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Evaluating treatment of obstructive sleep apnea comorbid with insomnia disorder using an incomplete factorial design

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Abstract

Chronic insomnia disorder is a prevalent condition and a significant proportion of these individuals also have obstructive sleep apnea (OSA). These two sleep disorders have distinct pathophysiology and are managed with different treatment approaches. High comorbidity rates have been a catalyst for emerging studies examining multidisciplinary treatment for OSA comorbid with insomnia disorder. In this article, we describe a randomized clinical trial of Cognitive Behavioral Treatment for insomnia (CBT-I) and Positive Airway Pressure (PAP) for OSA. Participants are randomized to receive one of three treatment combinations. Individuals randomized to treatment Arm A receive sequential treatment beginning with CBT-I followed by PAP, in treatment Arm B CBT-I and PAP are administered concurrently. These treatment arms are compared to a control condition, treatment Arm C, where individuals receive PAP alone. Adopting an incomplete factorial study design will allow us to evaluate the efficacy of multidisciplinary treatment (Arms A & B) versus standard treatment alone (Arm C). In addition, the random allocation of individuals to the two different combined treatment sequences (Arm A and Arm B) will allow us to understand the benefits of the sequential administration of CBT-I and PAP relative to concurrent treatment of PAP and CBT-I. These findings will provide evidence of the clinical benefits of treating insomnia disorder in the context of OSA.

Keywords

Obstructive Sleep Apnea; Insomnia Disorder; Randomized Clinical Trial; Incomplete Factorial Design

1. Introduction

Insomnia Disorder (ID) is a highly prevalent sleep disorder, affecting about 6–10% of the general population¹, and is characterized by difficulty falling or staying asleep, with next-day sequelae. Historically, the sleep problem was viewed as a symptom of an underlying psychiatric or medical condition, but accumulating evidence has found that insomnia

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occurring in the context of another condition is not merely a symptom of the underlying disorder, but can have a distinct course that merits independent treatment. This paradigm shift was highlighted in the 2005 NIH State-of-the-Science Conference on Manifestations and of Chronic Insomnia in Adults ², which outlined concerns that the insomnia was perceived as merely a symptom of an underlying condition and thus undertreated. Effective treatment of ID in the context of depression, chronic pain, and cancer can be achieved with cognitive-behavior therapy for insomnia (CBT-I) ³. Furthermore, CBT-I can improve the outcomes of the “underlying” condition, as seen in the case of depression ^{4,5}. Therefore, treatment of ID using CBT-I appears capable of improving the ID and outcomes related to the “underlying” condition.

Obstructive sleep apnea (OSA) highlights another example where the co-occurring insomnia has been seen as merely a symptom of the “underlying” condition. OSA is a sleep-related breathing disorder characterized by repetitive collapsing of the upper airway during sleep causing sleep fragmentation and between 6% and 84% of individuals with insomnia are also diagnosed with OSA ^{6–16}. OSA comorbid with ID is associated with greater illness severity and an increased morbidity of psychiatric and medical disorders ^{12–14,16,17}. Treatment studies that target both insomnia and OSA are associated with improvements in insomnia symptoms, daytime functioning, sleep quality and total sleep time ^{18,19}. However, these studies did not test head-to-head comparisons of combined vs. single treatment approaches. The results of a crossover design study ²⁰ revealed superior effects for the sequential administration of upper airway surgery for OSA followed by CBT-I, however we do not know if these results would hold true for positive airway pressure (PAP) therapy as standard treatment for OSA. In fact, there is mounting evidence that the presence of ID can adversely impact adherence to PAP ^{12,17,21–25} suggesting that it might be preferable to treat insomnia first or at least simultaneously.

