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SCIENTIFIC INVESTIGATIONS

Effect of depression, anxiety, and stress symptoms on response to cognitive behavioral therapy for insomnia in patients with comorbid insomnia and sleep apnea: a randomized controlled trial

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Study Objectives: Patients with comorbid insomnia and sleep apnea (COMISA) report increased severity of depression, anxiety, and stress symptoms compared to patients with either insomnia or sleep apnea alone. Although cognitive behavioral therapy for insomnia (CBTi) is an effective treatment for COMISA, previous research suggests a reduced response to CBTi by patients with insomnia and depression, anxiety, and stress symptoms. Therefore, we used randomized controlled trial data to investigate the impact of depression, anxiety, and stress symptoms before treatment on changes in insomnia after CBTi vs control in patients with COMISA.

Methods: 145 patients with COMISA (insomnia as defined by the *International Classification of Sleep Disorders*, third edition and apnea-hypopnea index ≥ 15 events/h) were randomized to CBTi (n = 72) or no-treatment control (n = 73). One-week sleep diaries and standardized questionnaire measures of insomnia, sleepiness, fatigue, depression, anxiety, and stress were completed pretreatment and posttreatment. Mixed models were used to examine interactions between depression, anxiety, and stress symptoms before treatment, intervention-group (CBTi, control), and time (pretreatment, posttreatment) on insomnia symptoms.

Results: Approximately half of this COMISA sample reported at least mild symptoms of depression (57%), anxiety (53%), and stress (48%) before treatment. Patients reporting greater depression, anxiety, and stress symptoms before treatment also reported increased severity of insomnia, daytime fatigue, and sleepiness. Improvements in questionnaire and diary-measured insomnia symptoms improved during CBTi and were not moderated by severity of depression, anxiety, or stress symptoms before treatment (all interaction $P \geq .11$).

Conclusions: We found no evidence that symptoms of depression, anxiety, or stress impair the effectiveness of CBTi in improving insomnia symptoms in patients with COMISA. Patients with COMISA and comorbid symptoms of depression, anxiety, and stress should be referred for CBTi to treat insomnia and improve subsequent management of their obstructive sleep apnea.

Clinical Trial Registration: Registry: Australian New Zealand Clinical Trials Registry; Name: Treating comorbid insomnia with obstructive sleep apnea (COMISA) study: A new treatment strategy for patients with combined insomnia and sleep apnea; URL: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=365184; Identifier: ACTRN12613001178730.

Keywords: insomnia, obstructive sleep apnea, COMISA, cognitive behavioral therapy, continuous positive airway pressure therapy, depression, anxiety, stress

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Comorbid insomnia and sleep apnea (COMISA) is a highly prevalent disorder associated with increased depression, anxiety, and stress symptoms compared to either insomnia or sleep apnea alone. Previous research suggests that depression, anxiety, and stress symptoms may impair the effectiveness of cognitive behavioral therapy for insomnia (CBTi); however, this relationship has not been investigated in patients with COMISA. Therefore, we examined the impact of depression, anxiety, and stress symptoms before treatment on changes in insomnia after CBTi vs control.

Study Impact: We found no evidence that symptoms of depression, anxiety, or stress impair the effectiveness of CBTi in treating insomnia in patients with COMISA. Patients with COMISA and comorbid depression, anxiety, or stress symptoms should be referred for CBTi to treat their insomnia.

INTRODUCTION

Insomnia and obstructive sleep apnea (OSA) are the 2 most common sleep disorders and frequently co-occur.[1–3] For example, 30–50% of patients with OSA report clinically significant insomnia symptoms, and 30–40% of patients with insomnia fulfill diagnostic criteria for OSA when assessed with overnight polysomnography.[4] Patients with comorbid insomnia and sleep apnea (COMISA) not only experience difficulties initiating sleep and long nocturnal awakenings, but any sleep that is

