A Randomized Controlled Trial of CBT-I and PAP for Obstructive Sleep Apnea and Comorbid Insomnia: Effects on Nocturnal Sleep and Daytime Performance

Alice Y. Tu, MA[1,2], Megan R. Crawford, PhD[3], Spencer C. Dawson, PhD[4], Louis F. Fogg, PhD[5], Arlener D. Turner, PhD[6], James K. Wyatt, PhD[7], Maria I. Crisostomo, MD[8], Bantu S. Chhangani, MD[9], Clete A. Kushida, PhD[10], Jack D. Edinger, PhD[11], Sabra M. Abbott, MD, PhD[1], Roneil G. Malkani, MD[1,12], Hrayr P. Attarian, MD[1], Phyllis C. Zee, MD, PhD[1], Jason C. Ong, PhD[1,13]

[1] Center for Circadian and Sleep Medicine, Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL

[2] Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL

[3] School of Psychological Sciences and Health, University of Strathclyde, Glasgow, United Kingdom

[4] Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN

[5] College of Nursing, Rush University Medical Center, Chicago, IL

[6] Center for Translational Sleep and Circadian Sciences, Department of Psychiatry & Behavioral Sciences, University of Miami, Miami, FL

[7] Department of Psychiatry and Behavioral Sciences, Rush University Medical Center, Chicago, IL

[8] None, IL

[9] Department of Medicine, Rush University Medical Center, Chicago, IL

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[10] Division of Sleep Medicine, Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA

[11] Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, National Jewish Health, Denver, CO

[12] Neurology Service, Jesse Brown Veterans Affairs Medical Center, Chicago, IL

[13] Nox Health, Suwanee, GA

Corresponding Author:

Jason C. Ong, Ph.D.

Department of Neurology, Center for Circadian and Sleep Medicine

Northwestern University Feinberg School of Medicine

710 North Lake Shore Drive, Room 1004, Chicago, IL 60611

Email: Jason.Ong@northwestern.edu

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ABSTRACT

Study Objectives

This study examines the impact of cognitive-behavioral therapy for insomnia (CBT-I) and positive airway pressure (PAP) therapy for comorbid insomnia and sleep apnea (COMISA) on nocturnal sleep and daytime functioning.

Methods

A partial factorial design was used to examine concomitant treatment with CBT-I and PAP and the relative benefits of each treatment. 118 individuals with COMISA were randomized to receive CBT-I followed by PAP, self-monitoring followed by CBT-I concurrent with PAP, or self-monitoring followed by PAP only. Participants were assessed at baseline, PAP titration, and 30- and 90-days after PAP initiation. Outcome measures included sleep diary- and actigraphy-measured sleep, Flinders Fatigue Scale(FFS), Epworth Sleepiness Scale(ESS), Functional Outcome of Sleep Questionnaire(FOSQ), and cognitive-emotional measures.

Results

A main effect of time was found on improving sleep diary-measured (decreased sleep onset latency[SOL] and wake after sleep onset[WASO]; increased total sleep time[TST] and sleep

efficiency[SE]) and actigraphy-measured sleep (decreased WASO; increased SE) and daytime functioning (reduced ESS, FFS; increased FOSQ) across all arms (all $p< 0.05$). Significant interactions and planned contrast comparisons revealed that CBT-I was superior to PAP and self-monitoring on reducing diary-measured SOL and WASO and increasing SE; as well as improving FOSQ and FFS compared to self-monitoring.

Conclusions

Improvements in sleep and daytime functioning were found with PAP alone or concomitant with CBT-I. However, more rapid effects were observed on subjective sleep and daytime performance when receiving CBT-I regardless of when it was initiated. Therefore, concomitant treatment appears to be a favorable approach to accelerate treatment outcomes.

Keywords: Comorbid Insomnia and Sleep Apnea; Cognitive-Behavior Therapy for Insomnia; Positive Airway Pressure Therapy; Sleep; Daytime Functioning

BRIEF SUMMARY

Patients with COMISA often experience significant daytime dysfunction and greater sleep disturbance compared to each condition alone. Recent studies have focused on PAP adherence and insomnia remission, but the effect of concomitant treatment using PAP and CBT-I on nocturnal sleep parameters and daytime functioning remains unclear. This study addressed this research gap by examining secondary analysis on a randomized controlled trial using PAP and CBT-I in COMISA. The findings revealed more rapid effects on subjective sleep and daytime functioning when receiving CBT-I prior to, or concurrent with PAP compared to PAP alone. Concomitant treatment using CBT-I and PAP appears to be a favorable approach to accelerate treatment outcomes in sleep parameters and certain domains of daytime functioning.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder that affects approximately 10-30% of the populations[1,2]. OSA often coexists with insomnia disorder, which is characterized by persistent difficulty falling asleep, difficulty maintaining sleep, or early morning awakening. Patients with comorbid insomnia and sleep apnea (COMISA) often have mixed symptoms from both disorders, such as fragmented sleep, trouble falling asleep, and poor daytime functioning[3-5]. Several reviews have concluded that the comorbidity prevalence rate of COMISA is between 30% to 60%, with the variability likely due to different criteria used for insomnia and sleep-disordered breathing[3,6,7].

Clinical management for patients with COMISA has been challenging, as they present a broad range of symptoms that are difficult to manage using singular treatment approaches for OSA or insomnia[8]. A concomitant approach using positive airway pressure therapy (PAP) and cognitive-behavioral therapy for insomnia (CBT-I) has emerged as a potential strategy since both PAP and CBT-I are considered first-line treatments for OSA and insomnia respectively[9,10]. Recent clinical trials have found that this concomitant approach can be efficacious for reducing insomnia symptoms with mixed findings on improving PAP adherence[11-14].

