

Original Trial Protocol

Study objectives

The primary aim of this study is to determine if an ongoing curriculum-based MBI that is available to the general community, Mindful Awareness Practices (MAPs), leads to greater improvements in sleep quality, represented by reductions in global Pittsburgh Sleep Quality Index (PSQI) score, compared to SHE in older adults with sleep disturbances. We anticipate that SHE will improve sleep, but that MAPs will lead to greater improvements in PSQI scores. In order to accomplish this aim we will test the treatment effect of MAPs in comparison to SHE on PSQI scores. Secondary aims are to test if MAPs versus SHE leads to relative improvements in sleep-related daytime impairments (i.e., insomnia, fatigue, depressive, stress, and anxiety symptoms) as well as levels of Nuclear Factor (NF)- κ B. NF- κ B is a transcription factor that regulates genes responsible for the inflammatory response.

Study Design

In older adults with sleep problems, this single-site, parallel-group randomized controlled trial with a pretest and immediate posttest design will test the relative effect of the MAPs to SHE program for improving sleep and secondary outcomes of daytime impairment. Participants will be randomized into one of two experimental conditions: (1) the MAPs course at the University of California, Los Angeles or (2) sleep hygiene education (SHE). Both study conditions will be comprised of a standardized 6-week group-based intervention administered at the UCLA Westwood Medical Campus. The UCLA Institutional Review Board has approved all study procedures. This trial will be registered at clinicaltrials.gov.

Participants

Participants will include older adult community volunteers between the ages of 55 and 90 (an

average age of 65 is expected). Participants will be recruited over a six-month period through advertisement in the local newspaper and flyers posted at our university medical center and affiliated clinical institutes located in Los Angeles, CA. Trained data collectors will screen all interested participants via a 15-minute telephone interview to ascertain sleep problems and study eligibility. Participants will be compensated up to \$50 in gift cards and will receive parking vouchers for each visit at the medical center. Eight visits will be requested, including 1 pretest assessment, 6 intervention sessions, and 1 post-test assessment.

Power Analysis

A priori power analysis was conducted in Gpower, and is based on previous research showing that MBIs and psychoeducational interventions can have between-group medium- sized effects on self-reported sleep quality (e.g., PSQI) in adults with sleep problems.[23] Given 80% power, $p < .05$ (two-sided), 2 treatment groups with 2 assessment points, and a .60 test-retest r (PSQI),[24] the estimated final sample size needed to detect a significant effect is 42. Based on our previous research with older adults, an attrition rate of ~10% is anticipated, making our target enrollment 47.

Eligibility Requirements

Inclusion criteria: Participants will be eligible for the study if they experience active insomnia symptoms as indicated by a PSQI score > 5 , [25] are 55 years of age or older, and agree to randomization to conditions. Those who are eligible will be community-based volunteers who will self-enroll based on their sleep disturbances. Exclusion criteria: Participants will be ineligible for the study if they have an inflammatory disorder, illness, or infection (e.g., autoimmune disease, type 1 diabetes, Hepatitis C, cancer, acute infection in past 2 weeks), significant current practice of any form of meditation (>15 minutes per day), [26] cognitive impairment (Mini-Mental State Examination, MMSE < 26), [27], current unresolved sleep apnea diagnosis, inability

to speak English, current smoking and/or substance dependence, class II or greater obesity (BMI > 34.9), and depression (Patient Health Questionnaire, PHQ-9 > 14). Class II obesity and depression are set as exclusion criteria to prevent confounding, due to the association between depression and sleep disturbance [28] and because of the effect of both depression and obesity on inflammatory markers.[29, 30] Trained study staff will complete the eligibility assessments at initial contact to participants over the phone in a one-to-one interview. During this initial contact, PSQI and illness exclusions will be assessed to ensure eligibility. The MMSE and BMI measures will be completed during a one-to-one visit by trained data collectors at a follow-up assessment. Participants that remain eligible from the MMSE and BMI assessment will complete the baseline survey at the same visit. The remaining eligibility criteria will be collected by self-report.

