CLINICAL PROTOCOL

The Clinical Utility of DLMO in the Treatment of Delayed Sleep-Wake Phase Disorder: A Randomized Trial

Study Agents: Melatonin 0.5 mg

HUM #: 00145052

IND: 141269

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PROTOCOL SYNOPSIS

Sponsor: American Sleep Medicine Foundation
Name of Finished Product: N/A
Study Title: The Clinical Utility of DLMO in the Treatment of Delayed Sleep-Wake Phase Disorder: A Randomized Trial
Study Phase: 3
Primary Objective: The objective of the proposed study is to evaluate the clinical utility of obtaining field-based dim light melatonin onset (DLMO) to time melatonin administration for patients with delayed sleep-wake phase disorder. Note that the efficacy of the intervention used to time the administration of melatonin is being tested, not the efficacy of melatonin per se.
Study Design: The study is a randomized, controlled, parallel double-blind 4-week trial of 0.5 mgs of exogenous melatonin timed to either 3 h before actual dim light melatonin onset (DLMO) based on in-home measurement (M-DLMO, n = 25) or 3 h before DLMO estimated at 2 h before average sleep onset time based on actigraphy and sleep diary (E-DLMO, n = 25) in adult participants with delayed sleep-wake phase disorder. All participants will receive melatonin 0.5 mgs. Outcomes include change in DLMO, subjective and objective sleep parameters, and daytime symptoms.
Study Population: Adults 18-65 years of age who meet diagnostic criteria for current delayed sleep-wake phase disorder.
Diagnosis and Main Criteria for Inclusion: To be enrolled in the study, participants must be 18-65 years of age, and meet diagnostic criteria for delayed sleep-wake phase disorder (DSWPD) per the International Classification of Sleep Disorders-3 (ICSD-3). Diagnostic criteria include: (1) have evidence of a delayed phase of the sleep-wake pattern on daily sleep diaries and actigraphy maintained for at least 7 days (e.g., a $\geq$ 2 h delay in the timing of habitual sleep episode between work/school and free days); (2) report difficulty falling asleep and difficulty awakening at desired/required times for $\geq$ 3 months.
Test Product; Dose; and Mode of Administration: Melatonin; 0.5 mgs; oral fast dissolve
Reference or Placebo Therapy; Dose; and Mode of Administration: N/A (all participants will receive melatonin 0.5 mgs).
Duration of Treatment: 4 weeks (28 days)
Variables: Time of DLMO in minutes; Epworth Sleepiness Scale score (ESS); Multidimensional Fatigue Inventory score (MFI-20); Short-Form Health Survey (SF-12);

from diary and actigraphy: total sleep time, initial sleep latency, sleep onset time, sleep offset time.
Statistical Methods: Statistical analyses will include 2-tailed t-tests and linear mixed models to test group differences on outcomes.

1 INTRODUCTION

1.1 Indication

Treatment of delayed sleep-wake phase disorder by timing melatonin administration to either measured or estimated dim light melatonin onset.

1.2 Background and Rationale

Delayed sleep-wake phase disorder is common and debilitating

The most common circadian rhythm sleep-wake disorder, delayed sleep-wake phase disorder (DSWPD) is estimated to affect up to 7-16% of adolescents and young adults, and more than 10% of patients presenting to sleep clinics with insomnia symptoms (American Academy of Sleep Medicine 2014). The prototypical patient with delayed sleep-wake phase disorder presents with chronic difficulty falling asleep and waking at required or socially desired times (American Academy of Sleep Medicine 2014). When free to select their own sleep schedule, patients with DSWPD have significantly later sleep onset and wake times relative to convention, with preserved sleep quality and normal sleep duration (American Academy of Sleep Medicine 2014). Delay of the circadian timing system relative to the required or socially desired timing of the sleep episode is posited to be one of the major etiological factors (Micic et al. 2016). This is corroborated by numerous studies, which show delays ranging from 2-6 h in DSWPD patients' circadian phase relative to normal sleepers (Oren et al. 1995, Ozaki et al. 1996, Shibui et al. 1999, Uchiyama et al. 2000, Watanabe et al. 2003).

The inability to maintain a sleep-wake schedule consistent with social and occupational requirements often leads to chronic sleep loss and significant daytime impairments. Consequences of DSWPD are wide-ranging and include absenteeism and presenteeism, and impairment in social and family life (Rajaratnam et al. 2015). Indeed, role disability is greater, and quality of life is more impaired, in adults with DSWPD relative to other chronic disorders, including sleep apnea, migraine, and depression (Nagtegaal et al. 2000).

Effective treatment of DSWPD is challenging under current treatment paradigms

Despite its prevalence, treatment of DSWPD is challenging. Effective treatment requires correcting the circadian phase so that it is optimally aligned with the desired sleep-wake schedule. Treatment options include light therapy, hypnotic medications, prescribed sleep-wake scheduling, timed physical activity, and wakefulness promoting medications. Among the available treatment options, the American Academy of Sleep Medicine (AASM) Clinical Practice Guideline for treatment of DSWPD in adults recommends only one therapy: timed exogenous melatonin (Auger et al. 2015). As noted in both the Clinical Practice Guideline and its accompanying editorial, there is a significant lack of research on clinical populations with circadian sleep-wake rhythm disorders, and treatment of circadian rhythm sleep-wake disorders such as DSWPD, with a particular need for field-based studies (Auger et al. 2015). Previous placebo-controlled studies of melatonin for DSWPD in adults show improvements in objectively measured sleep parameters, including increased total sleep time, reduced sleep onset latency, advanced DLMO time, and an advanced time of sleep onset time for melatonin relative to placebo (Kayumov et al. 2001, Mundey et al. 2005, Rahman et al. 2010).

