Awareness and Self-Compassion Enhancing Narcolepsy Treatment (ASCENT)

NCT04306952

11/14/2018

Protocol

Overview of Research Plan

The overall approach taken for this R34 follows recommendations for early stage treatment-development activities aimed at establishing the parameters of the intervention and research protocols before conducting a full-scale randomized controlled trial (RCT). Building upon our preliminary data, this project focuses on treatment-development, recruitment, and assessment by conducting a feasibility trial to determine the optimal parameters for adapting and delivering an MBI for people with narcolepsy. The first phase of this project consists of preparatory activities, including completion of the study protocol and training of treatment providers. Phase II consists of a feasibility trial in which 60 individuals will be randomized to receive one of three MBI doses of varying length: 4-week MBI (short), 8-week MBI (standard), or 12-week MBI (extended). All MBIs will feature similar content and structure and will be delivered in groups (n=4) using live videoconferencing.

Phase I: Protocol refinement and training of MBI Providers

The main goal of Phase I is to prepare for the feasibility trial. Preparatory activities include refining and completing the MBI protocols, developing a manual of operations, establishing a data and safety monitoring plan, and obtaining IRB approval. We have a preliminary outline of the three MBI doses that will be developed into a formal treatment manual that can be used for training and delivery.

MBI Provider Training. The next step is to recruit and train at least 6 MBI providers. The purpose of this step is to determine the feasibility of recruiting MBI providers for a large-scale study and to evaluate the level of training needed for providers to work effectively with people with narcolepsy (see Specific Aim 1). We will select providers who have experience in delivering a traditional MBI, such as MBSR or MBCT, and who have a personal mindfulness meditation practice but do not have to be licensed clinicians (e.g., psychologist, social workers). This is consistent with the requirements for MBSR and MBCT, which should enhance the potential pool of providers. We will then provide training workshops, providing education on narcolepsy and the challenges that patients have described. We will also provide training on delivering each of the MBI doses (see C.8. and Table 3 below), emphasizing the adaptations from traditional MBIs and the application of mindfulness principles to working with symptoms of narcolepsy. Based on feedback from our focus groups (see C.2), we will educate providers on the symptoms of narcolepsy as well as the unique challenges that are common among people with narcolepsy (e.g., stigma, negative public perception, unpredictability of symptoms). We expect to conduct workshops via video-conferencing to enhance flexibility in recruiting MBI providers, but will also conduct these in-person for those who are in the local area. Each provider will be required to demonstrate competency in delivering the MBI protocols based on evaluation by the PI or Co-I. We will also gather input from MBI providers regarding the intervention and finalize the MBI protocols. The major milestones of this phase are to finalize the manual of operations for the study protocol, establish a treatment manual for each MBI dose, and train 6 MBI providers to deliver MBI.

Phase II: Feasibility Trial

Phase II consists of a feasibility trial to gather data on the feasibility, acceptability, and clinical impact of MBI. Participants will be randomly assigned to receive one of three MBI doses (short, standard, or extended course) to determine the optimal parameters for length of the MBI program for people with narcolepsy. An important consideration at this stage is to optimize clinical impact and acceptability with cost-effectiveness as a secondary consideration in determining the optimal MBI dose. All MBIs will be delivered in small groups (n=4) using live videoconferencing. Recruitment and screening will begin upon completion of Phase I (month 6)

and we anticipate running 5 cycles. Given the focus on optimization, we will conduct an interim review after completing Cycle 2 to evaluate the need for modifications to the MBI protocol or study protocol. We plan to complete the interventions and assessment in Year 3, between months 6 to 8, leaving the remaining time for data analysis, dissemination of results, and preparation of a U01 or R61/R33 application depending on the findings of this study.