The purpose of this prospective clinical trial is to examine the efficacy and implementation sequence of CBT-I and PAP for individuals with OSA comorbid with ID. The primary aim is to determine the efficacy of a combined multidisciplinary approach using CBT-I and PAP compared to PAP alone. The secondary aim is to examine the relative benefits in the sequence of initiating CBT-I. A unique incomplete-factorial design is used to carry out these aims. Participants will be randomly allocated to one of three treatment arms: A) CBT-I and PAP treatment sequentially, starting with CBT-I; B) CBT-I and PAP concurrently; or C) PAP alone. The potential impact of this study will be to provide an evidence base to inform clinical guidelines for patient with OSA comorbid with ID.

2. Methods and Design

2.1. Study Design

In this study, participants will be randomized to one of three arms with each arm consisting of different treatment pathways (see Figure 1). In Arm A, participants begin their first phase (Phase I) with 4 weekly CBT-I sessions. Once the CBT-I is completed, participants return to the lab for an overnight PAP titration (see Interventions section below). They will begin PAP at home, marking the start of Phase II, and return for an assessment after 30 and 90 days of using PAP. At the 3-month follow up, they will return the machine to the study staff,

transition to routine clinical care, and return for a follow-up evaluation at 180 days post PAP initiation. Thus, Arm A represents the treatment sequence CBT-I then PAP and is designed to test the impact of treating insomnia prior to initiation of PAP. In Arm B, participants will begin Phase I with a 4-week monitoring program, where they will be asked to monitor their sleep using diaries and will have weekly contact with study staff, to match the CBT-I program for attention and therapist contact. Phase II starts with participants using their PAP at home, while concurrently starting the 4-session CBT-I program. PAP titration and follow-up visits at 30- 90- and 180-days will be identical to Arm A. Thus, Arm B represents the treatment sequence CBT-I+PAP, and is designed to test the impact of treating insomnia concurrent with PAP. In Arm C, participants will also begin their Phase I with a monitoring program, but in Phase II use PAP alone, with no CBT-I intervention. PAP titration and follow-up visits will be identical to the other two arms. Thus, Arm C represents the treatment sequence PAP alone and is designed to test the impact of current standard care for OSA without direct intervention on insomnia. In order to ensure that all participants are given the ability to receive all forms of treatment, participants in Arm C will be offered the 4-session CBT-I as an option for those who continue to experience insomnia after collection of our study endpoints (at the end of the 90 days).

This study is a three-arm randomized controlled trial using an incomplete factorial design²⁶ (see Table 1). Factorial designs traditionally enable the assessment of interactions between two or more treatments (factors), or combinations of treatment each with different levels (typically two levels, for example high or low dose of a drug)²⁷. These types of clinical trials are typically designed to compare the relative benefits of treatments and their interactions by systematically varying the administration of these interventions. For incomplete factorial designs, the factorial structure is preserved, but some of the possible treatment combinations are omitted. The omission of treatment groups may be for reasons of cost saving, of not requiring certain groups to test interactions of interest, or for ethical concerns that a treatment combination or treatment omission (placebo control) would put the participant at risk²⁶. This study as a full-factorial design would have 9 possible combinations because there are two factors (treatment: PAP and CBT) and each have three levels (not present, present and delivered first, or present and delivered second), see table 1. This would provide us with 9 possible combinations (two factors with three levels each, or a 3² factorial design). Some of these combinations bear ethical concerns (i.e., no treatment at all [combination 1 in table 1], or no PAP treatment [combination 8 and 9 in table 1]), other combinations would not contribute anything unique to our primary aims (PAP first then CBT second [treatment combination 5 in table 1]) and were thus not selected as possible treatment arms in this study. Because some combinations are omitted, this can be considered an incomplete factorial design.