Beyond these clinical endpoints, there is a need to understand the impact of treatments on other key aspects of COMISA, including nocturnal sleep parameters and daytime functioning. These factors are likely to drive patient complaints and subsequent adherence to treatments. Previous studies have found that people with COMISA have longer sleep onset latency (SOL) and more difficulty maintaining sleep compared to people with OSA only[15-18], as well as longer wake after sleep onset (WASO) compared to people with insomnia alone[15]. In addition, COMISA is associated with significant daytime sleepiness[19], dysfunctional sleep-related beliefs,

depression, anxiety[17,20], and medical consequences (e.g. cardiovascular diseases)[21]. Gooneratne and colleagues[22] also reported significantly lower global scores on the Functional Outcomes of Sleepiness Questionnaire (FOSQ) in individuals with COMISA compared to healthy controls. In a recent study[23], Alessi et al. found that an integrated behavioral treatment using CBT-I and PAP adherence techniques improved FOSQ-10 scores and daytime sleepiness at 3-month follow-up in people with COMISA. Additionally, they observed greater improvements in sleep diary-measured SOL as well as sleep diary- and actigraphy-measured sleep efficiency (SE) from baseline to 3-month follow-up in participants who received CBT-I and PAP adherence program compared to the control group (general sleep education). In a series of studies, Sweetman and colleagues also found that CBT-I improved both polysomnography- and sleep diary-measured sleep outcomes, including SOL, WASO, and SE in people with COMISA[12,14]. Furthermore, they found that sleepiness levels immediately returned to pretreatment level after a 15% increase in the first week of receiving CBT-I, indicating that increases in sleepiness are transient during treatment. In addition, they reported a reduction in dysfunctional sleep-related beliefs in those who received the combined treatment of CBT-I and PAP compared to PAP alone. However, no other between-group difference was found in their studies in the improvements of daytime functioning, including daytime sleepiness and fatigue[12,14].

The purpose of this study was to examine clinical measures of sleep and daytime performance as part of a planned series of analyses from a randomized controlled trial on PAP and CBT-I in people with COMISA. This report builds upon the main outcomes previously reported (PAP adherence, self-reported sleep quality, insomnia severity index)[13] to investigate other key clinical domains relevant to COMISA. The primary aim of this study was to examine the effects of the treatment combinations using CBT-I and PAP, and the relative benefits of each

treatment on sleep parameters and daytime functioning. We hypothesized that the combination of CBT-I and PAP would improve sleep outcomes (reductions in SOL and WASO, and lead to increases in total sleep time [TST] and SE) and improvement in daytime functioning compared to PAP treatment alone. In addition, a novel aspect of this study was the use of a partial factorial design. Therefore, the secondary aim was to conduct planned comparisons to examine the changes during each treatment condition (CBT-I, PAP) in these outcome measures.

METHODS

Study Design and Procedure

This study was a three-arm randomized controlled trial using a partial factorial design[24]. All three treatment arms consisted of two phases, Arm A: CBT-I in Phase 1 followed by PAP in Phase 2; Arm B: self-monitoring in Phase 1 followed by concurrent CBT-I and PAP in Phase 2; and Arm C: self-monitoring in Phase 1 followed by PAP only in Phase 2 (see Figure S1 in supplemental material for study procedure flow chart). Eligible participants were randomized to one of three study arms based on a randomization scheme, which was created by random size blocks of 3 or 6 and stratified by OSA severity (mild: apnea-hypopnea index [AHI] ≥ 5 and < 15; moderate-to-severe: AHI ≥ 15). Outcome measures of sleep, daytime functioning, and cognitive-emotional measures were collected during the in-person screening evaluation at baseline (Assessment 1). Same measures were also assessed at the end of Phase 1 / the time PAP titration was conducted (Assessment 2), after Phase 2 / 30 days after PAP initiation (Assessment 3), and 90 days after PAP initiation (Assessment 4).

Participants

The study was conducted at two sites (Rush University Medical Center, Northwestern University Feinberg School of Medicine). Participants were recruited from the community and through referrals from health care providers at each site from 2013 to 2018. A three-step screening process was administered to potential participants, consisting of (1) a preliminary eligibility screening through telephone, (2) an in-person evaluation using the Structured Diagnostic Interview for DSM-IV[25], the Duke Structured Interview Schedule for Sleep Disorders[26], and physical and medical history examination, and (3) an overnight in-laboratory polysomnography to determine OSA criteria and other exclusion criteria. The study protocol was approved by the Institutional Review Board at each site (Rush University #11090801-IRB01; Northwestern University #STU00203478). Written informed consents were obtained from all participants at the beginning of the in-person screening interview. See Figure 1 for the CONSORT flowchart diagram.

Inclusion criteria were (1) age 18 and over; (2) International Classification of Sleep Disorders, Version 2 criteria for OSA (AHI $\geq$ 5 on a full-night in-lab baseline polysomnography and the presence of 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); (3) International Classification of Sleep Disorders, Version 2 criteria for insomnia disorder, including a presence of difficulty initiating sleep, maintaining sleep, or waking too early for at least 3 months, coupled with at least one area of significant daytime impairment or distress. In addition, participants had to show a sleep onset latency or wake after sleep onset > 30 minutes for at least 3 nights per week through a 1-week sleep diary.

Exclusion criteria included (1) medical and psychiatric conditions that was unstable or judged to interfere with the study protocol or required immediate treatment (e.g. substance abuse, cognitive disorder, suicidal ideation); (2) other comorbid sleep disorders that required treatment outside of the study protocol; (3) severe OSA that required immediate treatment (AHI > 100, or arterial oxygen saturation < 80% for more than 10% of total sleep time); (4) active use of sedative-hypnotics; (5) excessive daytime sleepiness (Epworth Sleepiness Scale [ESS] > 16, or a score of 3 on the ESS question about risk of dozing "In a car, while stopped for a few minutes in traffic", or reporting excessive sleepiness while operating a motor vehicle); (6) use of CBT-I or PAP within 6 months prior to screening; and (7) unstable living environment for PAP set-up and home use.

< Insert Figure 1 >

Interventions

Positive Airway Pressure Therapy (PAP)

All participants received PAP treatment during Phase 2 following the standard of care procedures recommended by the American Academy of Sleep Medicine. Participants were given a standard PAP machine (Phillips Respironics PAP / Auto PAP Model 460 and 560) in an in-home setting instructed by a trained health care provider. The PAP titration sleep study was conducted at the beginning of Phase 2 (Assessment 2) by a board-certified sleep physician to determine the prescribed pressure or pressure range. Participants were contacted by the research

staff one week after set-up to verify the initiation of PAP use. No behavioral interventions for insomnia or PAP adherence were provided to the participants during this process. Participants were given a 90-day period to use the PAP machine and adherence data were collected at 30 and 90 days.

Cognitive-Behavioral Therapy for Insomnia (CBT-I)

This study used a 4-session, in-person CBT-I protocol. The components of CBT-I included sleep restriction, stimulus control, relaxation, sleep hygiene, and cognitive strategies (e.g. cognitive restructuring) (see Table S1 in supplemental material for protocol outline). CBT-I was delivered to the participants in Arm A during Phase 1 and Arm B during Phase 2 by a trained clinician (postdoctoral fellow or staff sleep psychologist) under the supervision of a Behavioral Sleep Medicine certified clinical psychologist (JCO). No instructions related to OSA management or treatment were provided to the participants during the CBT-I.

