnitus or ringing in the ears s. Feeling cold Evaluation of medical record, patient assessments to quantify adverse events and unexpected problems collected as a dichotomized yes/no and number of events	Thematic analysis Descriptive percent and mean with standard deviation; Chi-square (yes/no) and Mann-Whitney U test (continuous) to compare intervention arms
Satisfaction (**30-day**)	Quantitative rankings on a likert scale survey: experiences with the study overall, consent process, study team, study intervention, questionnaires, Actigraphy devices, care received	Descriptive median and interquartile range; Mann-Whitney U tests

	clinically in the hospital, care received clinically after hospital discharge Qualitative response to survey: "If you were provided sleep education, and did not use it or find it helpful, please describe reasons:"; "If you were provided sleep education, and found it helpful, please describe how you utilized the resources"; "How can the study team improve the experience of participants in future studies"	to compare intervention arms Thematic analysis
Reasons for Non-adherence (**30-day**)	Qualitative responses to survey: "Please describe reasons for not taking the study medication"; "Please describe reasons for not using the sleep educational resources provided at hospital discharge"; "How could the study team improve the design of the study in the future"; "How could the study be improved in the future"	Thematic analysis
Exploratory Clinical Effectiveness Outcomes		
*Sleep wake disturbance (**Baseline, 30-day**)	Sleep Disturbances Scale for Children (SDSC) total score	Descriptive mean and standard deviation; linear regression to compare intervention arms
Sleep wake disturbance phenotypes (**Baseline, 30-day**)	SDSC subscale scores, Children's Chronotype Questionnaire, actigraphy measures (total sleep time, sleep onset latency, wake after sleep onset, sleep efficiency, night sleep:total sleep time, sleep onset, sleep offset, daytime sleep episodes, duration of daytime sleep)	Descriptive mean and standard deviation; linear regression to compare intervention arms
Global health (**Baseline, 30-day**)	Pediatric Quality of Life Inventory (PedsQL) scales for core, fatigue	Descriptive mean and standard deviation; linear regression to compare intervention arms
Emotional health (**Baseline, 30-day**)	PROMIS measures for anxiety and depression	Descriptive mean and standard deviation; linear regression to compare intervention arms
Physical function (**Baseline, 30-day**)	PROMIS measures for pain; Functional Status Scale	Descriptive mean and standard deviation; linear regression to compare intervention arms
Cognitive function (**Baseline, 30-day**)	Behavior Rating Inventory of Executive Function, Second Edition	Descriptive mean and standard deviation; linear regression to compare intervention arms

*Primary outcomes

Subjects can withdraw from the study at any time, including discontinuation of the intervention. Subjects can choose to withdraw consent for use of their data during the study, and they will be fully removed. Subjects can also choose to withdraw from the intervention, but continue in the study where their data will be collected and analyzed.

7. Data and Specimens

Data and protected health information will be safeguarded in multiple ways. First, all study forms will include only a study ID number. Actigraphy devices will be configured with only an ID number and will not store any identifiers. The key to study ID and patient identifiers will be maintained by the PI in a secure REDCap database that is password protected and hosted on the OHSU secure server. All study data will be inputted into REDCap by members of the study team. The PI will maintain the REDCap database and provide access only to study team members. All exports of data from REDCap will be coded.

All potential physical discomforts related to actigraphy devices will be minimized by allowing participants to remove the device if discomfort occurs and to withdraw from this portion of the study if desired. The actigraphy data will be collected using Fitbit devices.