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obtained is often fragmented by repetitive respiratory events and arousals.[5,6] As insomnia and OSA are both independently associated with daytime impairments, including fatigue, depressive symptoms, and reduced quality of life,[7] it is unsurprising that individuals with COMISA report greater levels of depression, anxiety, and stress symptoms and reduced quality of life compared to individuals with either insomnia or OSA alone.[3–5,8–10]

In 2004 Smith and colleagues[9] examined a sample of 105 consecutive patients referred to a sleep clinic with suspected OSA and found that patients with comorbid insomnia reported levels of depression, anxiety, and stress in the moderate to severe range, while patients with confirmed OSA alone reported normal or nonclinical levels of each. Lang and colleagues[8] also recently examined a cross-sectional survey of sleep, daytime functioning, and health outcomes in a community-based sample of 700 Australian men, and reported that the severity and prevalence of depressive symptoms were greater in those with COMISA (42.6% depression prevalence) compared to those with either insomnia (21.6%) or OSA alone (8.4%). This was despite similar severity of respiratory disturbance between the COMISA and OSA groups and similar manifestations of insomnia severity between the COMISA and insomnia groups.

Cognitive behavioral therapy for insomnia (CBTi) is the recommended "first line" treatment for insomnia.[11–13] CBTi is a multicomponent nonpharmacological treatment that targets underlying psychological, physiological, and behavioral factors of insomnia over the course of 4–8 weekly individualized or small group sessions.[14–17] CBTi is an effective and appropriate treatment for insomnia among patients with COMISA, which improves insomnia severity,[18–20] reduces OSA severity,[21] and may increase subsequent acceptance and use of continuous positive airway pressure (CPAP) therapy.[20,22,23] Therefore, patients with COMISA may benefit from CBTi as the first line treatment before commencing CPAP therapy.[4]

Patients with comorbid insomnia and depression, anxiety, or stress symptoms may experience a reduced response to CBTi compared to patients without these symptoms.[24–32] While several studies have reported that depression,[25] anxiety,[27] distress,[26] and overall psychiatric symptoms[24,25] impair the effectiveness of CBTi in treating insomnia, others have reported no relationship.[28–31,33] For example, van de Laar and colleagues[24] reported that psychiatric symptoms predicted a reduced response to CBTi by posttreatment in 60 patients treated at a tertiary sleep medicine center. Manber and colleagues[28] also investigated the effect of high and low symptoms of comorbid depression (according to the Beck Depression Inventory) during a 7-session CBTi intervention in 301 patients with insomnia. There was no difference between the high-depression and low-depression groups in reduction in Insomnia Severity Index (ISI) scores during treatment or between-group difference in insomnia "response" posttreatment. However, the high-depression group reported reduced adherence to the bedtime restriction therapy component of CBTi.

Although COMISA and mental health symptoms commonly co-occur[8,34] and CBTi may represent an effective first line treatment for COMISA,[4,22] no previous study has examined the impact of depression, anxiety, or stress symptoms on response to CBTi in patients with this prevalent COMISA condition. Therefore, we aimed to use recent randomized controlled trial data in patients with COMISA to investigate the impact of depression, anxiety, and stress symptoms before treatment on changes in insomnia severity after CBTi and control.

METHODS

We used data from a recently completed randomized controlled trial including 145 patients with comorbid insomnia (ICSD-3 psychologist diagnosis[7]) and OSA (apnea-hypopnea index; AHI ≥ 15 events/h, physician diagnosis) to investigate the effect of depression, anxiety, and stress symptoms and CBTi vs no-treatment control on changes in insomnia symptoms pretreatment to posttreatment.[22] Patients from 2 hospital sites (Repatriation General Hospital, Adelaide, South Australia and The Prince Charles Hospital, Brisbane, Queensland) were randomized (via minimization[35]) to receive either 4 weekly 45-minute CBTi sessions or a no-treatment control. Questionnaire batteries and 1-week sleep diaries were completed pretreatment and posttreatment. The posttreatment assessment occurred approximately 1 week after completion of final CBTi session/control. No patients were receiving treatment for OSA during this study phase. Patient eligibility criteria, screening, and retention are reported in our main study[22] and summarized in **Figure 1**. Briefly, 2,870 patients were screened through clinical sleep laboratory and online screening arms, of whom 551 attended sleep physician screening, 342 attended research coordinator screening, 182 attended psychologist screening, and 145 were subsequently randomized.

