A Sleep Intervention to Improve Rehabilitation in Veterans with Chronic mTBI

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Title:
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Investigators:
Principal Investigator: Jonathan Elliott, PhD

Specific Aims/Purpose:
Each year ~2.5 million people sustain a traumatic brain injury (TBI).[1] Also a prominent general public health issue, TBI is particularly prevalent in Veterans, with 60-80% reporting a history of TBI.[2,3] Over 80% of all TBI are categorized as mild TBI,[3] which is associated with a myriad of short- and long-term complications. Two of the principal complicating factors associated with TBI are sleep-wake disturbances (e.g., insomnia,[4] excessive daytime sleepiness,[5] and circadian rhythm sleep disorders[6]) and chronic pain, including headache and diffuse/global pain.[7,8] Sleep-wake disturbances and chronic pain have an independent prevalence of ~70%,[8–10] individually impair quality of life,[11–16] impede effective rehabilitative therapies, and have staggering functional and economic impacts.[17,18]

Furthermore, there is a strong bidirectional relationship between sleep-wake disturbances and pain such that impaired sleep exacerbates pain, which leads to greater impairments in sleep and worse pain.[19–21] This vicious cycle between sleep disturbances and pain, which is a particularly prevalent and detrimental condition in Veterans with TBI, represents a central challenge precluding effective treatment and ultimately, improving Veteran quality of life.[22–25] Although there are pharmacological and non-pharmacological therapies for chronic pain, the presence of TBI significantly complicates the effectiveness of these treatment options,[26,27] and have significant adverse effects (e.g., long-term prescription opioid dependence, misuse, or overdose[28–30]). *We believe there is profound potential to intervene at the sleep level, and, by improving sleep quality, enable Veterans with TBI to better manage their pain and end this vicious cycle.*

This proposal aims to apply a sleep intervention to improve chronic pain in Veterans with TBI. We propose to use morning bright light therapy (MBLT), a readily deployable, cost-effective, non-pharmacologic, and home-based sleep intervention, to improve sleep-wake disturbances and therefore ameliorate chronic pain and improve quality of life in Veterans with TBI. There is substantial scientific precedent for MBLT to be effective in improving sleep quality, as outlined by a recent meta-analysis of 53 MBLT-based studies.[31] Indeed, the potential of MBLT to improve sleep quality in Veterans with TBI remains unexplored, and yet, highly promising. Outcomes will be assessed pre- and post-intervention, and at a 3-month follow-up time point. *Our central hypothesis is that MBLT will improve sleep quality and ameliorate pain, resulting in improved quality of life in Veterans with TBI*.

Specific Aim 1: Determine the effect of MBLT on *sleep quality* in Veterans with TBI.
- Hypothesis: Self-reported sleep quality, and sleep efficiency using actigraphy, will improve following 4-weeks of MBLT compared to sham in Veterans with TBI.

Specific Aim 2: Determine the effect of MBLT on *pain* in Veterans with TBI.
- Hypothesis: Self-reported pain, and pain testing via pressure algometry, will improve following 4-weeks of MBLT compared to sham in Veterans with TBI.

Specific Aim 3: Determine the effect of MBLT on *quality of life* in Veterans with TBI.
- Hypothesis: Self-reported quality of life will improve following 4-weeks of MBLT compared to sham in Veterans with TBI.

Scientific Rationale and Significance:

Sleep-Wake Disturbances Following TBI. It is nearly universally accepted that one of the principal complicating factors associated with TBI is sleep-wake disturbances. The functional and economic impact of sleep disturbances is staggering[18] and well-known to *directly impair quality of life*,[11] preclude independent functioning, reintegration into civilian life, return to duty or success in vocational endeavors.

The prevalence of sleep-wake disturbances following TBI is estimated to be 50-70%, based on a meta-analysis of 21 studies that included 1,706 subjects with TBI.[9] The most commonly cited sleep-wake disturbances include insomnia,[4] excessive daytime sleepiness,[5] and circadian rhythm sleep disorders.[6] Impaired sleep quality is also commonly observed following TBI. A recent meta-analysis of 16 studies with 637 TBI patients and 567 controls, reported that individuals with TBI showed less total sleep time, more wake after sleep onset, reduced sleep efficiency, and a longer sleep onset latency.[10]

Although insomnia and excessive daytime sleepiness are often considered to be the most prevalent issues,[32,33] recent work suggests circadian rhythm disorders (i.e., irregular sleep and/or wake onset times, or regular yet shifted early/late sleep-wake onset times) are grossly under diagnosed and mistaken for insomnia.[34] Indeed, complaints of insomnia *and* excessive daytime sleepiness are common occurrences and symptoms of an underlying circadian rhythm sleep disorder, which arise when individuals sleep-wake rhythm is improperly synchronized to environmental (i.e., bright light) and social stimuli.[35] Although actigraphy allows for objective monitoring of sleep-wake cycles, the gold standard assessment of circadian rhythm in humans is via the measurement of melatonin and body temperature, which should reach their peak and nadir, respectively, at the onset of sleep in ideal conditions.[34] Based on melatonin assays and body temperature, the most common circadian rhythm sleep disorder in patients with TBI is delayed sleep phase syndrome, again presenting very similar to insomnia with an inability to fall asleep at the preferred time.[34,36]

Sleep-wake disturbances commonly do not resolve in the acute recovery phase post-TBI (i.e., <6 months) and persist as a chronic sequelae (i.e., >several years).[37–39] Indeed, recently published work by our group supports the existing literature, and not only report sleep-wake disturbances in Veterans persist 15-25 years post-TBI, but these sleep problems positively correlate with post-concussive symptoms.[40,41]

Chronic Pain Following TBI. Pain that persists for an extended period of time (i.e., >3-6 months) and initially accompanies a disease process or bodily injury that has subsequently resolved or healed may be referred to as chronic pain.[42] Chronic pain represents one of the nations, including the within the VA, largest economic burdens[17] and similar to sleep disturbances, is well-known to *impair quality of life*.[12,43]