The Fitbit mobile app and device require the creation of individual accounts with Fitbit for all study participants within the Fitbit app on a smart phone or tablet. Participants will be asked to use an email address of their choosing and accept Terms and Conditions for use of the Fitbit app. The data collected from the Fitbit devices will NOT be integrated with the medical record of the patient or used for clinical decision making. FitBit data will be collected through syncing with the FitBit app on a smart phone or tablet at least weekly by the participant. The Fitabase platform will be used to remotely collect real-time physical activity and sleep data from study participants' Fitbit accounts, and also to send personalized text messages to participants' cell phones. Participants will be asked to accept the Fitabase Terms and Conditions for linking with the Fitbit App. Fitabase is a secure password-protected web-based platform hosted in a HIPAA-compliant server. Fitabase comprises user-friendly visualization and data exportation tools that allow key research personnel to view participants' Fitbit data in the form of graphs every time participants sync their wearable tracker with the Fitbit mobile app. Study participants will not have access to Fitabase; they will only interact with the Fitbit mobile app and activity tracker. The text messaging feature is integrated with Fitabase and utilizes Twilio's application programming interface to send messages via the SMS protocol. Participants will be consented to utilize their smart phone devices for syncing with the Fitbit app and to receive text messages from the platform to serve as reminders to sync devices and to utilize the online resources for those in the intervention phase. The only identifier shared with the Fitabase platform and Twilio, Inc. is the telephone number for the smart phone device the participant consents to utilize. Participants will be asked to use and email address of their choosing to create an account within the Fitbit App.

All risks associated with the intervention will be minimized by allowing participants to discontinue the intervention at their discretion and the study team will regularly assess adverse effects of the intervention.

If participants suffer any unforeseen harms including psychological, emotional, physical, they will be encouraged to contact the PI or the IRB. Contact information will be provided in the consent forms including telephone, mail, and email.

a. Sharing of Results with Subjects

Data from this clinical trial will not be shared directly with participants. The results of the clinical trial and de-identified data will be made in accordance with NIH regulations and clinicaltrials.gov.

b. Data and Specimen Banking

No specimens will be stored. Study records will be retained for the longest regulatory retention period. After that time, records will be destroyed in a confidential manner.

8. Data Analysis

See Table 1 for outline of data analysis planned for study outcomes. As this is a pilot intervention trial, the focus will be on feasibility and acceptability of the pragmatic intervention trial. We will also explore effectiveness outcomes, but recognized we will be underpowered for a definitive effectiveness trial within this heterogeneous population selected to be representative of the population of interest. We will use our pilot trial to inform a future larger trial that will include longitudinal real world health outcomes relevant to the pediatric TBI population if supported by our preliminary results.

Prior to evaluating outcomes, we will perform a thorough descriptive analysis of participant baseline characteristics (age, race, ethnicity, gender, pre-injury comorbidities, TBI characteristics including severity, location, and type). We will examine patterns of missingness in our outcomes collected at 1-month, differences in participant and non-participant characteristics, and differences in participants who completed versus dropped out of the study to ascertain potential bias. Additionally, we will describe and compare the distribution of patient and clinical characteristics, including age and TBI severity, across treatment groups to ensure our randomization protocol was successful. Comparisons between groups will be made using chi-square tests for categorical variables. Depending on characteristics of the data, t-tests and Mann-Whitney U tests will be used to compare continuous variables between groups. We plan to perform both intention to treat and per protocol analyses.

Quantitative feasibility outcomes will be presented as a percentage of patients, the denominators of which are listed in Table 1. Comparisons between groups will be made with chi-square tests. Quantitative acceptability outcomes for adverse events will be dichotomized to yes/no and evaluated as a total number for each patient summarized using percent and median with interquartile range (IQR), respectively. Acceptability outcomes for satisfaction will be measured using Likert scales for which we will present results as medians and IQR. Chi-square tests will be used to compare dichotomized outcomes between treatment groups, and Mann-Whitney U tests will be used to compare total number of events. Effectiveness outcomes will be summarized using means and standard deviations, except for daytime sleep episodes which will be summarized as a median and IQR; these outcomes will be summarized for the overall study population and by treatment group. We will primarily examine the effectiveness of our intervention using linear regression to assess differences in the total SDSC score across treatment groups at 1-month. Linear regression will allow us to assess differences in effectiveness outcomes while controlling for covariates that may confound this relationship; covariates of particular interest will include age and TBI characteristics. Covariates identified in our initial descriptive analysis as significantly different between treatment groups, and covariates significantly associated with SDSC total score in bivariate analyses will also be explored with multiple linear regression.