However, on average, these improvements are relatively modest and development of treatment protocols that enhance the efficacy of melatonin therapy is needed. Clinical strategies that allow for home-based measurement of DLMO and the administration of melatonin personalized to each patient's DLMO hold promise to improve the efficacy of melatonin. Indeed, evidence from laboratory-based studies of healthy adults suggests that melatonin must be administered at the correct time in the phase response curve relative to the individual's circadian phase to achieve a shift in circadian timing (Burgess et al. 2008, Burgess et al. 2010). One previous study has demonstrated the importance of the timing of melatonin administration in maximizing phase advances in adults with DSWPD, with a more robust phase advance observed for earlier administration times (Mundey et al. 2005). Nevertheless, to date, no study has evaluated the clinical superiority of timing the administration of melatonin to an individual's circadian time vs. clock time using a randomized design.

Dim light melatonin onset can be readily measured in the field

The time of melatonin onset in dim light (or dim light melatonin onset; DLMO) is the gold standard circadian marker (Lewy et al. 1989) and most reliable circadian phase marker in humans (Klerman et al. 2002). Dim light melatonin onset can be obtained via blood, urine, or saliva; advantages of saliva relative to other methods include practicality and reliability (Benloucif et al. 2008). Historically, research utilizing DLMO has been conducted in laboratory settings, which limits clinical utility. However, our group has pioneered the development of, and established the validity for, a kit for home-based saliva sampling to measure DLMO in the field. Dr. Burgess (Co-I) has developed a novel in-home DLMO kit, which she has validated against laboratory DLMOs, with a very high correlation between the in-home and in-laboratory DLMOs ($r = 0.91$, $p < 0.001$), and excellent compliance, as 92% of the in-home samples were valid (Burgess et al. 2015). Crucially, Dr. Burgess has also validated the kit in adults with DSWPD, with high correlations ($r = 0.93$, $p < 0.001$) relative to in-laboratory DLMOs and high compliance, as 83% of the in-home samples were valid (Burgess et al. 2016). In conjunction with Dr. Burgess, Dr. Swanson (PI) has used the in-home DLMO kit with postpartum women with depression, with excellent compliance (98% of the DLMOs were valid; (Swanson et al. 2017)).

Objective of the proposed study

The objective of the proposed study is to evaluate the clinical utility of obtaining field-based DLMO in the treatment of DSWPD using a randomized controlled study design. Our central hypothesis is that timing exogenous melatonin administration using measured DLMO will result in a more robust treatment response after 4 weeks of therapy relative to timing exogenous melatonin administration using an estimation of DLMO. The rationale for the proposed project lies in the critical need to understand whether use of objective circadian markers, particularly field-based markers, enhances treatment outcomes in DSWPD to reduce the burden of this circadian rhythm sleep disorder. This proposal leverages our unique expertise with field-based, validated in-home assessment of DLMO and clinical treatment of DSWPD. We plan to test our central hypothesis with a double-blind randomized trial of measured DLMO (M-DLMO, $n = 25$) vs. estimated DLMO (E-DLMO, $n = 25$) for timing exogenous melatonin administration in adults with DSWPD.

1.3 Hypothesis

Specific Aims

Aim 1: Compare pre- to post-treatment changes in DLMO in M-DLMO vs. E-DLMO conditions.

Hypothesis 1: Participants in the M-DLMO condition will show greater improvements in DLMO (i.e., greater advance of DLMO) relative to participants in the E-DLMO condition after 4 weeks of exogenous melatonin.

Aim 2: Compare pre- to post-treatment changes in objective and subjective sleep parameters and daytime symptoms in M-DLMO vs. E-DLMO conditions.

Hypothesis 2: Participants in the M-DLMO condition will show greater improvements in objective (per wrist actigraphy) and subjective (per daily sleep-wake diary) sleep parameters (specifically, total sleep time, initial sleep latency, sleep onset time, sleep offset time) after 4 weeks of exogenous melatonin. They will also show greater improvements in daytime symptoms.

1.4 Previous Human Experience

Melatonin is designated as a dietary supplement by the FDA. A recent, randomized, double-blind clinical trial to assess the toxicology of chronic melatonin tested 10 mg of oral melatonin administered daily for 28 days (n = 30) versus placebo (n = 10) in healthy adults (Seabra et al. 2000). Measurements included the following laboratory tests: complete blood count, urinalysis, sodium, potassium and calcium levels, total protein levels, albumin, blood glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), urea, creatinine, uric acid, glutamic-oxalacetic transaminase phosphate, gama-glutamic transaminase, T_3, T_4, TSH, LH/FSH, cortisol, and melatonin serum concentrations. Additional measurements included the Epworth Sleepiness Scale, and participants were also asked about side effects. No toxicological changes were noted in participants in the melatonin group. There were no differences between melatonin and placebo on any of the laboratory tests or Epworth Sleepiness Scale. There were no differences between melatonin and placebo in side effects. The most common side effects reported in the melatonin group included somnolence and headache.

Other studies in healthy adults have investigated psychomotor performance and melatonin. One of the studies examined the effects of 5 mg of oral melatonin vs. placebo on driving performance using a randomized, placebo-controlled, double-blind, crossover design in 20 healthy adults (Suhner et al. 1998). Measures included a medical examination, subjective sleepiness, body sway measurement, and a standardized driving computer battery (which tested attention, reaction time, power of concentration, and sensomotor coordination). All measures were administered 60 minutes after the melatonin was ingested. No differences were observed between melatonin and placebo on any of the driving performance measures, although subjective sleepiness was greater in the melatonin group vs. placebo. A second study evaluated the psychomotor effects of time-release oral melatonin 6 mg in 23 healthy adults; measures included serial reaction time, logicial reasoning, serial subtraction, and

multitask (Paul et al. 2003). Participants completed testing 7 hours after ingestion of melatonin. Melatonin did not impair performance on any task.

