LIGHT THERAPY FOR THE TREATMENT OF MS-ASSOCIATED FATIGUE

Protocol

NCT03060759

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Light Therapy for Multiple Sclerosis Fatigue
Detailed Protocol; version 3

I. BACKGROUND AND SIGNIFICANCE:

Historical background, rationale behind the proposed research, and potential benefits to patients and/or society.

Fatigue is the most commonly reported symptom among people living with multiple sclerosis (pMS).[1-4] More than a quarter of pMS state fatigue is their most disabling symptom.[5] Despite the impact of fatigue in MS, there are few effective treatment options. Many pMS seek non-pharmacological options for their symptoms but have limited evidence upon which to make important treatment decisions.

Fatigue may have multiple mechanisms in MS including dysfunction of the dopaminergic neurons in the basal ganglia,[6,7] endocrine dysfunction due to suppression of the hypothalamic pituitary adrenal axis,[8] cytokine induction in a continuous, pro-inflammatory state of the brain,[9] and/or reduced function of the frontal cortices.[6] We hypothesize that supplemental exposure to bright white light will be associated with a reduction in MS-associated fatigue. In a prospective study following pMS, self-reported sunlight exposure was correlated with lower levels of fatigue.[10] Although causality cannot be determined from that study, this suggests a possible therapeutic benefit of light for fatigue in pMS. Light therapy has also been associated with reduction of fatigue in other neurological and medical disorders including Parkinson's disease[11], traumatic brain injury[12], seasonal affective disorder[13] and cancer-related fatigue[14]. If mechanisms of fatigue are overlapping across disorders in which bright LT has shown therapeutic benefits, LT may be an unrecognized therapeutic option for fatigue among pMS. The beneficial effects of light on fatigue may be mediated through its direct alerting effects or through its effects as the main synchronizer of the circadian system.

II. SPECIFIC AIMS

Objectives and hypotheses to be tested:

1. To determine whether bright white light (BWL) (active condition) compared to dim red light (DRL) (control condition) will reduce self-reported fatigue among pMS when administered twice daily in one-hour sessions for four consecutive weeks.

Hypothesis 1: Bright white LT will reduce the average self-reported fatigue score on the Fatigue Severity Score (FSS) by ≥10 points among pMS with fatigue, compared to pMS treated with dim red LT.

2. To determine the feasibility and tolerability of LT as an intervention strategy to reduce fatigue in pMS by reporting the adherence data with the study intervention and participant-reported side effects.

Hypothesis 2: LT will be both feasible and well-tolerated in pMS.

III. SUBJECT SELECTION:

A. Inclusion/Exclusion Criteria:

a. *Inclusion Criteria*: (1) relapsing remitting or secondary

progressive MS based on McDonald Criteria (2010)[15] (2) ≥18 and ≤70 years old, (3) presence of fatigue defined as FSS ≥36 on screening (range 7-63 possible points).[16]

b. *Exclusion criteria*: (1) change in an anti-depressant, (2) fatigue medication regimen, or MS disease modifying therapy up to 4 weeks prior to study screening, (3) Beck Depression Inventory II score >20, (4) shift work, (5) use of photosensitizing medication, (6) presence of eye trauma or acute optic neuritis within the preceding 3 months or presence of macular degeneration or other retinal disease, (7) history of traumatic brain injury or (8) probable (untreated) sleep apnea based on Berlin questionnaire (9) significant anemia (10) history of mania, (11) MS relapse in the preceding four weeks, (12) current pregnancy, (13) known photosensitivity (14) other complicating illness preventing study completion. Patients will be withdrawn from study participation if they experience a clinical relapse requiring hospitalization or treatment with steroids during the study period. They will also be withdrawn if there is a change in disease modifying therapy for MS, depression or fatigue during the study period.

B. **Subject Recruitment:**

Participants will be recruited from the MS Clinic at Massachusetts General Hospital (MGH). 700 pMS are followed in this clinic. In preliminary screening, ~2/3 of MS patients at MGH have a FSS ≥36 (mean 45.9, standard deviation 15.2 points) and will be eligible for participation. We will use flyers placed throughout the hospital as well as letters to eligible patients in order to assist with recruitment. We will use MGH's Research Subject Volunteer Program (RSVP), a participant matching service, to identify subjects with enthusiasm for the project. If the participant is a patient of the principal investigator, a research physician or study coordinator will explain the study so they do not feel obligated to participate. Subjects between 18-**7**0 years old will be recruited for they study. For older subjects, best clinical judgment will be used to determine if participation is feasible.

