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SCIENTIFIC INVESTIGATIONS

A randomized controlled trial of cognitive behavioral therapy for insomnia 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; Bantu S. Chhangani, MD[8]; Clete A. Kushida, PhD[9]; Jack D. Edinger, PhD[10]; Sabra M. Abbott, MD, PhD[1]; Roneil G. Malkani, MD[1,11]; Hrayr P. Attarian, MD[1]; Phyllis C. Zee, MD, PhD[1]; Jason C. Ong, PhD[1,12]

[1]Center for Circadian and Sleep Medicine, Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois; [2]Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, Illinois; [3]School of Psychological Sciences and Health, University of Strathclyde, Glasgow, United Kingdom; [4]Department of Psychological and Brain Sciences, Indiana University, Bloomington, Indiana; [5]College of Nursing, Rush University Medical Center, Chicago, Illinois; [6]Center for Translational Sleep and Circadian Sciences, Department of Psychiatry and Behavioral Sciences, University of Miami, Miami, Florida; [7]Department of Psychiatry and Behavioral Sciences, Rush University Medical Center, Chicago, Illinois; [8]Department of Medicine, Rush University Medical Center, Chicago, Illinois; [9]Division of Sleep Medicine, Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California; [10]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, National Jewish Health, Denver, Colorado; [11]Neurology Service, Jesse Brown Veterans Affairs Medical Center, Chicago, Illinois; [12]Nox Health, Suwanee, Georgia

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 on nocturnal sleep and daytime functioning.

Methods: A partial factorial design was used to examine treatment pathways with CBT-I and PAP and the relative benefits of each treatment. One hundred eighteen individuals with comorbid insomnia and sleep apnea 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, Epworth Sleepiness Scale, Functional Outcome of Sleep Questionnaire, and cognitive emotional measures.

Results: A main effect of time was found on diary-measured sleep parameters (decreased sleep onset latency and wake after sleep onset; increased total sleep time and sleep efficiency) and actigraphy-measured sleep parameters (decreased wake after sleep onset; increased sleep efficiency) and daytime functioning (reduced Epworth Sleepiness Scale, Flinders Fatigue Scale; increased Functional Outcome of Sleep Questionnaire) across all arms (all $P < .05$). Significant interactions and planned contrast comparisons revealed that CBT-I was superior to PAP and self-monitoring on reducing diary-measured sleep onset latency and wake after sleep onset and increasing sleep efficiency, as well as improving Functional Outcome of Sleep Questionnaire and Flinders Fatigue Scale 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 self-reported 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.

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Keywords: comorbid insomnia and sleep apnea, cognitive behavior therapy for insomnia, positive airway pressure therapy, sleep, daytime functioning

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Patients with comorbid insomnia and sleep apnea often experience significant daytime dysfunction and greater sleep disturbance compared to each condition alone. Recent studies have focused on positive airway pressure (PAP) adherence and insomnia remission, but the effect of concomitant treatment using PAP and cognitive behavioral therapy for insomnia 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 cognitive-behavioral therapy for insomnia in comorbid insomnia and sleep apnea.

Study Impact: The findings revealed more rapid effects on self-reported sleep and daytime functioning when receiving cognitive behavioral therapy for insomnia prior to or concurrent with PAP, compared to PAP alone. Concomitant treatment using cognitive behavioral therapy for insomnia 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 population.[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 prevalence rate of COMISA is between 30–60%, 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 (PAP) therapy 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 (eg, cardiovascular diseases).[21] Gooneratne et al[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 et al 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 (SQ), and 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 increases in total sleep time [TST] and SE) and 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 and PAP) in these outcome measures.