The prevalence of chronic pain following TBI is estimated to be ~75%, based on a systematic review of 20 studies comprising a population of 3,289 predominantly civilian patients.[8] Veterans with TBI are particularly likely to experience chronic pain.[44] In a recent analysis of Veterans with TBI at a polytrauma rehabilitation facility, 96% reported experiencing at least one significant pain problem during their rehabilitation period.[45] The most common pain complaints are headaches and head pain;[46–49] however 60-70% of Veterans with TBI report pain at more than one site, including throughout the neck, shoulders, back, and upper/lower limbs.[7] Complaints of widespread/global pain are also commonly reported following TBI, with the severity of this diffuse pain reported to be moderate to severe pain.[50] Consistent with recent work by our group,[41] chronic pain following TBI appears to be independent of co-existing psychologic disorders such as post-traumatic stress disorder (PTSD) and depression.[8]

The pathophysiology of chronic pain cannot always be tied directly to the activation of normal pain pathways,[51] and therefore, fundamentally differs from acute pain, which can generally be well controlled using analgesic drugs or by blocking these normal sensory pain pathways. Accordingly, chronic pain, such as that experienced by Veterans following TBI can be extraordinarily challenging to manage clinically. This pain is instead thought to be due to “sensitization” of pain-processing circuits in the spinal cord and brain (usually called “central sensitization”). In a sensitized state, spinal and supraspinal nociceptive pathways are hyper-responsive to non-injurious peripheral stimuli, allowing innocuous inputs to be experienced as painful. Central sensitization is well supported in preclinical models of persistent pain where it has been shown to explain lower pain thresholds and hyperalgesia. In humans, central sensitization can only be inferred from indirect measures.

One such measure that probes human pain processing circuits is pressure algometry, which is a reliable[52] and quantitative pain testing measure validated across a variety of pain states.[53,54] The pressure pain threshold, defined as the minimum amount of pressure that induces pain or discomfort, can be used to predict the response to a therapeutic intervention in either clinical practice or research. Conditioned pain modulation is a pain processing paradigm that tests the ability of a painful stimulus applied to one body region, to inhibit another painful stimulus applied simultaneously, to a remote body region. This test reflects the function of spino-bulbo-spinal loops underlying the 'pain inhibiting pain' phenomenon termed 'Diffuse Noxious Inhibitory Control'.[55] Accordingly, conditioned pain modulation examines the endogenous analgesic system and thus, the ability to modulate (i.e., inhibit) pain.

Reciprocal Relationship Between Sleep-Wake Disturbances and Pain. There is an unequivocal reciprocal relationship between sleep-wake disturbances and chronic pain, such that impaired sleep exacerbates pain, which leads to greater sleep impairments and worse pain.[19–21,56] Several studies have investigated sleep and pain specific outcomes in rehabilitation programs: Haythornthwaite et al. showed pain intensity and duration (among other pain related variables) was significantly and positively correlated with delayed sleep onset, less total sleep time and worse sleep efficiency;[57] Wilson et al. reported sleep disturbances were associated with higher ratings of pain severity;[58] Wittig et al. reported patients with chronic pain showed lower sleep efficiency, increased wake after sleep onset, and hypothesized that pain tolerance decreases with lack of sleep.[59] Indeed, poor sleep quality and sleep-wake disturbances exacerbate pain and TBI symptoms,[60] impact the individual's ability to cope with these symptoms,[44] and inhibit full participation in rehabilitation treatment programs.[22] Thus, in the presence of TBI, sleep-wake disturbances greatly compound the issue by impeding rehabilitative effectiveness.

As outlined above, the relationship between TBI, sleep-wake disturbances, chronic pain, and poor quality of life is a highly prevalent, complex and multifaceted issue affecting Veterans. However, it is well established that sleep-wake disturbances and chronic pain, independent of TBI, individually correlate to reduced quality of life.[7,61,62] Both sleep disturbances and chronic pain exact profound negative consequences individually,[63] their combined impact in terms of personal suffering and lost productivity is likely magnified.[20,64] This should not be surprising given the seemingly inextricable relationship between sleep and pain, and the well-documented contribution of both on quality of life.

This vicious cycle between sleep disturbances and pain, which is particularly prevalent and detrimental in Veterans with TBI, is a central challenge precluding effective treatment and ultimately, improving Veteran quality of life. *We believe there is profound potential to intervene at the sleep level, and, by improving sleep quality, enable Veterans with TBI to better manage their pain and end this cycle.*

Proposed Sleep-Based Intervention to Improve Pain and Quality of Life. Existing strategies to improve sleep or manage chronic pain are limited by either being associated with considerable patient-provide burden, being costly, poor effectiveness, and/or have significant side effects (e.g. long-term prescription opioid dependence).[27] Pharmacologic mechanisms for managing both sleep impairments and chronic pain are by far the most common, although both classes of medication can also directly impair sleep quality (e.g., by suppressing rapid eye movement or slow-wave sleep). *We have identified a simple readily deployable, cost-effective, non-pharmacologic, and home-based sleep intervention - morning bright light therapy - that has not yet been evaluated in Veterans with TBI*.

Scientific Rationale for Bright Light Therapy to Improve Sleep. Ocular light exposure is a critical environmental mechanism for regulating sleep and wakefulness in humans. The physiologic mechanism linking light exposure with its control over sleep and wakefulness are specialized retinal ganglion cells that are functionally independent from retinal rods and cones (i.e., the 'classic' retinal ganglion cells responsible for visual function). These novel retinal ganglion cells are 'intrinsically photosensitive' and contain a unique photopigment, melanopsin, which again differs functionally from rhodopsin and photopsin (i.e., the photopigment inside rods and cones, respectively).