Randomization

Using a computer-generated randomization table, a treatment-blinded statistician (R.O.) will randomize enrollees to treatment conditions. The randomization procedure will use a computer generated 1:1 ratio. Group assignment will be concealed from participants and study staff.

Interventions

Intervention phases will occur during a six-week period. Participants in each condition will attend weekly 2-hour group-based classes for a total of 6-weeks. Treatment fidelity will be assessed by check box lists that teachers in each condition will use to report the components of the standardized lessons that are delivered.

Mindful Awareness Practices (MAPs)

MAPs is a weekly, 2-hour, 6 session, group-based manualized course in mindfulness meditation which is available for community residents to take in-person within the Los Angeles area or

online. A certified teacher with over 20 years of mindfulness practice will deliver the program curriculum to participants. Session titles by week include: (1) Introduction to mindfulness, (2) Listening, embodiment and obstacles, (3) Working with pain, (4) Difficult emotions and cultivating positive emotions, (5) Thoughts and mindful interactions, and (6) Loving kindness and class wrap-up. Mindfulness exercises embedded in the curriculum include mindful sitting meditation, body scan meditation, eating meditation, daily life meditation, relational mindfulness, appreciation meditation, loving-kindness meditation, walking meditation, standing meditation, and movement meditation, and practices to develop positive emotions. An average of 10 to 30 minutes of mindful experiential practice is engaged in during each class in addition to the teacher-delivered didactic material and group discussion. Participants are also provided with a textbook on mindfulness accompanied by a meditation compact disc.[31] Mindfulness practice is assigned as homework beginning with 5 minutes daily and advancing to 20 minutes daily at program's end. The MAPs curriculum will not include any sleep-specific content.

Sleep Hygiene Education (SHE)

SHE is a weekly, 2-hour, 6 session, group-based manualized course in sleep hygiene and sleep education developed by the lead author (DSB) that matches the MAPs condition for time, attention, group interaction, and expectancy of beneficial effects. A trained health educator with a Master of Public Health degree will deliver the program curriculum to participants. Active components of the SHE seminar include increasing knowledge of sleep biology, characteristics of healthy and unhealthy sleep, sleep problems, stress biology and stress reduction, relaxation methods for improving sleep, self-monitoring of sleep behavior, and weekly tips for better sleep. Educational and behavioral change content is based on the National Sleep Foundation's tips for better sleep, including changing poor sleep habits, avoiding stimulants such as coffee and tea near bedtime, exercise and relaxation, adequate exposure to natural light, establishing a relaxing bedtime routine, and modification of sleep environment to be relaxing and not

distracting.[32] Practice of the sleep hygiene behaviors and reading on healthy sleep is assigned as homework each week of the intervention to match the homework assigned in the MAPS condition.

Assessments and Measures

All assessments and classes will be completed at the UCLA Medical Center at the Cousins Center for Psychoneuroimmunology. Eight visits to the study site will be requested, including 1 pre-treatment assessment visit, 6 intervention sessions, and 1 post-treatment assessment visit. Pre- and post- treatment visits will include body measure assessment (i.e., height, weight, waist and hip circumference), administration of self-report questionnaires, and blood draw via venipuncture. Measures will be completed prior to the intervention and immediately post-intervention.

Sleep Quality

For the primary outcome, self-reported sleep quality will be measured with the Pittsburgh Sleep Quality Index (PSQI),[25] a validated 19-item self-report questionnaire that assesses sleep disturbances over the past month. The questionnaire assesses seven domains including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep-related medication use, and daytime dysfunction, which are quantified into a global score (range: 0–21). Lower scores indicate better sleep quality.

