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Title: Light therapy for multiple sclerosis-associated fatigue: a randomized, controlled phase II trial

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Abstract

Background: Bright white light therapy (LT) can improve fatigue in several disease states but has not been studied in multiple sclerosis (MS).

Objective: To determine whether controlled home-based LT is feasible, tolerable, and well-adhered to in MS-associated fatigue.

Methods: A randomized, controlled trial of twice-daily 1-hour bright white LT (BWLT) (10,000 lux, active arm) versus dim red LT (DRLT) (<300 lux, control arm) was performed. Adults with MS-associated fatigue were enrolled for 10 weeks: two-week baseline, four-week intervention, four-week washout.

Results: 41 participants were enrolled; 35 were randomized (average age 42 years, 80% female; BWLT n=20; DRLT n=15). 31 were in the intention to treat analysis. The average duration of LT sessions was similar between groups (BWLT: 60.9 minutes, DRLT: 61.5 minutes, $p=0.70$). The most commonly reported adverse event was headache. There were no events that led to discontinuation. Baseline fatigue was severe in both arms (each 53/63 points on the Fatigue Severity Scale (FSS), $p=0.92$). FSS was lower following BWLT (FSS 45.8 post-LT, $p=0.04$; 44.9 and post-washout, $p=0.02$ intra-group compared to baseline FSS) and DRLT (FSS 46.7 post-LT, $p=0.03$; 43.9 post-washout, $p=0.002$ intragroup compared to baseline FSS). There was no difference between BWLT and DRLT groups in the magnitude of reduction of FSS scores ($p=0.81$ after LT; $p=0.77$ after washout for between group comparisons). Similarly, MS quality of life metrics improved in both arms but were not significantly different between groups after LT ($p=0.22$) or washout.

Conclusions: LT is safe, feasible, and well-tolerated in people with MS-associated fatigue. Improvement in both light spectra likely indicates a strong placebo effect for the DRLT group.

Introduction:

Fatigue is the most common symptom in multiple sclerosis (MS)[1-4], with most patients reporting it to be the most disabling of all MS symptoms.[5] After evaluating for treatable comorbid conditions such as hypothyroidism or depression, treatments for MS-associated fatigue are largely pharmacological. Currently prescribed medications include amantadine, amphetamines, and modafinil, with variable evidence for their effectiveness in improving MS-associated fatigue.[6] These medications can be associated with significant unwanted adverse events or potential adverse interactions with other medications. Non-pharmacological treatments for MS fatigue include exercise, cognitive behavioral therapy, and educational programs, for which the long-term evidence of efficacy is limited.[7]

Bright white light therapy (LT), administered by exposure to broad spectrum light repeatedly over time, has been demonstrated to reduce fatigue levels in individuals with seasonal affective disorder,[8] Parkinson disease,[9] cancer-related fatigue,[10] and traumatic brain injury.[11,12] In a 3-year observational study of 203 MS participants in Tasmania, higher sunlight exposure was correlated with reduced fatigue.[13] The authors found no evidence that serum vitamin D levels were associated with fatigue, suggesting that the underlying interplay between light and fatigue in MS occurs independent of the vitamin D pathway.

Mechanistically, light is the most potent synchronizer of the suprachiasmatic nucleus (SCN) to light-dark periods via the intricate connections between photosensitive retinal ganglion cells (ipRGC) and the SCN. The SCN, often referred to as the body's pacemaker, orchestrates circadian rhythms that influence all physiological and behavioral processes.[14,15]

Given the possibility that supplemental light exposure may improve MS-associated fatigue, and the absence of any published reports on this therapy in this patient population, we conducted a

phase II randomized, controlled trial of LT in MS patients. We aimed to determine whether bright white LT (BWLTL) was feasible and tolerable as an intervention in people with moderate to severe MS-associated fatigue. As secondary endpoints, we measured the change in the Fatigue Severity Scale (FSS) score and MS quality of life (MSQOL) scale after a four-week course of LT.