Secondary effectiveness outcomes that specifically evaluate sleep phenotypes (measured by questionnaire and actigraphy) will be similarly evaluated with linear regression, except daytime sleep episodes which will be modeled using a count model, such as Poisson or negative binominal regression. For these secondary effectiveness outcomes, our focus is the magnitude of the association rather than statistical significance, as multiple comparisons will be made. Our primary goal with this secondary analysis will be to determine if the intervention appears effective for particular phenotypes that could be targeted in future studies. Results of these secondary analyses will be used as estimates for effect sizes in future intervention study design.

Qualitative analysis of survey responses for feasibility and acceptability outcomes (Table 1) will be analyzed with thematic network analysis. Transcription of survey responses will be coded using a hybrid approach: 1)based on the pre-specified survey questions administered (deductive approach); 2)creating new codes as needed based on participant responses to open ended questions (inductive approach). Coded transcripts will be used to construct thematic networks identifying global and organizing themes reported among responses. Exploration and description of thematic networks will be used to identify patterns within data for interpretation.

9. Privacy, Confidentiality, and Data Security

Data and protected health information will be safeguarded in multiple ways. All data will be stored on and OHSU secure drive or in the OHSU secure REDCap database, which is encrypted, and password protected. Access to REDCap will be controlled by the PI and is stored on an OHSU encrypted and password protected server. All study forms will include only a study ID number. All study data will be inputted into REDCap by members of the study team trained in Human Subjects Research and Responsible Conduct of Research as well as study procedures. The PI will maintain the REDCap database and provide access only to study team members. All exports of data from REDCap will be coded.

10. Provisions to Monitor the Data to Ensure the Safety of Subjects

Adverse events related to the intervention trial will be assessed at hospital discharge, and at 30-days via clinic visit, survey, and medical record review. All adverse events will be recorded and reported as required.

A Data and Safety Monitoring Plan (DSMP) including the provision of an institutional Data Safety Monitoring Board (DSMB) will be submitted as a separate documents for approval to the IRB.

As this trial is a pilot investigation, we do not have prespecified stoppage criteria. Trial progress and safety will be closely monitored by the PI and DSMB. The PI will review Serious Adverse Events (SAEs) as they occur and the DSMB will review SAEs at each meeting and on an as-needed basis. The DSMB will review trial progress and safety. The DSMB recommendations may include study continuation without modification, study termination, study continuation with protocol modification, or temporary suspension of enrollment until further evaluation is completed. The DSMB will review each death occurrence. Cumulative SAEs for each study arm will be provided to the DSMB and reports will be submitted to the study team, IRB, program staff at the National Institutes of Health, and the Food and Drug Administration as required. If the PI is notified of any SAE that is thought possibly related to the study, the participant will be immediately withdrawn.

11. Risks and Benefits

a. Risks to Subjects

Intervention risks will be considered more than minimal risk, but with potential to directly benefit the participant. Melatonin has demonstrated a good safety profile in multiple studies involving children and is available as a dietary supplement over the counter. A concern regarding use of over the counter melatonin is the variability in content and contaminants within supplements noted from lack of FDA oversight of dietary supplements.[87] We have minimized this risk by working with a manufacture that has provided Chemistry and Manufacturing Control data reviewed and approved for use by the FDA IND application. No serious adverse events have been reported with melatonin use in short or long-term studies as noted above. Studies using melatonin have reported symptoms including: dermatologic (itchy skin, rash), gastrointestinal (stomach upset, appetite changes, emesis), neurologic (drowsiness, blurred vision, vivid dreams), and bodily pain. Placebo studies report similar symptoms. Melatonin may affect levels of medications metabolized in the liver (particularly through CYP1A2 and CYP450 enzymes) or that are conjugated in the liver to sulfuric or glucuronic acid. There are unclear effects of melatonin on auto-

immune disorders and immune function. Melatonin is considered a dietary supplement, and as such, not regulated by the Food and Drug Administration. All risks will be communicated to the participant and included in the written consent provided to participants.

