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ORIGINAL ARTICLE

The effect of cognitive and behavioral therapy for insomnia on week-to-week changes in sleepiness and sleep parameters in patients with comorbid insomnia and sleep apnea: a randomized controlled trial

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Abstract

Study Objectives. While cognitive and behavioral therapy for insomnia (CBTi) is an effective treatment in patients with comorbid moderate and severe obstructive sleep apnea (OSA), there is concern that the bedtime restriction component of CBTi might dangerously exacerbate daytime sleepiness in such patients. We examined randomized controlled trial data to investigate the effect of OSA severity, and pretreatment daytime sleepiness on week-to-week changes in daytime sleepiness and sleep parameters during CBTi and no-treatment control.

Methods: One hundred and forty-five patients with untreated physician-diagnosed OSA (apnea–hypopnea index ≥15) and psychologist-diagnosed insomnia (ICSD-3) were randomized to a 4-week CBTi program (n = 72) or no-treatment control (n = 73). The Epworth sleepiness scale (ESS) and sleep diaries were completed during pretreatment, weekly CBTi sessions, and posttreatment. Effects of OSA severity, pretreatment daytime sleepiness, and intervention group on weekly changes in daytime sleepiness and sleep parameters were investigated.

Results: The CBTi group reported a 15% increase in ESS scores following the first week of bedtime restriction (M change = 1.3 points, 95% CI = 0.1–2.5, p = 0.031, Cohen's d = 0.27) which immediately returned to pretreatment levels for all subsequent weeks, while sleep parameters gradually improved throughout CBTi. There were no differences in changes in daytime sleepiness during treatment between CBTi and control groups or OSA-severity groups. Higher pretreatment ESS scores were associated with a greater ESS reduction during CBTi.

Conclusions: CBTi appears to be a safe and effective treatment in the presence of comorbid moderate and severe OSA. Nevertheless, patients living with comorbid insomnia and sleep apnea and treated with CBTi should be monitored closely for increased daytime sleepiness during the initial weeks of bedtime restriction therapy.

Clinical Trial Registration: Treating comorbid insomnia with obstructive sleep apnoea (COMISA) study: A new treatment strategy for patients with combined insomnia and sleep apnoea, https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id = 365184 Australian New Zealand Clinical Trials Registry: ACTRN12613001178730. Universal Trial Number: U1111-1149-4230.

Statement of Significance

Comorbid insomnia and sleep apnea is a prevalent condition that presents unique diagnostic and treatment challenges. Although several researchers recommend that such patients should be initially treated with cognitive and behavioral therapy for insomnia (CBTi), there is some concern that the bedtime restriction component of CBTi may exacerbate daytime sleepiness among patients with untreated moderate and severe sleep apnea. This trial demonstrated that patients with moderate and severe sleep apnea show a small increase of daytime sleepiness following the initiation of bedtime restriction therapy, which immediately returned to pretreatment levels. Compared to control, CBTi did not lead to increased sleepiness by posttreatment. When managed appropriately, CBTi is an effective and safe insomnia treatment in the presence of moderate and severe sleep apnea.

Key words: insomnia; cognitive behavioral therapy for insomnia; sleep restriction therapy; comorbid insomnia; obstructive sleep apnea; COMISA; excessive daytime sleepiness

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Introduction

Insomnia and obstructive sleep apnea (OSA) are the two most common sleep disorders, each occurring in 10% of the general population [1, 2]. Insomnia is characterized by chronic complaints of difficulties initiating sleep, maintaining sleep, or early morning awakenings, with associated daytime functional impairments [3], while OSA is characterized by repetitive brief closure (apnea) or narrowing (hypopnea) of the upper airway during sleep, leading to frequent intermittent hypoxemia, transient arousals, and surges in sympathetic nervous system activity [3]. OSA is also associated with increased daytime sleepiness and an increased risk of motor vehicle accidents [4–7]. The presence and severity of OSA are most commonly determined from the apnea–hypopnea index (AHI) that represents the average number of respiratory events occurring per hour of sleep. Moderate and severe OSA are commonly indicated by an AHI of at least 15 to less than 30 and at least 30, respectively [8].

Comorbid insomnia and sleep apnea (COMISA) is a highly prevalent condition [9, 10]. For example, 30%–70% of patients with preexisting OSA also report clinically significant insomnia symptoms, while 29%–67% of patients living with insomnia are found to have comorbid OSA when tested with overnight polysomnography (PSG) [9, 10]. Patients with COMISA experience more severe sleep disruption [11, 12], and daytime impairments [7, 11, 13], increased symptoms of depression and psychiatric disorders [11, 13, 14], and reduced quality of life [15], compared to patients with either insomnia or OSA alone [10].

Although COMISA is a common and debilitating condition, it is also more difficult to treat compared to either disorder in isolation [9, 10]. For example, the recommended treatment for moderate and severe OSA is continuous positive airway pressure (CPAP) therapy [8], which may be more difficult for patients to accept and regularly use when sleep of those living with insomnia is already difficult to initiate and/or maintain without the added encumbrance of a mask forcing air into the nose/mouth. Despite the presence of more severe sleep disruption and daytime impairments, patients with OSA with comorbid insomnia are less likely to accept and use CPAP therapy compared to those with OSA alone [16–19]. This finding has led several groups to suggest that patients with COMISA should be referred for insomnia treatment prior to commencing CPAP therapy [10, 20–24].

Cognitive and behavioral therapy for insomnia (CBTi) is the recommended treatment for insomnia [25–27]. CBTi is a multicomponent, non-pharmacological therapy that aims to modify cognitive [28], behavioral [29, 30], and physiological [31] processes and factors believed to perpetuate insomnia, over the course of 6–8 weekly sessions [25, 26]. Several pilot studies [32–37], experimental studies [24, 38, 39], and a quasi-experimental study [40] support the effectiveness of CBTi in patients with COMISA [9]. For example, we recently reported a randomized controlled trial demonstrating that compared to a control group, CBTi leads to greater improvement of global insomnia severity, dysfunctional sleep-related cognitions, and perceived sleep parameters in patients with COMISA [24]. In addition to demonstrating the efficacy of CBTi, it is also important to examine the suitability and safety of CBTi in the presence of both moderate and severe OSA and among patients with COMISA beginning treatment with elevated daytime sleepiness.

One of the most effective components of CBTi is *bedtime restriction therapy* (BRT; also *sleep restriction therapy*) [30, 41, 42]. BRT aims to gradually reduce conditioned relationships between the bedroom environment or routine and a state of arousal and alertness, thereby decreasing nighttime wakefulness [30]. During BRT, therapists guide patients to temporarily restrict time spent in bed over several consecutive nights, to increase homeostatic pressure, reduce the length of awakenings, and consolidate sleep periods [30, 42–44]. After patients begin sleeping for the majority of the time that they spend in bed (e.g. >85%), time in bed is extended from week to week, until a comfortable and satisfying equilibrium between time in bed, sleep time, and daytime sleepiness is achieved.

During the initial weeks of BRT, patients with insomnia commonly experience mild partial sleep deprivation and increased levels of daytime sleepiness, which promote the consolidation of sleep periods throughout the night [43, 44]. For example, Kyle et al. [44] examined changes in daytime sleepiness and objective sleep parameters before, during, and after 4 weekly sessions of BRT in 16 patients with insomnia. Patients reported increased sleepiness during the first 3 weeks of BRT; however, sleepiness returned to pretreatment levels by a 3-month follow-up. This initial increase in sleepiness was associated with a 91-min decrease in objective total sleep time during the first night of BRT. However, sleep time gradually increased over the subsequent weeks, as patients' conditioned insomnia responses decreased, and therapists gradually extended time in bed. Given that insomnia is characterized by chronic hyperarousal and increased *sleeplessness*, rather than increased *sleepiness* [31], acutely increased sleep propensity during the early stages of BRT has been viewed as a therapeutic target for clinicians and a manageable impact to most patients [43].