There exists almost 3 decades of research surrounding the physiologic relevance and function, with respect to the regulation of sleep and wakefulness, of intrinsically photosensitive retinal ganglion cells and their corresponding neural network, the retinohypothalmic tract. Accordingly, the central role that intrinsically photosensitive retinal ganglion cells have in controlling sleep and wakefulness has been well-described. Both classic and intrinsically photosensitive retinal ganglion cells project to visual processing areas, namely the lateral geniculate nucleus of the thalamus. However, input to other non-visual brain areas comes predominantly from intrinsically photosensitive retinal ganglion cells.[65] Perhaps their most important input is to the suprachiasmatic nucleus, a region in the hypothalamus that controls circadian rhythms,[66,67] which also regulates melatonin secretion via the pineal gland.[68,69] Indeed, ocular light exposure is the central mechanism for entraining the human circadian pacemaker and tracking environmental time. In the absence of light, the suprachiasmatic nucleus is said to be "free running" in that it follows its endogenous rhythm which produces rhythms of physiologic processes that do not conform to normal light-dark cycles (i.e., 24-hour periods).

In addition to the suprachiasmatic nucleus, intrinsically photosensitive retinal ganglion cells also project to several other key non-visual brain regions. First, the locus coeruleus (i.e., the noradrenergic arousal system), a key component of the ascending arousal system that regulates cortical arousal and alertness, while also facilitating optimal thalamic and cortical connections.[70,71] This is the physiological basis for feeling more alert in bright environments. Second, the ventrolateral preoptic area, a key sleep promoting region. Indeed, input from intrinsically photosensitive retinal ganglion cells to the ventrolateral preoptic area is inhibitory, and therefore promotes wakefulness. Third, the medial amygdala, which is a key regulator of mood and emotion,[72] and the proposed underlying mechanism for the utility of bright light therapy to treat depression.[73]

Thus, the scientific precedence for light exposure to influence sleep and wakefulness is substantial, but there is also data to support the use of light therapy in improving pain, although the mechanism for this connection remains to be established.[62,74] The potential for light therapy to modulate non-sleep factors, such as pain, would therefore indirectly further contribute to improvements in sleep quality.[75] For this reason light therapy can both *directly and indirectly* influence sleep quality.[75,76]

Morning Bright Light Therapy: Precedent and Protocol. In a recent systematic review and meta-analysis of the effects of light therapy on sleep problems that included 53 studies, the largest effect sizes (Hedge's *g* range: 0.38 to 1.13) were found on insomnia symptoms and circadian outcomes.[31] Within these categories, subjective sleep complaints were also found to have larger effect sizes compared to objective sleep-time variables. For example, studies employing bright light therapy to improve insomnia showed Hedge's *g* effect sizes of 1.13 for complaints of fatigue, 0.80 for insomnia symptoms, 0.77 for sleep quality, and 0.44 for daytime sleepiness. Within this same group of studies, objective sleep-time variables showed Hedge's *g* effect sizes of 0.45 for sleep onset latency, 0.44 for total sleep time, 0.47 for wake after sleep onset, and 0.38 for sleep efficiency. Similar effect sizes and pattern between subjective and objective sleep metrics were also reported for studies using bright light therapy to address circadian rhythm sleep disorders. Accordingly, the majority of the expected effect sizes for outcomes we propose in the present application have been shown to be moderate to large, albeit in a non-TBI civilian population.

The key moderator of the response to morning bright light therapy was found to be the administered light intensity (i.e., lux), although treatment duration was also relevant. In the aforementioned studies employing bright light therapy to treat insomnia the mean light intensity was 4,800 lux and corresponded to an overall effect size of 0.47. The moderator effect of light intensity was 0.08, meaning the estimated effect size for a light intensity of 10,000 lux increases to ~0.85. Additional relevant, albeit non-significant, moderators were noted to be treatment duration and treatment instructions. Previous work has also established that treatment intensity and duration are key moderators for the effectiveness for bright light therapy,[77] which should not be surprising given the neuroanatomical connection underlying these processes being dependent on total photopic flux (i.e., photopic input activating intrinsically photosensitive retinal ganglion cells). Finally, although non-significant, instructions for carrying out the light therapy protocol also appeared important. We have also found clear instruction to be critical toward effective implementation and have developed several strategies to improve communication.

Our MBLT protocol is based off much of this previous work,[31] including studies using MBLT to treat sleep-wake disturbances in patients with neurodegenerative conditions (e.g., dementia, Alzheimer's, Huntington's and Parkinson's disease),[78–80] and fatigue in cancer patients[81] healthy office workers,[82,83] and civilians with TBI.[84] *Specifically, Veterans will engage in 60 minutes of MBLT at 10,000 lux for 4-weeks, for which there is a large body of evidence*.[31]

Innovation and Impact. The high prevalence, profound disability, and economic impact associated with combat derived TBI in Veterans is undeniable and underscored by TBI-related research being among the highest priorities within Veteran Affairs Office of Research and Development and specifically Rehabilitation Research & Development.[45,85,86] The pathophysiology of TBI-related disability is multifaceted, complex, and creates an extremely complicated patient to treat, with poor sleep quality and chronic pain playing a central role. For this reason, there is substantial scientific precedence for rehabilitative strategies that target improved sleep quality to not only improve these quality of life metrics, but likely also improve the efficacy of ongoing symptom directed rehabilitation.[22,87–89]

The primary product of the proposed study is empirically validating MBLT to be effective for improving sleep quality in Veterans with TBI, as well as ameliorating chronic pain and improving quality of life. In doing so, we will gain a better understanding of the impact that improved sleep has on these, and other, highly relevant functional outcomes in Veterans with TBI. Several factors set MBLT aside as a potentially extremely high-yield therapeutic option, such as it being rapidly deployable, cost-effective, non-pharmacologic, and home-based. Therefore, the proposed study is likely to have a significant effect on the quality and effectiveness of rehabilitative services offered to our Veterans.

Relevance to the VA Patient Care Mission. The number of OEF/OIF Veterans seeking care and rehabilitation services within the VA Health Care System is increasing rapidly. As such, the VA is faced with an increasing demand to provide evidence-based, treatment for Veterans. Sleep-wake disturbances with secondary impairments in functional outcome measures, cognitive function and increased chronic pain can adversely affect a Veteran's ability to reintegrate into civilian life, return to duty, succeed in competitive employment, or function independently. Failure to provide appropriate interventions and rehabilitation can also result in an increased need for health care services and VA benefits in the future. The knowledge gained from the current application, concerning the interacting relationship between cognitive/emotional health, headache/chronic pain and sleep, may help the VA improve interventions and outcomes with returning Veterans from combat in Iraq, Afghanistan, or elsewhere. Indeed, the development of sleep-based therapies with the strong potential to improve rehabilitation that optimally address the complex and unique needs of combat Veterans is critical to the VA patient care mission.

