

Official title:

Blocking nocturnal blue light to treat insomnia: A pilot randomized controlled trial

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Study Design:

The current proposal is for a randomized, placebo-controlled, crossover trial to test the effects of blocking nocturnal blue light exposure on sleep, sleep habits, and melatonin secretion in individuals with insomnia. This will be a combined ambulatory and laboratory investigation. The intervention will consist of wearing BB lenses which block 97% of blue light (Uvex amber lenses, Bandit wraparound glasses, Honeywell Safety, Smithfield, RI) or non-BB placebo lenses (Uvex clear lenses, Bandit wraparound glasses, Honeywell Safety, Smithfield, RI) for the 2 h preceding bedtime each night for 1 wk (**Fig. 2**). Intervention phases will be separated by a 4-wk washout period, to reduce carry-over effects and study premenopausal women at the same menstrual cycle phase. This will be followed by crossover to the alternate intervention phase. Each 1-wk intervention phase will conclude with an in-

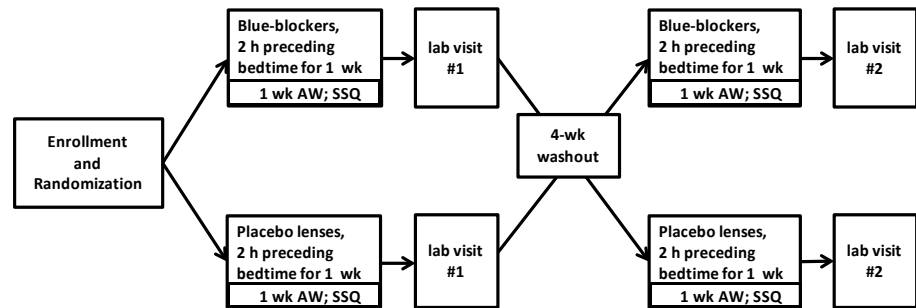


Figure 2. The randomized, placebo-controlled, crossover design. AW: actiwatch; SSQ: subjective sleep quality.

patient laboratory visit to characterize the effects of the intervention on sleep and circadian physiology (**Fig. 3**). During the ambulatory portion, participants will be free-living and will expose themselves to their habitual light levels and choose their sleep timing. During the laboratory portion, an 8-h sleep episode will be scheduled based on participant's habitual sleep times during the week preceding entry. For standardization, and to demonstrate the beneficial effects of the BB lenses for preserving nocturnal melatonin secretion, participants will be uniformly exposed to an LED light source for 2 h preceding bedtime during the laboratory portion (**Fig. 3**).

Potential participants who reply to posted advertisements will be told about the study. They will then be scheduled to meet with research staff to sign consent forms and determine eligibility. Inclusion criteria will include age 18-65 y, and a report of insomnia for ≥ 1 month. To determine insomnia, participants will have scores indicative of the case definition of insomnia based on the Insomnia Symptoms Questionnaire. This validated questionnaire assesses the presence, frequency, and duration of symptoms, as well as daytime consequences. Symptoms assessed include difficulty initiating sleep, difficulty maintaining sleep, and experiencing sleep that is unrefreshing. Participants with a diagnosis of obstructive sleep apnea of at least moderate severity (apnea-hypopnea index ≥ 15 events/h), a STOP-BANG score > 5 indicative of a high risk of sleep apnea, or other sleep disorders such as periodic limb movement disorder or narcolepsy will be excluded. History of deep vein thrombosis will be exclusionary. Night or rotating shift workers, those who have traveled across time zones in the 2 wk preceding procedures, will be excluded, since these can affect circadian physiology. Participants will be free of any psychiatric or neurological disorders, as these can affect sleep/circadian rhythms. Participants will be excluded if they are smokers or taking beta-blockers (26), since these decrease melatonin release, or if they consume excessive caffeine (>500 mg/d). Hypnotics/sedatives for sleep can have been used, but participants will refrain from use for 2 wk preceding the start and throughout

the study. Participants with children <1 y-old will not be included. Women will not be pregnant or breastfeeding. CUMC research staff will be involved in the recruitment and enrollment efforts.