However, untreated OSA is commonly associated with elevated daytime sleepiness [4, 7, 45, 46]. Therefore, there is some concern that partial sleep restriction occurring over consecutive nights during BRT may produce a more marked and potentially serious increase in daytime sleepiness and risk of motor vehicle accidents in some patients with COMISA [6, 47, 48]. For example, patients with severe OSA may be at a greater risk of experiencing excessive daytime sleepiness during BRT compared to those with moderate OSA [7]. Alternatively, patients with COMISA entering treatment with higher daytime sleepiness may experience an additional increase and potentially dangerous levels of daytime sleepiness during BRT.

Given the recommendation that patients with COMISA should be treated with CBTi before commencing CPAP therapy, it is important to examine the effect of CBTi on week-to-week changes in daytime sleepiness and sleep parameters among patients with moderate and severe OSA and patients entering treatment with preexisting daytime sleepiness. These data are needed to inform treating physicians of the most appropriate treatment approaches and considerations for different patients with COMISA.

Methods

Study design

We used data from a previously reported randomized controlled trial examining the effect of a four-session CBTi program versus no-treatment control, on subsequent CPAP acceptance and long-term use in patients with COMISA [24]. The current study included pre-CPAP data from both experimental groups. The four

aims of the current study were (1) to investigate weekly changes in self-reported sleepiness and diary-measured sleep parameters during CBTi, (2) to compare the effect of CBTi and a control group on weekly changes in sleepiness and sleep parameters, (3) to compare the effect of moderate versus severe OSA on weekly changes in sleepiness and sleep parameters during CBTi, and (4) to investigate the effect of pretreatment daytime sleepiness on weekly changes in sleepiness and sleep parameters during CBTi. We used a combination of single-arm and experimental/quasi-experimental mixed factorial designs to examine the effect of intervention group (CBTi, control), OSA severity (moderate, severe), and pretreatment daytime sleepiness (Epworth sleepiness scale [ESS] [49]), on changes in daytime sleepiness and diary-measured sleep parameters during each week of treatment (time: pretreatment, CBTi weeks 1–4, posttreatment).

BRT was initiated during the first week of CBTi and titrated by psychologists over the subsequent 3 weeks. Therefore, the pretreatment and week 1 measures both effectively represent "pre-BRT" measures of sleepiness and sleep parameters, while measures collected during and after week 2 represent outcomes after the initiation of BRT. The Pharmacy Department of the Repatriation General Hospital in South Australia randomized patients to either a CBTi or control group using minimization (MinimPy [50]) to equate potential confounders including site, gender, insomnia severity, age, AHI, and prior CPAP use. All patients completed a PSG sleep study, the ESS, and a 1-week sleep diary at pretreatment and following 4 weeks of CBTi (or control). Patients in the CBTi group also completed sleep diaries and the ESS during each week of CBTi.

This research was approved by the Southern Adelaide Clinical Human Research Ethics Committee (Southern Adelaide Local Health Network, Adelaide, Australia), the Human Research Ethics Committee (The Prince Charles Hospital, Brisbane, Australia), Queensland University of Technology Human Research Ethics Committee, and the External Request Evaluation Committee (Department of Human Services, Australia).

Patient screening and eligibility

Patients included 145 adults with psychologist-diagnosed insomnia (ICSD-3) [3] and physician-diagnosed OSA, who were recommended for treatment with CPAP therapy (Table 1). Detailed screening information is reported in the Supplementary Materials. Patients were screened through a website screening arm (n = 739) and clinical sleep study screening arm (n = 2,131) at two teaching hospitals in Australia: The Adelaide Institute for Sleep Health and Sleep Health Service, Repatriation General Hospital, Southern Adelaide Local Health Network, Adelaide, South Australia and The Prince Charles Hospital, Brisbane, Queensland from November 2013 to April 2016.

Inclusion criteria were AHI of at least 15 according to full-night PSG recording, appropriate age range (18–75 years), a diagnosis of OSA and sleep physician recommendation for CPAP therapy, and a psychologist diagnosis of insomnia according to sleep diary and questionnaire criteria. Criteria to diagnose insomnia included an insomnia severity index [51] score of at least 14 *and* a composite score of at least 4 on the first three "nocturnal" items; average diary-measured sleep onset latency of at least 30 min, *or* average wake after sleep onset of at least 45 min, *or* sleep efficiency of not greater than 75%; *and* self-reported significant daytime impairment. Patients were required to hold an insomnia complaint for at least 6 months. Conservative sleep diary and questionnaire inclusion criteria were used to limit the likelihood that insomnia symptoms were an artifact of the untreated OSA (e.g. multiple post-apneic awakenings and sleep-related dissatisfaction) [52].

Exclusion criteria were any additional sleep disorder (e.g. restless legs syndrome and narcolepsy) or medical disorder requiring immediate treatment; any significant memory, perceptual, or behavioral disorder; neurological deficits preventing the self-administration of CPAP equipment; significant language barriers; current employment as a commercial driver; episodes of falling asleep while driving in the past 6 months; or patients who resided significantly remotely from the clinic to preclude follow-up visits. Any prospective patients who elected an initial OSA treatment approach other than CPAP (e.g. surgery and mandibular advancement splint) were also excluded. We elected to conduct a pragmatic trial likely to be generalizable to patients with COMISA in clinical settings. Thus, we included a wide age range and did not exclude any patients with rotating/night-shift schedules or patients with additional medical or psychiatric comorbidities not requiring immediate treatment (other than additional sleep disorders).

Outcome measures

One-week sleep diaries

Sleep diaries are the recommended outcome measure of sleep in insomnia treatment research [53]. Sleep diaries were completed at pretreatment, during the 4-week CBTi program, and at posttreatment. Patients' average weekly time in bed, sleep onset latency, wake after sleep onset, and total sleep time were calculated for each week/follow-up. Average sleep efficiency was also calculated by dividing the average weekly total sleep time by time in bed and multiplying by 100.

PSG sleep studies

Home-based overnight PSG studies were completed at pretreatment (Somté portable full PSG recorders; Compumedics, Melbourne, Australia). Experienced technicians scored all sleep studies according to AASM 2007 criteria, and 2009 ASTA recommendation of AASM "alternate" criteria for respiratory events and AHI cutoffs [54, 55]. OSA was defined according to an AHI cutoff of at least 15 per hour, and moderate and severe OSA were defined according to an AHI of at least 15 to less than 30 and at least 30 per hour, respectively [8]. Technicians were blind to patients' treatment group (see Supplementary Materials for more information).

Epworth sleepiness scale

The ESS [49] is an eight-item self-report scale measuring perceived likelihood of falling asleep in various situations (e.g. watching TV, sitting and talking to someone). Scores range from 0 to 24 with greater scores indicating more daytime sleepiness. A cutoff of greater than 10 was used to indicate excessive daytime sleepiness [56].

Cognitive and behavioral therapy for insomnia

CBTi was administered by seven psychologists with previous CBTi experience during 4-weekly, 45-min individual or small-group sessions. As reported previously, there was no difference

in the effectiveness of CBTi between delivery modalities [24]. A short four-session CBTi program was necessary to avoid delaying patients' progression to CPAP therapy (all patients progressed to CPAP therapy following the CBTi intervention [24]), while maintaining an adequate number of sessions to treat insomnia [57]. CBTi did not include any information about OSA or CPAP therapy. Components of CBTi included basic sleep education and sleep hygiene information, BRT, PSG and sleep misperception feedback, cognitive therapy, and relapse prevention. Stimulus control therapy is a common component of CBTi [26], however was not included in the current intervention due to our limited number of sessions, and our intention to reduce prolonged nighttime awakenings triggered by post-apneic arousals from sleep (in the presence of untreated OSA). A psychologist independent of the trial performed a CBTi fidelity check that demonstrated adequate treatment fidelity (see Supplementary Materials) [24].