Self-Monitoring Program

During Phase 1, participants in Arm B and Arm C were instructed to complete sleep diaries for 4 weeks and were contacted by the research staff to review the diaries. This self-monitoring strategy has been used in previous research as a control condition, and was also used to control over the contextual factors (e.g. participants' self-monitoring of sleep, therapist contact) in this study. No therapeutic intervention was given by the research staff during this phase.

Outcome Measures

The measures selected for this study focused on three key domains below that provide a detailed clinical profile relevant to COMISA beyond the primary endpoints of the trial, which focused on regular PAP use and insomnia remission[13].

Sleep Parameters

Standardized prospective sleep diaries were used to assess self-reported sleep patterns along with a rating of sleep quality[27]. Participants were asked to fill out the diary daily with questions regarding daily sleep pattern, such as "what time did you get into bed", "how long did it take you to fall asleep", "how many times did you wake up, not counting your final awakening", etc., for 7 consecutive days at each assessment point. Diaries with at least 4 days of data were counted as valid and the averages of sleep parameters were calculated at each assessment point. Sleep parameters include SOL, WASO, time in bed (TIB), TST, SE, and sleep quality (SQ). In addition to self-reported sleep, wrist actigraphy (Actiwatch by Phillips Respironics) was used to collect objectively-measured sleep[28,29]. Scoring of actigraphy data followed a protocol used in previous study (see Figure S2 in supplemental material for scoring protocol).

Daytime Functioning

Several self-reported measures were collected to assess the impact of the interventions on daytime functioning. The FOSQ is a 30-item scale that measures the impact of daytime sleepiness on multiple daily activities across 5 factor subscales (activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome) with higher scores

representing less difficulties in carrying the activities[30]. The ESS is a 8-item scale that measures the general level of daytime sleepiness by assessing the tendency of dozing off/ falling asleep under 8 different situations. ESS scores have been found to correlate with the severity of OSA and be responsive to the treatment effects after PAP therapy for OSA[31,32]. The Flinders Fatigue Scale (FFS) is a 7-item scale that assesses the extent of insomnia-related fatigue and its impact on everyday functioning[33]. Higher scores on both the ESS and FFS indicate greater impairment.

Cognitive-emotional Measures

Several cognitive-emotional measures were collected to examine changes in cognitions related to insomnia, hyperarousal, and emotional functioning. The Beliefs and Attitudes about Sleep (BAS) is a 30-item scale that assesses dysfunctional beliefs and attitudes about sleep, which might contribute to initiation and persistence of insomnia[34]. Questions include unrealistic sleep expectations, perceptions of diminished control over sleep, and beliefs about sleep-promoting behaviors rated from 0 to 10 for each item, with a higher total score indicating greater dysfunctional cognition. The Glasgow Sleep Effort Scale (GSES) is a 7-item self-report measure of sleep effort during the past week. It scored on a 3-point Likert scale, with higher score indicating greater sleep effort[35]. The Sleep Locus of Control (SLOC) is an 8-item, 6-point Likert scale that measures the degree of how much an individual believes his or her sleep experiences are the result of personal control, as opposed to due to chance or external factors, with higher scores representing a greater internal locus of control[36]. The Pre-Sleep Arousal Scale (PSAS) is a 16-item self-report measure that assesses somatic and cognitive arousal (subscales) in the period prior to sleep[37]. This scale uses a 5-point Likert scale to rate the extent to which each item is experienced, with higher scores indicating greater pre-sleep arousal experience. The Center for

Epidemiologic Studies Depression (CES-D) is a 20-item scale used to evaluate the level of depression throughout the interventions[38]. The State Trait Anxiety Inventory – Trait (STAI-T) is a 20-item scale to measure participants' trait anxiety[39]. Items are scored on a 4-point Likert scale, with higher scores indicating greater anxiety level.

Data Analysis

Statistical analyses were conducted through IBM SPSS Statistics 25 (IBM Corp., Armonk, NY). A two-tailed alpha level of 0.05 was used to determine significance for all statistical tests. A series of 3 (treatment arm) x 4 (time/ assessment point) linear mixed models with a nested factor of recruitment site were performed on each outcome measure to examine the effect of CBT-I and PAP treatment combination across assessment points. The models were adjusted for age, educational level (attended graduate school or not), marital status (married or not), sex, OSA severity (mild [AHI $\geq$ 5 and < 15] or moderate-to-severe [AHI $\geq$ 15]), and average PAP use (average minute of usage over the 90-day period).

This study used a three-arm partial factorial design (see Figure S1). The factorial model was built by treatment type (CBT-I/ PAP) x treatment presence (not present/ present and delivered first/ present and delivered second), and was informed by the combinations that were most relevant to the specific research questions (i.e., timing and benefits of CBT-I in addition to PAP)[24]. To test the relative benefits of each intervention (CBT-I, PAP, or self-monitoring), planned contrast comparisons based on the study's factorial model were used when significant arm x time interactions were found in linear mixed model analyses (see Table S2 in the supplemental material for contrast design). To compare the effect of different treatments, between-assessment point differences of each outcome measure were calculated (e.g., time

period 1 = score changes from Assessment 1 to 2, period 2 = Assessment 2 to 3). 3 arms x 3 time periods were then decomposed into 9 levels (e.g., level 1 = Arm A at time period 1, level 2 = Arm A at period 2). By designating contrast weights toward each level, this study extracted specific treatment phases to compare between treatment conditions. A total of 6 special contrasts (including 1 for intercepts) were built in each post-test to examine the relative benefits of each treatment and its combination, (1) Arm A, B vs. Arm C (CBT-I + PAP vs. PAP-alone), (2) Arm A vs. Arm B (the timing of CBT-I initiation), (3) CBT-I vs. self-monitoring, (4) PAP vs. self-monitoring, and (5) CBT-I vs. PAP (see Table S2).

In addition, exploratory analyses from the previous main outcome study[13] identified significant relationships between certain demographic variables (i.e., level of education, marital status) and PAP adherence. To explore the potential impact of demographic factors, OSA severity, and PAP use on nocturnal sleep and daytime performance in COMISA, this study examined the relationships between these covariates and the outcome measures.