Melatonin has also been investigated in human clinical populations. A recent randomized, double-blind, placebo-controlled study of oral melatonin 6 mg vs placebo, taken daily for 3 months, on depression symptoms in adult females who were undergoing surgery for breast cancer found that melatonin reduced depressive symptoms, and there were no differences on side effects between the groups (Hansen et al. 2014). In a randomized, double-blind, placebo-controlled trial of 12 weeks of oral melatonin 3 mg (60 participants) vs. placebo (59 participants) and amitriptyline 25 mgs (59 participants) for the prevention of migraine headaches in adults, participants in the melatonin group reported a similar rate of side effects/adverse events to placebo, with the most common side effect of sleepiness; further, melatonin was equal, or superior to, amitriptyline on the migraine endpoints (Goncalves et al. 2016). In a trial of 1 or 3 mg of oral melatonin vs. placebo nightly for 12 months in 81 postmenopausal women with osteopenia, melatonin was not different from placebo with respect to side effects/adverse events; further, no hangover effect affecting balance- and muscle function was found following the intake of melatonin (Amstrup et al. 2015).

Melatonin has also been studied in adult humans as a treatment of delayed sleep-wake phase disorder (the indication for the present study). One of the earliest randomized controlled, trials was a crossover study conducted in 8 adults with delayed sleep wake phase syndrome, which evaluated oral melatonin 5 mgs vs placebo nightly for 4 weeks. Results indicated that melatonin was produced at a significantly earlier sleep onset time and wake time relative to placebo, with no next-day hangover effects (Dahlitz et al. 1991). Later randomized, controlled trials in adults with delayed sleep-wake phase syndrome have demonstrated the efficacy of melatonin for this disorder, including: 20 participants randomized to 4 weeks of nightly oral melatonin 5 mg or placebo, which found that melatonin produced improvements in sleep onset latency, with no difference from placebo in sleepiness, fatigue, and alertness (Kayumov et al. 2001); 30 participants in a crossover trial studying 2 weeks of nightly 5 mg oral melatonin vs. placebo, showing that melatonin produced significant advancement of the endogenous melatonin profile, advance of sleep onset, and shortened sleep latency (Nagtegaal et al. 1998); in 20 participants in a crossover trial of 4 weeks of nightly oral melatonin (5 mg) or placebo, melatonin improved sleep continuity and depression symptoms (Rahman et al. 2010); and for 13 participants who were randomized to 4 weeks of nightly oral melatonin (0.3 or 3 mg) or placebo, melatonin (regardless of dose) advanced the circadian phase of exogenous melatonin and sleep onset (Mundey et al. 2005). The dose of melatonin (0.5 mgs) was selected based on work by Burgess (Co-I; (Burgess et al. 2010)) and others (Mundey et al. 2005), which has shown similar phase shifting effects between smaller (0.3-0.5 mgs) and larger (3.0 mg) doses. As earlier administration produces maximal phase shifts, we propose to use the lowest effective dose to minimize possible soporific effects of taking melatonin during waking hours.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

The objective of the proposed study is to evaluate the clinical utility of obtaining field-based DLMO in the treatment of DSWPD using a randomized controlled study design. Our central

hypothesis is that timing exogenous melatonin administration using measured DLMO will result in a more robust treatment response after 4 weeks of therapy relative to timing exogenous melatonin administration using an estimation of DLMO. The rationale for the proposed project lies in the critical need to understand whether use of objective circadian markers, particularly field-based markers, enhances treatment outcomes in DSWPD to reduce the burden of this circadian rhythm sleep disorder. This proposal leverages our unique expertise with field-based, validated in-home assessment of DLMO and clinical treatment of DSWPD. We plan to test our central hypothesis with a double-blind randomized trial of measured DLMO (M-DLMO, n = 25) vs. estimated DLMO (E-DLMO, n = 25) for timing exogenous melatonin administration in adults with DSWPD.

2.2 Endpoints

Endpoints were selected to include those identified as "critical" and "important" by the AASM Clinical Practice Guideline (Auger et al. 2015).

2.2.1 Primary Endpoint

The primary endpoint is change in time of DLMO from pre- to post-treatment.

2.2.2 Secondary Endpoint

Secondary endpoints include:

- Change in sleep parameters per wrist actigraphy and sleep diary (specifically, total sleep time, initial sleep latency, sleep onset time, sleep offset time) from pre- to post-treatment.
- Change in daytime symptoms and functioning (as assessed by the Epworth Sleepiness Scale, Multidimensional Fatigue Inventory-20, Sheehan Disability Scale, Patient Health Questionnaire-9, Generalized Anxiety Disorder-7) from pre- to post-treatment.
- Change in self-report sleep quality and symptoms (as assessed by the Pittsburgh Sleep Quality Index, Morningness Eveningness Questionnaire, PROMIS-Sleep Disturbance scale, PROMIS-Sleep Related Impairment scale).

3 STUDY DESIGN

Overview of research design

This study is a randomized, controlled, parallel double-blind 4-week trial of 0.5 mg of exogenous melatonin (Emens et al. 2015) timed to either 3 h before actual DLMO based on in-home measurement (M-DLMO, n = 25) or 3 h before DLMO estimated at 2 h before average sleep onset time based on actigraphy and sleep diary (E-DLMO, n = 25). Note that the intervention tested is the method used to time melatonin administration--not melatonin per se, as all participants will receive the same dose of melatonin for the duration of the study.

4 SUBJECT SELECTION

4.1 Subject Recruitment

Fifty participants will be recruited over 2 years. Recruitment will occur within the greater Ann Arbor community, the Michigan Medicine Behavioral Sleep Medicine (BSM) clinics,

affiliated with the Michigan Medicine Sleep Disorders Center, where Drs. Swanson (PI), Arnedt (Co-I), and Conroy (Co-I) provide direct clinical care, and the University of Michigan's University Health Service (UHS) Collegiate Sleep Disorders Clinic (CSDC), directed by Dr. Hershner (Co-I). The UHS provides health care to all students enrolled at University of Michigan (> 40,000 students). Between the CSDC and BSM Clinics, an average of 63 new patients are seen per month, 8 of whom are diagnosed with DSWPD. Thus, we anticipate a pool of at least 95 patients annually from which we will recruit to meet our enrollment target of 25 participants per year.