2.2. Participants

A total of 140 participants will be recruited for this study. Recruitment will come from the three following sources: 1) responses to advertisements posted at Rush University Medical Center, on public transportation (both buses and trains), and on community bulletin boards (both online and physical); 2) referrals from other health care providers, word of mouth, and participants from previous research studies who have agreed to be contacted; and 3) referrals

from physicians of patients who present to the Rush Sleep Disorders Center. Males and females age 18 and over will be considered eligible for this study if they meet criteria for ID and OSA. The presence of OSA according to the International Classification of Sleep Disorders, Version 2 (ICSD-2)²⁸ will be demonstrated by an Apnea-Hypopnea Index (AHI) = 5 on a full-night in-lab baseline polysomnography (PSG) and at least one of the following clinical symptoms: daytime sleepiness or fatigue, unrefreshing sleep, gasping, choking, or holding breath at night, witnessed apneas or loud snoring. ICSD-2²⁸ and Research Diagnostic Criteria for insomnia²⁹ will be used to establish presence of ID characterized by either a complaint of difficulty initiating sleep, maintaining sleep, or waking too early, despite adequate opportunity and circumstances for sleep, coupled with at least one area of significant daytime impairment or distress. In addition, the sleep disturbance will have to be present for at least 3 months. Participants will also have to meet quantitative criteria as evaluated by a sleep diary showing sleep onset latency or wake after sleep onset > 30 minutes, at least 3 nights per week.

A full medical history and physical examination will be conducted to exclude individuals with severe and unstable comorbid medical conditions, where the delay in OSA treatment could compromise the overall health of the individual. Similarly, individuals will be excluded if they revealed a comorbid psychiatric condition that is judged to interfere with the study protocol, including substance abuse, psychotic disorder, cognitive disorder, current suicidal ideation, or any uncontrolled psychiatric condition that requires immediate treatment. Comorbid sleep disorder that requires treatment outside of this study protocol, for example other sleep-related breathing disorder besides OSA, such as complex sleep apnea and central sleep apnea will be excluded from this study. To allow for the delivery of 4-week CBT-I prior to PAP treatment (Arm A), PAP will not be introduced until about 4 weeks after randomization in all arms. Thus for safety reasons, we will exclude individuals with very severe OSA, where the delay in treatment could compromise their health. This will be defined as an AHI > 100, or arterial oxygen saturation (SaO₂) < 80% for > 10% of total sleep time. Because CBT-I can result in an increase in daytime sleepiness, we will also exclude those who reported active use of sedative-hypnotics and those who reported excessive daytime sleepiness (defined by an Epworth Sleepiness Scale [ESS] score >16 or a score of 3 (high chance) on the ESS question about risk of dozing “In a car, while stopped for a few minutes in traffic”, or reports of falling asleep at the wheel, a MVA, or near-miss accident due to sleepiness). These definitions of risk were determined in collaboration with the study physician and members of the study’s independent Data and Safety Monitoring Board (DSMB). Individuals who are excluded for these reasons will be referred to an appropriate clinic for immediate care. Individuals who have used PAP or CBT-I within the past 6 months of screening will not be eligible for this study.

2.3. Screening Process

Upon contact with the study personnel, individuals will undergo a telephone screen to evaluate general eligibility for the study. After this initial evaluation participants will be invited to an in-person screening visit, where research staff will first obtain written informed consent. After informed consent is obtained, each participant will complete a screening evaluation with a trained research staff member supervised by a licensed clinical

psychologist, to assess mental health status via the Structured Clinical Interview for DSM Disorders (SCID) version for the DSM-IV-TR³⁰ and determine the presence of sleep disorders in accordance with the DSM-IV and ICSD-2 via the Duke Structured Interview for Disorders Sleep Disorders³¹. In addition, a board certified sleep physician will obtain a brief medical history and perform a physical examination to determine the presence of any medical or sleep disorder that would preclude study involvement. At this stage, participants will also complete their first baseline questionnaire assessment (Assessment 1, see Clinical and Laboratory Assessments section below). The final stage in the screening evaluation is an in-lab full-night PSG (see Clinical and Laboratory Assessments section below for details) to further assess inclusion (presence of OSA) and exclusion criteria (medical and other sleep disorders e.g., tachycardia or REM behavior disorder). To minimize the potential for subject attrition and missing data, participants will be informed about the time commitment required to participate, and potential barriers to participating will be discussed during the screening process.