RESULTS

Demographic characteristics

118 participants were included for final analysis. The mean age was 49.99 ± 13.12 years with a range from 25 to 79, with 53.4% of the sample female. As shown in Table 1, no demographic or OSA severity difference was found between treatment arms.

<Insert Table 1 >

Sleep

Sleep Diary

A main effect of time was found on all sleep parameters, indicating that there was a significant decrease across all study arms on SOL ($F[3, 81.63] = 8.49$, $p < 0.001$), WASO ($F[3, 96.43] = 14.04$, $p < 0.001$), and TIB ($F[3, 88.97] = 4.58$, $p = 0.005$), and an increase on TST ($F[3, 91.01] = 4.29$, $p = 0.007$), SE ($F[3, 91.49] = 15.68$, $p < 0.001$), and SQ ($F[3, 86.53] = 20.29$, $p < 0.001$) from baseline (Assessment 1) to end-of-treatment (Assessment 4) (Table 2). In addition, significant arm by time interactions were found on SOL ($F[6, 81.52] = 6.25$, $p < 0.001$), WASO ($F[6, 96.48] = 3.73$, $p = 0.002$), TIB ($F[6, 89.23] = 7.30$, $p < 0.001$), SE ($F[6, 91.40] = 8.48$, $p < 0.001$), and SQ ($F[6, 86.56] = 3.42$, $p = 0.004$) (see Figure 2a and Figure 3).

Planned contrast analyses based on the factorial model showed that CBT-I significantly reduced SOL ($p = 0.001$), WASO ($p < 0.001$), and TIB ($p < 0.001$), and increased SE ($p < 0.001$) compared to self-monitoring, consistent with expectations of the effects of sleep restriction and stimulus control components. Additionally, CBT-I showed superior effects on improving these sleep parameters (SOL, WASO, TIB, and SE) compared to PAP (all $p < 0.001$). No significant difference was found in the comparison of treatment combinations (Arm A and B vs. Arm C) (see Table S3 and Table S4 in supplemental material for contrast result tables).

Actigraphy

Linear mixed models showed a main effect of time on reducing WASO ($F[3, 66.32] = 3.53$, $p = 0.019$) and TIB ($F[3, 73.22] = 4.12$, $p = 0.009$), as well as increasing SE ($F[3, 74.23] = 3.18$, $p = 0.029$) from baseline to end-of-treatment across all study arms. There was also a significant arm by time interaction in TIB ($F[6, 73.59] = 2.48$, $p = 0.031$). Specifically, the reductions on

TIB in Arm A and B occurred during CBT-I delivery (Figure 2b), indicating evidence of participants' adherence to the sleep restriction protocol in CBT-I. Planned contrast analyses showed a significant reduction in TIB during CBT-I compared to self-monitoring ($p = 0.025$) as well as to PAP ($p = 0.004$).

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Daytime Functioning

Linear mixed models revealed a main effect of time on FOSQ ($F[3, 95.08] = 25.84$, $p < 0.001$) (Figure 4), FFS ($F[3, 95.91] = 21.84$, $p < 0.001$), and ESS ($F[3, 95.72] = 31.35$, $p < 0.001$), indicating that participants in all groups reported improvements in daytime functioning from baseline to end-of-treatment across all study arms. In addition, significant arm by time interactions were found in FOSQ ($F[6, 95.13] = 4.25$, $p = 0.001$) and FFS ($F[6, 96.14] = 2.78$, $p = 0.016$). Planned contrast analyses showed that compared to self-monitoring, there was an increased FOSQ score ($p = 0.031$) and a reduced FFS score that approached significance ($p = 0.050$) in participants receiving CBT-I.

< Insert Figure 4 >

Cognitive-emotional Measures

Linear mixed-models conducted on cognitive-emotional measures revealed a main effect of time in all scales with significant reductions from baseline to end-of-treatment across study arms

on BAS ($F[3, 96.83] = 19.35$, $p < 0.001$), CES-D ($F[3, 96.03] = 19.50$, $p < 0.001$), STAI-T ($F[3, 95.74] = 15.48$, $p < 0.001$), PSAS (Total Score: $F[3, 96.04] = 21.43$, $p < 0.001$; Cognitive subscale: $F[3, 94.53] = 19.70$, $p < 0.001$; Somatic subscale: $F[3, 96.28] = 9.10$, $p < 0.001$), and GSES ($F[3, 97.53] = 19.93$, $p < 0.001$) scores, and a significant increase from baseline to end-of-treatment on SLOC scores ($F[3, 97.39] = 8.79$, $p < 0.001$).

The significant arm by assessment point interaction in BAS ($F[6, 96.82] = 8.96$, $p < 0.001$) and its contrast analysis indicated that CBT-I significantly reduced dysfunctional beliefs about sleep in relation to PAP and self-monitoring (both $p < 0.001$).PAP also had an effect on reducing BAS score compared to self-monitoring ($p = 0.037$).

The linear mixed model on SLOC score also showed a significant interaction ($F[6, 97.54] = 4.47$, $p < 0.001$). Planned comparisons revealed a significant effect of CBT-I over PAP ($p = 0.008$) on increasing the degree of participants attributing their experiences of sleep to internal causes.

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Exploratory Analyses

To explore the impact of demographic factors on the outcome measures, contributions of the covariates (i.e., age, education level, marital status, sex, OSA severity, and PAP use) to each linear mixed model were examined. Age was found to be positively associated with diary-measured SOL ($F[1, 92.88] = 4.54$, $p = 0.036$, estimate = 0.32) and WASO ($F[1, 93.28] = 5.21$, $p = 0.025$, estimate = 0.39), and negatively associated with diary-measured SE ($F[1, 93.49] = 10.89$, $p = 0.001$, estimate = -0.23).

In addition, marital status had a significant association with objective sleep measures. Mixed models of actigraphy-measured sleep outcomes showed that compared to people who were married, those who were not married tended to have longer objective SOL ($F[1, 71.37] = 7.17$, $p = 0.009$, estimate = 11.30) and WASO ($F[1, 86.43] = 7.84$, $p = 0.006$, estimate = 14.25), as well as shorter TST ($F[1, 79.18] = 5.25$, $p = 0.025$, estimate = -28.65), and lower objective SE ($F[1, 81.17] = 16.06$, $p < 0.001$, estimate = -7.31). No effect of educational level or sex was found in these analyses.