METHODS

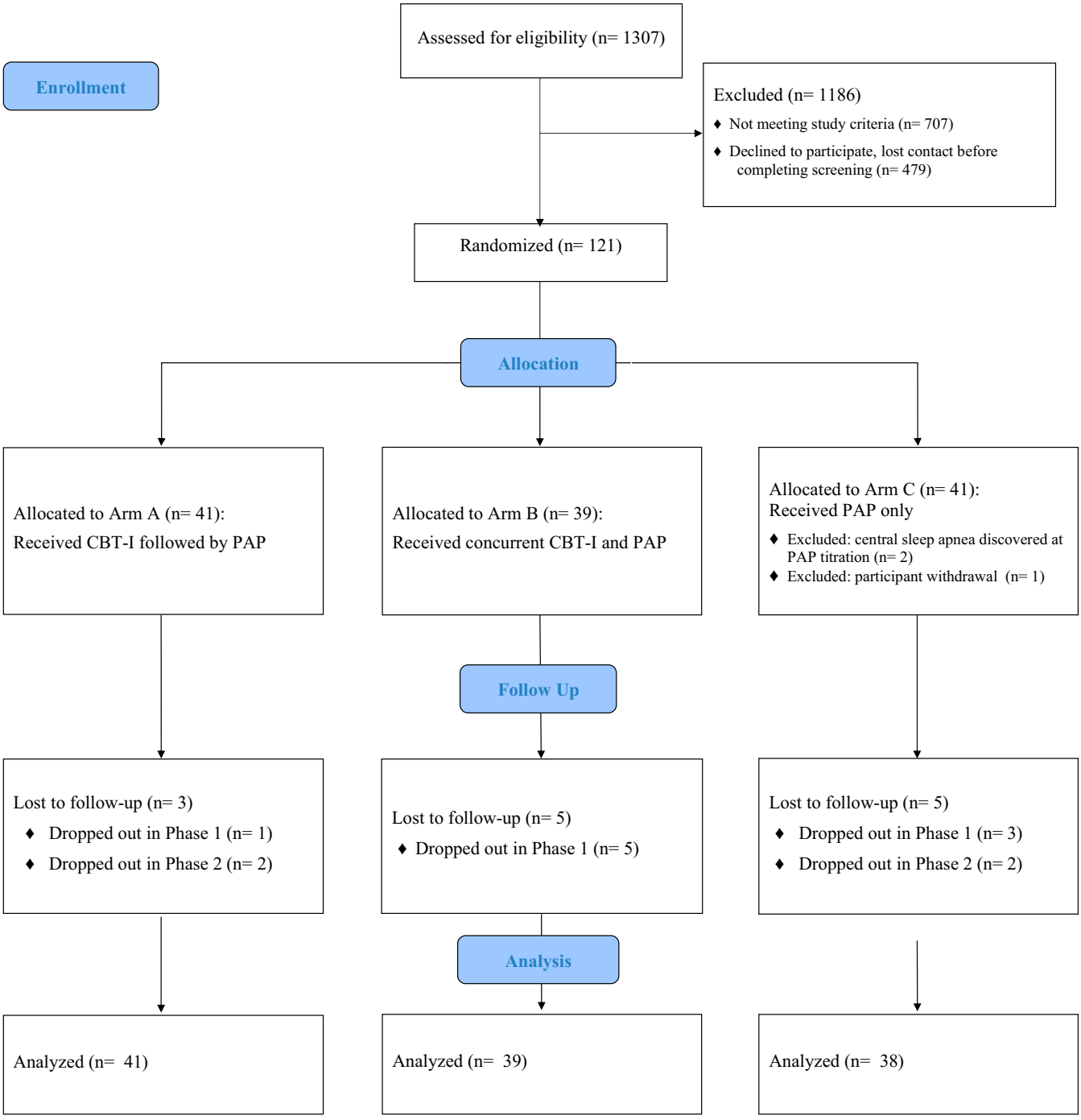
Study design and procedure

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 CBT-I and PAP initiated concurrently in Phase 2; and Arm C, self-monitoring in Phase 1 followed by PAP only in Phase 2 (see **Figure S1** in the 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 events/h and < 15 events/h; moderate-to-severe: AHI ≥ 15 events/h). Outcome measures of sleep, daytime functioning, and cognitive-emotional measures were collected during the in-person screening evaluation at baseline (Assessment 1). The 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 and 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

Figure 1—CONSORT flowchart.



CBT-I = cognitive behavioral therapy for insomnia, CONSORT = Consolidated Standards of Reporting Trials, PAP = positive airway pressure.

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.