No serious adverse events were reported in recent meta-analyses of studies using melatonin conducted in children with neurodevelopmental disorders, including epilepsy, or in a recent adult trial comparing melatonin and placebo, but melatonin appeared to effectively improve sleep. No serious adverse events were reported in a recent randomized trial in pediatric concussion using doses up to 10mg (double this trial's maximum dosing).[76] The potential benefit of improved sleep after TBI in our study compared to the risk associated with melatonin is likely as favorable to standard care given >50% have disturbed sleep after discharge without treatment and SWD are associated with worse cognitive functions and quality of life in pediatric TBI patients.

Given the ubiquitous use of melatonin in pediatric clinical care and research studies in a variety of pediatric populations with medical, developmental, and psychiatric disorders, no patients will be excluded for underlying medical conditions or concomitant medication use, outside of exclusion criteria above. Patients will be excluded from the trial if the clinical care Attending Physician deems the patient unable to tolerate enteral medications or otherwise has safety concerns regarding use of melatonin.

There will be no requirement for use of contraception in female participants of child-bearing age given no known adverse effects of melatonin in pregnancy and short duration of the intervention. Pregnant patients will be excluded from the trial or withdrawn immediately from the trial if become pregnant.

The educational intervention proposed in this study is of minimal risk given it is a handout with resources to promote healthy sleep. As part of our acceptability outcomes, we will evaluate utilization and usefulness of this portion of the intervention.

Data collection, questionnaire and survey risks include loss of confidentiality. Participants will provide questionnaire and survey data via paper forms, electronic survey through REDCap, or telephone interview at 30-day time points. Paper forms will only contain the subject study ID without other identifiable information to minimize risk of loss of privacy and confidentiality. Paper forms will be entered by a Research Assistant into REDCap. Access to identifiable information will be limited to study personnel and not shared with anyone outside the research group. Every effort will be made to minimize risk of loss of confidentiality. All study related paper forms will be destroyed after completion of the study.

Actigraphy risks include loss of confidentiality and minor physical discomfort. Participants will wear actigraphy devices for a period of one month that pose no more than minimal risk to subjects. Actigraphy devices will be distributed to participants during clinical visits or via mail. System generated text messages are sent weekly to remind participants to sync with the smartphone app to collect actigraphy data. Participants will be consented for use of text messaging and can opt out at any time by contacting the research team.

Study computers are password protected and encrypted within the OHSU network firewall and access will only be granted to study team members to minimize risk of loss of confidentiality. Actigraphy devices are non-invasive and can be freely removed by participants, but there is a small risk of discomfort related to the device. Participants will be allowed to withdraw from this portion of the study if desired.

b. Potential Benefits to Subjects

Participants may directly benefit from the intervention given the high prevalence of sleep disturbances after TBI, and literature supporting melatonin and sleep educational interventions in pediatric populations with SWD targeting the most prevalent sleep problems seen after pediatric TBI. While the placebo arm may not benefit directly from intervention, the increased focus on sleep through

recruitment into the trial may provide indirect benefit to all participants. There is a notable lack of interventions implemented in the hospital available to improve outcomes after pediatric TBI. SWDs represent a modifiable target associated with a variety of poorer post-discharge outcomes in pediatric TBI patients; thus, improving sleep may lead to improvement in multiple morbidities in pediatric TBI.

12. Drugs or Devices

The OHSU Research Pharmacy will oversee compounding and distribution of the study interventions (melatonin and placebo) per their standard operating procedures.