Besides demographic factors, OSA severity and PAP use were also associated with sleep parameters and daytime performance. Compared to moderate-to-severe OSA, people with mild OSA had longer actigraphy-measured TST ($F[1, 79.90] = 6.89$, $p = 0.01$, estimate = 29.99) and lower diary-measured sleep quality ($F[1, 95.52] = 16.63$, $p < 0.001$, estimate = -0.41). In addition, average PAP use was found to be a significant contributor to the FOSQ ($F[1, 89.13] = 4.32$, $p = 0.041$, estimate = 0.003), BAS ($F[1, 92.50] = 7.10$, $p = 0.09$, estimate = -0.06), and STAI ($F[1, 92.46] = 4.18$, $p = 0.044$, estimate = -0.012) models, indicating better daytime functioning, less dysfunctional beliefs about sleep, and lower anxiety level in participants who used PAP more regularly.

DISCUSSION

The goal of this study was to provide further insights into the clinical impact of using CBT-I and PAP on nocturnal sleep and daytime functioning for individuals with COMISA. In general, the findings indicate that using PAP, alone or concomitant with CBT-I, resulted in significant improvements from baseline to 90 days of PAP use on several measures of sleep and daytime

functioning. However, the addition of CBT-I to PAP therapy accelerated the improvements on several clinical measures, regardless of when it was initiated relative to PAP. Collectively, these findings reinforce the benefits of PAP use for COMISA but also indicate that adding CBT-I to PAP as part of a concomitant approach can achieve more rapid improvements in nocturnal sleep and daytime functioning.

Significant improvements were observed on self-reported and objective measures of sleep across all treatment arms. Self-reported sleep efficiencies increased by about 10% - 12% from baseline to end-of-treatment (Arm A [CBT-I, followed by PAP]: 12.2%; Arm B [CBT-I concurrent with PAP]: 11.0%; Arm C [PAP only]: 10.1%), reaching a sleep efficiency around 87% at the end of treatment in all arms. This level of sleep efficiency is considered within the normal range[40]. All treatment approaches also significantly reduced SOL and WASO in sleep diary with all three treatment arms reporting SOL and WASO < 30 minutes at the end of treatment, which is a common clinical cut-off for insomnia. Planned comparisons of CBT-I, PAP, and self-monitoring found that CBT-I was superior to self-monitoring and PAP on improving self-reported SOL, WASO, TIB, and SE, consistent with expectations of sleep restriction and stimulus control delivered during CBT-I. A significant reduction was also found across all treatment arms on actigraphy-measured WASO, TIB, and SE. Importantly, the significant reduction in actigraphy-measured TIB was most prominent during the period when participants received CBT-I, which provides objective evidence of adherence to the sleep restriction component of CBT-I in people with COMISA. Consistent with previous findings on global insomnia symptoms[12,13], these findings underscore the benefits of CBT-I on sleep parameters and further support the use of CBT-I for improving sleep in COMISA population. It is notable that even participants in Arm C, who received PAP with no CBT-I, reported

significant improvements in several sleep parameters, indicating that PAP can be an effective singular treatment in improving sleep in people with COMISA.

Similar results were found to support the benefits of all three treatment conditions on daytime performance. Significant improvements were observed from baseline to end-of-treatment on the FOSQ and significant decreases were found on fatigue and sleepiness with planned contrasts showing that CBT-I was superior to self-monitoring for improvements on the FOSQ and reducing fatigue. These findings suggest that CBT-I can optimize daytime functioning in patients with COMISA. Significant reductions were found on BAS with planned contrasts indicating that CBT-I was significantly better at reducing maladaptive sleep-related cognitions compared to PAP and self-monitoring, and PAP was significantly better than self-monitoring at reducing dysfunctional cognitions. It was expected that CBT-I would be superior to the other treatment conditions but the benefits of PAP on sleep-related cognitions were unexpected. Furthermore, exploratory analyses revealed that higher average PAP use per night was associated with better outcomes on the FOSQ, BAS, and STAI. Taken together, these findings indicate the improvements in sleep achieved from PAP alone could be another means of reducing maladaptive sleep-related beliefs and negative affect in people with COMISA, similar to changes reported after behaviour therapy alone in insomnia patients (Eidelman et al. 2016). Whether these shifts are sustained long-term remains to be explored further.

In addition to the treatment effects, this study observed some potential factors that were associated with these clinical outcome measures. Age was found to be associated with nocturnal sleep quality. Younger participants in this sample tended to have better self-reported sleep. Interestingly, marital status also predicted objective sleep quality whereby people who were married, in relation to those who were not, had better actigraphy-measured sleep efficiency. One

possible explanation of these data could be the impact of having a bed partner on patient's adherence to treatment and subsequent outcomes in COMISA population[41]. Beyond the sociodemographic factors, OSA severity was found to be another predictor for nocturnal sleep in this sample. Compared to those with a moderate-to-severe OSA, participants with mild OSA had more actigraphy-measured TST.

Two main limitations should be taken into account when interpreting and generalizing the findings from this study. First, multiple comparisons were used to conduct separate analyses for each outcome measure, which could inflate Type I error. Given these are secondary analyses from a clinical trial, the findings should be interpreted with caution, and are intended to complement the primary endpoints of the study. Second, the study design did not include all possible treatment combinations and sequences and thus we are unable to draw conclusion about certain treatment sequences such as administering CBT-I first compared to PAP first. Compared to full factorial designs, partial factorial designs may be more prone to potential bias when interactions exist[42]. However, the factorial design allowed for efficiency in the sample size and conducting planned comparisons of the treatment components of interest, which revealed important new data pertaining to the specific changes associated with CBT-I and PAP in the context of COMISA treatments.

The findings of this study indicate that people with COMISA can achieve significant improvements in sleep and daytime functioning when receiving PAP for 90 days, which is generally consistent with the known treatment effects of PAP on OSA[43-46]. Adding CBT-I as a concomitant treatment appears to enhance the treatment effects by accelerating the rate of improvement in sleep and daytime functioning. Therefore, the concomitant approach using CBT-I and PAP appears to optimize the speed of response and effectiveness of treating COMISA.

Given that these were secondary analyses, further research should be conducted to confirm these findings.