Individuals meeting inclusion criteria will be enrolled and randomized to receive either BB or placebo lenses in phase 1. Participants will be instructed to wear lenses each night, from 2 h before bedtime until lights out. Throughout the intervention, upon awakening participants will note their bedtime and waketime, and time of wearing lenses, on a sleep-log, and will complete a daily post-sleep questionnaire (**PSQ**). The PSQ entails quantitative estimates of SOL, total sleep time (**TST**), time awake during sleep episode, and number of awakenings, as well as ratings on a 7-point scale of overall evaluation of sleep (1: extremely bad, 7: extremely good), soundness of sleep (1: extremely light, 7: extremely sound), current feeling of sleepiness (1: not sleepy at all, 7: extremely sleepy), and current feeling of refreshed (1: not refreshed at all, 7: extremely refreshed) (42). This will allow us to confirm compliance with intervention and to collect data on ambulatory sleep quality and habits across the trial. During each intervention, participants will wear a wrist-mounted Actigraph GT3X+ to monitor TST, SOL, and sleep efficiency (**SE**). At the beginning of the intervention, participants will complete a brief computer-based adaptive neuropsychological battery (NIH Toolbox Cognition Battery; www.nihtoolbox.org) to assess their functioning in the domains of executive function, attention, episodic memory, language, processing speed, and working memory. This assessment will last about 30 minutes. CUMC research staff will interact with participants and setup the study.

Upon completing the 1-wk intervention, participants will be admitted to the Inpatient Unit at the Clinical Research Resource (CRR) of CUMC at ~18:00 for the lab testing period (Fig. 3). Upon admission, an in-dwelling forearm catheter will be inserted to allow continuous blood sampling which will not interrupt the sleep episode. Blood (3 ml/sample) will be collected continuously (1x/h) from 19:00-09:00 under “constant posture conditions”. Participants will remain in dim lights (<30 lux) and in a semi-recumbent position during wakefulness. The sleep episode will occur in total darkness in a fully recumbent position. In lieu of meals, small isocaloric servings of BOOST Plus Complete Nutritional Drink (Nestle) will be served each hour during wake episodes. Participants will be asked to stretch their legs each hour while in the bed during the lab portion, without getting out of bed.

Within the first 2 hours of arrival in the lab, participants will complete the Pittsburgh Insomnia Rating Scale-65 (**PIRS65**), which quantifies insomnia symptom severity. They will also repeat the same brief (~30 min) neuropsychological battery (NIH Toolbox Cognition Battery) administered at the intervention. Each hour spent awake in the laboratory, participants will complete a 15-item visual analogue scale (**VAS**) to assess their levels of alertness, hunger, and appetite. CUMC research staff will interact with participants and conduct the study/collect data.

Beginning 2 hours before the sleep episode, participants will be exposed to bright light (500 lux) and will wear either BB or placebo lenses. The sleep episode will be scheduled based on their habitual sleep patterns during the previous week at home. They will have an 8-hour sleep opportunity in the lab. This will include a polysomnographic sleep recording. Upon awakening, participants will remain in bed in semi-recumbent position for the next 3 hours. Participants will complete the PSQ, and will resume the VAS scales, as well as have servings of BOOST Plus. At

9:00, blood sampling will end and the catheter will be removed. Participants will be discharged at 10:00. Blood samples will be analyzed for plasma content of melatonin (RIA, ALPCO, Salem, NH). After discharge, participants will begin a 4-week washout period. At the conclusion of this, they will cross over to the alternate lenses condition. They will be given the alternate lense type (BB or clear) and also the actigraph for the 7-day ambulatory tracking period. They will resume using the lenses 2-h before bedtime for 7 days, and completing the sleep-log and post-sleep questionnaires. After this, they will return to the lab for the second overnight visit. At the conclusion of the second overnight visit, they will have completed all experimental procedures.

Statistical Procedures:

Two-way within subjects ANOVA for repeated measures (factors: condition x time) will be used to analyze continuous melatonin, VAS, and neuropsychological values obtained during the laboratory visits. Simple main effects tests will be used to analyze significant interactions. Paired-samples t-tests will be used to analyze single-value sleep parameters (subjective, actigraphic, and PSG), as well as sleep related questionnaires (PIRS65 and PSQ). Data will be tested for normality, and non-parametric equivalent tests will be used if data are deemed not normally distributed. Significance will be $p < 0.05$