BRT was initiated during the first week of CBTi, by restricting patients' time in bed to match average pretreatment diary-measured total sleep time, with a minimum of 5.5 h. Psychologists reviewed patients' pre-completed sleep diaries, ESS scores, and verbally reported sleepiness each week to inform decisions to continue, modify, or discontinue BRT. Given concerns regarding the use of BRT in the presence of untreated OSA and elevated daytime sleepiness, psychologists were also provided with a set of pragmatic suggestions to consider when implementing BRT. If a patient scored from 0 to 9 on the pretreatment ESS (i.e. no excessive daytime sleepiness), it was suggested that time in bed should be restricted to the average pretreatment total sleep time, with a minimum of 5.5 h. If a patient scored from 10 to 14 (i.e. moderate daytime sleepiness), it was suggested that minimum restriction should equal whichever was greater of the patient's pretreatment objective total sleep time during their overnight PSG study or their self-reported total sleep time from their pretreatment sleep diary. Finally, if a patient scored 15 or greater on the ESS at pretreatment (i.e. severe daytime sleepiness), it was suggested that psychologists consider regularizing their bedtimes and rise times and discourage daytime napping rather than restricting their time in bed. It was expected that these suggested modifications and psychologists' clinical judgments would replicate clinical practice and hence increase the generalizability of the current findings. If a patient's sleep efficiency was greater than 85%, bedtime parameters were extended by 15–30 min for the subsequent week. More information regarding CBTi, therapist training, accompanying materials, and treatment fidelity is reported in the Supplementary Materials.

Control

Patients randomized to the control group attended all screening and diagnostic appointments with psychologists, sleep physicians, and research staff, however did not receive any active intervention between the pretreatment and posttreatment follow-ups. Control patients completed sleep diaries and the ESS at pre- and posttreatment only (i.e. no sleep diary or ESS data were collected from control patients during the weeks between the pre- and posttreatment follow-up). The current study reports data from a larger randomized controlled trial in which control patients subsequently progressed to CPAP therapy for the treatment of their OSA [24]. Control patients were offered access to CBTi after they completed the larger trial.

Data analysis

Data were analyzed with SPSS version 22 (IBM Statistics, USA) software on an intention to treat basis. Linear mixed model analyses were used to examine weekly changes in a sleep diary and ESS outcomes between repeated measures (pretreatment, weeks 1–4, and posttreatment), intervention groups (CBTi vs. control), pretreatment daytime sleepiness (ESS), and OSA-severity groups (moderate vs. severe). Significant overall interactions and main effects were examined, before using Bonferroni adjusted comparisons within each model to perform pairwise comparisons. Sensitivity analyses including effects of AHI (a continuous measure of OSA severity) were also performed (see Supplementary Materials). Chi-square and Fisher's exact tests were used to compare rates "excessive daytime sleepiness" (ESS > 10) between OSA-severity groups and intervention groups, during each follow-up.

Outcomes were inspected for outliers and normality. A logarithmic transform was used for non-normally distributed outcomes, and analyses were run using both transformed and untransformed data. Interaction effects were identical for all analyses for any given outcome, so the results using the untransformed data are reported. Missing data were defined as missing at random or missing completely at random according to predefined criteria [24, 58]. Descriptive statistics are reported with 95% confidence intervals (CIs) and an alpha significance level of 0.05 was used.

Results

Missing data and patient attrition

At pretreatment, all sleep diary and ESS data were collected. Pretreatment AHI data were missing for two CBTi patients due to one patient immediately withdrawing from the study and one failed oximetry trace during the PSG study. Missing posttreatment data were observed for 4% and 10% of ESS forms and 7% and 21% of sleep diaries in the CBTi and control groups, respectively. Patients failing to complete posttreatment sleep diaries were more likely to be in the control than the CBTi group ($p = 0.01$), due to some patients in the control group progressing to CPAP therapy before posttreatment sleep diaries could be collected (part of the larger trial [24]). One patient in the control group withdrew due to time commitments and two in the CBTi group withdrew due to an unrelated illness and loss of interest before the posttreatment assessment.

During CBTi weeks 1–4, missing ESS data occurred in 6%, 6%, 6%, and 11% of CBTi patients, while missing sleep diary data occurred in 14%, 7%, 6%, and 10% of patients, respectively. There were no differences in rates of missing data between OSA-severity groups (all $p > 0.35$) or patients with excessive versus no excessive daytime sleepiness at pretreatment (ESS > 10) during any week of CBTi (all $p > 0.14$).

Pretreatment patient characteristics

Table 1 indicates pretreatment daytime sleepiness, insomnia severity, self-reported and objective sleep parameters, and demographic variables between CBTi and control groups and in patients with moderate and severe OSA. As reported previously [24], there were no differences in demographics, questionnaire,

Table 1. Demographic and pretreatment descriptive data

	CBTi *M* (SD)		Control *M* (SD)		OSA-severity group difference	
	Moderate OSA	Severe OSA	Moderate OSA	Severe OSA	*t*	*p*
Total *n*	36	34	39	34	0.6*	0.811
Male *n* (%)	16 (44)	23 (68)	18 (46)	22 (65)	6.3*	0.012
Age	58.5(10.3)	59.9 (9.9)	56.1 (8.6)	58.8 (11.1)	1.3	0.207
Body mass index	34.6 (6.1)	33.7 (5.5)	36.5 (7.1)	35.8 (5.8)	0.79	0.431
Insomnia severity index	18.4 (5.4)	18.3 (5.3)	17.9 (4.7)	18.0 (4.7)	0.0	0.976
ESS	9.3 (5.4)	8.7 (4.6)	9.6 (4.6)	9.7 (4.5)	0.3	0.772
ESS > 10	15	11	20	11	3.1*	0.081
Sleep diary						
Sleep time (min)	332.4 (67.9)	363.9 (71.5)	351.0 (73.6)	350.3 (89.5)	1.19	0.237
Sleep onset latency (min)	58.7 (44.4)	43.2 (29.7)	55.3 (39.4)	42.9 (27.8)	2.4	0.020
Wake after sleep onset (min)	105.5 (76.2)	86.2 (34.8)	94.6 (59.1)	104.7 (85.7)	0.4	0.694
Time in bed (min)	504.6 (68.6)	538.1 (91.0)	519.4 (83.4)	521.7 (74.5)	1.3	0.188
Sleep efficiency (%)	66.2 (12.0)	68.4 (12.0)	58.2 (13.1)	62.7 (16.1)	0.4	0.706
PSG study						
AHI	19.0 (6.1)	48.2 (18.2)	19.1 (6.8)	55.0 (22.0)	12.7	<0.001
Arousal index	24.7 (11.6)	41.6 (17.6)	22.2 (9.6)	51.1 (22.7)	8.2	<0.001
Sleep time (min)	379.6 (89.3)	371.2 (84.9)	383.6 (66.2)	329.4 (99.4)	2.2	0.031
Sleep onset latency (min)	36.6 (84.7)	28.7 (30.9)	26.7 (30.7)	32.0 (36.2)	0.1	0.898
Wake after sleep onset (min)	79.1 (59.2)	114.0 (64.1)	74.8 (44.6)	90.4 (54.1)	2.7	0.008
Sleep efficiency (%)	76.6 (15.2)	71.7 (12.7)	78.0 (10.2)	71.5 (12.9)	2.7	0.009

AHI = apnea–hypopnea index; CBTi = cognitive and behavioral therapy for insomnia; ESS = Epworth sleepiness scale; PSG = polysomnography.
*Chi-square statistic.

PSG, or sleep diary data between CBTi and control groups at pretreatment. According to an ESS cutoff of greater than 10, excessive daytime sleepiness occurred in 27 (38%) CBTi and 31 (43%) control patients at pretreatment ($p = 0.541$). As seen in Table 1, patients with severe OSA experienced higher pretreatment AHI and arousal index scores, more PSG wake after sleep onset, and less diary-measured sleep onset latency, PSG total sleep time, and PSG sleep efficiency compared to those with moderate OSA. More males than females were classified with severe OSA at pretreatment (66% vs. 34%, respectively).