2.4. Randomization

The study statistician (LF) who is blind to the participants' medical history created the randomization scheme in random size blocks of 3 or 6 to minimize bias using the statistical software package Excel (Microsoft Excel 2007). The randomization scheme was also stratified by OSA severity using AHI = 5 and < 15 for mild OSA and AHI = 15 for moderate-to-severe OSA. Once a participant meets all study criteria, the Principal Investigator (JCO) will assign the participant to one of the three treatment arms based on the randomization scheme. This is not a blinded study, both participants and study staff will be not be blinded to the condition the participant is randomized to. In order to reduce bias, the technologist and durable medical equipment company staff who set up the PAP machines will be blinded to treatment assignment. In addition, to avoid any selection bias, the study staff who conduct the screenings (MRC, ADT) will not have access to the randomization scheme prior to assignment.

2.5. Interventions and Clinical Assessment Measures

2.5.1 Interventions

Positive Airway Pressure (PAP): During Phase II, all participants will receive PAP following the standard of care procedures recommended by the American Academy of Sleep Medicine outlined in the clinical treatment guidelines³². The standard of care procedures include conducting a PAP titration sleep study with the participant (Assessment 2) followed by instructions on use and set up of PAP within 7 days by a trained health care provider, typically a respiratory therapist from a durable medical equipment company. During the study, participants will use a standard PAP machine using a prescribed pressure or pressure range determined by study physician. Participants will be allowed to choose a PAP mask from a few options (e.g., nasal masks, full face masks or nasal pillows). One week after receiving the PAP machine participants will be contacted by the research staff to verify initiation of PAP treatment, as well as discuss any issues related to the PAP equipment. The study physician, who is permitted by the study protocol to discuss issues related to equipment or use of the PAP, will oversee PAP therapy. Behavioral interventions for

insomnia or PAP adherence (e.g., desensitization, motivational techniques) will not be discussed in these interactions related to PAP therapy. Participants will be provided a 90-day period to use their PAP machines with assessments occurring 30 days and 90 days after initiation (described below). At the 90 day assessment the participant will be asked to return the PAP machine. At this point, participants will be transferred to long-term care in the Rush Sleep Disorders Center or an outside sleep center, enabling them to continue with sleep treatments. Participants will return for a follow-up assessment 180 days after receiving PAP.

Cognitive Behavior Therapy for Insomnia (CBT-I) ^{33,34}: CBT-I is a multicomponent intervention consisting of behavioral (sleep restriction ^{35,36}, stimulus control ^{36–38}, relaxation ^{36,39–42} and sleep hygiene ³⁶) and cognitive approaches (e.g., cognitive restructuring ⁴³). Table 2 summarizes the key treatment components that are to be discussed in each session of CBT-I and the corresponding treatment goals. The protocol for CBT-I in this study consists of 4 individual sessions (approx. 50 minutes each) and will be delivered by a trained clinician (postdoctoral fellow or staff sleep psychologist) under the supervision of a clinical psychologist certified in Behavioral Sleep Medicine. During the course of CBT-I the clinician will not be allowed to discuss instructions for OSA treatments (e.g., PAP adherence). Each session will be recorded and at least 1 of each participant's recordings will be reviewed to evaluate therapist fidelity using measures that were developed specific to this protocol. In addition, we will assess patient adherence to CBT-I via bedtime and wake time, which is obtained from the sleep diaries. Transient daytime sleepiness and lapses in attention/vigilance are potential adverse events related to CBT-I and specifically sleep restriction ^{44–46}. Therefore, weekly sleepiness ratings and other adverse events will be reviewed to ensure patient safety. We also reduced the number of CBT-I sessions from the traditional 6 to 8 session CBT-I to a 4-session intervention to minimize the delay prior to PAP. Participants who are unable to attend a session will be scheduled for a makeup session to review the materials from the missed session.