Inclusion criteria were (1) age 18 years and over; (2) *International Classification of Sleep Disorders*, second edition criteria for OSA (AHI ≥ 5 events/h 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); and (3) *International Classification of Sleep Disorders*, second edition 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 an SOL or WASO > 30 minutes for at least 3 nights per week through a 1-week sleep diary.

Exclusion criteria included (1) medical and psychiatric conditions that were unstable or judged to interfere with the study protocol or required immediate treatment (eg, 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 events/h or arterial oxygen saturation < 80% for more than 10% of TST); (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 setup and home use.

Interventions

PAP therapy

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 (PAP/Auto PAP Models 460 and 560; Phillips Respironics, Murrysville, PA) 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 1 week after setup 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.

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 (eg, cognitive restructuring) (see **Table S1** in the 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 (J.C.O.). 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 (eg, participants' self-monitoring of sleep and 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 SQ.[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 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** for scoring protocol). Consistent with diaries, averages for each sleep parameter (ie, SOL, WASO, TIB, TST, and SE) were calculated at each assessment point if there were at least 4 days of valid data.

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 subscales (activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome) with higher scores representing less difficulties in carrying out the activities.[30] The ESS is an 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 is a 7-item self-report measure of sleep effort during the past week, scored on a 3-point Likert scale, with higher scores indicating greater sleep effort.[35] The Sleep Locus of Control 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 chance or external factors, with a higher scores representing a greater internal locus of control.[36] The Pre-Sleep Arousal Scale 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 presleep arousal experience. The Center for Epidemiologic Studies Depression is a 20-item scale used to evaluate the level of depressive symptoms.[38] The State Trait Anxiety Inventory – Trait 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, New York). A two-tailed alpha level of 0.05 was used to determine significance for all statistical tests. A series of 3 (treatment arm) × 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 ≥ 5 events/h and < 15 events/h] or moderate-to-severe [AHI ≥ 15 events/h]), and average PAP use (average minutes 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) × 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 (ie, 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 × time interactions were found in linear mixed model analyses (see **Table S2** for contrast design). To compare the effect of different treatments, between-assessment point differences of each outcome measure were calculated (eg, time period 1 = score changes from Assessment 1 to 2, period 2 = Assessment 2 to 3). Three arm × 3 time periods were then decomposed into 9 levels (eg, 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 posttest 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 (ie, level of education and 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

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

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 < .001), WASO (F[3, 96.43] = 14.04, P < .001), and TIB (F[3, 88.97] = 4.58, P = .005) and an increase on TST (F[3, 91.01] = 4.29, P = .007), SE (F[3, 91.49] = 15.68, P < .001), and SQ (F[3, 86.53] = 20.29, P < .001) from baseline (Assessment 1) to end of treatment (Assessment 4) (**Table 2**). In addition, significant arm × time interactions were found on SOL (F[6, 81.52] = 6.25, P < .001), WASO (F[6, 96.48] = 3.73, P = .002), TIB (F[6, 89.23] = 7.30, P < .001), SE (F[6, 91.40] = 8.48, P < .001), and SQ (F[6, 86.56] = 3.42, P = .004) (see **Figure 2A** and **Figure 3**).

Planned contrast analyses based on the factorial model showed that CBT-I significantly reduced SOL (P = .001), WASO (P < .001), and TIB (P < .001) and increased SE (P < .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 < .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** for contrast result tables).

Actigraphy

Linear mixed models showed a main effect of time on reducing WASO (F[3, 66.32] = 3.53, P = .019) and TIB (F[3, 73.22] = 4.12, P = .009) as well as increasing SE (F[3, 74.23] = 3.18, P = .029) from baseline to end of treatment across all study arms. There was also a significant arm × time interaction in TIB (F[6, 73.59] = 2.48, P = .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 = .025) as well as to PAP (P = .004).

Table 1—Sample characteristics.