CBTi compliance, adherence, and implementation

Eight patients (11.4%) did not complete the CBTi protocol due to withdrawal, loss of interest, and sickness. Five patients discontinued BRT due to health reasons, refusal, responsibilities to care for a sick partner, and anxiety. All analyses of weekly changes in ESS and diary-measured sleep parameters were re-run without these five patients and descriptive and inferential statistics remained unchanged, so original intention-to-treat analyses are reported.

As psychologists were instructed to use their clinical judgment, along with a set of suggested ESS cutoffs to inform BRT decisions (see Methods section), we examined changes in weekly psychologist-prescribed time in bed between patients in the CBTi group categorized with "no excessive daytime sleepiness" ($n = 41$; ESS 0–9), "moderate daytime sleepiness" ($n = 17$; ESS 10–14), and "severe daytime sleepiness" ($n = 12$; ESS 15–24) at pretreatment. There was no significant interaction effect between time and ESS category ($F(186.7) = 1.52$, $p = 0.175$) or main effect of ESS category ($F(67.5) = 1.0$, $p = 0.375$) on psychologist-prescribed time in bed, indicating that psychologists recommended a similar degree of bedtime restriction for patients with different levels of pretreatment daytime sleepiness during CBTi. A sensitivity analysis including fixed effects of time and pretreatment ESS scores (retained as a continuous predictor) on psychologist-prescribed time in bed did not change this interpretation of interaction or main effects (both $p \geq 0.29$; see Figure 3 for the diary-measured time in bed between intervention groups and pretreatment ESS scores).

Changes in daytime sleepiness

Aim 1: Weekly changes in sleepiness during CBTi

Among patients in the CBTi group, a main effect of time ($F(315.4) = 6.3$, $p < 0.001$) indicated that patients experienced a significant 15% increase in daytime sleepiness between the first and second week of CBTi (i.e. immediately after commencing BRT; *M* difference = 1.3, CI = 0.1, 2.5, $p = 0.031$, Cohen's $d = 0.27$), before returning to pretreatment levels for each subsequent week (all $p \geq 0.13$ compared to pretreatment and week 1; see "CBTi group average" in Figure 1).

Aim 2: Weekly changes in sleepiness between CBTi and control groups

There was no significant intervention group by time interaction on ESS scores ($F(540.0) = 1.0$, $p = 0.316$; see Figure 1), indicating that CBTi did not lead to a significantly greater increase or maintenance of sleepiness from pre- to posttreatment compared to the control group, consistent with our previous analysis [24].

Aim 3: Effect of OSA severity on weekly changes in sleepiness

Among patients in the CBTi group, there was no significant OSA severity by time interaction effect (Table 2) or main effect of OSA-severity group ($p = 0.212$) on ESS scores, indicating that patients with moderate and severe OSA did not experience significantly

different weekly changes in daytime sleepiness during CBTi. A sensitivity analysis including pretreatment AHI (retained as a continuous predictor) intervention group and time confirmed these interaction/main effects (see Figure 1 and Supplementary Materials). An additional mixed model including effects of intervention group, OSA-severity group, and time indicated that there was no significant difference in weekly changes in daytime sleepiness between CBTi and control groups, between patients with moderate and severe OSA (interaction $p = 0.90$).

Aim 4: Effect of pretreatment daytime sleepiness on weekly changes in sleepiness

Among CBTi patients, a significant pretreatment ESS by time interaction effect ($F(308.1) = 5.6$, $p < 0.001$) indicated that patients beginning treatment with higher ESS scores experienced a greater decrease in daytime sleepiness during CBTi (Figure 2). For example, CBTi patients beginning treatment with an ESS of 5 experienced no change in ESS scores by posttreatment (*M* difference = 0.3-point increase, CI = –1.0, 1.6, $p = 0.693$), while those beginning treatment with an ESS of 20 experienced a 7.1-point decrease in ESS scores by posttreatment (CI = 4.6, 9.5, $p < 0.001$; Figure 2).

A mixed model including fixed effects of intervention group, pretreatment ESS, and time revealed a significant three-way interaction ($F(498.9) = 6.8$, $p = 0.009$; Figure 2) indicating that CBTi led to a greater decrease in daytime sleepiness compared to the control group in patients beginning treatment with greater daytime sleepiness, compared to patients beginning treatment with lower daytime sleepiness. For example, among patients beginning treatment with an ESS score of 20, those in the CBTi group showed a significant 7.1-point decrease in ESS scores during treatment (CI = 4.6, 9.5, $p < 0.001$), while those in the control group showed no change ($p = 0.326$). Alternatively, among patients beginning treatment with an ESS score of 5, neither the CBTi or the control group showed a significant change in ESS scores by posttreatment (both $p > 0.44$).

Changes in sleep parameters

Aim 1: Weekly changes in sleep parameters during CBTi

Among CBTi patients, a significant main effect of time ($F(295.4) = 52.1$, $p < 0.001$; Figure 3) indicated that time in bed was significantly decreased by the second week of treatment (i.e. immediately after commencing BRT), compared to pretreatment (*M* reduction = 114.7 min, CI = 88.9, 140.4, $p < 0.001$, Cohen's $d = 1.33$) and week 1 (*M* reduction = 105.8 min, CI = 85.5, 126.2, $p < 0.001$, Cohen's $d = 1.44$). Although time in bed remained restricted during each subsequent week of therapy compared to pretreatment (all $p < 0.001$, Cohen's $d = 0.95$–1.35), gradual upward titration of time in bed during CBTi resulted in a significant increase in time in bed between week 2 (i.e. initial restriction) and posttreatment (*M* difference = 38.7 min, CI = 9.0, 68.5, $p = 0.002$, Cohen's $d = 0.49$).

Total sleep time was significantly reduced by the second week of CBTi compared to pretreatment (*M* reduction = 25.9 min, CI = 3.0, 48.8, $p = 0.014$, Cohen's $d = 0.34$; Figure 4) and week 1 (*M* reduction = 25.4 min, CI = 7.5, 43.2, $p = 0.001$, Cohen's $d = 0.34$). Following the reduction of sleep during week 2, there was a gradual increase of total sleep time over the subsequent weeks, until posttreatment sleep time was 30.2 min greater than week 1 (CI = 0.6, 60.0, $p = 0.041$, Cohen's $d = 0.40$) and 55.6 min greater than week 2 (CI = 28.7, 82.4, $p < 0.001$, Cohen's $d = 0.74$).

A main effect of time ($F(291.2) = 28.7$, $p < 0.001$; Figure 5) indicated that among patients in the CBTi group, sleep efficiency was significantly greater than pretreatment by week 2 (*M* increase = 12.2%, CI = 7.5, 16.8, $p < 0.001$, Cohen's $d = 0.92$), week 3 (*M* increase = 17.1%, CI = 11.9, 22.3, $p < 0.001$, Cohen's $d = 1.29$), week 4 (*M* increase = 19.2%, CI = 13.7, 24.7, $p < 0.001$, Cohen's $d = 1.45$), and posttreatment (*M* increase = 17.4%, CI = 11.7, 23.1, $p < 0.001$, Cohen's $d = 1.31$).

A main effect of time ($F(269.1) = 6.05$, $p < 0.001$) indicated that CBTi-treated patients reported significantly shorter sleep onset latencies during weeks 3 (*M* reduction = 28.8 min, CI = 6.7, 50.9, $p = 0.002$, Cohen's $d = 0.81$), 4 (*M* reduction = 30.2 min, CI = 7.8, 52.6, $p = 0.001$, Cohen's $d = 0.85$), and posttreatment (*M* reduction = 31.8 min, CI = 9.5, 54.1, $p < 0.001$, Cohen's $d = 0.90$), compared to pretreatment.