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).

Insomnia diagnosis

Insomnia was diagnosed by 1 of 7 registered psychologists with extensive experience in the diagnosis and management of insomnia, according to 1-week sleep diary and questionnaire data completed before the diagnostic appointment. Insomnia diagnosis reflected ICSD-3 and quantitative criteria, including at least 1 of either; sleep onset latency > 30 minutes, wake after sleep onset > 45 minutes, or sleep efficiency of < 75%, and self-reported daytime impairments associated with insomnia symptoms.[7]

Sleep apnea diagnosis

OSA was diagnosed by 1 of 18 sleep physicians, according to an AHI ≥ 15 events/h measured during overnight at-home polysomnography (Compumedics, Melbourne, Australia) and physician recommendation for a trial of CPAP therapy. No upper AHI limit was used. Recording channels included 2 electroencephalogram channels (C_3-M_2, C_4-M_1), 2 electrooculogram channels, 1 electromyogram channel, 2 leg movement channels, 1 electrocardiogram channel, 2 respiratory effort bands, a

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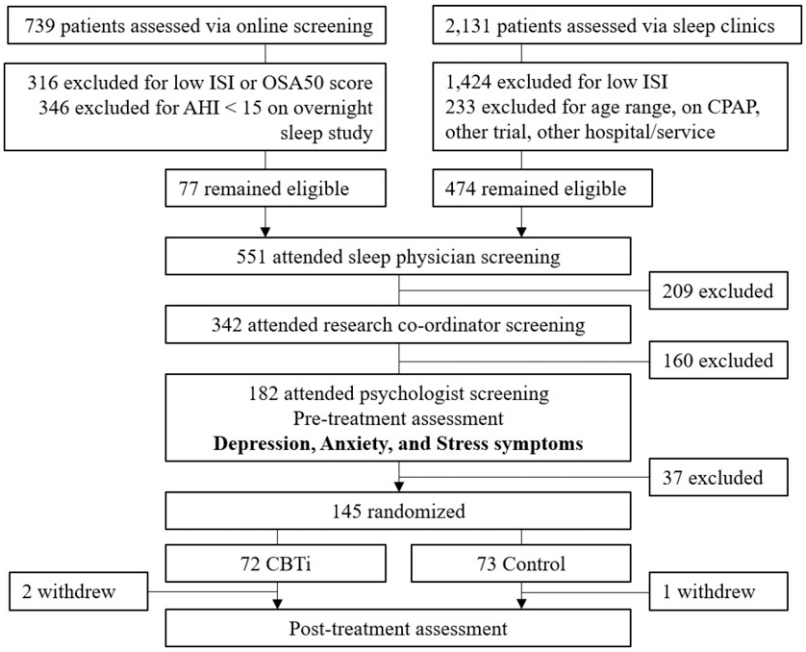
Figure 1—Study design, and patient recruitment and retention.



AHI = apnea-hypopnea index, CBTi = cognitive behavioral therapy for insomnia, CPAP = continuous positive airway pressure, ISI = Insomnia Severity Index, OSA50 = Obstructive Sleep Apnea screening questionnaire.

nasal cannula to record nasal pressure, an oronasal thermistor to record oronasal airflow, and a finger oximeter to record continuous oxyhemoglobin saturation. Studies were scored according to AASM 2007 criteria and a 2009 ASTA commentary.[36,37]

Materials

Depression, anxiety, and stress scale

Depression, anxiety, and stress symptoms were assessed with the 3 subscales of the 21-item version of the Depression, Anxiety, and Stress Scale (DASS).[38,39] Each subscale score ranges from 0 to 42, with greater scores indicating increased severity of depression, anxiety, and stress symptoms, respectively. Standardized cut-offs for the 3 subscales of the DASS are presented in the supplemental material. The DASS has good psychometric properties.[38,40,41]

Insomnia Severity Index

The ISI[42] is a 7-item self-report measure of nighttime (difficulties initiating sleep, maintaining sleep, and early morning awaking) and daytime (dissatisfaction, daytime functional impairment, quality of life, worry/distress) insomnia symptoms, which has been used in previous COMISA research.[4] Scores range from 0 to 28, with greater scores indicating increased insomnia severity.