	Arm A		Arm B		Arm C		
	(n = 41)		(n = 39)		(n = 38)		*P*
Age (M, SD)	47.7	12.6	53.2	11.1	49.2	15.1	.15
Sex (n, %)							.26
Male	21	51.2%	14	35.9%	20	52.6%	
Female	20	48.8%	25	64.1%	18	47.4%	
Race (n, %)							.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	0.0%	2	5.3%	
OSA severity (n, %)							.99
Mild (AHI ≥ 5 and < 15 events/h)	18	43.9%	17	43.6%	16	42.1%	
Moderate/severe (AHI ≥ 15 events/h)	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	.63
Marital status (n, %)							.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	0.0%	
Occupational status (n, %)							.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	0.0%	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)	.18

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); Arm 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. AHI = apnea-hypopnea index, M = mean, OSA = obstructive sleep apnea, PAP = positive airway pressure, SD = standard deviation.

Daytime functioning

Linear mixed models revealed a main effect of time on FOSQ (F[3, 95.08] = 25.84, P < .001) (**Figure 4**), FFS (F[3, 95.91] = 21.84, P < .001), and ESS (F[3, 95.72] = 31.35, P < .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 × time interactions were found in FOSQ (F[6, 95.13] = 4.25, P = .001) and FFS (F[6, 96.14] = 2.78, P = .016) (**Table 3**). Planned contrast analyses showed that compared to self-monitoring, there was an increased FOSQ score (P = .031) and a reduced FFS score that approached significance (P = .050) in participants receiving CBT-I.

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 < .001), Center for Epidemiologic Studies Depression (F[3, 96.03] = 19.50, P < .001), State Trait Anxiety Inventory – Trait (F[3, 95.74] = 15.48, P < .001), Pre-Sleep Arousal Scale (total score: F[3, 96.04] = 21.43, P < .001; cognitive subscale: F[3, 94.53] = 19.70, P < .001; somatic subscale: F[3, 96.28] = 9.10, P < .001), and Glasgow Sleep Effort Scale (F[3, 97.53] = 19.93, P < .001) scores and a significant increase from baseline to end of treatment on Sleep Locus of Control scores (F[3, 97.39] = 8.79, P < .001).

Table 2—Sleep diary and actigraphy measures of nocturnal sleep at each assessment point by each treatment arm.

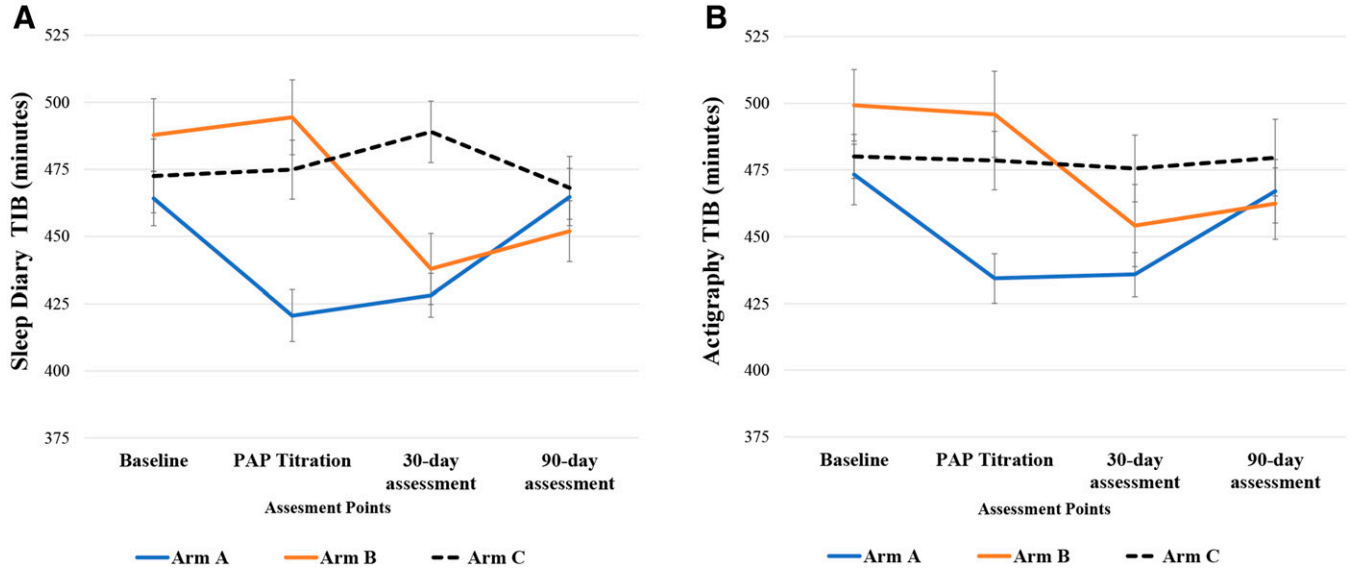
		Baseline		PAP Titration		30-Day Assessment		90-Day Assessment	
		n	M (SD)	n	M (SD)	n	M (SD)	n	M (SD)
Sleep diary									
SOL***†††	Arm A	39	35.08 (24.28)	38	14.28 (10.85)	32	18.27 (15.74)	34	23.37 (23.25)
	Arm B	38	42.37 (48.97)	33	38.16 (44.85)	31	16.58 (17.81)	30	16.72 (13.99)
	Arm C	37	36.73 (33.30)	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)