Finally, CBTi-treated patients reported significantly reduced wake after sleep onset by weeks 2 (*M* reduction = 51.8 min, CI = 32.7, 70.7, $p < 0.001$, Cohen's $d = 0.78$), 3 (*M* reduction = 57.1 min, CI = 36.6, 77.5, $p < 0.001$, Cohen's $d = 0.86$), 4 (*M* reduction = 58.2 min, CI = 36.8, 79.6, $p < 0.001$, Cohen's $d = 0.87$), and posttreatment (*M* reduction = 50.8 min, CI = 29.1, 72.5, $p < 0.001$, Cohen's $d = 0.76$), compared to pretreatment.

Aim 2: Weekly changes in sleep parameters between CBTi and control groups

A significant intervention group by time interaction effect ($F(523.1) = 13.4$, $p < 0.001$; Figure 3) indicated that CBTi patients experienced a greater reduction of time in bed from pre- to posttreatment (*M* reduction = 75.8 min, CI = 41.8, 109.8, $p < 0.001$, Cohen's $d = 0.95$) compared to control patients (*M* reduction = 14.5 min, CI = –9.4, 38.4, $p = 0.233$, Cohen's $d = 0.18$), confirming the results of our previous report [24]. Despite this significant difference in time in bed, we found no difference in changes in total sleep time between the CBTi and control groups from pre- to posttreatment (interaction $p = 0.611$; Figure 4).

As previously reported, the CBTi group experienced significantly greater improvement of sleep efficiency and wake after sleep onset by posttreatment compared to the control group (interaction $p < 0.001$ and 0.016, respectively; Figure 5) [24]. Although we previously found a greater reduction of sleep onset latency in the CBTi than the control group when examining changes between pre- and posttreatment [24], after including weekly measures of sleep parameters collected during CBTi, this effect was no longer statistically significant ($p = 0.053$).

Aim 3: Effect of OSA severity on weekly changes in sleep parameters

Among patients in the CBTi group, there was no significant difference in changes in any sleep parameter between OSA-severity groups (see Table 2). Sensitivity analyses including AHI as a continuous predictor of OSA severity confirmed these results (see Supplementary Materials). Main effects of OSA severity indicated that compared to patients with severe OSA, those with moderate OSA experienced 33.9 min less overall time in bed (CI = 7.1, 60.7; $F(75.8) = 3.4$, $p = 0.014$, Cohen's $d = 0.43$) and 35.6 min less total sleep time (CI = 8.6, 62.7; $F(74.9) = 6.9$, $p = 0.011$, Cohen's $d = 0.47$), but no difference in sleep efficiency ($p = 0.252$), sleep onset latency ($p = 0.292$), or wake after sleep

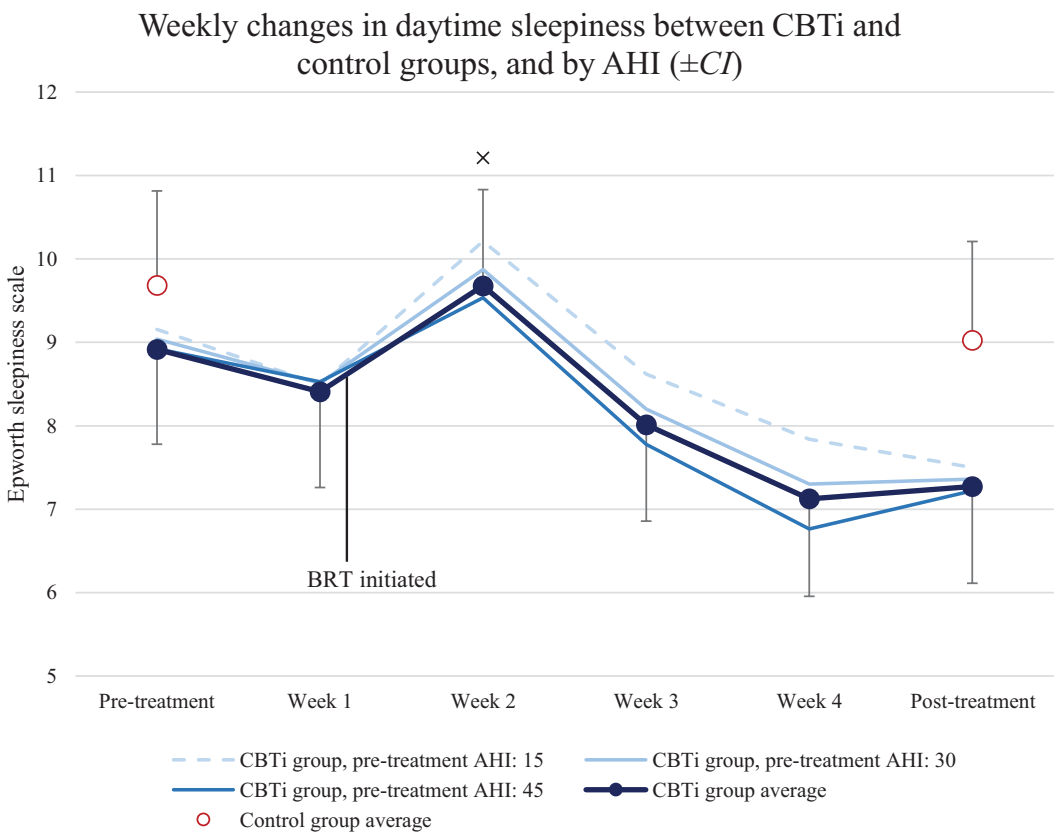

Figure 1. Weekly changes in daytime sleepiness between CBTi and control groups and by pretreatment AHI (±CI). "x" indicates a significant difference in daytime sleepiness from week 1 in the CBTi group. AHI = apnea–hypopnea index; BRT = bedtime restriction therapy; CBTi = cognitive and behavioral therapy for insomnia.

onset ($p = 0.456$) during CBTi. An additional set of analyses including the effects of intervention group, OSA severity, and time did not indicate any significant three-way interactions on any sleep diary outcome (all $p \geq 0.25$).

Aim 4: Effect of pretreatment daytime sleepiness on weekly changes in sleep parameters

Among the CBTi group, there were no interactions between pretreatment ESS and time on any diary-measured sleep parameter (all $p > 0.67$), indicating that patients beginning treatment with different levels of reported sleepiness did not experience significantly different changes of any sleep parameters during CBTi (Figures 3 and 5). The main effect of pretreatment ESS scores indicated that patients with higher levels of daytime sleepiness at pretreatment reported lower total sleep time ($F(75.5) = 4.3$, $p = 0.042$) and greater wake after sleep onset ($F(85.1) = 8.9$, $p = 0.004$) throughout treatment.

A series of mixed model analyses including fixed effects of intervention group, pretreatment ESS, and time on sleep parameters were also performed. A significant three-way interaction was observed for sleep efficiency ($F(496.4) = 6.3$, $p = 0.013$), indicating that CBTi was associated with a greater increase of sleep efficiency from pre- to posttreatment compared to the control group among patients with lower daytime sleepiness than higher daytime sleepiness at pretreatment (Figure 5). For example, among patients beginning treatment with an ESS score of 20, an increase in sleep efficiency was observed for patients in both the CBTi (M increase = 11.4%, CI = 1.7, 21.0, $p = 0.021$) and control groups by posttreatment (M increase = 15.6%, CI = 6.4, 28.7, $p = 0.002$). Alternatively, among patients beginning treatment with an ESS score of 5, those in the CBTi group showed a 19.6% increase in sleep efficiency by posttreatment ($CI = 14.4$, 24.7, $p < 0.001$), while those in the control group showed no change (M increase = 1.5%, CI = –4.7, 7.6, $p = 0.6.3$; Figure 4). There were no other significant three-way interactions between intervention group, pretreatment ESS, and time on any other sleep parameters (all $p > 0.15$).

Serious adverse events and excessive daytime sleepiness

During the posttreatment follow-up, patients reported the occurrence of serious adverse events including any event resulting in a hospital appointment or admission, or any untoward medical occurrences. One serious adverse event was recorded during the BRT protocol in which a patient reported experiencing chest pain after physical exertion. An angiogram revealed mild coronary artery disease and the patient was subsequently recommended medical management and weight loss. This event was deemed to be unrelated to the BRT protocol.