Monitoring Program: In treatment Arms B and C, participants will begin their Phase I by monitoring their sleep with sleep diaries. They will have weekly contact with study staff, who evaluate their progress with the sleep diaries and assess for adverse events. This type of self sleep-monitoring has been successfully used as a credible control condition in our previous research ⁴⁷, and allows for the control of contextual factors such as support and therapist contact. In addition, the effects of sleep self-monitoring, which itself has been reported to yield changes in sleep ^{48,49}, are controlled for. No therapeutic intervention will be introduced during the monitoring program.

2.6. Clinical and Laboratory Assessments

Table 3 outlines the timeline for the assessment of the key primary and secondary variables. Our main interest is to see if the treatment of insomnia (and successful resolution of insomnia symptoms) can improve PAP adherence. While PAP adherence is itself an important endpoint, it is a health behavior that is only clinically meaningful if sleep quality also improves. Therefore, both PAP adherence and sleep quality are considered primary variables. Baseline measures of sleep and nocturnal symptoms, daytime functioning, sleepiness, and fatigue will be collected during the in-person screening visit (Assessment 1).

To examine the efficacy of the treatments, we will assess these symptoms after the first phase (Assessment 2), after the second phase, which is 30 days after PAP initiation (Assessment 3), and again at the study endpoint or 90 days after PAP initiation (Assessment 4). A follow-up will be conducted at 180 days after the initial PAP set up (Assessment 5). To minimize possible missing data or subject attrition, reminders will be sent prior to each session via telephone or e-mail to increase attendance and completion of weekly measures. Participants will also be offered a small monetary compensation (\$20) for completing each assessment visit.

2.6.1 Measures of Sleep and Nocturnal Symptoms—The measures used to determine efficacy are:

Pittsburgh Sleep Quality Index (PSQI): The PSQI is a 19-item self-report measure of sleep quality and sleep disturbances ⁵⁰. A PSQI cut-off score of ≥ 5 will be used to define our clinical endpoint of good sleepers.

PAP Adherence: Objective adherence data for PAP will be obtained at the 30-day and 90 day assessments (% of nights used & hours per night) via the nightly use tracker onboard the device. Regular users of PAP will be defined as PAP use = 4 hours on 70% of nights and this is the second of our two clinical endpoints ⁵¹.

Sleep Diaries: Prospective sleep daily diaries that include ratings of sleep quality will be used to assess self-reported sleep patterns. The format and instructions for the sleep diaries in this study will follow the recommendations of the Consensus Sleep Diary (core version)⁵². The sleep diary-derived measure of sleep efficiency $> 85\%$ will be used in addition to the PSQI to define good sleepers. Sleep efficiency is the percentage of time asleep relative to the time in bed.

2.6.2 Secondary Measures

Insomnia Severity Index (ISI): The ISI is a brief 5-item scale assessing nocturnal and daytime symptoms of insomnia over the past week ⁵³.

Laboratory Polysomnogram (PSG): A standard technician-monitored, in-laboratory PSG is conducted at the baseline diagnostic PSG assessment and at PAP titration. Each recording will be scored, and interpreted in accordance with the AASM Manual for the Scoring of Sleep and Associated Events ⁵⁴. The diagnostic PSG will include 19 channels: 6 channels of EEG (F4/M1, C4/M1, O2/M1, F3/M2, C3/M2, O1/M2), 2 channels of EOG (ROC/M1, LOC/M2), 4 channels of EMG (2 chin EMG channels from 3 mentalis/submentalis sites, and left and right anterior tibialis), 1 channel of ECG (modified Lead II), 1 channel of snoring sounds, 2 channels of airflow (nasal/oral thermistor for apneas, nasal pressure transducer for hypopneas), 2 channels of respiratory effort (thoracic and abdominal inductance plethysmography belts), and 1 channel of finger pulse oximetry. For the PAP titration study, the 2 channels of airflow used for the diagnostic PSG will be replaced with 2 PAP channels (PAP pressure and mask leak pressure). The PAP titration study will utilize a standard PAP

titration protocol published by Dr. Kushida⁵⁵. The PSGs will be scored by a registered polysomnography technologist and reviewed by a board certified sleep medicine physician.