ABBREVIATIONS LIST

AHI – Apnea-Hypopnea Index

BAS – Beliefs and Attitudes about Sleep

CBT-I – Cognitive Behavioral Therapy for Insomnia

CES-D – Center for Epidemiologic Studies Depression

COMISA – Comorbid Insomnia and Sleep Apnea

ESS – Epworth Sleepiness Scale

FFS – Flinders Fatigue Scale

FOSQ – Functional Outcomes of Sleepiness Questionnaire

GSES – The Glasgow Sleep Effort Scale

OSA – Obstructive Sleep Apnea

PAP – Positive Airway Pressure Therapy

PSAS – Pre-Sleep Arousal Scale

SE – Sleep Efficiency

SLOC – Sleep Locus of Control

SOL – Sleep Onset Latency

STAI-T – State Trait Anxiety Inventory

TIB – Total Time in Bed

TST – Total Sleep Time

WASO – Wake After Sleep Onset

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Table 1 – Sample characteristics.

	Arm A (n = 41)		Arm B (n = 39)		Arm C (n = 38)		*P*
Age (M, SD)	47.7	12.6	53.2	11.1	49.2	15.1	0.15
Gender (n, %)							0.26
Male	21	51.2%	14	35.9%	20	52.6%	
Female	20	48.8%	25	64.1%	18	47.4%	
Race (n, %)							0.35
American Indian/Alaskan Native	0	0.0%	0	0.0%	1	2.6%	
Asian	3	7.3%	1	2.6%	3	7.9%	
Black or African American	15	36.6%	19	48.7%	16	42.1%	
White	23	56.1%	19	48.7%	16	42.1%	
More than one race	0	0.0%	0	0%	2	5.3%	
OSA Severity (n, %)							0.99
Mild (AHI ≥ 5 and <15)	18	43.9%	17	43.6%	16	42.1%	
Moderate/Severe (AHI ≥15)	23	56.1%	22	56.4%	22	57.9%	
Education Years (M, SD)	15.9	2.9	15.8	2.9	16.4	3.0	0.63
Marital Status (n, %)							0.24
Married	14	34.2%	10	25.6%	14	36.8%	
Single	21	51.2%	19	48.7%	21	55.3%	
Divorced	3	7.3%	8	20.5%	3	7.9%	
Live-in partner	1	2.4%	2	5.1%	0	0.0%	
Widowed	2	4.9%	0	0%	0	0.0%	
Occupational Status (n, %)							0.37
Employed	28	68.3%	23	59.0%	24	63.2%	
Student	2	4.9%	0	0.0%	2	5.3%	
Retired	5	12.2%	10	25.6%	6	15.8%	
Homemaker	0	0.0%	2	5.1%	0	0.0%	
Disabled	0	0.0%	0	0%	1	2.6%	
Unemployed	6	14.6%	4	10.3%	5	13.2%	
PAP Use [n, M(SD)] Average minutes of use per night	38	159.58 (135.88)	34	174.06 (153.34)	30	223.12 (142.81)	0.18

Note. PAP = Positive Airway Pressure Therapy; OSA = Obstructive sleep apnea; AHI = Apnea-Hypopnea Index; M = mean; SD = standard deviation. Arm A: Cognitive-behavioral therapy for insomnia (CBT-I) in Phase I (Baseline to PAP Titration) and PAP in Phase II (PAP Titration to 90-day assessment); Arms B: self-monitoring in Phase I and CBT-I + PAP in Phase II; Arm C: self-monitoring in Phase I and PAP in Phase II.

Table 2 – Sleep Diary and Actigraphy measures of nocturnal sleep at each assessment point by each treatment arm.

		Baseline		PAP Titration		30-day assessment		90-day assessment	
Sleep Diary		*N*	M (SD)	*N*	M (SD)	*N*	M (SD)	*N*	M (SD)
SOL *** †††	**Arm A**	*39*	35.08 (24.28)	*38*	14.28 (10.85)	*32*	18.27 (15.74)	*34*	23.37 (23.25)
	Arm B	*38*	42.37 (48.97)	*33*	38.16 (44.85)	*31*	16.58 (17.81)	*30*	16.72 (13.99)
	Arm C	*37*	36.73 (33.30)	*34*	26.14 (17.72)	*29*	26.53 (23.75)	*28*	17.52 (13.44)
WASO *** ††	**Arm A**	*39*	47.40 (37.59)	*38*	21.06 (26.94)	*32*	18.27 (18.64)	*34*	23.87 (30.54)
	Arm B	*38*	41.73 (29.33)	*33*	47.46 (44.45)	*31*	27.25 (36.93)	*30*	20.36 (18.77)
	Arm C	*37*	38.77 (25.69)	*34*	33.35 (28.74)	*29*	20.41 (21.92)	*28*	16.94 (13.19)
TIB ** Δ †††	**Arm A**	*39*	464.14 (63.46)	*38*	420.57 (59.29)	*32*	428.12 (45.93)	*34*	464.70 (62.30)
	Arm B	*38*	487.82 (83.38)	*33*	494.42 (80.23)	*31*	437.90 (73.52)	*30*	451.94 (62.13)
	Arm C	*37*	472.54 (83.64)	*34*	474.90 (64.16)	*29*	489.00 (61.66)	*28*	468.10 (62.08)
TST **	**Arm A**	*39*	352.19 (89.19)	*38*	368.78 (76.04)	*32*	377.27 (47.13)	*34*	405.83 (57.80)
	Arm B	*38*	375.47 (103.64)	*33*	379.69 (89.69)	*31*	383.46 (77.40)	*30*	396.57 (70.48)
	Arm C	*37*	358.01 (87.30)	*34*	375.04 (58.42)	*29*	402.05 (63.01)	*28*	400.65 (53.76)
SE *** †††	**Arm A**	*39*	75.25 (14.83)	*38*	87.20 (11.59)	*32*	88.40 (7.87)	*34*	87.45(8.34)
	Arm B	*38*	76.83 (16.11)	*33*	77.18 (16.03)	*31*	87.60 (10.58)	*30*	87.83(8.70)
	Arm C	*37*	75.87 (14.51)	*34*	79.44 (10.50)	*29*	82.59 (12.44)	*28*	85.98(8.23)
SQ *** Δ ††	**Arm A**	*38*	2.92 (0.60)	*38*	3.29 (0.76)	*32*	3.48 (0.80)	*34*	3.44 (0.75)
	Arm B	*37*	2.86 (0.78)	*33*	2.95 (0.67)	*31*	3.39 (0.67)	*30*	3.51 (0.72)
	Arm C	*37*	2.54 (0.62)	*34*	2.73 (0.65)	*29*	3.03 (0.81)	*28*	3.39 (0.66)
Actigraphy									
SOL	**Arm A**	*36*	24.20 (25.95)	*31*	21.94 (25.40)	*24*	13.33 (14.07)	*27*	26.91 (37.45)
	Arm B	*30*	31.00 (26.29)	*26*	28.51 (37.86)	*27*	20.65 (17.67)	*23*	20.78 (13.03)
	Arm C	*27*	28.40 (32.53)	*28*	37.47 (36.99)	*26*	27.00 (21.48)	*24*	26.38 (20.38)
WASO *	**Arm A**	*36*	59.40 (26.37)	*31*	47.57 (21.98)	*24*	45.56 (27.36)	*27*	54.65 (29.38)
	Arm B	*30*	63.66 (28.56)	*26*	63.88 (30.09)	*27*	54.73 (24.99)	*23*	52.48 (22.23)
	Arm C	*27*	55.22 (19.98)	*28*	63.12 (26.22)	*26*	56.78 (29.27)	*24*	52.89 (24.62)
TIB ** †	**Arm A**	*36*	473.28 (68.09)	*31*	434.34 (51.41)	*24*	435.78 (40.26)	*27*	467.01 (61.88)
	Arm B	*30*	499.27 (73.47)	*26*	495.88 (82.53)	*27*	454.12 (80.12)	*23*	462.36 (64.26)
	Arm C	*27*	480.05 (42.92)	*28*	478.52 (58.16)	*26*	475.54 (63.91)	*24*	479.61 (70.56)
TST	**Arm A**	*36*	369.31 (70.53)	*31*	342.43 (60.12)	*24*	356.32 (52.71)	*27*	366.92 (59.09)
	Arm B	*30*	383.96 (61.70)	*26*	381.61 (68.89)	*27*	364.08 (73.08)	*23*	369.98 (59.44)
	Arm C	*27*	373.29 (47.63)	*28*	352.67 (67.31)	*26*	371.54 (57.11)	*24*	377.39 (59.46)
SE *	**Arm A**	*36*	78.12 (10.70)	*31*	78.69 (10.97)	*24*	82.18 (10.50)	*27*	79.19 (12.16)
	Arm B	*30*	77.37 (7.74)	*26*	77.37 (9.23)	*27*	80.45 (8.79)	*23*	80.04 (7.02)
	Arm C	*27*	77.20 (9.30)	*28*	74.01 (11.29)	*26*	78.21 (7.77)	*24*	79.10 (8.33)