Methods:

Ethical approval: This study was reviewed and approved by the Partners Human Research Committee. Each participant provided individual informed consent. A patient advocate with MS participated in the design, conduct, and reporting of the study. The study was registered on clinicaltrials.gov (NCT03060759).

Recruitment and enrollment: Patients were recruited through the Multiple Sclerosis Clinics at Massachusetts General Hospital and Brigham and Women's Hospital, via study recruitment flyers distributed to outpatient physical therapy practices, through the National MS Society's New England chapter website, and through the Partners online recruitment website, *Rally* (rally.partners.org). Interested patients were screened for eligibility via an online REDCap™ questionnaire.

Study Instruments:

1) The FSS[16] queries fatigue levels through nine Likert scales of agreement (from 1=totally disagree to 7=totally agree). Respondents circle the number that best corresponds to their level of agreement (range 9=least fatigue, 63=most fatigue). The FSS was chosen as a fatigue outcome because it is well represented in the MS fatigue clinical trials literature, was originally designed for use in MS patients, can detect clinically meaningful differences in fatigue with

relative sensitivity, and correlates with other clinically significant factors in MS, such as perceived burden of disease and quality of life.[16-23]

2) The MSQOL-54[24] survey is a 54-item survey querying self-perceived quality of life (QOL) (range 0=lower perceived QOL, 100=higher perceived QOL).

3) The Pittsburgh Sleep Quality Index[25] (PSQI) queries self-reported sleep quality over 19 indices combined into 7 components (range 0=high sleep quality, 21=low sleep quality). A PSQI score above 5 is considered disturbed sleep.

4) The Beck Depression Inventory[26] (BDI) assesses depressive symptom burden. The BDI evaluates depressive symptoms over 20 questions each with 4 possible answers. To reduce the risk of causing undue stress and discomfort, we removed one question from the BDI that queried suicidal ideation (range in this study, 0=no depressive symptoms, 57=most depressive symptoms).

5) The Berlin Questionnaire[27] assesses risk of having undiagnosed sleep apnea via a 10-question survey. Possible scores on the Berlin Questionnaire were: high risk or low risk of undiagnosed obstructive sleep apnea.

6) The Epworth Sleepiness Scale[28] (ESS) assesses excessive daytime sleepiness. The ESS is an 8-component survey that evaluates a respondent's self-reported likelihood of dozing during different times of day (range 0=low sleepiness, 24=high sleepiness).

Study Population:

Inclusion criteria: (1) Diagnosis of relapsing-remitting or secondary progressive MS based on the 2017 McDonald Criteria[29]; (2) age 18-70 years; and (3) fatigue, defined as FSS Score ≥ 36 . [19,30,31]

Exclusion Criteria: Recent change in either (1) antidepressant, (2) anti-fatigue (e.g. modafanil, amantadine, methylphenidate), or (3) MS disease modifying therapy within 4 weeks prior to screening; (4) MS relapse within 4 weeks prior to screening; (5) significant depressive symptom burden defined as BDI score >20 ; (6) history of eye trauma, optic neuritis, or other retinal disease within 3 months prior to screening; (7) history of traumatic brain injury; (8) co-existent sleep disordered breathing, based on a score of “high risk” on the Berlin Questionnaire; (9) significant anemia (<11 g/dL); (11) pregnancy; (12) treatment with photosensitizing medications; (13) history of prior light sensitivity; (14) shift work; (15) history of mania; (16) history of another significant illness that would prevent study completion.

Eligible participants were enrolled at the Neurological Clinical Research Institute at MGH. Confirmation of the diagnosis of MS was made by a study physician based on medical records review at enrollment. An expanded disability scale status (EDSS) score was performed.

Study Intervention: Participants were randomized 1:1 at the baseline visit to either BWLT or DRLT. LT was administered via the *SunRay* desk light box (The SunBox Co., Gaithersburg, MD, USA), containing full-spectrum 10,000 lux bulbs. A single-layer dim-red light filter was used for the control condition. The devices were calibrated to produce 10,000 lux (BWLT) or <300 lux (DRLT).