Preliminary Studies:

We have conducted several studies that highlight the need for this project and inform experimental design. Our preliminary data has examined; 1) the prevalence of sleep disturbances in Veterans – a cohort which identifies a large, immediately available pool of subjects for recruitment for this study, and 2) the feasibility of the MBLT intervention in Veterans with sleep disturbances.

MIRB #3641 and 3636

Title: *Factors that affect response to treatment for obstructive sleep apnea and related sleep disorders*

Publications:

Balba NM*, **Elliott JE***, Weymann KB, Opel RA, Duke JW, Oken BS, **Morasco BJ**, Heinricher MM, **Lim MM**. Increased sleep disturbances and pain in Veterans with comorbid TBI and PTSD. *Journal of Clinical Sleep Medicine*, 2018. *denotes equally contributing authors

Elliott JE, Opel RA, Papesh MA, Weymann KB, Chau AQ, Callahan ML, Storzbach D, **Lim MM**. Sleep disturbances in TBI: Associations with sensory sensitivity. *Journal of Clinical Sleep Medicine*, 2018.

Relevance:
This protocol recruited 670 Veterans across an ~3-year time frame from the VA Sleep Disorders Clinic, demonstrating our ability to access and recruit large numbers of Veterans with sleep problems.

MIRB #4085 and 4086
Title: *Morning bright light to improve sleep quality in Veterans*

Publications:
Data collection ongoing.

Relevance:
This protocol has recruited 91 participants over 18 months, 60 of which underwent MBLT for 4 weeks. The primary purpose of this protocol was to assess feasibility outcomes, including recruitment rate, retention rate, and adherence to the light therapy. Of the participants with TBI, 88% of subjects remained adherent to light therapy for the full 4 weeks. Overall, 91% of subjects said they liked using the lightbox. We additionally found that MBLT improves self-reported sleep, mood, and quality of life in our pilot cohort, however, this study lacks a placebo device for comparison.

Research Design and Methods:
Veterans within the VA Portland Healthcare System (VAPORHCS) and non-Veterans will be recruited for participation in this study. This study will consist of at least 4 visits over the span of ~5-6 mo.

Study Overview and Timeline.

	Visit 1	Visit 2	At Home	Visit 3	Visit 4 Follow up
Time point:	Day 0	Week 2	Week 2-6	Week 6	Week 10
Informed consent	X				
Subject given actiwatch		X		X	
Conduct pain assessment		X		X	X
Subject given lightbox or sham		X			
Questionnaires		X		X	X
Daily use of intervention for 1 hour			X		
Total time	**~120 min**	**~120 min**	**28 hours**	**~120 min**	**~120 min**

- *Informed consent and HIPAA authorization*. Written and verbal informed consent will be obtained before all other Visit 1 activities and may take place on an earlier date if DocuSign is able to be used to facilitate the consent conversation.
    - In cases where DocuSign is not feasible, consent conversations will take place in office space available at the VAPORHCS Sleep Disorders Clinic (building 100-6C), in related outpatient clinical space, or in Research Service space approved for human subjects use

(building 101, rooms 432A, 430, 404), or in subjects' homes. Alternatively, consent may take place remotely via phone or video conferencing via mailed documents.
    - Where DocuSign is feasible, study staff will initiate email of a DocuSign envelope providing subjects access to the consent and authorization forms ahead of the consent discussion. Subjects will then be guided through downloading the fully executed consent form.
- Participants will be asked to fill out demographics information which will include their name (including name at birth), date of birth, city/town of birth, email and physical address, phone number, health history, and military history.
- Individuals without a medical record at the VA will be asked permission for study staff to request their medical record pertaining to sleep and traumatic brain injury.

Visit 2

- Visit 2 will occur ~2 weeks after visit 1. It can take place within the VAPORHCS Sleep Disorders Clinic (building 100-6C), in Research Service (building 101, rooms 432A, 430, 404, and 533), remotely via phone/video conferencing, or at the subject's home.
- *Questionnaires*. Subjects will complete baseline questionnaires. They take ~30 min to complete and include past medical history and self-reported measures on sleep, social habits, quality of life, mental health, pain, and other metrics related to subject's prior trauma exposure history. All questionnaires are validated and will be completed via pen and paper. Medical history and testing related to sleep will be accessed from the participants' VA medical records by study staff with VA credentials. Subjects may elect to complete these questionnaires at either this or subsequent visits as needed. Questionnaires may be mailed if completed remotely.
- *Equipment*. Subjects will be randomized to receive a lightbox (LightPad mini, Aurora Light Solutions) or sham-control modified negative ion generator. Devices will be modified by completely disconnecting the electrical wiring required for negative ion generation. This will be verified using a voltmeter. A small fan may be installed to emit a low humming noise as an indicator of activity. They will be instructed to use either device for 60 min every morning after waking up starting 2 weeks following this visit and continuing for 4 weeks. Light sensitive devices, called HOBOs, will be attached to the lightboxes which will track when the lightbox is turned on or off, as a secondary measure of light delivery.
- *Actigraphy*. Subjects will be asked to wear an individually configured actigraphy watch (Phillips Respironics Actiwatch 2) for the entirety of the study. This actiwatch collects data related to subject's sleep-wake cycle, including activity (via a built-in accelerometer) and light exposure (via a built-in luxometer). Watches are user friendly, requiring no user input to operate, and batteries last for ~6 weeks. Subjects will be reminded to keep clothing from covering up the luxometer on the actiwatch as much as possible.
- *Study diary*. Subjects will be asked to fill out a study diary, with daily entries for the entirety of the study. They will record when they went to bed, when they woke up, when they used the lightbox, and days they went to work. At this point subjects will be educated on principles of good sleep hygiene, such that all subjects start at the same baseline with respect to their understanding of good sleep hygiene principles. Study diaries will be coded via subject's ID with no other identifiable information listed.
- *Pain testing*, Pressure algometry.Pressure-pain threshold and tolerance will be quantified using a pressure algometer (AlgoMed Computerized Pain Pressure Algometer), a validated device used both experimentally and clinically with the pressure stimulus delivered to the thumbnail/thenar region of the non-dominant hand. Threshold will be determined by the amount of pressure that the subject perceives as mildly painful. Tolerance will be determined by the amount of pressure that causes the subject to withdraw their hand. This test takes ~20 min to complete.
- *Pain testing*. Cold Pressor Test. The cold pressor test may be used at VAPORHCS and at visits that are conducted remotely. This test will consist of an ice bath that subject's are instructed to submerge