Daytime sleepiness, fatigue, and dysfunctional beliefs

Additional questionnaires completed pretreatment and posttreatment included the Epworth Sleepiness Scale,[43] the Flinders Fatigue Scale,[44] and the 16-item version of the Dysfunctional Beliefs and Attitudes About Sleep (DBAS) scale[45] (a description of these questionnaires is in the supplemental material).

One-week sleep/wake diaries

One-week sleep diaries were completed at pretreatment, posttreatment, and during each week of CBTi. Average diary-measured total sleep time, sleep onset latency, wake after sleep onset, time in bed, and sleep efficiency (sleep time/time in bed × 100) were calculated during each occasion. Among patients in the CBTi group, we examined adherence to psychologist-prescribed time in bed restriction by subtracting psychologist-prescribed time in bed from diary-measured time in bed during each session of CBTi (eg, a patient with 400 minutes of diary-measured time in bed and 360 minutes of prescribed time in bed spent 40 minutes greater time in bed than was prescribed).

Treatment expectations and satisfaction questionnaire

During the third CBTi session, patients completed an adapted treatment credibility/expectancy questionnaire.[46] Treatment credibility and expectation subscales are derived from 3 items regarding treatment credibility (eg, "At this point, how logical does therapy offered to you seem?") and 3 items regarding expectation of improved symptoms (eg, "At this point, how successfully do you think this treatment will be in reducing your symptoms").[46] Average responses to each subscore range from 0 to 100, with higher scores indicating greater perceptions of treatment credibility and expectations of improvement, respectively.

Medication use

Prescriptions of antidepressant (amitriptyline, citalopram, doxepin [higher antidepressant dose], escitalopram, fluoxetine, mirtazapine, quetiapine, sertraline, etc.) and benzodiazepine

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medicines (alprazolam, diazepam, temazepam, oxazepam, etc.) were measured before and during treatment via health records data. Patients were categorized into those receiving any antidepressant prescription (yes, no) and any benzodiazepine prescription (yes, no) during the 60 days preceding randomization and the 60 days following randomization.

Data and statistical analyses

Data were analyzed with SPSS version 22 (IBM Statistics Armonk, New York). Linear mixed models with an autoregressive covariance structure were used to examine interactions between severity of depression, anxiety, and stress symptoms before treatment, intervention group (CBTi, control), and time (pretreatment, posttreatment) on questionnaire and diary measures of insomnia severity. Pretreatment DASS subscale scores were retained as continuous predictor variables for primary mixed model analyses and were separated into 5 categorical levels of increasing severity for secondary analyses (ie, none, mild, moderate, severe, and extremely severe; see supplemental material).

An alpha significance cut-off of $P < .05$ and 95% confidence intervals (CIs) were used. Cohen's *d* effect sizes were calculated with pooled pretreatment standard deviations. Overall mixed model interaction terms were examined for significant interactions before interpreting pairwise comparisons with a Sidak correction. All data were inspected for normality and outliers. Logarithmic transformations were performed on nonnormally distributed data to correct skewness. As there were no differences in main/interaction effects between transformed and untransformed data, the original untransformed data are reported to facilitate understanding of descriptive statistics. Missing data were categorized as missing at random according to predefined criteria.[22,47]

RESULTS

Patient characteristics at pretreatment

A total of 145 patients with COMISA (age mean = 58.2 years, standard deviation = 9.9, 55.2% male) were included in this study. As previously reported, there were no differences between intervention groups in patient demographic data, disease severity, or average depressive, anxiety, or stress symptoms before treatment.[22] Similarly, there were no between intervention group differences in the proportion of patients categorized with none, mild, moderate, severe, or extremely severe depression (χ^2 $P = .77$), anxiety ($P = .37$), or stress ($P = .91$) before treatment (**Table 1**). At least mild depression (57%), anxiety (53%), and stress (48%) were reported by approximately half of the patients before treatment.