Study procedures: This trial had 3 segments: a 2-week baseline phase, a 4-week intervention phase, and a 4-week washout phase. At baseline, participants were administered the FSS,

ESS, PSQI, and MSQOL-54. Participants were educated on how to use a light box, and were provided the box at the end of this visit. Participants were requested to complete a sleep diary daily throughout the trial to record 1) hours asleep, 2) number of caffeine uses, 3) number of hours exercised, and 4) number of medication uses in a daily 24 hour period. During the four-week treatment period, participants were instructed to use the box for one hour twice per day, in the morning starting two hours after waking, and in the evening starting 3 hours before bedtime. Participants were instructed to sit in front of the light box with eyes approximately 36" from the light source to achieve desired LT exposure. Phone calls to participants were made at week 4 (two weeks following initiation of LT). During the intervention phase, the participants were asked to log daily LT use.

Participants were evaluated in person at 6 weeks. They were administered the FSS and MSQOL-54 and asked to describe their experience using LT. Participants were evaluated at 10 weeks via an online REDCap™ survey, which included administration of the FSS, MSQOL-54, and qualitative questions in their experience in the study. Each participant received 125 USD.

Blinding: All study physicians were blinded to participant group assignment. Participants were necessarily aware of the color of their assigned light but were told that the goal of the study was to examine the effect of different spectra of light on fatigue. The blinded study evaluator was not aware of the treatment condition when assessing participants.

Outcomes: The primary outcomes were the tolerability, safety, and adherence of the LT intervention. Adherence was measured via participant self-report through a daily adherence log. The secondary outcomes were a preliminary measure of efficacy, as captured by the FSS, the change in MSQOL-54 at the end of LT, and the differences in MSQOL-54 and in FSS post-LT.

Data Analysis: Comparison between participants in the two study arms at the pre-specified timepoints of the study was made using *student's t-tests*. The assessment of tolerability and safety was both qualitative and quantitative based on the severity and frequency of participants' self-reported adverse events. An intention to treat analysis was performed for the impact of LT on the outcome measures of FSS and MSQOL-54 at 6 weeks and 10 weeks and the change in scores between baseline and the end of the LT intervention (6 weeks) and after the washout phase (10 weeks). A two-tailed distribution p-value of <0.05 was considered to be statistically significant.

Data Availability Statement: De-identified data from this study will be made available to qualified investigators upon request to the authors.

Results:

Participant enrollment: Participants were recruited between March 2017 and August 2019. 141 potential participants were screened. Of the 41 participants enrolled, 6 voluntarily withdrew their consent prior to being made aware of their LT assignment, leaving 35 participants randomized to DRLT or BWLT. Twenty participants were randomized to BWLT condition and 15 to DRLT. Participants in the BWLT arm were on average older and had a longer duration of MS, although these differences were not statistically significant. The average age of BWLT-assigned participants was 47.2 years compared to DRLT at 41.9 years ($p=0.13$). The average duration of disease since MS diagnosis was 12.4 years in the BWLT group compared to 8.9 years in the DRLT group ($p=0.20$). (Table 1). The study arms were balanced in terms of gender, ethnicity, baseline EDSS score, and baseline FSS score. At the 6-week timepoint, 2 participants (1 BWLT, 1 DRLT) were lost to follow up, 1 participant (BWLT) voluntarily withdrew from the study due to a lack of perceived effect, and 1 participant (BWLT) was administratively withdrawn for

continuing with LT past the directed time of discontinuation. At the 10-week timepoint, 3 participants (2 BWLT, 1 DRLT) were lost to follow-up and 1 participant in the DRLT group was administratively withdrawn due to a change in anti-fatigue medication dosage in the final 2 weeks of the study. 31 participants had data for the complete intention to treat analysis (Figure 1).