their non-dominant hand into. Threshold and Tolerance will be measured with a stop watch. Threshold will be determined by the amount of time that the subject perceives the temperature as mildly painful. Tolerance will be determined by the amount of time that causes the subject to withdraw their hand. This will be done during a single trial. The upper limit of allowing the hand in the icebath is 5 minutes.

- *Pain testing*. Ischemic Pain Test. Ischemic pain testing may be used at VAPORHCS and at visits that are conducted remotely. This test will consist of a manual blood pressure cuff that is placed on the subject's non-dominant upper arm and inflated to 300 mmHg. Threshold will be determined by the amount of time that the subject perceives the constriction as mildly painful. Tolerance will be determined by the amount of time that the subject allows the constriction to continue. This will be done during a single trial. The upper limit of allowing the hand the constriction is 5 minutes.
- *Department of Defense Head Trauma Events Checklist (DoD HTEC)*. Determination of TBI status occur through a semi-structured diagnostic interview following the DoD HTEC guidelines. This interview will take ~15 min to complete.
- *Reimbursement*. Subjects will be compensated with up to $20

Visit 3

- Visit 3 will occur ~4 weeks after Visit 2 and will take place within the VAPORHCS Sleep Disorders Clinic (building 100-6C), in Research Service (building 101, rooms 432A, 430, 404, and 533), remotely via phone/video conferencing, or at the subject's home.
- *Measures*. The same series of questionnaires and pain testing conducted at Visit 1 will be repeated.
- *Equipment*. Subjects will return all equipment, including the actiwatch, lightbox and/or sham device.
- *Reimbursement*. Subjects will be compensated with up to $60

Visit 4

- Visit 4 will occur ~4 weeks after Visit 3 and will take place within the VAPORHCS Sleep Disorders Clinic (building 100-6C), in Research Service (building 101, rooms 432A, 430, 404, and 533), remotely via phone/video conferencing, or at the subject's home.
- *Measures*. The same series of questionnaires and pain testing conducted at Visit 1 will be repeated.
- *Reimbursement*. Subjects will be compensated with up to $20
- *End of study debrief*. Subjects will be debriefed about our experimental design, given the inclusion of a placebo-controlled condition. We will provide subjects with a written description that we will describe to them in person and address any questions they may have.

Mailed forms and equipment. In an effort to reduce subject's time at the Portland VA we may mail consent forms, questionnaires, equipment and pre-addressed, pre-paid return envelopes directly to their homes. Instructions will be provided via phone or video conferencing.

Video Conferencing. If the subject is comfortable and equipped, we may conduct visits using video conferencing, such as VA Video Connect or other VA approved methods (skype, facetime, google hangouts, etc.). A link to the video chat will be emailed participants via Azure RMS encrypted email. For VA Video Connect (VVC), this email is entered into the VCC platform and an email is automatically generated.

At home visits. In special circumstances study personnel may travel to the subject's homes in order to conduct the visit more comfortably. Equipment, data, and specimens will travel in between the home and the VA only.

Phone calls. In between visits subjects will be contacted up to 2 times per week as needed. They will be assessed for understanding and compliance and given the opportunity to asked questions. Questions will be asked about their sleep, pain, and quality of life metrics.

Emails. Communication via RMS Azure encrypted email may be established between the subject and study coordinator in order to allow subjects to freely ask any questions they may have.

Study Population:

Number of subjects. The target population will consist of n=100 subjects. In order to meet this enrollment target we anticipate that up to 400 individuals may need to be recruited (consented) and screened.

Eligibility Criteria. Only Veterans and non-Veterans who are physically and mentally able to provide written and verbal informed consent and have a medical record-confirmed or physician confirmed diagnosis of TBI, will be included in this study. Additional criteria are as follows:

1) Current self-reported sleep-wake disturbances (defined by clinically abnormal Insomnia Severity Index and/or Functional Outcomes of Sleep scores)
2) Moderate to severe pain (defined as a score of ≥4 on an 11-point scale[90]) persisting for longer than 6 months
3) Do not have a diagnosis for dementia
4) Are not currently using a lightbox or negative ion generator
5) Are not night-shift workers
6) Are English speaking with phone access
7) Are 18 years of age or older
8) Do not have macular degeneration or bipolar disorder (both are relative contraindications to regular bright light exposure)
9) No suicidal ideation
10) No cancer diagnosis in the past 6 months
11) At least 6-12 months of being surgery free
12) No evidence of drug and alcohol dependency (defined by the substance abuse and dependency scale).
13) Are currently living within the United States.

Our inclusion/exclusion criteria will not exclude any specific class of persons who might benefit from the proposed research. Every effort will be made to include women and minority groups in this study. All Volunteers meeting inclusion/exclusion criteria will be invited to participate in the study, regardless of gender or racial/ethnicity status. Women comprise 8.5% of the Veterans included in the established VAPORHCS Sleep Disorders Data Repository (MIRB #3636) and minorities 8.3%. The same inclusion/exclusion criteria are applied for all participants which ensures that there is no recruitment bias to confound the results.

Every effort will be made to recruit Veterans for the completion of this project. However, we will plan to recruit non-Veterans as necessary to ensure sufficient data to answer study questions. The Veteran population is disproportionately male and often burdened with significant health issues. Thus, the inclusion of non-Veteran recruitment will help ensure greater recruitment eligibility and enrich for the inclusion of more women and underrepresented minorities. While we will not specifically target active military personnel for recruitment, we will also include them when they reach out to project staff about participating.