Sleep-related Daytime Impairments

For the secondary sleep-related daytime impairment outcomes, insomnia symptoms, depressive symptoms, anxiety symptoms, perceived stress, and fatigue symptoms will be assessed using self-report measures. Insomnia symptom will be measured with the Athens Insomnia Scale (AIS),[33] a validated 8-item self-report questionnaire that assesses sleep difficulty. A sum score

is calculated (range: 0–24), with lower scores indicating less sleep difficulty. Depressive symptoms will be measured with the Beck Depression Inventory-II (BDI-II),[34] a validated 21-item questionnaire that assesses depressive symptom severity over the past two weeks. A sum score is calculated (range: 0–64), with lower scores indicating less depression. Anxiety symptoms will be measured with the Beck Anxiety Inventory (BAI),[35] a validated 21-item questionnaire that assesses anxiety severity over the past month. A sum score is calculated (range: 0–63), with lower scores indicating less anxiety. Perceived stress will be measured with the Perceived Stress Scale (PSS),[36] a validated 10-item questionnaire that assesses the degree to which one appraises life situations as stressful over the past month. A sum score is calculated (range: 10–50), with lower scores indicating less stress. Fatigue symptoms will be measured with the Fatigue Symptom Inventory (FSI),[37] a validated 14-item questionnaire that assesses fatigue. Two sub-scales are yielded from the FSI, FSI-Interference and FSI-Severity. FSI-Interference (a sum score of 9 items, range: 0–90) assesses the degree to which fatigue has interfered with daily life over the past week, with lower scores indicating less interference of fatigue on daily life. FSI-Severity (a sum of 4 items, range 0–40) assesses the severity of fatigue experienced over the past week, with lower scores indicating less severe fatigue.

Blood Draw and Inflammatory Assay

Covariates

For the secondary inflammatory signaling outcome, blood will be collected via venipuncture between 8:30AM and 11:30AM by a certified phlebotomist while the participant is in a normal sitting and upright resting state. Whole blood samples will be collected by venipuncture into Cell Preparation Tubes with sodium citrate anticoagulant (BD, Franklin Lakes, NJ), held at room temperature and processed within two hours to obtain peripheral blood mononuclear cells (PBMC) according to the manufacturer's protocol. Nuclear extracts will be prepared using 6–10

million PBMC, then stored at -80°C as previously described. [38] Total protein concentration of each nuclear extract will be determined using a Pierce 660 nm Protein Assay (Thermo Scientific, Rockford, IL). Concentrations of activated NF- κ B p65 in pristine aliquots of nuclear extracts will be determined using the TransAM NF- κ B p65 ELISA kit (Active Motif, Carlsbad, CA) with recombinant NF- κ B p65 (0.3–10 ng/well) as the reference standard. Each extract will be assayed in triplicate at 1–4 μg total protein per well. A positive control (stimulated Jurkat cell extract) provided by the manufacturer will be included in each assay at 2.5 μg /well. NF- κ B concentrations will be expressed as ng p65/ μg total protein.

Demographic covariates to be measured will include age, gender, ethnicity, education, income, occupation, and marital status. Biobehavioral covariates will include substance use, BMI, and waist-to-hip ratio. Treatment compliance/fidelity will be assessed in both conditions with a standardized teacher-completed checklist of activities completed during each treatment session.

Statistical analyses

Analyses will be performed in SPSS v21 (IBM Corp., Armonk, NY). Between-group change in mean PSQI score at post-intervention will be the primary outcome in the intent-to-treat population. Between-group contrasts in outcomes across the intervention period will be tested using generalized linear mixed modeling (MIXED command) with pairwise comparisons, adjusted for pre-intervention levels of the outcome. Other covariates that have at least a marginally significant correlation ($p < .10$) with both the predictor and outcome variable will be adjusted for in the models if substantively relevant. Estimated mean differences and bias corrected effect sizes (Hedge's g) with their 95% confidence intervals will be provided. We will assess whether data provide evidence of benefit of MAPs versus SHE on sleep quality (PSQI) and secondary daytime impairment/inflammatory signaling outcomes. Value comparisons of baseline PSQI scores between those with and without missing data at post-intervention will be

compared with t-tests.