Adherence: Of the 31 participants who completed LT, 4 did not return their logbooks, leaving 27 participants with self-reported adherence data. The average time spent using LT per session among sessions that occurred did not differ between groups (BWLT: 60.9 minutes, standard deviation: 3.2 minutes vs. DRLT: 61.5 minutes, standard deviation: 4.2 minutes; $p=0.70$). Of 840 possible sessions among the BWLT group, there were 111 (13%) completely missed LT sessions (i.e. 0 minutes), 80 of which were among three participants who self-discontinued early. Of 672 possible sessions among the DRLT group, 32 (5%) were completely missed. Two participants in the BWLT and 2 participants in the DRLT group reported completing every session for no less than 60 minutes. On average, 80% of BWLT sessions and 89% of DRLT sessions lasted 60 minutes or more ($p=0.118$). The reason for missing an LT session was not systematically recorded.

Out of all attended LT sessions, 16 were recorded as being under 30 minutes. Of these sessions under 30 minutes, 9 were in the BWLT and 7 were in DRLT. On average, of all attended LT sessions, 99% in BWLT and 99% in DRLT ($p=0.97$) were at least 30 minutes or longer.

Adverse events: There were no serious adverse events or adverse events that led to discontinuation of LT. There were more adverse events in the BWLT arm at both 2 weeks (7 events out of 20 participants, 35%) and 4 weeks (8 events out of 17 participants, 47%) after

starting LT (Table 2). There was one reported adverse event after 2 weeks (1/15 participants, 6%) and 2 adverse events after 4 weeks (2/14 participants, 14%) in the DRLT arm. The most common adverse event was headache. Several participants had a known history of headaches.

Fatigue severity: Fatigue severity was high at baseline (~53 out of 63 points in both study arms). In the BWLT arm, the mean FSS score was reduced to 45.8 after 4 weeks ($p=0.04$) of LT and to 44.9 after the washout period ($p=0.02$, compared to baseline) (Table 3). In the DRLT arm, the mean FSS score was reduced to 46.7 after completing LT ($p=0.03$) and to 43.9 points after the washout period ($p=0.002$, compared to baseline). The mean improvement in FSS scores after LT completion was 6.5 points in the BWLT arm and 7.3 points in the DRLT arm, with no statistically significant difference between the two study arms ($p=0.8$) (Table 3) (Figure 2).

Quality of Life: MSQOL-54 score was moderate and similar at baseline between the BWLT and DRLT arms (58.5 and 55.7 respectively). MSQOL-54 score improved post-LT in both study arms and remained improved after the washout phase. Improvements in MSQOL-54 only reached statistical significance when the entire study population's scores were compared from baseline to post-LT (baseline average: 57.6, post-LT average: 63.6, $p=0.049$). MSQOL-54 scores improved by 7.1 points in the BWLT arm and 4.7 points in the DRLT arm after LT.

Discussion:

We report a randomized, controlled clinical trial of LT for MS-associated fatigue. LT was well tolerated, and participants mostly adhered to their assigned LT regimen. Fatigue level and quality of life improved in both study arms. This trial has several important findings that can inform future research in this area.

First, the use of LT in the MS patient population is feasible. In order to have a homogeneous study population, we employed stringent criteria to include participants who had only MS-associated fatigue, and to the extent possible, excluded other causes of fatigue and sleepiness through our detailed screening process. The requirement to use the light box for 1 hour twice daily for 4 weeks in addition to 6 additional weeks of sleep and fatigue tracking was time-consuming. Many patients were unable to participate given the specific schedule for LT administration and its duration. We were unable to enroll all people living with MS who had interest in the intervention. Therefore, the number and characteristics of patients who would benefit from LT may differ considerably from the number who were eligible to be in this early phase trial.

Second, LT was well tolerated. The most common event was headache. In no case did an adverse event of the LT lead to trial discontinuation. The proportion of adverse events was higher with BWLT. Since headaches are a common occurrence, and a history of headaches was not an exclusionary criterion, it is uncertain whether BWLT exacerbates headaches in participants with a tendency towards them, induces new headaches, or is a spurious finding. Overall, our results were reassuring and did not lead to additional exclusionary criteria for future research.