IV. SUBJECT ENROLLMENT:

A. **Methods of enrollment, procedures for obtaining informed consent, and randomization**: Following a redcap screening survey (Beck Depression Inventory, Fatigue Severity Scale, Berlin Questionnaire, Inclusion/exclusion criteria) and a baseline visit, eligible participants will be consented and randomized using a computer-based randomization generator 1:1 to (a) white LT (10,000 lux), or (b) dim red LT (<300 lux). Dim red LT is a widely accepted controlled condition in clinical studies of LT. In attempt to reduce placebo effect, the participants will be informed that this study will examine the effect of two different light spectra on fatigue and that one will be placebo. They will be informed that they will not know the

group they are in. Informed written consent will be obtained at the time of enrollment at the screening/baseline visit.

V. STUDY PROCEDURES:

A. Study visits and parameters to be measured, data to be collected and when the data is to be collected:

Interested patients will be identified through the MS clinic at MGH, the RSVP, the Partners Clinical Trials website or alerted by flyer/letter. Following a phone call to explain the details and requirements of the study, interested participants will undergo a screening survey administered through redcap, link sent by email. This survey will include questions regarding the inclusion/exclusion criteria, the Fatigue Severity Scale (≥36), the Beck Depression Inventory (≤20), and the Berlin Questionnaire to screen the participant for eligibility. Participants who are eligible and remain willing to participate will then be scheduled for an in-person visit with either the principal investigator (PI) or another physician involved in the study for a baseline visit. The following assessments will be administered by the study PI/research physician at the baseline visit: (1) the Kurtrzke Extended Disability Status Scale (EDSS), (2) FSS, (3) Pittsburg Sleep Quality Index (PSQI), (4) Epworth Sleepiness Scale (ESS), (5) Multiple Sclerosis Quality of Life-54 (MSQOL-54). Additionally data will be obtained from patient report and chart review on the patient's history of RRMS or SPMS including time from diagnosis, disease modifying therapy, baseline neurologic symptoms, imaging features such as presence or absence of spinal cord lesions as well as data on medical comorbidities and medications used. Data on the use of caffeine, alcohol and tobacco will also be collected. The participants most recent Vitamin D level will also be obtained from their medical record. This will be collected in order to assess whether response to light therapy differs amongst patients with differing levels of vitamin D deficiency. Studies in patients with MS fatigue show mixed results regarding the relationship of fatigue with vitamin D level and supplementation [19-21].

At the baseline visit, participants will be randomized to BWL or DRL. The research coordinator will be aware of the assignment and will distribute the appropriate light therapy boxes during the visit. The PI and research physician will be blinded to treatment assignment so as not to bias follow-up visit assessments. The group assignments will be kept in an excel file that only the research coordinator has access to to maintain blindedness.

After randomization the subjects will begin the study period. The study period will include a 2-week baseline period without any light therapy treatment, a four week treatment period and a four week follow-up (wash-out) period. Throughout the study period, participants will record their fatigue using the Visual Analogue Fatigue Scale (VAFS) four times daily, starting after waking up, and

every four hours thereafter (at least 3x per day). The VAFS is a simple, validated 10-point scale ranging from 1 to 10 in which participants can report their fatigue as a snapshot at that particular moment.[18] Data collection will occur by participants in self-report fashion on paper that will be returned to the study staff at then end of the study period. During the entirety of the study period including baseline and wash-out, patients will also collect a sleep diary which requires filling out once per day (<1 minute). During the four week treatment period patients will record their use of light therapy in a log as well as any side effects they are experiencing. Patients will be instructed to sit in front of the light box with eyes approximately 18.5 inches from the light source. They will use the box for one hour twice per day, in the morning starting two hours after awakening and in the evening starting 3 hours before bedtime. Eyes should be open while using LT but patients do not have to look directly at the light and can eat, read, watch television etc. during use.

There will be two visits with the principal investigator (PI) including the baseline visit described above, a visit with the PI at the end of the treatment period in which participants will perform a FSS, MSQOL-54 and discuss their experiences with LT. Final follow up surveys (FSS and MSQOL54) will be sent using redcap by email following the 4-week washout period. Patients will be reminded not to reveal their treatment assignment to the examining blinded physician.