References

1. Williams, C.N., A. Kirby, and J. Piantino, *If You Build It, They Will Come: Initial Experience with a Multi-Disciplinary Pediatric Neurocritical Care Follow-Up Clinic.* Children (Basel), 2017. **4**(9): p. 1-8.
2. Williams, C.N., et al., *The Burden of Pediatric Neurocritical Care in the United States.* Pediatr Neurol, 2018. **89**: p. 31-38.
3. Faul M, X.L., Wald MM, Coronado VG. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002-2006. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Cotnrol*. 2010 10/5/2017]; Available from: https://www.cdc.gov/traumaticbraininjury.
4. Williams, C.N., M.M. Lim, and S.A. Shea, *Sleep disturbance after pediatric traumatic brain injury: critical knowledge gaps remain for the critically injured.* Nat Sci Sleep, 2018. **10**: p. 225-228.
5. Williams, C.N., et al., *Sleep wake disturbances after acquired brain injury in children surviving critical care.* Pediatr Neurol, In Press.
6. Aaro Jonsson, C.C., I.M. Emanuelson, and A. Charlotte Smedler, *Variability in quality of life 13 years after traumatic brain injury in childhood.* Int J Rehabil Res, 2014. **37**(4): p. 317-22.
7. Beebe, D.W., et al., *Brief report: parental report of sleep behaviors following moderate or severe pediatric traumatic brain injury.* J Pediatr Psychol, 2007. **32**(7): p. 845-50.
8. Sandsmark, D.K., J.E. Elliott, and M.M. Lim, *Sleep-Wake Disturbances After Traumatic Brain Injury: Synthesis of Human and Animal Studies.* Sleep, 2017. **40**(5): p. 1-18.
9. Gagner, C., et al., *Sleep-Wake Disturbances and Fatigue after Pediatric Traumatic Brain Injury: A Systematic Review of the Literature.* J Neurotrauma, 2015. **32**(20): p. 1539-52.
10. Crichton, A., et al., *Fatigue Following Traumatic Brain Injury in Children and Adolescents: A Longitudinal Follow-Up 6 to 12 Months After Injury.* J Head Trauma Rehabil, 2017.
11. Tham, S.W., et al., *The longitudinal course, risk factors, and impact of sleep disturbances in children with traumatic brain injury.* J Neurotrauma, 2012. **29**(1): p. 154-61.
12. Baumann, C.R., et al., *Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study.* Brain, 2007. **130**(Pt 7): p. 1873-83.
13. Kempf, J., et al., *Sleep-wake disturbances 3 years after traumatic brain injury.* J Neurol Neurosurg Psychiatry, 2010. **81**(12): p. 1402-5.
14. *Healthy People 2020*. 01/25/2019]; Available from: https://www.healthypeople.gov/2020/topics-objectives/topic/sleep-health.
15. Chang, C.H., S.J. Chen, and C.Y. Liu, *Pediatric sleep apnea and depressive disorders risk: A population-based 15-year retrospective cohort study.* PLoS One, 2017. **12**(7): p. e0181430.
16. Wang, F., et al., *Sleep Duration and Overweight/Obesity in Preschool-Aged Children: A Prospective Study of up to 48,922 Children of the Jiaxing Birth Cohort.* Sleep, 2016. **39**(11): p. 2013-2019.

