Official title: Napping, Sleep, Cognitive Decline and Risk of Alzheimer's Disease

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SleepTIGHT Statistical Analysis Plan

(Sleep Therapeutics Intervention to improve coGnitive HealTh)

Full Study Title: Napping, Sleep, Cognitive Decline and Risk of Alzheimer's Disease

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STUDY AIMS

The overall objective is to develop a CBT-I program for people with MCI/ mild Alzheimer's disease and sleep disturbances, pilot test its feasibility, and elucidate its preliminary effects on sleep, cognition and quality of life, with the ultimate aim of decreasing risk of Alzheimer's onset or progression.

Aim 1: To develop a CBT-I program and test its feasibility and acceptability in patients with MCI/ mild Alzheimer's disease and sleep disturbances.

Aim 2: To elucidate the effects of the CBT-I program on patients' subjective and objective sleep quality.

Exploratory Aim: To collect pilot data and explore preliminary effects of 1) the CBT-I program on cognition and quality of life and 2) involving caregivers in the program.

PROCEDURES

We plan to study older adults (aged 65 and above) with MCI or mild AD. Patients will be identified from a combination of online sources, including the UCSF CTSI Electronic Health Record services (MyChart), Researchmatch.org and social media postings, as well as the UCSF Memory and Aging Center (MAC, Director: Dr. Bruce Miller, co-founders include Dr. Kristine Yaffe). *The attached figure* outlines the study visits and related measurements.

1. Baseline screening/ Randomization
When a potential participant is identified or expresses interest in the study, study staff will contact them to explain study procedures and go through the key points of the consent form. Once consented, study staff will administer clinical interviews via zoom to assess insomnia, medical history, mood and QDRS-derived global CDR to determine eligibility and obtain visual proof of written informed consent. Eligible participants who consent will be scheduled for a baseline assessment via zoom within 2 weeks of enrollment. The measures described above will also serve as part of the baseline measures.

Baseline Visit: At the baseline zoom visit, study staff will administer detailed assessment of sleep quality, quality of life and cognitive function, using the Pittsburgh Sleep Quality Index (PSQI) (general sleep quality), Epworth Sleepiness Scale (excessive daytime sleepiness), the 36-Item Short Form Survey (SF-36) (quality of life) and a standardized battery of neurocognitive tests selected for their sensitivity in evaluating multiple potentially relevant cognitive domains, feasibility of administration during either in-person or telehealth visits, and manageable burden to participants and study personnel in the setting of a full-scale randomized trial. In addition, study staff will give detailed instructions on the use of sleep assessment device (Actiwatch Spectrum® from Philips Respironics, Inc for the measure of 24-h sleep-wake activities) and the corresponding sleep diary (questions such as bed time, wake time, nap times, and any times when watch is removed and for what reason).

2. Intervention (9 weeks). We will randomize patients, using computer-generated random numbers, to one of two treatment arms: a) an FDA-authorized prescription digital CBT-I therapeutic called the Somryst or b) an interactive, attention-matched, internet-based placebo control program. At the beginning of the intervention, study staff will give instructions on the use of the programs via zoom. Throughout the intervention, study staff will call the participants weekly to give further clarifications and answer questions. Somryst is a 9-week program that delivers digital CBT-I therapeutic content, and can be used on a mobile device, such as a smartphone or tablet. CBT-I is a neurobehavioral treatment which focuses on addressing the maladaptive behaviors, routines, and dysfunctional thoughts that perpetuate sleep problems, regardless of the cause of sleep problems. CBT-I is typically delivered by a specialty-trained clinician, either 1:1 or in group format. Standard delivery of CBT-I usually occurs in weekly sessions over 6-8 weeks. CBT-I can be conceptualized as six sessions or cores that deliver proven behavioral and cognitive treatment strategies. The Somryst program is intended to deliver 6 treatment Cores, with the following specific CBT-I therapy content: 1. Get Ready: This Core sets the stage for the therapeutic experience. It lets the participant know what they will need to learn and do to improve sleep and sets goals for success. 2. Sleep Window: This Core focuses on the concept of sleep restriction and identifies a Sleep Window - a recommended Bedtime and Arising Time – the participant should follow. 3. Behaviors: This Core focuses on stimulus control and establishes guidelines for participants to follow while implementing their Sleep Window. 4. Thoughts: This Core explains how a participant's thinking can contribute to insomnia. The participant will learn to identify, and shift thought patterns. 5. Education: This Core helps the participant identify changes to be made in their lifestyle and environment that can promote better sleep. 6. Looking Ahead: This Core pulls together what the participant has learned, prepares the participant for the future, and teaches them what to do if they experience a relapse. Somryst also includes a daily Sleep Diary in which the participant records information about their sleep.

3 Follow-up and outcome measures. The primary goal of this research is to pilot test the feasibility of implementing this CBT-I program in patients with MCI or mild AD. Following the last session of CBT-I, participants will be asked to report their satisfaction and acceptability of the treatment. We will also assess eligibility, consent, and retention rates, as well as data quality and completeness. To explore the initial effects of this treatment on sleep and cognition, we will repeat baseline measurements, including the neuropsychological battery and the questionnaires (ISI, PSQI, ESS and SF-36) towards the end of the intervention.

STATISTICAL ANALYSES

To assess the randomization, baseline demographic and clinical characteristics will be compared between arms using parametric (e.g. t-test) or nonparametric test (e.g. chi-square, Wilcoxon tests); variables that are not balanced across treatment arms will be adjusted for in subsequent analyses. The primary analysis will use the intent-to-treat principle. Secondary subgroup analyses will assess the role of treatment adherence on outcomes, using measures of compliance applicable to both study arms, thus avoiding the well-known biases of a "compliers only" analysis.

For Aim 2 and the Exploratory Aim, we will use t-tests, Wilcoxon or chi-square tests to compare between the treatment and non-treatment groups the change scores in: 1) circadian rhythms parameters (e.g. amplitude, and overall rhythmicity); 2) frequency and length of day naps; 3) quality of nocturnal sleep (e.g. change in ISI scores; increased sleep duration and efficiency; decreased sleep onset time); 4) reported quality of life (SF-36 scores); 5) cognitive scores. Standardized measures of cognitive performance (z-scores) will be calculated for each participant for each neuropsychological test in the battery. Repeated measures models will be used to examine longitudinal treatment effects. These models will include subject-specific (i.e. intercept term) and fixed effects (treatment group, time and the time*treatment interaction). A significant time*treatment interaction will indicate that changes in outcome measures over time are different in the treatment arms. In order to explore the impact of involvement of caregivers, we will repeat the above analysis between the treatment group with and without involvement of the caregiver. The resulting estimates will be imprecise, and thus useful for trial planning only in combination with external data, expert opinion, and established norms for clinically meaningful effects.