Note. PAP = Positive Airway Pressure Therapy; SOL = sleep onset latency; WASO = wake after sleep onset; TIB = time in bed; TST = total sleep time; SE = sleep efficiency; SQ = sleep quality; M = mean; SD = standard deviation; * represents the significance of the fixed effect of time (assessment points) in the linear mixed models, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$; Δ represents the significance of the fixed effect of arm in the linear mixed models, $p < 0.05$; †

represents the significance of arm x time interaction in the linear mixed models, †: $p < 0.05$, ††: $p < 0.01$, †††: $p < 0.001$. Arm A: Cognitive-behavioral therapy for insomnia (CBT-I) in Phase I (Baseline to PAP Titration) and PAP in Phase II (PAP Titration to 90-day assessment); Arms B: self-monitoring in Phase I and CBT-I + PAP in Phase II; Arm C: self-monitoring in Phase I and PAP in Phase II.

Table 3 – Daytime functioning and cognitive-emotional measures at each assessment point by each treatment arm.

		Baseline		**PAP Titration**		**30-day assessment**		**90-day assessment**	
		N	M (SD)	*N*	M (SD)	*N*	M (SD)	*N*	M (SD)
FOSQ *** ††	**Arm A**	*40*	15.94 (2.67)	*41*	16.93 (2.29)	*38*	18.05 (1.84)	*35*	18.25 (1.99)
	Arm B	*39*	15.60 (2.76)	*34*	15.22 (2.84)	*33*	18.22 (1.70)	*34*	18.44 (2.04)
	Arm C	*37*	15.91 (2.72)	*35*	16.61 (2.34)	*32*	17.83 (2.10)	*33*	17.70 (2.54)
FFS *** †	**Arm A**	*40*	13.47(7.50)	*41*	10.33 (6.21)	*38*	9.54 (6.54)	*35*	8.09 (6.37)
	Arm B	*39*	14.44 (6.40)	*34*	14.35 (5.78)	*33*	9.03 (5.85)	*34*	7.76 (5.77)
	Arm C	*37*	13.97 (7.43)	*35*	12.40 (6.98)	*32*	10.69 (7.89)	*33*	9.58 (8.15)
ESS ***	**Arm A**	*40*	8.85(4.97)	*41*	7.66 (4.39)	*38*	5.53 (3.45)	*35*	4.77 (3.33)
	Arm B	*39*	9.41 (4.39)	*34*	9.12 (5.07)	*33*	6.61 (4.25)	*34*	4.88 (3.33)
	Arm C	*37*	9.76 (5.01)	*35*	9.47 (4.90)	*32*	6.28 (3.60)	*33*	6.24 (4.47)
BAS *** ΔΔ †††	**Arm A**	*40*	123.50 (46.12)	*41*	93.00 (38.00)	*38*	84.08 (38.77)	*35*	83.91 (42.62)
	Arm B	*39*	126.55 (40.34)	*34*	133.78 (47.20)	*33*	96.88 (43.25)	*34*	87.71 (41.02)
	Arm C	*37*	122.81 (39.22)	*35*	117.11 (38.45)	*31*	114.13 (38.64)	*33*	102.64 (38.79)
CES-D ***	**Arm A**	*40*	20.00 (5.73)	*41*	19.32 (5.47)	*38*	17.37 (5.08)	*35*	17.26 (5.49)
	Arm B	*39*	19.62 (4.33)	*33*	20.09 (5.11)	*33*	18.00 (4.99)	*34*	15.82 (3.51)
	Arm C	*37*	20.08 (4.95)	*35*	20.03 (6.69)	*32*	18.06 (5.38)	*33*	17.09 (5.89)
STAI-T ***	**Arm A**	*40*	36.77 (10.16)	*41*	36.68 (10.42)	*38*	35.42 (10.00)	*35*	33.34 (8.28)
	Arm B	*39*	37.15 (8.31)	*34*	37.58 (10.68)	*33*	33.00 (8.42)	*34*	32.74 (9.65)
	Arm C	*37*	36.86 (10.19)	*35*	37.46 (12.58)	*31*	34.53 (11.44)	*33*	35.03 (13.19)
GSES ***	**Arm A**	*40*	6.65 (3.65)	*41*	4.93 (3.14)	*38*	4.32 (3.41)	*35*	3.97 (3.14)
	Arm B	*39*	7.00 (3.49)	*34*	6.35 (3.90)	*32*	4.47 (3.56)	*34*	3.21 (2.37)
	Arm C	*37*	6.16 (3.30)	*35*	5.43 (3.31)	*32*	5.16 (3.75)	*33*	4.09 (3.59)
PSAS ***	**Arm A**	*39*	31.92 (10.91)	*41*	28.22 (9.88)	*38*	27.11 (10.17)	*35*	26.00 (9.82)
	Arm B	*39*	31.08 (9.80)	*34*	31.91 (11.25)	*33*	24.88 (7.98)	*34*	24.00 (6.56)
	Arm C	*37*	29.86 (8.42)	*35*	28.11 (8.64)	*31*	25.03 (9.45)	*33*	24.67 (10.18)
PSAS-C ***	**Arm A**	*39*	18.82 (6.84)	*41*	16.29 (6.54)	*38*	15.50 (7.15)	*35*	14.86 (7.11)
	Arm B	*39*	18.69 (7.55)	*34*	18.76 (7.46)	*33*	14.45 (5.97)	*34*	13.85 (5.12)
	Arm C	*37*	17.76 (6.11)	*35*	16.94 (6.41)	*31*	14.74 (6.89)	*33*	13.73 (6.58)
PSAS-S ***	**Arm A**	*39*	13.10 (5.01)	*41*	11.93 (4.11)	*38*	11.61 (3.73)	*35*	11.14 (3.77)
	Arm B	*39*	12.38 (4.55)	*34*	13.15 (4.92)	*33*	10.42 (2.72)	*34*	10.15 (2.27)
	Arm C	*37*	12.11 (4.00)	*35*	11.17 (3.56)	*31*	10.29 (3.54)	*33*	10.94 (4.56)
SLOC	**Arm A**	*40*	28.40 (4.83)	*41*	31.56 (5.44)	*38*	31.37 (6.44)	*35*	31.49 (6.40)