Power analysis. From pilot data collected via MIRB #4085, as well as from literature regarding MBLT interventions, a power analysis was conducted in order to estimate the sample size needed to detect a statistically robust difference in the described primary outcome variables at an acceptable level of significance and power with a clinically meaningful level effect size. In order to account for the inclusion of the sham control, a placebo effect size was postulated at 50% of the observed MBLT effect with the same variance in outcomes as observed in the pilot cohort. This led to a postulated collection of effect sizes necessary to observe differences in the various outcomes between the MBLT and a sham control. Most fell between 0.5

and 1.0, after including a sham control group with postulated, one-treatment per arm sample sizes of 20-70, with a mean sample size of 47 and median of 50 post drop-out. This is consistent with prior studies that examined efficacy of MBLT therapy within comparable populations (e.g., circadian rhythm sleep disorders, insomnia, depression, or dementia), showing Hedges' g effect sizes ranging from 0.20 to 0.95 in sample sizes ranging between n = 26 to 42.[31] Therefore, we intend to recruit 50 subjects per group. This sample size should be sufficient to detect clinically meaningful shifts in our outcome variables at levels that are robust enough to be accurately modeled and statistically evaluated.

Subject Identification/Recruitment

Research subjects will be recruited through word of mouth and several other methods:

1. **Repositories:** Participants may be recruited from an existing data repository at VAPORHCS (VA MIRB #3636, PI: Lim, n=670 participants or VA MIRB #4086, PI: Lim, n=200), approximately 30% of whom report TBI. These individuals have all provided informed consent for their data to be kept in the data repository and have given their permission to be re-contacted for future research studies.
2. **Sleep Clinic:** Veterans may be recruited from the VAPORHCS Sleep Disorders Clinic, or other outpatient clinics at VAPORHCS that have referred participants to us. Veterans will be approached in person or called on the phone, evaluated for eligibility in this study, and if interested, invited to undergo verbal and written informed consent.
3. **Flyers**: Volunteers may be recruited by fliers posted within the VAPORHCS, OHSU, and in the community. In the Portland VA, these flyers will be posted in the building 104 elevator, in handout stands in various clinics, and other VA bulletin boards with approved space for research flyers. They will also be given to clinicians at outpatient clinics to give to interested subjects. Interested subjects who contact us will then be screened over the phone with our phone script. If the participant is eligible and interested after the phone screen, we will plan to meet in person at VAPORHCS to get written and verbal informed consent.

Informed Consent & HIPAA Authorization:

Obtaining written informed consent, and HIPAA authorization, will be conducted in English by trained study personnel either remotely, at the subjects' homes, or in the VAPORHCS Sleep Disorders Clinic or other outpatient clinics within the VAPORHCS and will not differ between subjects for any cohort. Prior to obtaining informed consent, subjects will be given a short screening questionnaire to ensure that they meet eligibility criteria. Study personnel will guide subjects step-by-step through the informed consent document and ensure subjects have had all questions answered. Subjects will be reminded several times that participation is entirely voluntary, and they are free to discontinue participation at any point, and likewise, investigators are free to discontinue their participation at any point.

Informed consent may also occur remotely via phone or video conferencing which will require that we collect the interested potential participant's name, phone number, email address, and physical mailing address prior to consent. Remote consent conversations will occur in one of the following ways:

- *DocuSign* – Study staff will initiate the sending of a DocuSign envelope to furnish the potential participant with links to the consent and authorization forms for conducting the consent conversation. These will be sent with approved template wording that reminds the volunteer not to sign anything until instructed to do so by the consenter during the scheduled phone or video visit. After the consent discussion the consenter will aid the subject in executing the documents and then in retrieving their copies of the fully executed consent and HIPAA Authorization for their records.

  DocuSign will be used as the study's preferred method for fully remote HIPAA/Consent discussion. Choosing to use DocuSign will improve security and privacy for our research volunteers, will alleviate participants' burden in tracking and shipping these crucial study documents, and will help prevent the delays and errors that mail-in consent methods may encounter.

The study team has been approved by ORD for use of 350 envelopes (emails). Further details are located within the document 'Standard of Operating Procedure: DocuSign for Research'.

- *Mail- (This option will be used in cases where DocuSign is not feasible for any reason.)* Study staff will mail the consent form and HIPAA authorization form for the participant to review and then set up a meeting for study personnel to talk through the forms with the potential participant. Study personnel will go through each section of the consent form and HIPAA authorization form and address any questions the potential participant may have. If the subject agrees, they will be instructed to sign and date the forms and return them with the prepaid, pre-addressed envelopes provided. When the study team receives these forms, they will also sign and mail back the signed copy of the forms.

Risks and Side Effects:

The delivery of usual care is never altered by this study. Study risks include breach of confidentiality, psychological discomfort in completing study questionnaires, and mild physical discomfort from MBLT, and pain testing.

Psychological.

- Questionnaires and Neuropsychological testing: There is a small risk that completing questionnaires could be stressful, discomforting, or mildly embarrassing to the participants. The questionnaires take approximately ~30 min to complete. Since questions are asked about mood, including thoughts of self-harm and depression, there is a possibility that information about thoughts of suicide or evidence of depression will be gained that will require an intervention. How this information will be handled is discussed below in the *Suicidality* section.

Physical.