*Significance of the fixed effect of time (assessment points) in the linear mixed models, *P < .05, **P < .01, ***P < .001. ΔSignificance of the fixed effect of arm in the linear mixed models, P < .05. †Significance of arm × time interaction in the linear mixed models, †P < .05, ††P < .01, †††P < .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); Arm 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. M = mean, PAP = positive airway pressure, SD = standard deviation, SE = sleep efficiency, SOL = sleep onset latency, SQ = sleep quality, TIB = time in bed, TST = total sleep time, WASO = wake after sleep onset.

The significant arm × assessment point interaction in BAS (F[6, 96.82] = 8.96, P < .001) and its contrast analysis indicated that CBT-I significantly reduced dysfunctional beliefs about sleep in relation to PAP and self-monitoring (both P < .001). PAP also had an effect on reducing BAS score compared to self-monitoring (P = .037).

The linear mixed model on Sleep Locus of Control score also showed a significant interaction (F[6, 97.54] = 4.47, P < .001). Planned comparisons revealed a significant effect of CBT-I over PAP (P = .008) on increasing the degree of participants attributing their experiences of sleep to internal causes.

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

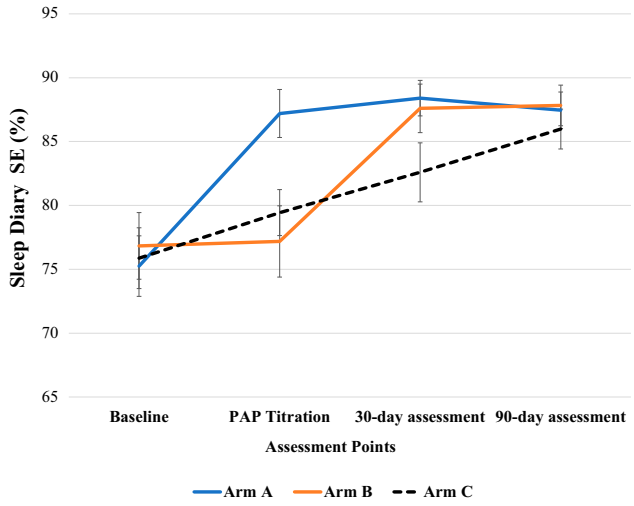


Arm A: Cognitive behavioral therapy for insomnia (CBT-I) in Phase I (Baseline to PAP Titration) followed by PAP in Phase II (PAP Titration to 90-day assessment); Arm B: self-monitoring in Phase I followed by CBT-I + PAP in Phase II; Arm C: self-monitoring in Phase I followed by PAP in Phase II. **(A)**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