Third, LT led to an overall reduction in fatigue and an overall improvement in quality of life in *both* study arms. We hypothesized that the BWLT would have a therapeutic benefit on fatigue in people with MS. The control condition of DRLT was not anticipated to reduce FSS or improve MSQOL scores. The impact of DRLT may reflect a placebo response in this group. It is also plausible that LT in our study improved quality of life and fatigue metrics via lifestyle changes imposed on the participants by the study protocol, e.g. the introduction of a significant daily routine around LT administration or heightened awareness of sleep, exercise, and caffeine

patterns. Since both FSS dropped and MSQOL-54 improved, using LT is potentially beneficial to most people living with MS, but the reasons may differ by person. The improvements in FSS scores have clinical significance. In two studies of patients with MS-associated fatigue, it was found that the minimally clinically important difference in FSS scores ranged from 0.45 to 1.9 points on a modified scale out of 7 points.[18,19] The range of 0.45 to 1.9 points in the averaged FSS would therefore correspond to a minimally clinically important difference in a summed FSS of 4.1 to 17.1 points on the scale used here. The average decrease in FSS scores at the end of LT of 6.7 points ($p=0.03$) and 6.2 points ($p=0.07$) in BWLT and DRLT respectively, could reflect clinically meaningful improvements in fatigue.

BWLT is biologically plausible as an intervention that could improve fatigue in MS. Although there is no adequate biomarker to measure MS fatigue, correlations to both cortical gray matter atrophy and thalamic atrophy have been recognized.[20,32] Since people with MS often have a history of optic neuritis, leading to chronic optic nerve atrophy, and reduced light exposure into the eye, BWLT may improve the direct inputs into the circadian rhythm generators that receive signals through the retina. BWLT may also alleviate fatigue and elevate mood in patients with depressive symptoms without MS. Since we excluded patients with moderate to severe depressive symptoms, the impact of LT on people living with both depression and fatigue in MS is not yet known.

The placebo effect is prominent in randomized, placebo-controlled trials of MS fatigue. A 1995 study of amantadine versus pemoline versus placebo found that 52% of MS patients treated with placebo preferred placebo to no drug for fatigue treatment.[21] This exceeded the number of patients who preferred pemoline (32%) but was less than those who preferred amantadine (79%). A separate study of amantadine versus placebo in 32 patients with MS found that 22%

had improved fatigue levels on placebo compared to 63% on amantadine.[33] Similarly, a randomized, placebo-controlled trial of modafinil in 115 patients with MS using the Modified Fatigue Impact Scale found that fatigue scores improved by day 35 in both study arms.[34] The modafinil-treated group showed a score reduction (i.e. reduced fatigue) from 61 to 52 points on average as compared to the placebo group which showed a reduction from 63 to 49 points. Rather than seeing no difference between groups due to no impact of either intervention, analysis of variance for repeated measures over time showed that the difference in fatigue scores from baseline to day 35 was significant in *both* placebo and modafinil-treated groups. In a multi-disciplinary fatigue management program,[22] the placebo intervention program was superior to the multidisciplinary program (44% placebo versus 17% in the designed program). Other studies, including a range of fatigue interventions, have reported similar findings.[23,35,36] This placebo effect may reflect a variety of situations but appears across pharmacological, educational, and device studies. It is also consistent across different measurements of fatigue, study years, and study countries of origin. Rather than a lack of measurable response to any interventions, patients with MS often report a strong placebo response, necessitating a very high magnitude of effect from an intervention to exceed it.

Our study had several limitations. We did not exclude participants with hypothyroidism, insomnia, or non-acute optic atrophy or visual impairment. These factors may have altered treatment outcomes. We did not have the statistical power to assess small effects of BWLT vs. DRLT on FSS. This would require >100 participants. We were unable to control for seasonal effects or time of calendar year. Several participants did not complete the study at 10 weeks for multiple reasons including medication changes. Not all reasons were unfavorable since one participant refused to discontinue LT because it was perceived to be helping too much to stop using it. Our trial enrolled during the introduction of several new-to-market disease modifying therapies, limiting the number of people who could enroll if they were awaiting a DMT switch

through their insurer. We enrolled participants across all DMTs, phases of MS, and included people stable on a current symptomatic medication. This heterogeneous group improves generalizability but limits our understanding of specific aspects of the disease course in detail. Due to our low sample size, we were unable to perform subgroup analyses, for example on patients with or without a certain disease characteristic. Our participants were overall severely fatigued. We are uncertain whether LT would have similar impacts across milder fatigue levels and in different patient populations, e.g. considerably younger or older groups.