- Morning Bright Light Therapy: Light from a lightbox is essentially indistinguishable from natural light from the sun and consists of broad-spectrum white light. Morning bright light from a lightbox poses very minimal and rare risks. One study showed that light intensity of 10,000 lux received for an average of 40+ min per day over a five-year period had no major side effects. Minimal and uncommon side effects included eye irritation, irritability, headache, nausea, sensation of glare, dryness of eyes, and dryness of skin (as can occur from natural sunlight exposure). A rare occurrence of mania or rapid-cycling may occur in those with Bipolar Disorder due to too much exposure to bright light. For this reason, this study will exclude those with Bipolar Disorder. The manufacturer notes in the user guide that people with macular degeneration may be more at risk of retinal damage from blue light and should avoid it. Although the lightbox emits very little blue light, those with macular degeneration will be excluded from the study, as stated above in *Inclusion and Exclusion Criteria*. If problems are experienced, participants are free to stop the study at any time and/or call the Study Coordinator with any questions or issues.
- Negative ion generator: The negative ion generator will be modified so that it does not emit negative ions, so there will be no side effects from negative ions.
- Actiwatch: Participants may experience skin irritation from the actigraphy watch wristband, although very uncommon. Participants will be told to remove the actigraphy watch if this occurs. This would not exclude subjects from further participation.
- Pressure algometer pain testing: Pressure algometry has minimal risk for discomfort. Some studies, like this one, have the potential to cause "peripheral nerve stimulation." Peripheral nerve stimulation is a light touching sensation on the skin surface, lasting only for a few seconds. It may cause mild discomfort but is not harmful. There is a possibility that participants may experience some temporary redness or report some tenderness after the test. If at any point a participant expresses more than mild discomfort and/or wants to stop the test, we will stop.
- Cold pressor pain testing. The cold pressor test has minimal risk for discomfort. There is a possibility that participants may have some temporary redness or sensitivity after the test. If at any point a

participant expresses more than mild discomfort and/or wants to stop the test, they will be instructed to remove their hand from the ice bath. We will not allow the research subject to have they hand submerged for more than 5 minutes to prevent any tissue damage.

- Ischemic pain testing. The ischemic pain test has minimal risk for discomfort. There is a possibility that participants may have some temporary numbness or sensitivity after the test. If at any point a participant expresses more than mild discomfort and/or wants to stop the test, they blood pressure cuff will be immediately deflated.

Other.

- Because this study collects protected health information, there is always a risk of a breach of confidentiality. This risk is addressed below under *Privacy and Confidentiality*.

The possible benefits to the participants and to future understanding and improvements in delivery of sleep-related care to Veterans are reasonable and outweigh the risks of minor and rare physical harm, emotional distress, or breach of confidentiality to study participants.

Participant Safeguards:

This study will not include any vulnerable populations. Potential participants will be gauged for their interest in the study prior to being provided a consent form. Those participants that can verbally acknowledge understanding of the study and agree to participate will be consented by trained study personnel. If it appears that the subject is experiencing decisional impairment or an inability to understand the study, such as failing to repeat back the basic concepts of the study, that person will not be permitted to participate.

Suicidality:

In the event that a participant expresses the thought of harming themselves when they are at the clinic for the overnight sleep test, the sleep lab technician or the researcher, if present, will accompany them to the Emergency Department for a warm-transfer.

If during a follow-up phone call after the sleep test the volunteer expresses thoughts of harming themselves, then the researcher will contact the VA national crisis line at 585-393-7938 or 1-800-273-8255 or the local suicide prevention line at x52857 and connect the individual to that help by phone. In the event a direct phone transfer cannot be completed, then the researcher will ask that the participant remain available by phone. The researcher will provide the VA National Suicide Prevention Hotline with the name and phone of the participant and the VA Hotline will then phone the participant. The researcher will follow-up afterwards by phone to ensure that the participant has received adequate help and is safe.

In the event that questionnaire answers indicate depression or suicidality, their primary mental health provider will be notified. If they do not have a mental health provider, then their primary care physician will be notified to make a referral. If there is an immediate suicidal ideation, we will walk the participant to the emergency room for a warm transfer.

Benefits:

Participants may directly benefit from this study through the designated morning bright light. Outcomes include improved quality of sleep, an increase in quality of life, improved cognition, and reduction of pain. Subjects will receive modest monetary compensation for their time (see *Subject Compensation*).

Protected Health Information:

The following protected health information (PHI) will be collected in this study: full name, phone number, dates of research visits, date of birth, full mailing address, email address, and last four digits of the social security number. Demographics such as identified race & ethnicity will be collected and history regarding diagnosis of a sleep disorder; medical history will be confirmed or examined in chart and information regarding TBI, PTSD, and/or depression may also be collected. Information regarding drug and alcohol dependency will be examined for the purpose of determining eligibility to participate in the study and research personnel

involved in the study will not identify, directly or indirectly, any individual subject in any report of the research, or otherwise disclose the subject identities to anyone outside the IRB-approved VA personnel for this study in any manner (e.g. manuscript or publication). In addition, to create the GUID for Federal Interagency Traumatic Brain Injury (FITBIR) we will collect name at birth and place of birth (though note that no PHI/PII is ever disclosed to FITBIR). Data will be transferred to FITBIR.

At consent, a participant ID code will be assigned to each participant, and this will be used as the identifier for all further data collection. Research questionnaires will be collected on paper copies (all coded with the unique participant ID number and no identifiable data). The originals will be stored in a locked file cabinet in a locked office on the 4th floor of VAPORHCS building 101, room 432A. Original hardcopy consent and HIPAA forms will be stored in a locked drawer and office in building 101, room 432A. Electronic consents will be stored on the VAPORHCS limited-access Research drive. (R01:\\Research\Elliott\), on VA OneDrive and other future VA-approved platforms. In order to help facilitate remote visits, questionnaires may be mailed.

PHI that is mailed or transported between a home visit and the VA will also be coded and stored in the locked file cabinet upon receipt.

Prior to consent, first and last name and email address will be provided to DocuSign in order to initiate the electronic consent process. The consent to be used will also be relayed to DocuSign and, for this study, the consent will list the subject's status as a veteran who may have had a TBI, problems sleeping, problems with memory, and/or problems with pain. Please see "Letter_DocuSign Memo for PO" provided with this protocol for details regarding the National VA's decision to deem DocuSign secure and appropriate for e-consent. Screening phone scripts have been developed which include discussion of this transfer of information and ask potential participants permission for transfer. Mail or in person consent is offered as an alternative within these documents.

Resources Available:

There is office space available at the VAPORHCS Sleep Disorders Clinic (building 100-6C), and provided by Research Service (building 101, rooms 432A, 430, 404, and 533) with locked file drawers in a dedicated, locked room (101/432A). Testing will occur at the VAPORHCS at the aforementioned rooms available to the study team. The local VAPORHCS Co-Investigator, Miranda Lim, M.D., Ph.D., is a clinical provider in the Sleep Disorders Clinic.