17. Bogdanov, S., S. Naismith, and S. Lah, *Sleep outcomes following sleep-hygiene-related interventions for individuals with traumatic brain injury: A systematic review.* Brain Inj, 2017. **31**(4): p. 422-433.
18. Larson, E.B. and F.S. Zollman, *The effect of sleep medications on cognitive recovery from traumatic brain injury.* J Head Trauma Rehabil, 2010. **25**(1): p. 61-7.
19. Singh, K., et al., *Sleep Disorders Associated With Traumatic Brain Injury-A Review.* Pediatr Neurol, 2016. **60**: p. 30-6.
20. Volk, C. and R. Huber, *Sleep to grow smart?* Arch Ital Biol, 2015. **153**(2-3): p. 99-109.
21. Ringli, M. and R. Huber, *Developmental aspects of sleep slow waves: linking sleep, brain maturation and behavior.* Prog Brain Res, 2011. **193**: p. 63-82.
22. Jan, J.E., et al., *Long-term sleep disturbances in children: a cause of neuronal loss.* Eur J Paediatr Neurol, 2010. **14**(5): p. 380-90.
23. Tononi, G. and C. Cirelli, *Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration.* Neuron, 2014. **81**(1): p. 12-34.
24. Kocevska, D., et al., *The Developmental Course of Sleep Disturbances Across Childhood Relates to Brain Morphology at Age 7: The Generation R Study.* Sleep, 2017. **40**(1): p. 1-9.
25. Kocevska, D., et al., *Prenatal and early postnatal measures of brain development and childhood sleep patterns.* Pediatr Res, 2018.
26. Mahmood, O., et al., *Neuropsychological performance and sleep disturbance following traumatic brain injury.* J Head Trauma Rehabil, 2004. **19**(5): p. 378-90.
27. Shay, N., et al., *Sleep problems and their relationship to cognitive and behavioral outcomes in young children with traumatic brain injury.* J Neurotrauma, 2014. **31**(14): p. 1305-12.
28. Owens, J.A., *Neurocognitive and behavioral impact of sleep disordered breathing in children.* Pediatr Pulmonol, 2009. **44**(5): p. 417-22.
29. Gozal, D. and L. Kheirandish-Gozal, *Neurocognitive and behavioral morbidity in children with sleep disorders.* Curr Opin Pulm Med, 2007. **13**(6): p. 505-9.
30. Gamaldo, C.E., A.K. Shaikh, and J.C. McArthur, *The sleep-immunity relationship.* Neurol Clin, 2012. **30**(4): p. 1313-43.
31. Kapsimalis, F., et al., *Cytokines and pathological sleep.* Sleep Med, 2008. **9**(6): p. 603-14.
32. Kapsimalis, F., et al., *Cytokines and normal sleep.* Curr Opin Pulm Med, 2005. **11**(6): p. 481-4.
33. Licastro, F., et al., *Peripheral Inflammatory Markers and Antioxidant Response during the Post-Acute and Chronic Phase after Severe Traumatic Brain Injury.* Front Neurol, 2016. **7**: p. 189.
34. Kumar, R.G., J.A. Boles, and A.K. Wagner, *Chronic Inflammation After Severe Traumatic Brain Injury: Characterization and Associations With Outcome at 6 and 12 Months Postinjury.* J Head Trauma Rehabil, 2015. **30**(6): p. 369-81.
35. Opel, R.A., et al., *Effects of traumatic brain injury on sleep and enlarged perivascular spaces.* J Cereb Blood Flow Metab, 2018: p. 271678X18791632.
36. Barlow, K.M., et al., *Melatonin as a Treatment after Traumatic Brain Injury: A Systematic Review and Meta-Analysis of the Pre-Clinical and Clinical Literature.* J Neurotrauma, 2018.
37. Ferracioli-Oda, E., A. Qawasmi, and M.H. Bloch, *Meta-analysis: melatonin for the treatment of primary sleep disorders.* PLoS One, 2013. **8**(5): p. e63773.
38. Mindell, J.A., et al., *Behavioral treatment of bedtime problems and night wakings in infants and young children.* Sleep, 2006. **29**(10): p. 1263-76.
39. Owens, J.A., Rosen C., Mindell J., *Medication Use in the Treatment of Pediatric Insomnia: Results of a Survey of Community-Based Pediatricians.* Pediatrics, 2003. **111**(5): p. e628-e635.
40. Ophoff, D., et al., *Sleep disorders during childhood: a practical review.* Eur J Pediatr, 2018. **177**(5): p. 641-648.