*** ΔΔ †††	**Arm B**	*39*	26.56 (6.78)	*34*	26.53 (4.83)	*33*	30.03 (6.59)	*34*	31.56 (6.03)
	Arm C	*37*	24.22 (6.91)	*35*	27.14 (5.13)	*32*	26.88 (4.96)	*33*	27.42 (5.47)

Note. PAP = Positive Airway Pressure Therapy; FOSQ = Functional Outcome of Sleep Questionnaire; FFS = Flinders Fatigue Scale; ESS = Epworth Sleepiness Scale; BAS = Beliefs and Attitudes about Sleep; CES-D = Center for Epidemiologic Studies Depression; STAI-T = State Trait Anxiety Inventory (Trait); GSES = Glasgow Sleep Effort Scale; PSAS = Pre-Sleep Arousal Scale; PSAS-C = Pre-Sleep Arousal Scale - Cognitive Subscale; PSAS-S = Pre-Sleep Arousal Scale - Somatic Subscale; SLOC = Sleep Locus of Control; SD = standard deviation. M = mean; SD = standard deviation; * represents the significance of the fixed effect of time (assessment points) in the linear mixed models, ***: $p < 0.001$; ΔΔ represents the significance of the fixed effect of arm in the linear mixed models, $p < 0.01$; † represents the significance of arm x time interaction in the linear mixed models, †: $p < 0.05$, ††: $p < 0.01$, †††: $p < 0.001$. Arm A: Cognitive-behavioral therapy for insomnia (CBT-I) followed by PAP; Arms B: self-monitoring followed by CBT-I + PAP; Arm C: self-monitoring followed by PAP.

FIGURE TITLES AND CAPTIONS

Figure 1 – CONSORT Flowchart Diagram.

CBT-I = cognitive-behavioral therapy for insomnia; PAP = positive airway pressure therapy.

Figure 2 – Sleep diary- and actigraphy-measured total time in bed (TIB) from baseline to 90-days after PAP initiation (mean ± standard errors).

PAP = positive airway pressure therapy. Arm A: Cognitive-behavioral therapy for insomnia (CBT-I) in Phase I (Baseline to PAP Titration) followed by PAP in Phase II (PAP Titration to 90-day assessment); Arms B: self-monitoring in Phase I followed by CBT-I + PAP in Phase II; Arm C: self-monitoring in Phase I followed by PAP in Phase II. Figure 2a depicts the reductions in self-reported TIB in Arm A and B during CBT-I delivery, and Figure 2b depicts a similar pattern of changes in actigraphy-measured TIB, both indicating evidences of participants' adherence to the sleep restriction protocol in CBT-I.

Figure 3 – Sleep diary-measured sleep efficiency (SE) from baseline to 90-days after PAP initiation (mean ± standard errors).

PAP = positive airway pressure therapy. Arm A: Cognitive-behavioral therapy for insomnia (CBT-I) followed by PAP; Arms B: self-monitoring followed by CBT-I + PAP; Arm C: self-monitoring followed by PAP.

Figure 4 – Functional Outcomes of Sleep Questionnaire (FOSQ) total score from baseline to 90-days after PAP initiation (mean ± standard errors).

PAP = positive airway pressure therapy. Higher scores represent less difficulties in performing daily activities. Arm A: Cognitive-behavioral therapy for insomnia (CBT-I) followed by PAP; Arms B: self-monitoring followed by CBT-I + PAP; Arm C: self-monitoring followed by PAP.

Figure S1 – Study procedure flow chart.

CBT-I = cognitive-behavioral therapy for insomnia, 4 weekly sessions in 30 days. PAP = positive airway pressure therapy. Assessment 2 was conducted at the conclusion of Phase 1. Assessment 3 was taken 30 days after initiation of Phase II. Assessment 4 was the study endpoint conducted 90 days after initiation of Phase II. Figure is adapted from [24].

Figure S2 – Scoring Protocol for Actigraphy Data.

Sleep diaries were used as the first line to determine the rest periods (period from lights out/ getting into bed to lights on/ getting out of bed). If there is more than an 1-hour discrepancy between the sleep diary periods and the data from the actigraph, other information would be considered in setting the rest interval, including (a) event marker; (b) pattern of light (e.g. light value decreases significantly); (c) decrease in activity level; (d) further inquiry with the participant; and (e) automatic detection using the Actiware program. If using the above information still did not lead to a reliable judgment, then the data would not be used for analysis.