Costs To Subjects:

Participants may incur a minor cost from operating the energy-efficient lightboxes or negative ion generators. The estimated electrical cost to power the lightbox amounts to <30 cents over the course of the study period. There are no other costs involved with participating in the study. Transportation for subsequent visits will not be provided or reimbursed by the study team.

Subject Compensation:

Subjects will receive compensation via gift cards or other cash equivalent. Each subject in each group (MBL or negative ion generator) will receive the same compensation (up to $100 in total).

- Visit 2 = $20
- Visit 3 = $60
- Visit 4 = $20

Privacy and Confidentiality:

All physical copies of study documents will be stored in a locked file in a locked room (Room 432A). All study related materials will be coded only by participant identification number. To protect privacy and confidentiality, the electronic master list of study participants and their unique study identification number will be stored on the VAPORHCS limited-access Research drive, the VA OneDrive and other future VA-

approved. These platforms will beprotected by password access to the VA computer system. Only IRB-approved study personnel will have access to this file.

De-identified study data will be disclosed to and uploaded onto the FITBIR Informatics System. Participants will be identified by the FITBIR GUID, the key to which will be accessible only to the investigators. The information gathered during this study will be kept confidential to the extent that the law allows. The subjects will be informed that these results may be published for scientific purposes, provided their identity is not revealed.

PHI that is mailed or transported between a home visit and the VA will also be coded and stored in the locked file cabinet.

Information and/or Specimen Management

Study information will be located at the VAPORHCS. Information collected from symptom questionnaires at clinical intake will include PHI such as name, mailing address, and phone number on the cover page. Questionnaires will be collected on physical copies with no identifiable data and only a coded participant ID on the cover page. The original hard copy questionnaires, as well as original consent and authorization forms, will be stored in a locked file cabinet in a locked office on the 4th floor of VAPORHCS in building 101, room 432A.

The actigraphy watches will be used to collect actigraphy data and will contain sleep patterns, overall light intake, and overall activity levels. The actigraphy watch has no ability to transmit wirelessly and must be connected to a proprietary charging dock via USB read by proprietary software in order retrieve the data. Data will be downloaded onto a password-protected OHSU computer containing said proprietary software for actigraphy devices. All actigraphy data downloaded from the actigraphy device is coded data; no PHI is associated with any of this downloaded data. Raw actigraphy data will be housed on the limited-access Research drive, VA OneDrive, and other future VA-approved platforms at VAPORHCS.

HOBOs will be attached to the lightboxes which will track when the lightbox is turned on or off. The HOBOs do not have the ability to transmit wirelessly and must be connected to a USB dock to retrieve data. Data will be downloaded onto a password-protected OHSU computer containing VA-approved software.

Data and Safety Monitoring Plan (DSMP)

Participant Safety

Dr. Elliott, the principal investigator will be responsible for complying with the reporting requirements. Dr. Lim is the Responsible Clinician on record and will be responsible for monitoring the safety of the study. Continuous, close monitoring of participant safety will include prompt and frequent reporting of safety data (i.e., adverse/serious adverse events) to the local site IRB and the VA. Serious adverse events will be reported to the local IRB, and the project officer within 48 hours of the time project staff become aware of the incident. It is unlikely that study outcomes will adversely affect the health or well-being of research participants in this experimental study. Participants are under usual care for all treatment they receive for their sleep complaint, in addition to the proposed study arms. If depression or risk of suicide are evident due to questionnaire data collected (e.g., question 9 on the PHQ-9), then the participant will be referred for follow-up. If a participant indicates thoughts of self-harm, then steps will be taken to protect and support the participant as described above in the sections on Suicidality and on Risks and Side Effects.

Data safety and management

Our team has extensive experience collecting and managing research data from Veterans. All research records will be maintained according to the current VA research retention schedule. Our current VA IRB-approved studies operate under a standard operating procedure with specific instructions for administration and entry of questionnaire data. Safeguards are in place to cross-check for duplicate or erroneous data.

Subjects will be assigned a unique subject code as soon as they are consented that will follow them through the study. Inclusion of personally identifiable patient information will be minimized, but some

personally identifiable data will be included to decrease errors and allow cross checking of information through, for example, medical chart review. Strict security measures will be used to protect the data, all of which meet or exceed HIPAA requirements. Personal identifiers will only be accessible to authorized study personnel for the purposes for which it was collected.

The goals of our data management system are to maintain data accuracy and security, and to ensure efficient access for monitoring and analysis. All study personnel doing data collection will be carefully trained in their tasks (i.e., collection methods, security, auditing and tracking, prevention and detection of intrusion, back-up and recovery, quality control, monitoring and reporting.

Step-by-Step Guidance on Conducting the Study

Recruit subjects from methods described in "Subject Identification/Recruitment" section

1. Complete Visit 1.
    a. Obtain written and verbal informed consent and HIPAA authorization from subjects
2. Schedule time to return to the VAPORHCS for Visit 2.
3. Complete Visit 2.
    a. Provide subjects with lightbox or disabled negative ion generator
    b. Collect subjects initial questionnaire data, complete pain testing, provide study diary
    c. Compensate subjects with up to $20
4. Schedule time to return to the VAPORHCS for Visit 3.
5. Complete Visit 3.
    a. Collect subjects post-study questionnaire packet and complete pain assessment.
    b. Collect subjects actiwatch, lightbox or negative ion generator, and study diary
    c. Compensate subjects with up to $60
6. Schedule time to return to the VAPORHCS for Visit 4.
    a. Collect subjects follow-up questionnaire packet and complete pain assessment.
    b. Compensate subjects with up to $20
7. Thank subjects for their participation.

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Appendix – Supporting Documents List

Contact info sheet filled out by subjects at consent
Demographics form
Modified HTEC
Flyer
Info sheet given to subjects
Questionnaire packet
Phone scripts

DocuSign Materials: Phone Script E-consenting, Email Script for DocuSign, Letter DocuSign Memo for PO, SOP DocuSign for Research, IAM Stand Alone eSig service training