Measures of Daytime Sleepiness and Fatigue: In order to characterize the impact of the intervention on daytime functioning, secondary measures will be collected, including daytime functioning⁵⁶, sleepiness⁵⁷, fatigue⁵⁸, emotional functioning⁵⁹ and objective indications of sleep and activity using wrist actigraphy.

Treatment Satisfaction: After completing the 90 days assessment period, each participant will complete a treatment satisfaction questionnaire⁶⁰.

2.7 Safety Monitoring

This protocol was reviewed and approved by the Institutional Review Board (IRB) at Rush University Medical Center. To ensure the maintenance of confidentiality for all participant materials, identifying information will be removed and an identification number will be assigned to each participant. Although this study carries minimal risk for participants, to ensure that safety is maintained, we will assess for adverse events at each study assessment using a symptom checklist⁶¹, and open-response questions about changes in medical or psychiatric symptoms, and sleepiness levels. Adverse events are defined as any reaction, side effect, or other untoward medical occurrence, regardless of the relationship to the study interventions, which occurs during the conduct of this clinical trial. Adverse events will be reported to the IRB and to the DSMB. Our DSMB consists of five external clinical experts with expertise in OSA, insomnia, sleep medicine, and/or clinical trials, and the committee was approved by the funding agency (NHLBI) prior to recruitment of any research participants. The DSMB will meet via telephone conference every six months to discuss any issues related to participant safety, including reports of adverse events, withdrawal from the study, and appropriate referrals for those who are excluded or withdrawn from the study.

2.8 Statistics and Data Analysis

2.8.1 Sample Size Justification—The sample size calculation for this study was based on effect sizes on PAP use from pilot data conducted with patients at the Rush Sleep Disorders Center with OSA comorbid with ID⁶² and effect sizes from previous studies in the literature, which indicate moderate to large pre-to-post treatment effect sizes associated with CBT-I + PAP. In efforts to be conservative, we calculated the sample size using a medium effect size of .50, a one-tailed alpha of .05, and a power of 0.80, which revealed a sample size of 35 per arm. Thus, the total sample size for completers is 105 (35 x 3 treatment arms). We established a target recruitment goal of 140 participants to account for 25% attrition in the sample, yielding 105 completers.

2.8.2 Statistical Analysis and Hypotheses—For all statistical tests a .05 significance level will be used. All analyses will be performed on an intent-to-treat basis. Missing data will be imputed using the SAS procedure, PROC MI⁶³. The specific aims and data analytic strategy for testing each study hypotheses are described below and in Table 4.

Specific Aim 1: To determine the efficacy of a treatment model combining CBT-I and PAP for individuals with OSA comorbid with ID: Multivariate Analysis of Variance (MANOVA) will be used to compare PAP adherence, and number of participants reaching the clinical endpoints between the combined treatment arms (Arms A + B) and PAP alone (Arm C). Repeated measures ANOVA will be used to compare improvements in sleep quality (from baseline to endpoint) between these groups. We hypothesize that combined treatment will yield superior results compared to PAP alone. From our pilot data ⁶², we evaluated that at an effect size of .50, a meaningful difference would be 18% more days with PAP use ≥ 4 hs in the active treatment (combined treatment=Arm A+B) compared to the control (PAP alone=Arm C).

Specific Aim 2: To determine if there are relative benefits in the sequence of treatment initiation: An ANOVA will be computed to compare PAP adherence between the two combined treatment arms (Arms A and B). Repeated measures ANOVA will be used to examine improvements in sleep quality (from baseline to endpoint) and sleep efficiency (from the baseline PSG to the PAP titration). To test the effects of CBT-I on sleep efficiency, we also hypothesize that CBT-I administered prior to PAP (Arm A) will be associated with increased improvements in PSG sleep efficiency compared to the other two treatment sequences (Arms B and C).