4.1.1 Inclusion Criteria

1. 18-65 years of age
2. ICSD-3 diagnosis of DSWPD: (1) have evidence of a delayed phase of the sleep-wake pattern on daily sleep diaries and actigraphy maintained for at least 7 days (e.g., a ≥ 2 h delay in the timing of habitual sleep episode between work/school and free days); (2) report difficulty falling asleep and difficulty awakening at desired/required times for ≥ 3 months.
3. Female participants of childbearing potential (i.e., they are not permanently sterilized (hysterectomy, bilateral salpingectomy and bilateral oophorectomy) or postmenopausal (12 months with no menses without an alternative medical cause) by report) must agree to use a reliable method of contraception from the screening visit until 4 weeks after the study has completed. Acceptable methods of birth control during participation in the study include: oral contraceptives, patch contraceptives, injection contraceptives, male condom with spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation), vasectomized partner(s), or total sexual abstinence.

4.1.2 Exclusion Criteria

1. Hypersensitivity to melatonin or any other component of the product
2. Suspicion of a sleep disorder other than DSWPD per interview (Edinger et al. 2004) and medical record review (when available)
3. Presence of chronic psychiatric conditions which may directly influence sleep per interview and medical record review (when available), including:
    - current illicit drug use,
    - current alcohol or drug abuse,
    - bipolar disorder,
    - psychotic disorder.
4. Presence of unstable chronic medical condition which may directly influence sleep (e.g., chronic pain, thyroid conditions)
5. Current or past history of medical conditions which may affected by melatonin per self-report and medical record review (when available), such as
    - Hypertension or hypotension
    - diabetes,
    - clotting/bleeding disorders,
    - epilepsy/seizures,
    - autoimmune disorders,
    - conditions requiring immunosuppressive management such as transplant.

6. Per self-report or medical record review (when available), current use of medications which may have interactions with melatonin:
    - nifedipine,
    - anti-hypertensive medications (including, but not limited to, chlortalidone, chlorothiazide, hydrochlorothiazide, indapamide, metolazone, Lisinopril, Benazepril, captopril, candesartan, losartan, amlodipine, diltiazem);
    - immunosuppressants (including, but not limited to, prednisone, budenoside, prednisolone, cyclosporine, tacrolimus, sirolimus, everolimus, azathioprine, leflunomide, mycophenolate);
    - sedative or hypnotic medications (including, but not limited to, zolpidem, suvorexant, butabarbital, quazepam, estazolam, flurazepam, triazolam, eszopiclone, temazepam, secobarbital, doxepin, zaleplon);
    - antidiabetes drugs (including, but not limited to, insulin, metformin, glyburide, glipizide, glimepiride, repaglinide, nateglinide, rosiglitazone, pioglitazone, canagliflozin, dapagliflozin, liraglutide);
    - anticoagulant/antiplatelet (including, but not limited to, heparin, warfarin, rivaroxaban, dabigatran, apixaban, edoxaban, enoxaparin, fondaparinux, clopidogrel, ticagrelor, prasugrel, dipyridamole, dipyridamole/aspirin, ticlodipine, eptfibatide.)
    - CYP4501A2 strong or moderate inhibitors or inducers (including, but not limited to, floroquinolones such as ciprofloxacin, fluvoxamine, verapamil, St. John's wort, modafinil, nafcillin, omeprazole)
7. Pregnancy (as determined by urinary pregnancy test at screening for women of child-bearing potential) or self-report of breastfeeding
8. Self-report of routine night shift work
9. Self-report of past month travel or planned travel during the study across more than one time zone
10. Self-report of use of melatonin in the past month
11. Current use of medications that may interfere with the measurement of melatonin (NSAIDs if used daily, and beta-blockers, (Benloucif et al. 2008)) per self-report and medical record review (when available)

5 STUDY TREATMENTS

5.1 Allocation to Treatment

Eligible participants will be randomized using the minimization method (Pocock et al. 1975) in a 1:1 ratio to M-DLMO or E-DLMO. Assignment to condition will be balanced by age and baseline sleep onset time on free days. For allocation of participants, a computer program (the Treatment Assignment System, created by UM's Consulting for Statistics, Computing, and Analytics Research) will be used by the study coordinator to generate the group assignment at enrollment for each participant.

Participants will be blinded to the specific study hypotheses and to their group assignment. The study clinician will be blinded to group assignment. The study coordinator, who communicates the time of melatonin administration to the study clinician, will not be blinded to the actual DLMO of participants in the M-DLMO condition; however, they will be blinded to the actual DLMO of participants in the E-DLMO condition until their participation is complete.

Due to individual variation in melatonin levels or errors in the saliva collection process, it is possible that DLMO will not be able to be determined for a small proportion of participants. To retain these participants in the protocol, if they are randomly assigned to the M-DLMO condition, the study coordinator may change their assignment to the E-DLMO condition. Data for these participants will be examined post-hoc upon completion of the study using sensitivity analyses before determining whether to retain or discard their data from analyses.

5.2 Breaking the Blind

The randomization can be broken, if necessary per the physicians caring for the subject to ensure subject safety.

5.3 Drug Supplies

5.3.1 Formulation, Preparation and Dispensing

Melatonin 0.5 mgs in a fast dissolve tablet manufactured by Natrol®, LLC (21411 Prairie St. Chatsworth, CA 91311) will be dispensed by study staff to participants. The manufacturer is providing the melatonin for this study free of charge. They will be provided with a 14-day supply at the start of the study and at the first follow-up treatment visit (week 1).