We did not set participant withdrawal criteria for non-adherence or changes to participants' daily caffeine, sleep, or exercise regimens. This was done in the interest of evaluating tolerability and feasibility of LT as an intervention in a real-world pragmatic study design; however, more stringent withdrawal criteria could have avoided potential confounders. By using a randomized study design, we anticipate that both measured and unmeasured confounding variables, both anticipated and unanticipated, would be balanced across study arms. We did not systematically record participants' reasons for missing an LT session. On the daily adherence logs, participants had space to record any side effects experienced that day; however, recording of side effects did not necessarily indicate that the participant skipped a session, nor did skipping a session necessarily indicate that the participant did so due to side effects. Finally, we relied on participant self-report to confirm completion of LT, rather than a more objective measure such as wearable sun and light tracking actigraphy options that measure environmental light exposure. We did require participants to record the actual distance from the light box that they used even though specific instructions on distance were provided. This potentially altered light intensity exposure and outcomes for this home-based intervention.

Our study also had several notable strengths. We used a robust study design to demonstrate that LT is both feasible and tolerable in most people with MS who choose to engage in a pre-defined intervention of LT. Our study participants are generally representative of MS patients in

an ambulatory practice in this setting in terms of gender, ethnic background, age, and disease severity. We have demonstrated that LT has a favorable impact on fatigue and have demonstrated a likely strong placebo effect. The placebo effect in non-pharmacological interventions in MS symptomatic management is not well studied but is likely strong, and changes the degree to which an intervention must demonstrate efficacy in order for it to show a statistically significant difference in people living with MS.

Future research in MS using LT could take several possible directions. A larger, randomized, double-blinded trial could determine whether BWLT is efficacious for the reduction of MS fatigue, including a trial of different durations, frequencies, and wavelengths of light exposure. MSQOL-54 scores improved in both study arms, leading to a question on the role of documentation, tracking, and self-awareness of sleep and fatigue and its potential impact on favorable outcomes, regardless of an intervention. The role of optic nerve atrophy and history of optic neuritis, as measured through optical coherence tomography as well as the relationship to MRI-based variables such as cortical gray matter atrophy, white matter lesion burden, and the location of lesions along hypothesized fatigue circuitry could be studied through advanced brain imaging in tandem with LT. Finally, electronic tracking of fatigue and sleep could provide more data than self-reported measurements have yielded, including inferences on the relationship to physical activity level, sun exposure, and sleep quality.

Taken together, we provide phase II trial data on the tolerability, feasibility, adherence, and preliminary efficacy of controlled LT in the MS population affected by severe fatigue. Given the few options for MS patients with this disabling symptom, and the safe, inexpensive, and well-tolerated nature of self-LT, we advocate for further studies of this non-pharmacologic intervention for MS.

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Declarations:

Conflicting Interests: The authors declare that there are no conflicts of interest.

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Ethics approval: This study was reviewed and approved by the Partners Human Research Committee.

Consent to participate: All participants provided written informed consent prior to enrollment.

Consent for publication: Not applicable.

Availability of data and material: Study data will be provided upon reasonable request to qualified investigators by the authors.

Code availability: Not applicable.

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Figure Legend:

Figure 1.

- Title: Diagram of participant flow through study

Figure 2.