Exploratory analyses

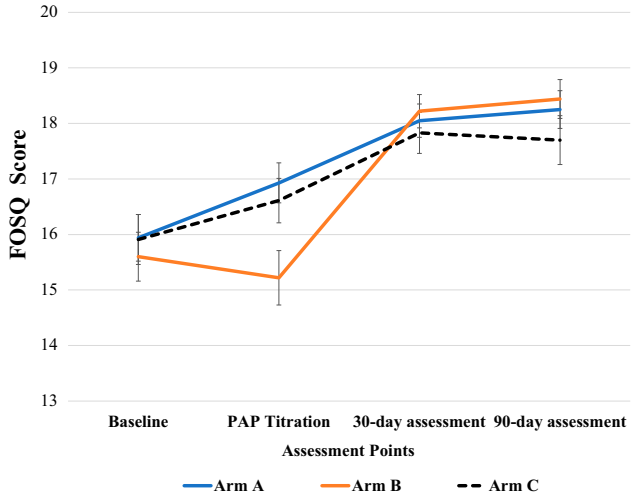
To explore the impact of demographic factors on the outcome measures, contributions of the covariates (ie, age, education level, marital status, sex, OSA severity, and PAP use) to each linear mixed model were examined. Age was found to be positively associated with diary-measured SOL (F[1, 92.88] = 4.54, P = .036, estimate = 0.32) and WASO (F[1, 93.28] = 5.21, P = .025, estimate = 0.39) and negatively associated

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



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

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



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

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***ΔΔ†††	Arm A	40	28.40 (4.83)	41	31.56 (5.44)	38	31.37 (6.44)	35	31.49 (6.40)
	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)

*Significance of the fixed effect of time (assessment points) in the linear mixed models,***$P < .001$. ΔΔSignificance of the fixed effect of arm in the linear mixed models, $P < .01$. †Significance of arm × time interaction in the linear mixed models, †$P < .05$, ††$P < .01$, †††$P < .001$. Arm A: Cognitive behavioral therapy for insomnia (CBT-I) followed by PAP; Arm B: self-monitoring followed by CBT-I + PAP; Arm C: self-monitoring followed by PAP. BAS = Beliefs and Attitudes about Sleep, CES-D = Center for Epidemiologic Studies Depression, ESS = Epworth Sleepiness Scale, FFS = Flinders Fatigue Scale, FOSQ = Functional Outcome of Sleep Questionnaire, GSES = Glasgow Sleep Effort Scale, M = mean, PAP = positive airway pressure, PSAS = Pre-Sleep Arousal Scale, PSAS-C = Pre-Sleep Arousal Scale – Cognitive Subscale, PSAS-S = Pre-Sleep Arousal Scale – Somatic Subscale, SD = standard deviation, SLOC = Sleep Locus of Control, STAI-T = State Trait Anxiety Inventory (Trait).

with diary-measured SE ($F[1, 93.49] = 10.89$, $P = .001$, 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 ($F[1, 71.37] = 7.17$, $P = .009$, estimate = 11.30) and WASO ($F[1, 86.43] = 7.84$, $P = .006$, estimate = 14.25) as well as shorter TST ($F[1, 79.18] = 5.25$, $P = .025$, estimate = −28.65) and lower objective SE ($F[1, 81.17] = 16.06$, $P < .001$, 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 = .01, estimate = 29.99) and lower diary-measured SQ (F[1, 95.52] = 16.63, P < .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 = .041, estimate = 0.003), BAS (F[1, 92.50] = 7.10, P = .09, estimate = −0.06), and State Trait Anxiety Inventory (F[1, 92.46] = 4.18, P = .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 SE around 87% at the end of treatment in all arms. This level of SE 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 reductions in 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 State Trait Anxiety Inventory. 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.

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 SQ. Younger participants in this sample tended to have better self-reported sleep. Interestingly, marital status also predicted objective SQ, whereby people who were married, in relation to those who were not, had better actigraphy-measured SE. 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 and examine patient factors that can predict the optimal treatment pathway.

ABBREVIATIONS

AHI, apnea-hypopnea index
BAS, Beliefs and Attitudes about Sleep
CBT-I, cognitive behavioral therapy for insomnia
COMISA, comorbid insomnia and sleep apnea
ESS, Epworth Sleepiness Scale
FFS, Flinders Fatigue Scale
FOSQ, Functional Outcomes of Sleepiness Questionnaire
OSA, obstructive sleep apnea
PAP, positive airway pressure
SE, sleep efficiency
SOL, sleep onset latency
SQ, sleep quality
TIB, total time in bed
TST, total sleep time
WASO, wake after sleep onset

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Address correspondence to: Jason C. Ong, PhD, 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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