41. Hartz, I., et al., *Paediatric Off-Label Use of Melatonin--A Register Linkage Study between the Norwegian Prescription Database and Patient Register.* Basic Clin Pharmacol Toxicol, 2015. **117**(4): p. 267-73.
42. Abdelgadir, I.S., M.A. Gordon, and A.K. Akobeng, *Melatonin for the management of sleep problems in children with neurodevelopmental disorders: a systematic review and meta-analysis.* Arch Dis Child, 2018. **103**(12): p. 1155-1162.
43. Gruber, R., et al., *Training, knowledge, attitudes and practices of Canadian health care providers regarding sleep and sleep disorders in children.* Paediatr Child Health, 2017. **22**(6): p. 322-327.
44. Bruni, O., et al., *Current role of melatonin in pediatric neurology: clinical recommendations.* Eur J Paediatr Neurol, 2015. **19**(2): p. 122-33.
45. Bock, D.E., et al., *Sleep-promoting medications in children: physician prescribing habits in Southwestern Ontario, Canada.* Sleep Med, 2016. **17**: p. 52-6.
46. Esposito, S., et al., *Pediatric sleep disturbances and treatment with melatonin.* J Transl Med, 2019. **17**(1): p. 77.
47. Cydni N. Williams, et al., *Sleep and Executive Functioning in Pediatric Traumatic Brain Injury Survivors after Critical Care.* Children (Basel), 2022, In Press.
48. Koopman-Verhoeff, M.E., et al., *Association of Sleep Problems and Melatonin Use in School-aged Children.* JAMA Pediatr, 2019. **173**(9): p. 883-885.
49. Maras, A., et al., *Long-Term Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children with Autism Spectrum Disorder.* J Child Adolesc Psychopharmacol, 2018.
50. Ivanenko, A., et al., *Melatonin in children and adolescents with insomnia: a retrospective study.* Clin Pediatr (Phila), 2003. **42**(1): p. 51-8.
51. Cortesi, F., et al., *Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial.* J Sleep Res, 2012. **21**(6): p. 700-9.
52. Jain, S.V., et al., *Melatonin improves sleep in children with epilepsy: a randomized, double-blind, crossover study.* Sleep Med, 2015. **16**(5): p. 637-44.
53. Appleton, R.E., et al., *The use of MElatonin in children with neurodevelopmental disorders and impaired sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS).* Health Technol Assess, 2012. **16**(40): p. i-239.
54. Abramova, R., et al., *Review of Melatonin Supplementation for Sleep Disorders in Pediatric Special Populations.* J Pharm Pract, 2019: p. 897190019845982.
55. Brown, K.M. and B.A. Malow, *Pediatric Insomnia.* Chest, 2016. **149**(5): p. 1332-9.
56. Duclos, C., et al., *Rest-Activity Cycle Disturbances in the Acute Phase of Moderate to Severe Traumatic Brain Injury.* Neurorehabil Neural Repair, 2014. **28**(5): p. 472-82.
57. Grima, N.A., et al., *Circadian Melatonin Rhythm Following Traumatic Brain Injury.* Neurorehabil Neural Repair, 2016. **30**(10): p. 972-977.
58. Claustrat, B., J. Brun, and G. Chazot, *The basic physiology and pathophysiology of melatonin.* Sleep Med Rev, 2005. **9**(1): p. 11-24.
59. Marseglia, L., et al., *Melatonin Secretion Is Increased in Children with Severe Traumatic Brain Injury.* Int J Mol Sci, 2017. **18**(5): p. 1-10.
60. Lorente, L., et al., *Serum melatonin levels in survivor and non-survivor patients with traumatic brain injury.* BMC Neurol, 2017. **17**(1): p. 138.
61. Shekleton, J.A., et al., *Sleep disturbance and melatonin levels following traumatic brain injury.* Neurology, 2010. **74**(21): p. 1732-8.
62. Alluri, H., et al., *Melatonin Preserves Blood-Brain Barrier Integrity and Permeability via Matrix Metalloproteinase-9 Inhibition.* PLoS One, 2016. **11**(5): p. e0154427.