3. Discussion

Despite a growing interest in the comorbidity of OSA and insomnia, research that systematically evaluates treatment approaches for this population is sparse. Here we have described a randomized clinical trial to compare combined treatment of CBT-I and PAP delivered either sequentially or concurrently with standard of care (PAP alone). The first aim of this study is to determine the efficacy of combined treatment relative to standard care of PAP therapy alone. The second aim is to elucidate the most effective treatment sequence of initiating CBT-I. We hypothesize that not only will combined treatment yield superior results, but initiating CBT-I prior to PAP will be associated with increased improvements in PAP adherence, sleep quality and sleep efficiency compared to the concurrent sequence.

To test our hypotheses, we are employing an incomplete factorial design (see Table 1 and Figure 1 for a visual representation of the design), and we believe this translates to three core strengths of this study. The first strength relates to the efficiency of the study design in testing the efficacy of three treatment pathways that patients are likely to encounter in sleep clinic. As mentioned above, incomplete factorial designs omit specific treatment groups for economical or ethical reasons, or because certain groups are not needed to test specific interactions. These arguments hold true for this study. The possible treatment groups not tested here are “CBT-I alone”, “PAP followed by CBT-I” and “no treatment/waitlist control”. These combinations would not provide any unique contribution to answering our primary research questions, thus including them would be associated with unnecessary cost. Furthermore, a “no treatment” arm (or elimination of a treatment group containing PAP) would not have been ethical, given that PAP and CBT-I are known effective treatments for OSA and insomnia respectively. Although it is now acceptable to include a sham treatment

when designing trials involving individuals with OSA (see ⁶⁴), there is no data on the use of sham PAP in this comorbid population.

The second strength relates to ability to elucidate possible temporal sequences, thus the results are more translatable to clinical practice. Through the factorial structure, we are able to compare different temporal sequences and determine which is associated with superior outcomes and should be implemented into clinical care. Treatment Arm C replicates the current standard treatment of care for individuals with OSA (alone or with insomnia): PAP only. The two experimental arms (Arms A and B) test treatment pathways that could be implemented into a clinic that cares for the needs of individuals with OSA comorbid with ID.

The third strength relates to the possibility of exploring mechanisms of change and the interactions between insomnia symptoms and PAP adherence. Although not one of our main aims, this study will allow us to generate data on the relationship between changes in insomnia symptoms before or during PAP use. This would support the emerging evidence revealing the negative impact of insomnia symptoms on PAP use ^{12,17,21–25}.

The generalizability of our results will be somewhat limited by the adaptations to the treatment and design considerations to address concerns of patient safety. To allow for the administration of 4-week CBT-I program prior to PAP treatment (Arm A) we have to delay the initiation of PAP by about 5 weeks after diagnosis. In Arm B and C, participants will be asked to monitor their sleep with diaries for 4 weeks. This delay prior to treatment initiation is a feature of this study design to ensure equal timeframes from baseline to study endpoint across all arms. To ensure participant safety with this delay in treatment, we exclude individuals who are in need of immediate treatment and for whom a delay in PAP could have increased the risk to health and safety. The shortest CBT-I program that was weighed against the possible delay in PAP was a 4-week treatment program, which is slightly shorter than the 6–8 week programs cited in most clinical trials. This decision was however supported from results of a dose-response study which demonstrated a 4-session (albeit biweekly) CBT-I program was superior to 1-, 2 and 8-week session CBT-I at 6 months follow-up ⁶⁵. In addition, we excluded individuals who are reporting excessive daytime sleepiness, and those who had severe OSA defined by results from the PSG, to ensure individuals are stable enough to delay their PAP treatment.

In summary, this study assesses the treatment of insomnia in the context of OSA using multidisciplinary approaches. The findings from this study will inform if there is added value to treating insomnia in the context of OSA. Our agenda now is to conduct high quality research that can elucidate the most efficacious, cost effective and acceptable multidisciplinary approach to provide best quality care for individuals with OSA comorbid with ID.