Pretreatment questionnaire and sleep diary data, between depression, anxiety, and stress categories are displayed in **Table 1**. A greater proportion of females (24.6%) than males (6.3%) reported "extremely severe anxiety" before treatment (χ^2 $P = .031$). There were no sex differences between depression or stress categories before treatment or age differences between any depression, anxiety, or stress categories before treatment. Increasing severity of depression, anxiety, and stress categories were associated with higher ISI and daytime impairment scores before treatment but were not related to OSA severity (see **Table 1**).

Rates of antidepressant and benzodiazepine prescriptions before and during treatment are described in the supplemental material. In the 60 days preceding randomization, 30% of patients were prescribed an antidepressant medication (between intervention group $\chi^2 = 2.3$, $P = .13$) and 6.2% of patients were prescribed a benzodiazepine (between intervention group $\chi^2 = 0.10$, $P = .75$). There was no difference in antidepressant prescriptions between depression or stress categories before treatment (both $P \geq .49$). A significant chi[2] analysis indicated that patients in the "extremely severe anxiety" group before treatment had the highest rates of antidepressant prescriptions in the 60 days preceding randomization (57%) compared to those reporting none, mild, or moderate anxiety (22–30% prescription rates; $P = .040$). There was no difference in benzodiazepine prescriptions between depression, anxiety, or stress categories before treatment (all $P \geq .24$; supplemental material).

Effect of depressive symptoms on response to cognitive behavioral therapy for insomnia

Mixed models were performed to examine the effect of depression severity before treatment (continuous score), intervention group, and time on insomnia symptoms. There were no 3-way interaction effects on the ISI ($P = .70$; see **Figure 2**), any sleep diary measure of insomnia severity (all $P \geq .63$), daytime sleepiness ($P = .27$), fatigue ($P = .47$), or the DBAS ($P = .11$), indicating that pretreatment depression symptoms did not attenuate the effect of CBTi vs control on reducing any nocturnal or daytime symptoms of insomnia. A group by time interaction ($P = .001$) indicated a greater reduction in ISI scores in the CBTi than the control group, confirming the previous results.[22] A main effect of depression ($P < .001$) indicated higher ISI scores across groups and repeated measures among patients with higher depressive symptom severity at pretreatment (**Figure 2**).

When examining patients in only the CBTi group, there was no interaction between depressive symptoms before treatment and time on the ISI ($P = .45$), any sleep diary parameters (all $P \geq .11$), daytime sleepiness ($P = .25$), fatigue ($P = .85$), or the DBAS ($P = .25$). This pattern of results did not change after controlling for antidepressant prescriptions and benzodiazepine or after excluding the 27 patients in the CBTi group who used these medications in the 60-day period preceding randomization. Sensitivity analyses were conducted with pretreatment depression categories (instead of continuous predictor scores), which resulted in a similar pattern of results (supplemental material).

Effect of anxiety symptoms on response to cognitive behavioral therapy for insomnia

Mixed models were performed to examine the effect of anxiety severity before treatment (continuous score), intervention group, and time on insomnia symptoms. The pattern of results was very similar to those observed when investigating the effect of depressive symptoms on treatment response. There were no 3-way interaction effects on the ISI ($P = .62$), any sleep diary measure of insomnia severity (all $P \geq .20$; see **Figure 3**), daytime sleepiness ($P = .51$), fatigue ($P = .83$), or the DBAS ($P = .45$), indicating that anxiety symptoms before treatment did not

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Table 1—Mean questionnaire and sleep diary data between depression, anxiety, and stress categories at pretreatment (± confidence intervals).