63. Osier, N., et al., *Melatonin as a Therapy for Traumatic Brain Injury: A Review of Published Evidence.* Int J Mol Sci, 2018. **19**(5).
64. Ozdemir, D., et al., *Protective effect of melatonin against head trauma-induced hippocampal damage and spatial memory deficits in immature rats.* Neurosci Lett, 2005. **385**(3): p. 234-9.
65. Ozdemir, D., et al., *Effect of melatonin on brain oxidative damage induced by traumatic brain injury in immature rats.* Physiol Res, 2005. **54**(6): p. 631-7.
66. Naseem, M. and S. Parvez, *Role of melatonin in traumatic brain injury and spinal cord injury.* ScientificWorldJournal, 2014. **2014**: p. 586270.
67. Carrillo-Vico, A., et al., *The modulatory role of melatonin on immune responsiveness.* Curr Opin Investig Drugs, 2006. **7**(5): p. 423-31.
68. de Castro-Silva, C., et al., *Melatonin improves sleep and reduces nitrite in the exhaled breath condensate in cystic fibrosis--a randomized, double-blind placebo-controlled study.* J Pineal Res, 2010. **48**(1): p. 65-71.
69. Marra, A., et al., *Melatonin in Critical Care.* Crit Care Clin, 2019. **35**(2): p. 329-340.
70. Clark, I.A. and B. Vissel, *Inflammation-sleep interface in brain disease: TNF, insulin, orexin.* J Neuroinflammation, 2014. **11**: p. 51.
71. Krueger, J.M., *The role of cytokines in sleep regulation.* Curr Pharm Des, 2008. **14**(32): p. 3408-16.
72. Krueger, J.M., J.A. Majde, and D.M. Rector, *Cytokines in immune function and sleep regulation.* Handb Clin Neurol, 2011. **98**: p. 229-40.
73. Vgontzas, A.N., et al., *Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-alpha antagonist.* J Clin Endocrinol Metab, 2004. **89**(9): p. 4409-13.
74. Grima, N.A., et al., *Efficacy of melatonin for sleep disturbance following traumatic brain injury: a randomised controlled trial.* BMC Med, 2018. **16**(1): p. 8.
75. Bramley, H., et al., *Sleep Disturbance Following Concussion Is a Risk Factor for a Prolonged Recovery.* Clin Pediatr (Phila), 2017. **56**(14): p. 1280-1285.
76. Barlow, K.M., et al., *Efficacy of Melatonin in Children With Postconcussive Symptoms: A Randomized Clinical Trial.* Pediatrics, 2020. **145**(4).
77. Barlow, K.M., et al., *Efficacy of Melatonin for Sleep Disturbance in Children with Persistent Post-Concussion Symptoms: Secondary Analysis of a Randomized Controlled Trial.* J Neurotrauma, 2021. **38**(8): p. 950-959.
78. Keegan, L.J., et al., *Effectiveness of melatonin for sleep impairment post paediatric acquired brain injury: evidence from a systematic review.* Dev Neurorehabil, 2014. **17**(5): p. 355-62.
79. Lubas, M.M., et al., *A randomized double-blind placebo-controlled trial of the effectiveness of melatonin on neurocognition and sleep in survivors of childhood cancer.* Pediatr Blood Cancer, 2022. **69**(1): p. e29393.
80. Zisapel, N., *Assessing the potential for drug interactions and long term safety of melatonin for the treatment of insomnia in children with autism spectrum disorder.* Expert Rev Clin Pharmacol, 2022. **15**(2): p. 175-185.
81. Schroder, C.M., et al., *[Therapeutic approaches for sleep and rhythms disorders in children with ASD].* Encephale, 2022.
82. Williams, C.N., et al., *Sleep-Wake Disturbances After Acquired Brain Injury in Children Surviving Critical Care.* Pediatr Neurol, 2020. **103**: p. 43-51.
83. Goldman, R.D., et al., *Myths and Evidence Regarding Melatonin Supplementation for Occasional Sleeplessness in the Pediatric Population.* Pediatr Ann, 2021. **50**(9): p. e391-e395.
84. Procaccini, D.E. and S.R. Kudchadkar, *Melatonin Administration Patterns for Pediatric Inpatients in a Tertiary Children's Hospital.* Hosp Pediatr, 2021. **11**(11): p. e308-e312.
85. Johnston, D.L., et al., *Phase I dose-finding study for melatonin in pediatric oncology patients with relapsed solid tumors.* Pediatr Blood Cancer, 2019. **66**(6): p. e27676.

86. Esses, S.A., et al., *Post-Intensive Care Syndrome: Educational Interventions for Parents of Hospitalized Children.* Am J Crit Care, 2019. **28**(1): p. 19-27.
87. Erland, L.A. and P.K. Saxena, *Melatonin Natural Health Products and Supplements: Presence of Serotonin and Significant Variability of Melatonin Content.* J Clin Sleep Med, 2017. **13**(2): p. 275-281.