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Figure 1.
Study Design and Consort Flow Diagram

Note. CBT = 4 weekly session in 30 days; Assessment 2 conducted at the conclusion of Phase I. Assessment 3 taken 30 days after initiation of Phase II. Assessment 4 is the study endpoint conducted 90 days after initiation of Phase II.

Table 1

This table highlights all possible combinations of a 3² factorial design. Each of the two treatments (PAP and CBT) have three levels (0,1,2). Level 0 is “not present”, Level 1 is “present and delivered first”, and Level 2 is “present and delivered second”. The rows with bold text represent the combinations that equate to Arms A, B and C in this study. The combinations “CBT only”, “no treatment” and “PAP→CBT” are not represented in this study.

Combination	FACTOR			Treatment Combination	ARM in study
	PAP treatment		CBT treatment		
1	Level 0	Not present	Level 0	No treatment	n/a
2	Level 1	Present (first)	Level 0	PAP only	ARM C
3	Level 2	Present (second)	Level 0	PAP only	ARM C
4	Level 1	Present (first)	Level 1	PAP and CBT concurrently	ARM B
5	Level 1	Present (first)	Level 2	PAP→CBT	n/a
6	Level 2	Present (second)	Level 1	CBT →PAP	ARM A
7	Level 2	Present (second)	Level 2	PAP and CBT concurrent	ARM B
8	Level 0	Not present	Level 1	CBT only	n/a
9	Level 0	Not present	Level 2	CBT only	n/a

Table 2

Outline of CBT-I for Insomnia

	Session 1	Session 2	Session 3	Session 4
Component	Sleep Restriction	Stimulus Control	Sleep Hygiene	Cognitive Therapy
Goals	Reduce excessive time in bed; increase sleep homeostatic drive	Re-condition bed and bedroom as a place to feel sleepy	Eliminate behaviors, that are counterproductive for sleep	Challenge maladaptive beliefs and attitudes about sleep and insomnia

Table 3

Timeline of Assessment of Key Measures

Key Measures	Assessment 1	Assessment 2	Assessment 3	Assessment 4	Assessment 5 (6-month follow-up)
Primary					
PSG	Diagnostic	Titration			
PAP Adherence			30-day	90-day	180-day
PSQI	X			X	X
Sleep Diaries	X	X	X	X	X
ISI	X	X	X	X	X
Secondary					
FOSQ-10	X	X	X	X	
ESS	X	X	X	X	
FSS	X	X	X	X	
CES-D	X	X	X	X	
Actigraphy	X	X	X	X	
Treatment Satisfaction				X	

Table 4

Summary of Study Hypotheses and Main Outcome Variables

Aim	Hypothesis	Dependent Variable
Aim 1	1a. CBT-I+PAP (A+B) > PAP alone (C) on adherence to PAP	% nights used and hours per night
	1b. CBT-I+PAP (A+B) > PAP alone (C) on Sleep Quality	PSQI (A4 – Baseline)
	2a. CBT-I+PAP (A+B) > PAP alone (C) on “regular use” of PAP	PAP use ≥ 4 hours on ≥ 70% of nights
	2b. CBT-I+PAP (A+B) > PAP alone (C) on “good sleeper”	PSQI < 6 and sleep efficiency > 85%
	3. CBT-I → PAP (A) > B and C on sleep efficiency after completing	
Aim 2	Phase I	PSG Sleep Efficiency (A2)
	4. CBT-I → PAP (A) > CBT-I + PAP concurrent (B) on adherence to PAP and sleep quality	% nights used, hours per night and PSQI (A4 – Baseline)

Note. CBT-I=Cognitive Behavioral Therapy for Insomnia; PAP= Positive Airway Pressure Therapy; PSQI=Pittsburgh Sleep Quality Index, A4= Assessment 4 or 90 days post PAP initiation, A2= Assessment 2 or PAP titration