According to an ESS cutoff of greater than 10 [56], excessive daytime sleepiness was observed in 38% of CBTi patients at pretreatment and 38%, 44%, 31%, 20%, and 25% of patients during weeks 1–4 and posttreatment, respectively. There were no differences in the proportion of patients in the CBTi group with excessive daytime sleepiness between patients with moderate and severe OSA during any follow-up (all Fisher's exact

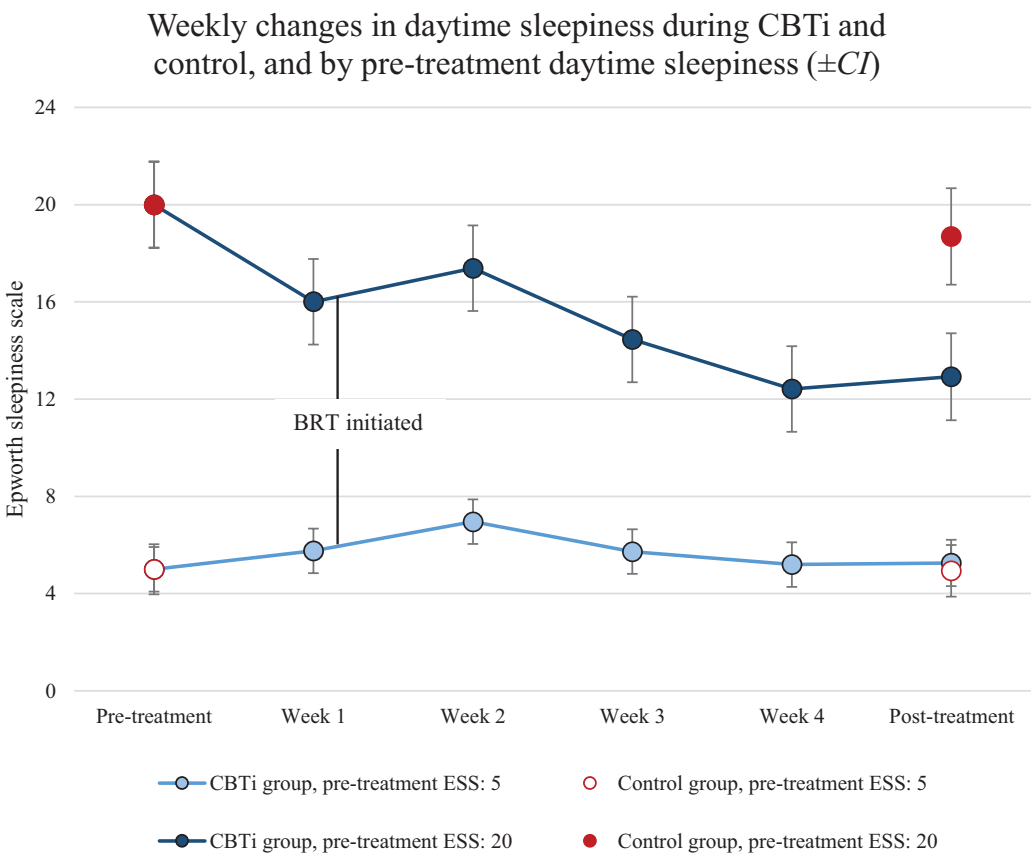

Figure 2. Weekly changes in daytime sleepiness during CBTi and control and by pretreatment daytime sleepiness (±CI). BRT = bedtime restriction therapy; CBTi = cognitive and behavioral therapy for insomnia; ESS = Epworth sleepiness scale.

$p > 0.21$). Furthermore, there was no difference in the proportion of patients with excessive daytime sleepiness between the CBTi (25%) and control groups (39%) by posttreatment (Fisher's exact $p = 0.10$).

Discussion

In a large sample of patients with COMISA, self-reported daytime sleepiness showed a significant but small increase after the first week of BRT. However, following the second week of BRT, sleepiness ratings returned to pretreatment levels and remained so for the rest of the treatment. The first week following the initiation of BRT (week 2) was also associated with a 106-min reduction of diary-measured time in bed and a 26-min reduction of total sleep time. Although total sleep time returned to pretreatment levels by the following week, time in bed remained restricted for the subsequent weeks of treatment. On the other hand, patients reported gradual improvement of sleep onset latency, wake after sleep onset, and sleep efficiency throughout treatment. Compared to the control group, CBTi did not lead to a greater increase or maintenance of sleepiness by posttreatment but was associated with greater improvement of sleep efficiency and wake after sleep onset. We observed no differences in weekly changes in ESS scores, diary-measured sleep parameters, or the proportion of patients with excessive daytime sleepiness (i.e. ESS > 10) between patients with moderate and severe OSA. Together, these results suggest that when managed appropriately, CBTi is a safe and effective insomnia treatment in the presence of co-occurring moderate and severe OSA.

Although CBTi is recommended as the initial treatment for patients with COMISA [10, 20–24], there has been an understandable degree of caution regarding the use of BRT in patients with untreated OSA who may enter treatment with elevated daytime sleepiness. The primary concern is that patients with OSA may experience an increased vulnerability to the effects of partial sleep restriction, which may exacerbate levels of daytime sleepiness and increase the risk of accidents [7, 47].

However, we observed only a small and short-lived 8% decrease in sleep time and an accompanying 15% increase in self-reported sleepiness following the first week of BRT. However, by the second week of BRT, self-reported sleepiness and total sleep time had returned to pretreatment levels. These acute changes reinforce the importance of closely monitoring symptoms and providing patients advice to manage sleepiness-related side effects during the early stages of BRT; however, we do not believe that these small increases in sleepiness should preclude physicians from referring future patients with COMISA for BRT when managed appropriately.

There has also been some concern that patients with COMISA with severe OSA may be more vulnerable to the effect of consecutive nights of partial sleep restriction during BRT. We compared changes in sleepiness and sleep parameters between patients with moderate and severe OSA (and by AHI; see Supplementary Materials), however did not observe any difference in weekly changes in sleepiness or sleep parameters