5.3.2 Drug Storage and Drug Accountability

Melatonin will be stored in the Sleep and Circadian Research Laboratory in a locked cabinet, to which only study staff will have access. Melatonin will be provided by study staff to participants in bottles equipped with a TrackCap to monitor the date and time at which the bottle was opened. Reconciliation of medication will be tracked at each study visit by pill count completed by study staff and by download of the TrackCap data at each study visit.

5.4 Concomitant medications

Medications that may interact with melatonin will not be allowed during the study (list of possible interactions obtained from the Food, Herbs, and Supplements Database available at https://naturalmedicines.therapeuticresearch.com). Participants enrolled in the study will not be allowed to take alcohol, nifedipine, anti-hypertensive medications (including, but not limited to, chlortalidone, chlorothiazide, hydrochlorothiazide, indapamide, metolazone, lisinopril, benazepril, captopril, candesartan, losartan, amlodipine, diltiazem); immunosuppressants (including, but not limited to, prednisone, budenoside, prednisolone, cyclosporine, tacrolimus, sirolimus, everolimus, azathioprine, leflunomide, mycophenolate); sedative or hypnotic medications (including, but not limited to, zolpidem, suvorexant, butabarbital, quazepam, estazolam, flurazepam, triazolam, eszopiclone, temazepam, secobarbital, doxepin, zaleplon); antidiabetes drugs (including, but not limited to, metformin, glyburide, glipizide, glimepiride, repaglinide, nateglinide, rosiglitazone, pioglitazone, canagliflozin, dapagliflozin, liraglutide); anticoagulant/antiplatelet (including, but not limited to, heparin, warfarin, rivaroxaban, dabigatran, apixaban, edoxaban, enoxaparin, fondaparinux, clopidogrel, ticagrelor, prasugrel, dipyridamole, dipyridamole/aspirin, ticlodipine, eptfibatide); CYP4501A2 strong or moderate inhibitors or inducers (including, but not limited to, floroquinolones such as ciprofloxacin, fluvoxamine,

verapamil, St. John's wort, modafinil, nafcillin, omeprazole). If they require one of the medications on this list, they will be discontinued from the study.

6 STUDY PROCEDURES

6.1 Screening Visit

Potential participants will be screened for initial eligibility using an in-person diagnostic interview, including the Mini-International Neuropsychiatric Interview (M.I.N.I) and a sleep interview. In order to maintain the integrity of the data, participants screening visits will not be scheduled around the start or end of daylight savings time.

During second level screening, participants will complete health history and demographic forms (including current and past medical history, and current medications) and female participants of childbearing potential will complete a urine pregnancy test. Participants who meet eligibility criteria following completion of the forms and pregnancy screen will maintain self-selected sleep-wake schedules at home for approximately 7-14 days with daily sleep-wake diaries and actigraphy monitoring to evaluate study criteria for DSWPD and determine full eligibility.

Participants who are eligible for the study following full screening will complete baseline study questionnaires and complete an orientation to the in-home DLMO collection protocol. Participants who do not meet eligibility criteria will be provided referrals for clinical care through the CSDC or BSM clinics.

6.2 Treatment Study Period

Visit 1 (Day 1)

Participants will have their first session with the study clinician at Visit 1. Prior to the session, study staff will meet with the participant to download their actigraphy. Study staff will provide the study clinician with the initial clock time at which each participant should take melatonin. The initial clock time of melatonin administration for participants assigned to the M-DLMO condition will be set at 3 h before their measured baseline DLMO. The initial clock time of melatonin administration for participants assigned to the E-DLMO condition will be set at 5 h before their average time of sleep onset at baseline per most recent 7 days of actigraphy. Participants be provided with a 14-day supply of melatonin 0.5 mgs, which they will begin taking that evening.

During the first visit, study staff will query whether participants have had any changes in their medications or medical history since the screening, and review concomitant medications. Participants' baseline sleep diary and actigraphy data will be reviewed by the study clinician. The study clinician will provide them with specific instructions regarding when to take melatonin, their bed time, their wake time, and when to dim ambient lighting and electronic devices to their lowest usable level (timed to be approximately 60 minutes before their scheduled bedtime). They will be provided with a handout summarizing this information.

6.2.1 Follow-up (Weeks 1-4)

Participants will continue to take melatonin 0.5 mg at the scheduled time daily for the 4 weeks of the study. At approximately Week 1, they will be provided with an additional 14-

day supply of melatonin. Each follow-up session (approximately Weeks 1-4) will follow an identical protocol:

1. Study staff will meet with the participant to query the following: review previously reported medications and current use of previously reported medications; any new medications; any side effects from the melatonin; any unexpected medical conditions since their last visit; any new medical diagnoses or changes in medical history since their last visit. They will also meet with the participant to download their actigraphy, TrackCap data, and complete a pill count. Compliance with melatonin administration timing per TrackCap, the pill count, changes in medical history or medications, and side effect information, will be provided to the study clinician. Only melatonin administration deviations ≥ 30 minutes will be considered non-compliant and be reported as protocol deviations.
2. During the follow-up treatment session, the study clinician will review side effects/adverse events, compliance with bed and wake times, adherence to melatonin administration time, and address any barriers to compliance. Participants will be instructed to advance the time of melatonin administration by 1 h and their bed-wake schedule by 1 h (without altering their total time in bed from their baseline average) at each weekly treatment session until they reach their desired bed-wake schedule. The study clinician may also choose to adjust the melatonin administration time or time in bed schedule using their discretion and clinical judgement as needed. At each follow-up session, participants will be provided with a handout summarizing the main components of the session.