- Title: Reported FSS score at three time-points
- Legend: BL = baseline, FU1 = follow-up 1, FU2 = follow-up 2

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Table 1. Demographic and Disease Characteristics at Baseline			
Characteristic	BWLT (n=20)	DRLT (n=15)	<i>p</i> ^a
Age - yr			
Mean (range)	47.2 (32-64)	41.9 (25-60)	0.133
Median (25th,75th percentile)	46.5 (41.3 - 54.5)	43 (35-49.5)	
Female sex - no. (%)	16 (80)	12 (80)	
Type of multiple sclerosis - no.(%)			
Relapsing-remitting multiple sclerosis	20	15	
Primary-progressive multiple sclerosis	0	0	
Time since first diagnosis – yr (as of 2020)			
Mean (range)	12.39 (1.00-30.00)	8.93 (2.00-20.00)	0.202
Median (IQR)	12.00 (11.75)	6.00 (9.25)	
Expanded Disability Status Scale			
Mean (range)	3.1 (1-6)	3.1 (1-6.5)	0.878
Median (25th,75th percentile)	3.0 (2.3-4)	2.5 (2-3.5)	
Beck Depression Inventory (0-57)			
Mean (range)	7.25 (2-20)	9.7 (1-21)	0.262
Median (25th,75th percentile)	6.5 (4-8.75)	7.0 (5-14)	
Epworth Sleepiness Scale			
Mean (range)	9.6 (2-27)	10.8 (0-18)	0.540
Median (IQR)	9.5 (6-12)	12.0 (6.5 - 15)	
Pittsburgh Sleep Quality Index ^b			
Mean	8.40 (4-13)	10.21 (3-20)	0.270
Median (IQR)	9 (5.75-11)	10.00 (6-13.50)	
Ethnicity			
Hispanic or Latinx	1	2	
Not Hispanic or Latinx	19 ^c	13 ^d	
Race			
Black or African American	1	3	
White	18	10	
Other	1 ^e	2 ^f	
^a Two-tailed <i>student's t-tests</i> for comparison of independent samples. ^b 1 participant chose not to complete this survey. ^c 2 participants preferred not to answer. ^d 1 participant preferred not to answer, 1 participant did not answer. ^e 1 participant preferred not to answer. ^f 1			

participant preferred not to answer, 1 participant did not answer.

	Baseline		Intergroup <i>p</i>	6-Week Followup (post-LT)		Intergroup <i>p</i>	10-Week Followup (post-washout)		Intergroup <i>p</i>
	BWLT (n=20)	DRLT (n=15)		BWLT (n=17)	DRLT (n=14)		BWLT (n=15)	DRLT (n=12)	
Mean FSS	52.600	52.867	0.918	45.824	46.714	0.814	44.933	43.917	0.769
Mean change in FSS from BL (within group <i>p</i>)	-	-	-	-6.529 (0.043)	-7.286 (0.030)	-	-6.4 (0.015)	-10.25 (0.002)	-
Mean change in FSS from 6-week follow-up (within group <i>p</i>)	-	-	-	-	-	-	0.867 (0.813)	-1.583 (0.413)	-
Mean MSQOL-54 Avg.	58.489	55.703	0.467	66.257	60.506	0.224	62.816	63.566	0.877
Mean change in MSQOL-54 Avg from BL (within group <i>p</i>)	-	-	-	7.136 (0.055)	4.734 (0.356)	-	4.264 (0.295)	5.259 (0.153)	-
Mean change in MSQOL-54 Avg from 6-week follow-up (within group <i>p</i>)	-	-	-	-	-	-	-4.266 (0.397)	0.801 (0.586)	-

All *p*-values were calculated using a two-tailed *t*-test for the means of two independent samples.

Table 3. Adverse Events at 2 and 4 weeks				
	BWLT		DRLT	
	2 weeks (n=20)	4 weeks (n=17)	2 weeks (n=15)	4 weeks (n=14)
Any adverse events ^a - n(%)	7 (35)	8 (47)	1 (6)	2 (14)
Adverse event leading to discontinuation of trial	0	0	0	0
Difficulty sleeping	1 (5)	2 (12)	0	0
Dizziness	1 (5)	0	0	0
Eye Issues				
Eye strain	0	0	1 (6)	0
Difficulty with night vision	1 (5)	0	0	0
Tearing issues	0	0	0	1 (7)
Fatigue ("worn out")	1 (5)	0	0	0
Headache	2 (10)	6 (35)	0	1 (7)
Hot flashes	1 (5)	0	0	0
^a Adverse events were queried at two timepoints: halfway through LT and at the end of LT				