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Evaluating the 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.

1. Introduction

Insomnia disorder (ID) is a highly prevalent sleep disorder, affecting about 6–10% of the general population [1], 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 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. 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 cross-over design study [19] 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 [12,17,20–24] 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

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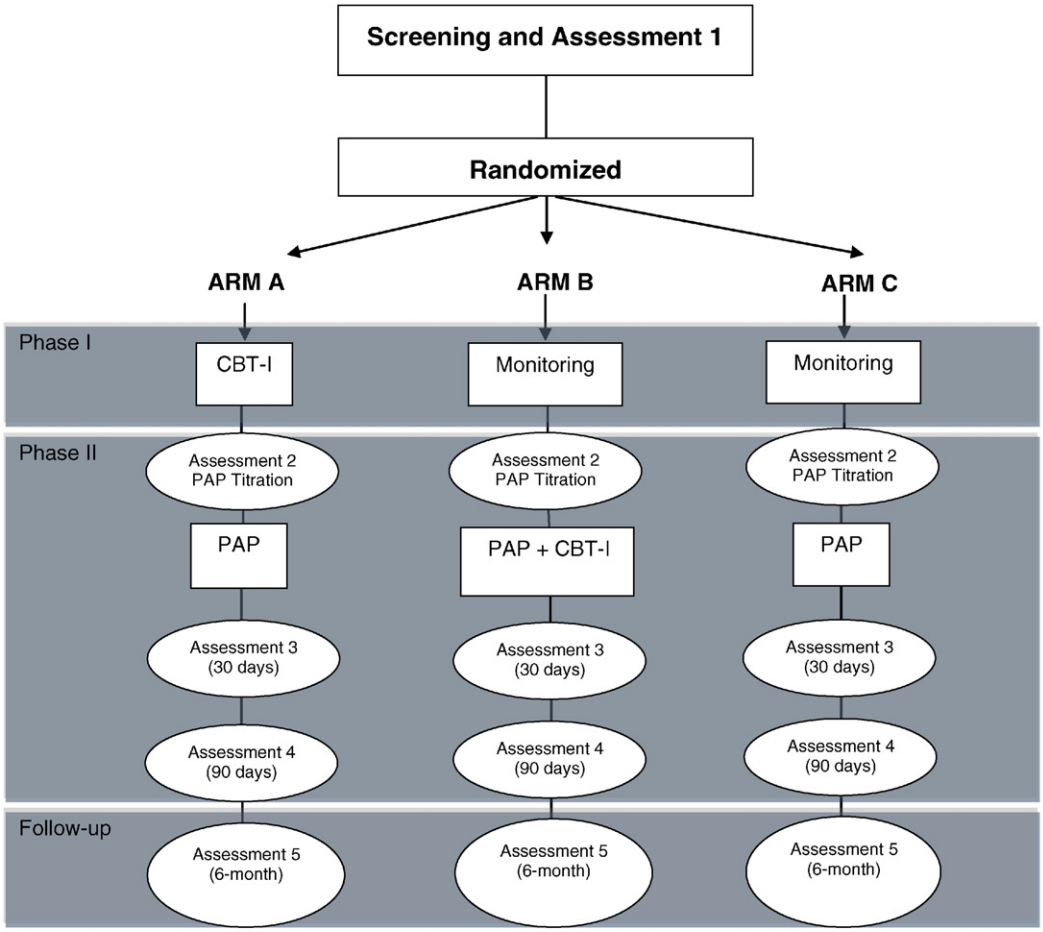
is used to carry out these aims. Participants will be randomly allocated to one of three treatment arms: A) CBT-I and PAP treatment sequentially, starting with CBT-I; B) CBT-I and PAP concurrently; or C) PAP alone. The potential impact of this study will be to provide an evidence base to inform clinical 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 Fig. 1, adapted from Ong and Crisostomo [25]). 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 design [26] (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



Note. CBT = 4 weekly sessions 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.

Fig. 1. Study design and consort flow diagram.