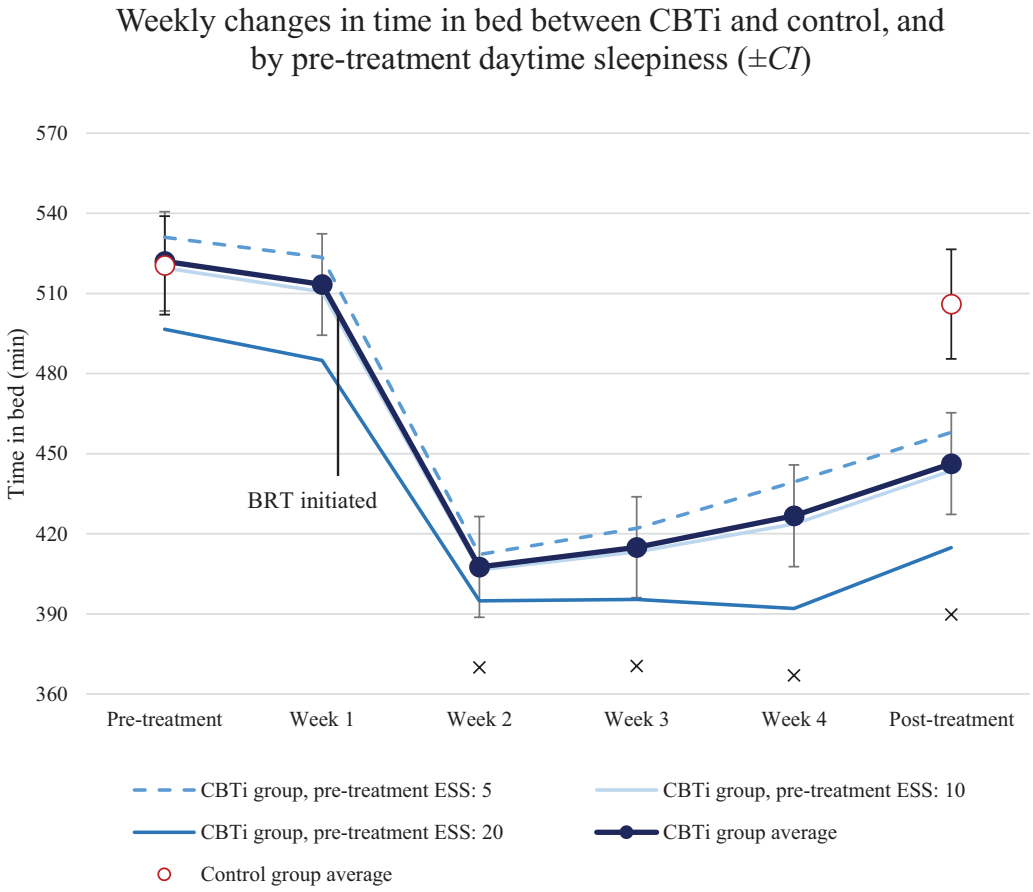

Figure 3. Weekly changes in time in bed between CBTi and control groups and by pretreatment daytime sleepiness (±CI). BRT = bedtime restriction therapy; CBTi = cognitive and behavioral therapy for insomnia; ESS = Epworth sleepiness scale. "x" indicates a significant reduction in time in bed from pretreatment and week 1 in the CBTi group.

Table 2. Weekly sleepiness and sleep parameters during cognitive and behavioral therapy for insomnia between patients with moderate and severe sleep apnea (mean ± CI)

			Bedtime restriction therapy				OSA-severity interaction	
	Pretreatment	Week 1	Week 2	Week 3	Week 4	Posttreatment	*F*	*p*
Epworth sleepiness scale								
Moderate OSA	9.3 (1.6)	9.0 (1.6)	10.6 (1.6)	9.0 (1.6)	8.0 (1.6)	7.5 (1.6)		
Severe OSA	8.7 (1.7)	8.0 (1.7)	9.0 (1.7)	7.2 (1.7)	6.3 (1.7)	7.1 (1.7)	0.69	0.633
Total sleep time (min)								
Moderate OSA	332.4 (25.7)	323.6 (25.0)	305.2 (25.9)	329.7 (25.9)	347.2 (26.1)	364.0 (26.1)		
Severe OSA	363.9 (26.4)	372.5 (26.9)	338.9 (26.7)	366.8 (26.6)	384.8 (26.7)	389.6 (26.6)	0.85	0.515
Time in bed (min)								
Moderate OSA	504.6 (25.8)	496.5 (26.2)	394.3 (26.1)	394.4 (26.1)	403.7 (26.2)	436.2 (26.3)		
Severe OSA	538.1 (26.6)	529.8 (27.2)	420.8 (27.0)	436.3 (26.8)	451.0 (26.9)	456.5 (26.7)	1.02	0.407
Sleep efficiency (%)								
Moderate OSA	66.2 (4.3)	66.2 (4.4)	77.8 (4.4)	83.4 (4.4)	86.1 (4.4)	83.1 (4.4)		
Severe OSA	68.4 (4.5)	71.0 (4.6)	81.0 (4.5)	84.9 (4.5)	86.0 (4.5)	85.4 (4.5)	0.53	0.756
Wake after sleep onset (min)								
Moderate OSA	105.5 (18.5)	94.0 (18.8)	46.8 (18.7)	34.8 (18.7)	33.9 (18.8)	46.4 (18.9)		
Severe OSA	86.2 (19.0)	85.4 (19.6)	39.5 (19.4)	40.9 (19.2)	40.0 (19.4)	41.0 (19.2)	0.84	0.523
Sleep onset latency (min)								
Moderate OSA	58.7 (13.0)	65.8 (13.6)	41.4 (13.2)	23.5 (13.2)	30.9 (13.4)	22.7 (13.4)		
Severe OSA	43.2 (13.4)	41.7 (14.4)	46.0 (14.0)	32.2 (13.6)	21.1 (14.0)	26.9 (13.6)	1.68	0.140

OSA = obstructive sleep apnea.

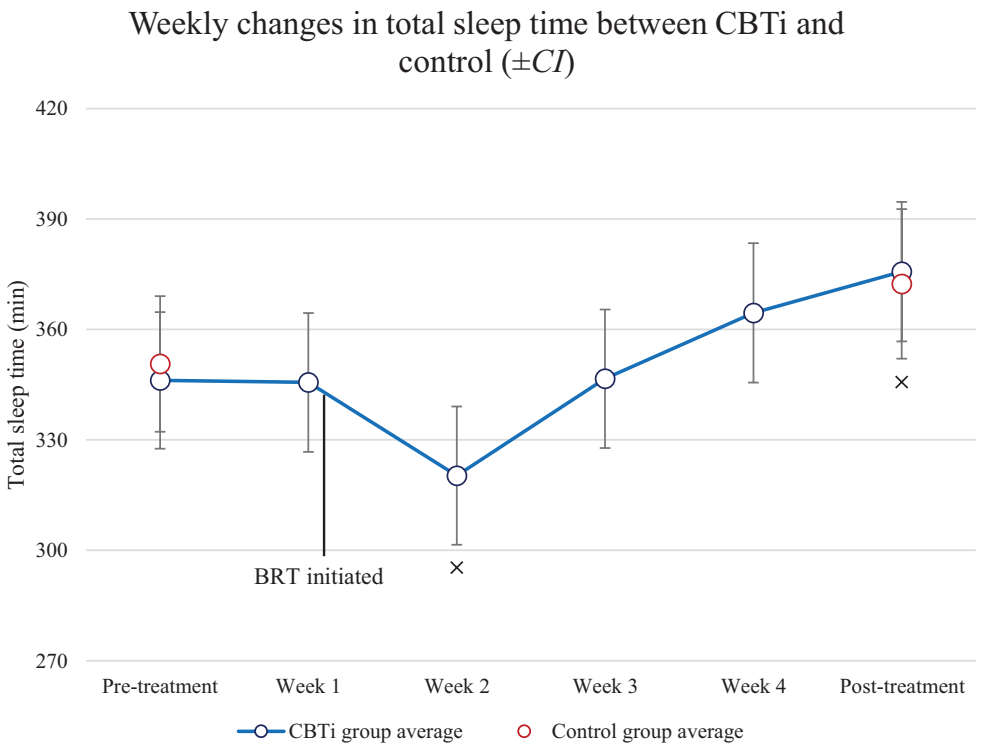

Figure 4. Weekly changes in total sleep time during CBTi and control (±CI). "x" indicates a significant change from week 1 in the CBTi group. BRT = bedtime restriction therapy; CBTi = cognitive and behavioral therapy for insomnia.

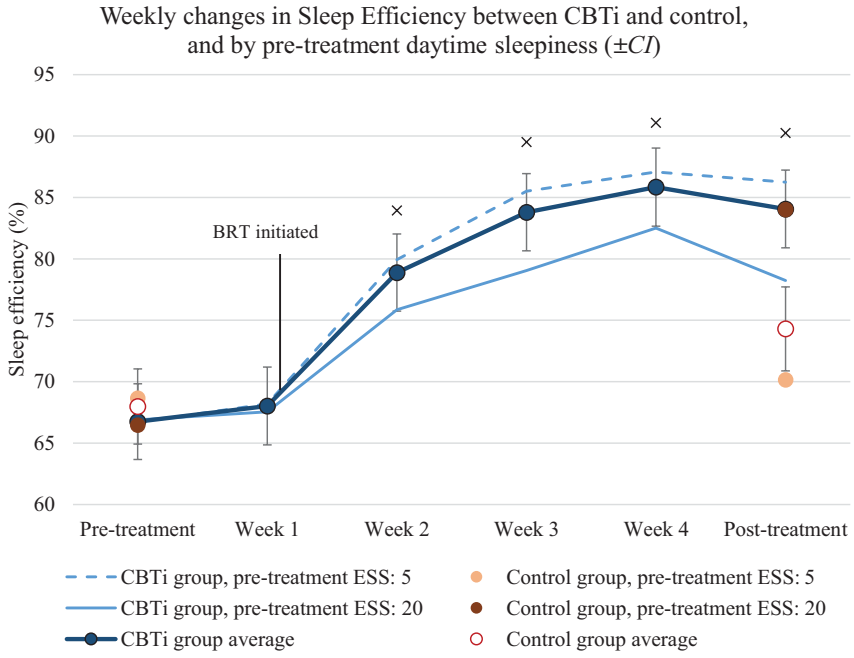

Figure 5. Weekly changes in sleep efficiency during CBTi and control and by pretreatment daytime sleepiness (±CI). "x" indicates a significant change from pretreatment in the CBTi group. BRT = bedtime restriction therapy; CBTi = cognitive and behavioral therapy for insomnia; ESS = Epworth sleepiness scale.

during BRT, or any difference in the proportion of patients reporting "excessive daytime sleepiness" during any week of CBTi.