7 ASSESSMENTS

Table 1. Protocol Activity by Visit

Protocol Activity	Screen/ Baseline	Visit 1	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4 (Final)
		Day 1	Day 7 ± 5 business days	Day 14 ± 5 business days	Day 21 ± 5 business days	Day 28 ± 5 business days
Week (approximate)	0	1	2	3	4	5
Visit #	0	1	2	3	4	5
Informed Consent	X					
Interview and Medical History	X					
Pregnancy Test (females of childbearing potential)	X					
Randomization	X					
DLMO	X					X
Daily sleep diary	X	X	X	X	X	X
Wrist actigraphy	X	X	X	X	X	X

Melatonin Treatment		**X**	**X**	**X**	**X**	**X**
Adverse Event Assessment			**X**	**X**	**X**	**X**
Concomitant Medication Assessment	**X**	**X**	**X**	**X**	**X**	**X**
Daytime functioning and sleep self-report measures	**X**					**X**

7.1 Primary Endpoint Assessments

Protocol activity and assessments are summarized in Table 1 above.

Primary endpoint: change in the time of DLMO from pre- to post-treatment.

To assess time of DLMO, all eligible participants (regardless of group assignment) will undergo in-home salivary DLMO collection at pre- and post-treatment, using the protocol established by Dr. Burgess (Co-I) (Burgess et al. 2015). Participants will be oriented to the collection procedures during their clinic visit. Participants will be in dim light starting 30 minutes prior to the first sample collection. Collection begins 6 hours prior to participants' habitual sleep onset per their most recent week of actigraphy at baseline. At post-treatment, collection begins 6 hours prior to participants' bed time as assigned at the final treatment session. Samples are collected via Salivette every 30 minutes until bedtime (13 samples total). They are provided with a kit, which includes: a checklist of procedures; a test tube rack; a toothbrush; a nightlight; blue-blocking Uvex glasses (with an Actiwatch attached to monitor compliance of use); an iPod programmed to alarm at collection times; a light medallion (an Actiwatch with light sensor worn around the neck to monitor compliance with light exposure); Salivette collection vials equipped with Track Cap, which will record when the vial was opened; and a label dispenser with pre-labeled labels. Participants wear the blue-blocking glasses throughout the dim light saliva collection and are required to remain seated in the 10 minutes before each sample. When the iPod alarms, participants brush their teeth without toothpaste, collect saliva by chewing on the Salivette, and deposit it in the vial. Participants are informed about the compliance measures utilized in the study. Samples will be stored in participants' freezers until they can be transported to our facility. Samples are centrifuged for two minutes, frozen, and assayed using Bühlmann Laboratory radioimmunoassay (ALPCO Diagnostics, Salem, NH) at Solidphase Inc. To ensure consistency and to minimize the effects of sleep schedule changes on the weekends/days off of work, whenever possible, all participants will complete DLMO collection on the third night of their typical workday sleep schedule (e.g., DLMO collection will occur on a Wednesday, Thursday, or Friday night for participants who work a traditional Monday-Friday schedule).

7.2 Secondary Assessments

Secondary Assessments: 1. Change from pre- to post-treatment in sleep parameters (total sleep time, initial sleep latency, sleep onset time, sleep offset time) measured using wrist actigraphy and daily sleep diaries; 2. Change in daytime symptoms and functioning (Epworth Sleepiness Scale, Multidimensional Fatigue Inventory-20, Sheehan Disability Scale, Patient Health Questionnaire-9, Generalized Anxiety Disorder-7,) from pre- to post-

treatment, 3. Change in self-report sleep quality and symptoms (as assessed by the Pittsburgh Sleep Quality Index, , Morningness Eveningness Questionnaire, PROMIS-Sleep Disturbance scale, PROMIS-Sleep Related Impairment scale).

Wrist Actigraphy Assessments: The Actiwatch Spectrum Plus will be worn by participants daily throughout the protocol for wrist actigraphy monitoring to approximate objective sleep/wake patterns. The Actiwatch Spectrum Plus is a kinesiology ambulatory recorder manufactured by Philips Respironics (Bend, Oregon), and is exempt from FDA premarket submission. Actigraphy data will be scored using Actiware®-Sleep software following standard scoring procedures (Patel et al. 2015).

Sleep Diary Assessments: Participants will maintain daily self-report sleep-wake diaries daily throughout the treatment protocol.

Daytime Symptoms Assessments: Participants will complete the self-report questionnaires (Epworth Sleepiness Scale, Multidimensional Fatigue Inventory-20, Sheehan Disability Scale, Patient Health Questionnaire-9, Generalized Anxiety Disorder-7,) to assess daytime symptoms.

Sleep Quality and Symptoms: Participants will complete the self-report questionnaires (the Pittsburgh Sleep Quality Index, Morningness Eveningness Questionnaire, PROMIS-Sleep Disturbance scale, PROMIS-Sleep Related Impairment scale) to assess sleep quality and symptoms.

Exploratory Assessment: Conners Adult ADHD Rating Scale-Short Form (Change from pre- to post-treatment)

8 ADVERSE EVENT REPORTING

Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

These events may be:

a. *Definitely related:* clearly associated with study drug/treatment
b. *Probably related*: likely associated with study drug/treatment
c. *Possibly related*: may be associated with study drug or other treatment
d. *Unlikely to be related*, or
e. *Definitely not related* to the study drug/treatment

For reporting purposes, an AE should be regarded as definitely or probably related to the regimen if the investigator believes that at least one of following criteria are met:

a. There is a clinically plausible time sequence between onset of the AE and the administration of the study drug or treatment.

b. There is a biologically plausible mechanism for the study drug or treatment causing or contributing to the AE.
c. The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.
d. A potential alternative cause does not exist.

Serious Adverse Events (SAE): An adverse drug experience occurring at any dose that results in any of the following outcomes:

a. Death
b. A life-threatening adverse drug experience
c. Inpatient hospitalization or prolongation of existing hospitalization
d. A persistent or significant disability &/or incapacity
e. A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A serious adverse experience includes any experience that is fatal or immediately life threatening, results in a persistent or significant disability/incapacity, requires or prolongs in-patient hospitalization, or is a congenital anomaly, cancer, or overdose.
Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously.