B. **Device to be used:** The light box used for LT (SunRay by *The Sunbox Company*, Gaithersburg, Maryland, USA) is approximately 15.5" tall x 23" wide x 3.25" deep and is designed to stand on a desk or tabletop. It can be used both in the home or office. The light is delivered at a downward angle to maximize the effectiveness. The box runs on 124 watts and contains full spectrum 5000k 10,000 lux bulbs. Bright light treatment requires at least 2,500 lux to be effective.[17]

The lights are tested by the supply company before distribution to ensure they meet advertised levels of lux output. Lights are turned on by the study team to make sure they work before being provided to study participants. In cases where bulbs burn out, they are replaced with new bulbs purchased from the same supply company.

VI. BIOSTATISTICAL ANALYSIS:

Specific data variables, study endpoints, statistical methods, power analysis

The primary outcome measure will be change in the average FSS after

the 4-week study period in the bright light "active" versus the dim light "control" groups. There are no available data on FSS in response to bright LT in pMS. To test the specific aim of change of ≥15 points, we used the conventional values of α=0.05 and β=0.80 for 2-tailed tests of probability with equally sized groups. For a difference in ≥15 points, with an estimated standard deviation of 15.2 points and mean of 45.9 points from preliminary data collection at the MGH MS Clinic, we require a minimum of 15 people in either group. The primary aim will compare the mean change in FSS scores before initiation and after completion of LT, in an intention to treat analysis comparing the active and control condition groups. The secondary outcome measure will be a change in the global VAFS scores after light therapy in both groups. Frequencies will be used to describe baseline characteristics across treatment arms. X_2 statistics or Fisher's exact test will be used to compare the differences between groups. VAFS will be evaluated using a mixed-effects model which accounts for correlation between repeated measurements. Participant logbooks will be used to generate summary statistics and to graphically display fatigue patterns throughout the day among pMS in both groups. Logbooks will also be used to qualitatively assess the safety and tolerability of LT.

RISKS AND DISCOMFORTS:

Device complications/malfunctions and Psychosocial (non-medical risks)

We anticipate light therapy to be well-tolerated. Potential side effects of light therapy include triggering photosensitivity in those prone to migraines as well as triggering mania in those with a history of mania (mania is an exclusion criteria to trial participation). Patients may find it burdensome to devote two hours per day to light therapy but may also be motivated to try this potential treatment for a disorder with minimal current treatment options. Patients may also find the frequent VAFS tracking burdensome although this has been used successfully in the past in trials of light therapy in Parkinson's disease patients[11]. We do not anticipate device malfunction to lead to any risks or safety issues. Should the device stop working, participants will be given instructions on how to contact the research team to obtain a new device.

VII. POTENTIAL BENEFITS

Potential benefits to participating individuals and to society

Participants may benefit by improvement of their fatigue severity with light therapy. Society and patients with MS stand to benefit if LT is found to be an effective, feasible, and tolerable non-pharmacologic therapy for a very common problem among MS patients for which there are currently limited treatment options. Data gathered from this study will be essential to inform a larger randomized study of LT for fatigue reduction in pMS in general or among subgroups of pMS with promising preliminary results.

VIII. MONITORING AND QUALITY ASSURANCE

A. **Independent monitoring of source data:** If participants in the bright white LT do not self-administer the intervention, it may underestimate the effect of LT. Participants will be called two weeks after the commencement of the light therapy treatment phase by the research coordinator, including addressing challenges to completion of LT. Honest reporting of LT use will be encouraged.
B. **Safety Monitoring:** As above, participants will be called two weeks after the commencement of the light therapy treatment phase to assess for tolerability problems with light therapy. They will be encouraged to contact the research team immediately to report any potential side effects of light therapy. The research coordinator will be available by phone during regular business hours, and the PI will be available to patients at all times by page.
C. **Outcomes Monitoring:** Outcomes including therapy efficacy, tolerability and feasibility will be reviewed at each treatment visit.
D. **Adverse Event Reporting Guidelines:** Patients will monitor adverse events/side effects on a daily basis and will be instructed how to contact the research coordinator or PI at any time to report adverse events. As above the research coordinator will review potential adverse events two weeks after the commencement of the light therapy treatment phase with patients and the research physicians will review treatment/side effect logs at the two post-treatment follow-up visits.

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