Short MBI (4-week). The short MBI consists of four weekly group sessions that are two hours each and follows the structure and format described above for each group and home meditation practice. Meta-analytic results of MBIs in lifestyle medicine trials have found that intervention effects are not dependent on the length of the MBI and that shorter-length MBIs (< 8 weeks) have demonstrated positive findings with effect sizes similar to MBI of 8 weeks or longer. Therefore, the rationale for testing the short MBI is to evaluate a low-dose (8 hours of contact) MBI that optimizes cost-effectiveness and minimizes patient burden.

Standard MBI (8-week). The standard MBI consists of eight weekly group sessions that are approximately two hours each. Group sessions will follow the structure and format described above. The length of this package is based on the standard length of MBSR as an 8-week program. The rationale for testing the standard MBI is to provide a comparison to a dose (16 hours of contact) that is most similar to the length of MBSR and has the fewest modifications, making it easier to train MBI providers.

Extended MBI (12-week). The extended MBI consists of four weekly group sessions followed by four group sessions every other week over the course of 12 weeks. Each group session will be two hours and follows the contents and structure described above. The group sessions will be identical to the standard package except for the timing (every other week) of the last four sessions. In addition to the group sessions, the MBI provider will offer “office hours” in between the bi-weekly group sessions, where participants will be able to schedule individual sessions with the MBI provider to discuss questions and troubleshoot their mindfulness practice. The rationale for testing the extended MBI is to optimize acceptability and uptake based on our focus group data by allowing for a slower, extended pace of learning mindfulness practices with an opportunity to have individual discussions with the instructor (16 hours of contact + individual office hours).

Data Analysis Plan

Overall Approach and Power Considerations. The overall goal of this project is to work out the parameters of a mindfulness program that will be feasible and acceptable for people with narcolepsy. Following recommendations for pilot studies, this stage of testing focuses on evaluation of benchmarks and refinement of the intervention, recruitment methods, and assessment protocol. Formal hypothesis testing of outcomes and clinical endpoints will be conducted at a later stage, once the optimal MBI dose and delivery format is selected and refined. Since sex is not a biological variable of key interest in this study, we plan to conduct all analyses aggregated across sex. However, if patterns emerge to indicate that sex could influence the results, we will explore post-hoc analyses as needed (e.g., sex as a covariate). As suggested for pilot studies, our sample size was selected based on balancing the research priorities established in the specific aims with the pragmatics of recruitment and the resources allowed in the R34 funding mechanism. Data gathered on recruitment pace and effect size on clinical measures will be used to inform power considerations and the feasibility of conducting a large-scale trial in future studies. A summary of the analytic plan is described below. See **Statistical Design and Power** for details about specific analyses and the data management plan.

Specific Aim 1. *Determine the feasibility and acceptability of MBI using videoconferencing for the purpose of improving psychosocial functioning in people with narcolepsy.* To carry out Aim 1, we will evaluate the short, standard, and extended doses of MBI on the pre-determined benchmarks below to determine the feasibility and acceptability.

- Benchmark 1 (feasibility of MBI providers): Recruit and train at least 6 qualified providers to deliver the MBI conditions (see section C.4. for details). No specific analyses are planned for this benchmark.
- Benchmark 2 (acceptability of MBI doses): An average attendance ≥ 80% of sessions per MBI condition will be used as a benchmark for determining acceptability of the videoconference delivery of MBI and patient uptake of MBI. This benchmark corresponds to attendance of all sessions (4 out of 4) for the short MBI and 7 out of 8 sessions for the standard MBI. For extended MBI, participants must attend at least 6 out of 8 group sessions plus at least one optional individual session scheduled during provider "office hours" or 7 out of 8 group sessions if no individual sessions are scheduled.
- Benchmark 3 (receipt of MBI targets): The benchmark for receipt of mindfulness and self-compassion will be an increase from baseline to post-treatment in the SCS and FFMQ with an effect size in the moderate range or higher (Cohen's $d \geq .5$) per MBI dose. This benchmark will be used to evaluate the feasibility that people with narcolepsy are capable of acquiring self-compassion and mindfulness skills from the MBI and also provide estimations of the effect size for each MBI dose (4, 8, 12 weeks). Given that our conceptual model (see Figure 1) posits that self-compassion, mindful awareness, and mindful action are key putative mechanisms by which MBI improves HRQOL, this benchmark will provide an initial test of our conceptual model.
- Benchmark 4 (feasibility of clinical impact): We will use a similar benchmark ($d \geq .5$) to evaluate the clinical impact from baseline to post-treatment for each MBI dose on the PROMIS global health, depression, anxiety, and psychosocial illness impact measures.