Expected adverse events are those adverse events that are listed in the protocol and the study informed consent document.

Unexpected adverse events are those that are not anticipated in the study informed consent. This includes adverse events for which the specificity or severity is not consistent with the description in the informed consent.

Unanticipated problem: Per FDA Procedural Guidance for Clinical Investigators, Sponsors, and IRBs (January 2009), A serious problem that has implications for the conduct of the study (requiring a significant and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent or investigator's brochure).

Unanticipated problem Reporting: Per 21 CFR 312.66, 312.53 (c)(1)(vii), and 56.108(b)(1), should an Unanticipated problem occur during the investigation, the investigator will promptly report all unanticipated problems involving risks to human subjects or others to IRBMED /FDA.

The severity or grade of an adverse event may be measured using the following definitions:

Mild: Noticeable to the subject, but does not interfere with subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.
Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.
Severe: Extremely limits the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve.
Event reporting: Information regarding potential adverse events (AE) will be collected by participant report at each study assessment/follow-up. Dr. Swanson will ensure that all protocol deviations, AEs, and SAEs are reported to the IRB and FDA according to the applicable regulatory requirements. AEs will be reported according to the study-specific reporting timeline outlined below. Only related adverse events will be reported.

Potential Risks of the Study:

1 Risk: Breach of confidentiality
Likelihood of risk: Rare
Seriousness to the subject: Minimal
2. Risk: Saliva collection. There is a risk of choking on salivette chewing swab.
Likelihood of risk: Rare
Seriousness to the subject: Serious
3. Risk: Actigraphy. Minimal risks exist with actigraphy. It is possible that participants may experience some discomfort from the band.
Likelihood of risk: Infrequent
Seriousness to the subject: Minimal
4. Risk: Clinical interview and questionnaires. Participants may feel psychological discomfort when being interviewed or completing questionnaires related to their insomnia, mood, or health.
Likelihood of risk: Rare
Seriousness to the subject: Minimal
5. Risk: Melatonin side effects. The safety of melatonin has been well-documented in both animal and human studies, with no studies showing evidence of serious adverse events from melatonin. Possible side effects include drowsiness, headache, dizziness, or nausea.
Likelihood of risk: Infrequent
Seriousness: Minimal

Potential Benefits:
Potential benefits of the proposed research to the participants include an active treatment for DSWPD, thus many can expect to experience improvement in their sleep and related functioning during the day. The study could potentially identify a more effective treatment for DSWPD than the current standard of care. Additionally, we will have other treatment referral services in place in the event that we identify other potential sleep disorders, such insomnia. Thus, the risks associated with participating are reasonable in light of the potential benefits to the participants and others.

Protection against Study Risks

Informed Consent Process. All subjects will provide written informed consent prior to beginning participation in the study. The consent process will inform potential subjects about the study, indicates that their participation is voluntary, and they have the right to stop participation at any time. Risks are enumerated in the informed consent form and described orally during the consent process.

Protection Against Risks.

Melatonin side effects: To minimize side effects from melatonin, a very small dose of melatonin (0.5 mgs) is utilized in the study, and for a short period of time (28 days). Further, individuals who take medications for which there are known interactions with melatonin, or who have medical conditions for which melatonin is contraindicated, will be excluded from participation in the study. Participants will be provided with written and verbal instructions to avoid driving or operating heavy machinery until they know how the melatonin will affect their alertness.

Saliva sample collection: Participants will be shown how to use the saliva collection swab to minimize the risk of choking.

Actigraphy: Participants will be instructed on how to dry the band should it become wet to minimize discomfort.

Violation of Confidentiality: To minimize the risk to confidentiality, we will ensure that data are protected and coded only by subject identification number. Further, only highly trained study team members will be interacting with participants or have access to study data. These protections are likely to be very effective in preventing loss of confidentiality.

Psychological discomfort: To minimize this risk, all interviews and questionnaire completion will be completed by skilled research staff in private offices. Participants will also be informed that they do not have to answer every question to participate in the study.

Although we do not anticipate screening or enrolling participants who are at risk for suicide, should the participant report suicidal ideation (on interview, the Patient Health Questionnaire-9, or in clinical interaction or any other study interaction), participants will be further screened for suicide risk using the Columbia Suicide Severity Rating Scale (C-SSRS). Note that the majority of cases in our current and previous research studies are generally determined to be minimal risk- no immediate threat to self or others, no plan in place, no means to carry out threat, etc. For minimal risk cases (positive answers to questions 1 or 2 on C-SSRS suicidal ideation scale with negative answers to questions 3-5), staff will express concern to the participant and provide resources (including a pamphlet from the National Suicide Prevention Lifeline, the phone number for Michigan Medicine Psychiatric Emergency Services), and referral information for treatment depending on the situation. For moderate risk (positive answers to question 3 on C-SSRS with negative answers to questions 4 and 5) or high/imminent risk (positive answers to questions 4 or 5 on C-SSRS) cases, Dr. Swanson (PI) will be immediately paged for consultation; Drs. Arnedt and Conroy (Co-Is) may also be paged if Dr. Swanson is unavailable/as necessary. For

moderate and high/imminent risk cases, staff will first discuss their concerns with the participant and ask their permission to arrange a liaison with study staff (i.e., as noted above, Drs. Swanson, Arnedt, or Conroy) for further assessment. If the participant refuses consultation, staff and the on-call supervisor determine safety plans and resources and notify medical staff and/or authorities in some cases.