Furthermore, we examined weekly changes in daytime sleepiness and sleep parameters among patients with COMISA beginning treatment with elevated ESS scores. Although we provided psychologists with suggestions to modify the BRT protocol based on ESS scores, there were no differences in psychologist-prescribed time in bed restriction between patients entering treatment with different levels of daytime sleepiness. Interestingly, we found that patients with higher pretreatment ESS scores reported a greater reduction of sleepiness during CBTi. Although this interaction effect may have partly resulted

from a floor effect among patients with lower pretreatment ESS scores, we also observed a three-way interaction effect which indicated that CBTi resulted in greater reduction of daytime sleepiness by posttreatment than the control group among patients beginning treatment with higher ESS scores, compared to patients beginning treatment with lower ESS scores. Hence, patients with COMISA entering CBTi with elevated sleepiness scores may experience an overall reduction of ESS during treatment, despite restricted time in bed, acutely reduced sleep time, and the persistence of untreated moderate and severe OSA. It is possible that the consolidation of sleep, reduced nocturnal wakefulness, and reduced symptoms of cognitive and physiological "hyper-arousal" during CBTi may result in reduced perceptions of sleepiness among such patients.

Together, these results support that patients with COMISA with moderate and severe OSA, and patients beginning treatment with preexisting daytime sleepiness warrant consideration for CBTi before initiating CPAP therapy. Given the established beneficial effect of CBTi on improved insomnia symptoms and increased subsequent CPAP use, a single week of mildly increased daytime sleepiness during CBTi will likely represent an acceptable and comparatively small impact to most physicians and patients with COMISA [10, 24].

Kyle et al. [44] previously observed that among patients with insomnia alone, BRT was associated with an immediate 90-min reduction of objective sleep time and a 3.7-point increase in ESS scores that remained elevated for the following 3 weeks. In contrast, the patients with COMISA in the current study experienced a smaller 26-min reduction of perceived sleep time and a 1.3-point increase in ESS scores after the initiation of BRT, which returned to pretreatment levels by the following week. Kyle et al.' study included a greater restriction of time in bed as evidenced by the 130-min decrease in time in bed during the first week, compared to the 106-min decrease observed in patients with COMISA in the current study. This difference in BRT protocols may have resulted in the larger and more sustained changes in daytime sleepiness in the patients with insomnia alone [44]. The previous patients with insomnia alone also began treatment with lower ESS scores compared to the patients with COMISA in the current study; however, both groups reported similar levels of daytime sleepiness by the final treatment session.

Future research should aim to confirm these changes in daytime sleepiness during CBTi in patients with COMISA, with a broader range of outcomes including cognitive functioning and simulated driving performance measures, and multiple sleep latency tests administered at key points during treatment. This latter suggestion is particularly salient given that the mean ESS score after the first week of treatment was 9.7 and 44% of the patients had an ESS score of greater than 10. It may also be possible for future research to investigate baseline predictors of patients who are most vulnerable to experiencing greater increases in objective sleepiness and impairment of cognitive functioning during CBTi, so BRT protocols can be modified accordingly [59].

The current CBTi protocol differs from other CBTi protocols in several important ways which may limit the generalizability of these results. Firstly, we delivered CBTi over the course of 4 weekly sessions rather than the standard six to eight sessions, to avoid delaying patients' progression to CPAP therapy [24]. Although previous research has demonstrated the effectiveness of shorter four to six sessions of CBTi programs [40, 57, 60], additional treatment sessions may allow for a more gradual (ramped) introduction of BRT to reduce the initial sudden increase in daytime sleepiness. Secondly, our CBTi program did not include stimulus control therapy [29]. Given the association between untreated OSA and daytime sleepiness, we predicted that patients with COMISA would express fewer difficulties initiating sleep at the start of the night and greater difficulties with prolonged nocturnal awakenings throughout the night precipitated by frequent post-apneic arousals from sleep. We therefore focused our CBTi intervention on BRT, known to produce moderate to large improvements in sleep onset latency, nighttime wakefulness, and sleep efficiency [42]. Finally, we utilized a modified BRT protocol to accommodate preexisting levels of elevated sleepiness. Psychologists were instructed to use their clinical discretion and were provided with a list of suggested ESS cutoffs to modify BRT decisions. In practice, psychologists relied largely on their clinical discretion and prescribed similar levels of restriction between patients commencing treatment with different levels of daytime sleepiness. Furthermore, psychologists prescribed an average of 6.2 h' time in bed during the first week of BRT, which is close to the recommended 5.5 h minimum, and similar to the degree of restriction applied in several other trials investigating the effect of CBTi in patients with insomnia alone [42, 60].

Several limitations should be considered when interpreting the results of this study. Firstly, the BRT protocol was delivered alongside other components of CBTi, including sleep education, sleep hygiene, and cognitive therapy. Therefore, we are unable to confirm the unique contribution of BRT to changes in sleep and sleepiness in the current sample. However, BRT is rarely delivered independently of other CBTi components and the delivery of a full CBTi package increases the generalizability of these findings to future patients with COMISA treated in clinical settings.

Secondly, control patients did not complete weekly ESS or sleep diaries outcomes between the pre- and posttreatment follow-up, which precluded direct between-group comparisons of sleepiness and sleep parameters during each week of treatment. Future studies may wish to employ weekly measures of sleep, sleepiness, and other daytime functioning/side effect outcomes in both the CBTi and control groups to examine between-group differences in weekly changes in each outcome.

Finally, although we recorded serious adverse events including medical events and hospital appointments/admissions, during the CBTi protocol, we did not capture non-medical side effects other than daytime sleepiness (e.g. reports of headaches, increased fatigue, and reduced motivation). As is the case in patients with insomnia alone, it is probable that BRT resulted in acutely elevated fatigue and reduced energy in the current COMISA sample [43]. Although such disturbances are commonly perceived as a manageable and short-lived consequence of treatment for most patients, it is important that future patients are warned of these potential side effects before beginning BRT.

Conclusions

This study demonstrates that when managed appropriately, CBTi is an effective and safe treatment in patients with insomnia with comorbid moderate and severe OSA. Patients showed a small increase in reported daytime sleepiness following the first week of BRT, which returned to pretreatment levels during all subsequent weeks. At the same time, patients experienced gradual

improvement of sleep onset latency, wake after sleep onset, and sleep efficiency across the weeks of treatment. Clinicians should closely monitor sleepiness of patients with COMISA during CBTi programs, especially during the initial sessions of BRT. Future research should examine weekly changes in a broader range of daytime functioning/impairment outcomes in patients with COMISA during CBTi, including cognitive functioning tasks, reaction time, and simulated driving performance measures.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Ethics Approval

This research was approved by the Southern Adelaide Clinical Human Research Ethics Committee (428.12; South Australian Local Health Network, Flinders University of South Australia), the Human Research Ethics Committee (1300000302; The Prince Charles Hospital, Brisbane), the Queensland University of Technology Human Research Ethics Committee, and the External Request Evaluation Committee (Department of Human Services, Australia).

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