Secondary Considerations. In addition to these benchmarks, we will conduct other analyses as secondary considerations of acceptability and feasibility. We will examine the amount of meditation practice from the daily diaries (total minutes of practice and number of sessions) to assess enactment of mindfulness meditation outside of the sessions. We will

conduct qualitative analyses from focus group data using thematic analysis to evaluate themes and patient feedback on each MBI dose. We will also conduct exit interviews with the MBI providers to gather input from the provider's perspective as to the optimal MBI dose. In addition to evaluating effect sizes at post-treatment (Benchmark 3 & 4), we will also conduct linear mixed models to examine the trend of each MBI dose over time (A1 to A4) on SCS, FFMQ, and exploratory clinical measures (ESS, FOSQ, sleep/wake patterns from actigraphy and sleep diaries, neurocognitive assessment). These exploratory analyses will be used to supplement the evaluation of the effect sizes given the variation in time at post-treatment across MBI doses. We will also review adverse events and consider the potential harms as a factor in selecting the MBI condition (i.e., least AEs will be selected). Finally, we will consider the cost-effectiveness of each MBI dose (number of sessions, amount of face-to-face contact, amount of provider training).

Selecting the optimal MBI dose. The major milestone of Specific Aim 1 is to select the optimal MBI condition using the parameters described above. We anticipate that each MBI dose will have a unique profile (e.g., short MBI will have high attendance but smaller effect size on SCS and FFMQ) and will select the MBI dose that is able to achieve the most benchmarks. If these benchmarks cannot determine a condition that is superior, we will use secondary considerations and cost-effectiveness (lowest-level of resources) to determine the optimal MBI dose. This MBI program will be used for further testing or optimization (see Future Directions).

Specific Aim 2: *Determine the feasibility of recruitment and assessment methods for MBI using videoconferencing.* The purpose of Aim 2 is to evaluate the pace of recruitment and the feasibility of remote data collection using the assessment instruments proposed for conducting a future large-scale trial. We will use the following benchmarks to carry out Aim 2:

- Benchmark 5 (recruitment feasibility): The benchmark for feasibility of recruitment will be enrollment of 12 participants who meet all eligibility criteria per 3-month cycle (or ≥ 4 participants per month). The criteria for this benchmark is based on the minimum rate of recruitment needed to support randomization into groups of four for each of the MBI conditions. It will provide data to inform recruitment decisions, the method of randomization, and the number of sites needed for a large-scale study in the future.
- Benchmark 6 (assessment feasibility): The benchmark for the assessment protocol is complete data for ≥ 80% of all participants (n=48 out of 60). Completion is defined as providing valid data from baseline (A1) through post-treatment for each MBI. This benchmark will inform the degree of missing data, the acceptability of the assessment protocol (e.g., neuropsychological assessment via videoconferencing), and the selection of instruments (e.g., reliability of collecting actigraphy data remotely).

Secondary considerations. In addition to these benchmarks, we will evaluate the assessment instruments for inclusion in future studies by reviewing the effect size, costs, and patient feedback from focus groups for each instrument. For example, if there is evidence that some PROMIS domains selected for this study are not relevant we will not include these in future studies. We will also examine issues such as practice effects or fatigue to evaluate the validity and feasibility of conducting the neurocognitive battery using videoconferencing for people with narcolepsy. The major milestone of Aim 2 is to establish operational guidelines for effective recruitment methods and an assessment protocol that can be used to support a future large-scale trial.