Table 2. Study-Specific AE Reporting Timeline

Reportable Events	**Timing of Report to IRB and FDA**
Unanticipated problem involving risks to subjects or others related to this research study	Serious: within 7 days Non-serious: with scheduled continuing review
Any physical, social, or psychological harm attributable to participation in this research study (e.g., an injury occurring during a study visit, infection at the site of a blood draw if antibiotics are required)	Serious: within 7 days Non-serious: with scheduled continuing review
Death while on study regardless of relatedness	Within 7 days
Privacy violation or breach of confidentiality	Within 7 days
Protocol deviations not related to an adverse event	With scheduled continuing review
Unanticipated problem related to the research that is not a serious adverse event	With scheduled continuing review
Expected, minor side effects commonly associated with melatonin use: • Dizziness • Sleepiness • Headache • Nausea • Transient depression • Insomnia • Nightmares or vivid dreams • Diarrhea • Irritability	With scheduled continuing review
Other serious events not attributable to the research except death as noted above	With scheduled continuing review

9. DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

We based our sample size estimation on the number of participants necessary to detect a 1 h change in DLMO; the sample size required to detect this change at 90% power with an alpha of 0.05 is 23 per group. Thus, our proposed sample of 25 participants per group (50 total) should be adequate to detect a clinically meaningful change in DLMO.

9.2 Data Analysis

Descriptive analyses will be completed by graphical and numerical summarization of key variables. Treatment groups will be compared on pre-treatment demographic and clinical variables using t-tests, chi-square tests, and Fisher's exact tests as appropriate. Variables that emerge as potential confounders from this analysis will be controlled for in the final analyses. Weekly averages will be calculated for total sleep time, initial sleep latency, sleep onset time, and sleep offset time for each week of the study for both actigraphy and sleep diary.

9.2.1 Analysis of Primary Endpoint

Change in DLMO from pre- to post-treatment will be calculated in minutes for each participant. A 2-tailed t-test will evaluate the difference between the change in DLMO between the two groups.

9.2.2 Analysis of Secondary Endpoints

Linear mixed models using a repeated measures group X time (weeks of study) model will be used to determine between-group main effects and interactions with week of study for the following actigraphy and sleep diary variables: sleep onset time, initial sleep latency, total sleep time, sleep offset time, wake after sleep onset, and sleep efficiency. T-tests (2-tailed) will compare group differences in the change from pre- to post-treatment on the following: ESS score; SF-12 score; MFI-20 score.

10 MONITORING

10.1 Data and Safety Monitoring Plan

At each follow-up visit, study staff will query participants about each of the following: review previously reported medications and current use of previously reported medications; any new medications; any side effects from the melatonin; any unexpected medical conditions since their last visit; any new medical diagnoses or changes in medical history since their last visit. Side effects and adverse events will be reviewed with the participant by the study clinician at each follow-up visit. The PI will have oversight of the medical history data, medications, and side effect data for each participant. Only changes to medications/medical history/side effects which occur after the first treatment session/treatment initiation will be recorded. Changes to medications/medical history/side effects deemed by the PI to be possibly, probably, and definitely related to melatonin use will be reported as adverse events.

The PI will be primarily responsible for monitoring data integrity. Monitoring is intended to protect participants' rights and safety, and to ensure the integrity and quality of the data collected. The PI will ensure that all relevant IRBMED and FDA policies, procedures, and stipulations are followed by the study team.

10.2 Frequency of Data and Safety Monitoring

Study staff will inform the PI of potentially related unexpected events as soon as they occur. The PI will be informed of related serious adverse events as soon as they occur and will notify the IRB and FDA within 7 days of notification.

11 DATA HANDLING AND RECORD KEEPING

11.1 CRFs / Electronic Data Record

All data, including Case Report Forms, will be collected and maintained in REDCap.

11.2 Record Retention

Per 21 CRF §312.62, study records will be retained for 2 years after the investigation is discontinued.

12 ETHICS

12.1 IRB/FDA

Prior to study commencement, an Investigator Initiated Investigational New Drug (IND) will be submitted to the Food and Drug Administration (FDA), for review and approval. The study will also be reviewed and approved by the Institutional Review Board (IRBMED, University of Michigan, Ann Arbor, MI).

This study will be carried out in compliance with the protocol and the principles of good clinical practice, as described below:

12.2 Institutional Review Board (IRB)

Before implementing this study, the protocol, the proposed informed consent form and other information to be provided to subjects, must be reviewed by a properly constituted Institutional Review Board (IRB). Any amendments to the protocol must be reviewed and approved by IRBMED.

12.3 Subject Information and Consent

The study team member will explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and will be submitted for IRB approval.

12.4 STUDY DISCONTINUATION CRITERIA

12.4.1 Stopping Rules for Safety reasons

The trial will be stopped if any serious adverse events occur that could possibly be related to the intervention.

12.4.2 Rules for Discontinuation of a Subject

In the event a patient drops out of the study or is discontinued due to protocol violations, all attempts will be made to exit the patient in accordance with the protocol requirements.

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14 APPENDIX

In order to maintain participant and study staff's safety, the following protocol changes may be made during a viral outbreak or pandemic, per clinical judgement and in line with all institutional guidance/requirements with subjects:

1. We will follow all institutional guidance/requirements regarding in person contact with subjects.
2. When appropriate, participants will be provided with all materials necessary so that they may complete their study participation, including intervention sessions, remotely per sponsor allowance for Virtual Clinic Visits per clinician/subject discretion/institutional or government allowance to reduce or eliminate in-person contact with the study team. Specifically, we will provide the participant with enough supplies to complete post treatment in-home saliva collection and a 28-day supply of melatonin.
3. We will continue to screen participants for initial eligibility; all screening will take place remotely and will not involve any in-person interactions with participants. Participants will complete e-consent through REDCap to provide their written consent prior to completion of remote screening.
4. Further screening for participants who meet initial eligibility will be deferred until in-person interactions with participants may be resumed. Participants who passed the initial eligibility screen and completed e-consent will be re-consented in-person at their, in-person second eligibility screen.
5. Screening interviews and intervention sessions may take place via an online video system (i.e., BlueJeans, Zoom Health), or over the phone.