Depression Category	**None (n = 62, 42.8%)**	**Mild (n = 17, 11.7%)**	**Moderate (n = 30, 20.7%)**	**Severe (n = 10, 6.9%)**	**Extremely Severe (n = 26, 17.9%)**	***P***
Apnea-hypopnea index (events/h)	36.1 (5.6)	35.4 (10.2)	35.0 (9.6)	31.6 (17.9)	30.5 (7.1)	.853
Insomnia Severity Index	15.6 (1.2)[c,e]	18.6 (1.9)	20.4 (1.8)[a]	17.9 (3.6)	21.8 (1.3)[a]	< .001
Epworth Sleepiness Scale	8.6 (1.2)[e]	7.1 (1.6)[e]	9.6 (1.8)	9.6 (2.8)	11.7 (2.1)[a,b]	.016
Dysfunctional Beliefs Scale	52.6 (4.2)[c,e]	56.7 (7.6)	65.0 (5.7)[a]	64.2 (9.8)	68.6 (6.5)[a]	< .001
Flinders Fatigue Scale	12.2 (1.2)[c,d,e]	16.6 (3.3)	17.7 (1.7)[a]	18.3 (4.1)[a]	20.9 (1.8)[a]	< .001
Sleep onset latency	40.1 (7.4)[e]	45.2 (18.1)	63.3 (17.1)	52.7 (21.5)	77.5 (24.8)[a]	.002
Wake time	94.2 (15.3)	97.2 (32.8)	84.5 (15.3)	84.0 (34.3)	122.7 (40.3)	.247
Total sleep time	366.1 (16.3)	340.5 (48.3)	337.9 (29.3)	353.0 (52.1)	321.8 (36.4)	.132
Sleep efficiency	70.7 (3.0)	66.2 (7.3)	66.0 (5.2)	65.4 (11.0)	62.5 (5.9)	.092
Anxiety Category	**None (n = 68, 46.9%)**	**Mild (n = 20, 13.8%)**	**Moderate (n = 21, 14.5%)**	**Severe (n = 15, 10.3%)**	**Extremely Severe (n = 21, 14.5%)**	***P***
Apnea-hypopnea index (events/h)	34.0 (4.9)	31.9 (9.6)	39.5 (14.2)	35.6 (11.3)	33.3 (9.9)	.841
Insomnia Severity Index	16.4 (1.2)[d,e]	18.3 (2.1)	19.1 (2.1)	21.6 (2.2)[a]	20.7 (1.9)[a]	< .001
Epworth Sleepiness Scale	8.2 (1.0)	10.1 (2.4)	9.9 (2.1)	11.1 (3.0)	10.4 (2.4)	.091
Dysfunctional Beliefs Scale	51.7 (3.7)[c,d,e]	57.6 (7.0)	67.3 (6.5)[a]	70.5 (7.2)[a]	70.5 (7.2)[a]	< .001
Flinders Fatigue Scale	13.7 (1.6)[c,d,e]	15.0 (2.8)	18.1 (2.9)[a]	19.1 (2.0)[a]	19.7 (1.8)[a]	< .001
Sleep onset latency	39.5 (7.4)[c]	59.9 (14.3)	79.6 (29.9)[a]	54.7 (18.3)	62.5 (23.7)	.002
Wake time	86.6 (10.2)	96.0 (30.9)	95.8 (35.3)	129.0 (49.8)	109.5 (42.5)	.207
Total sleep time	366.6 (15.5)[d]	331.1 (28.7)	333.6 (41.5)	294.9 (53.5)[a]	359.0 (38.6)	.009
Sleep efficiency	71.2 (2.6)[d]	64.1 (5.5)	64.3 (8.5)	57.7 (8.3)[a]	68.0 (5.1)	.003
Stress Category	**None (n = 75, 51.7%)**	**Mild (n = 22, 13.8%)**	**Moderate (n = 22, 13.8%)**	**Severe (n = 21, 14.5%)**	**Extremely Severe (n = 5, 3.5%)**	***P***
Apnea-hypopnea index (events/h)	36.2 (5.0)	34.0 (12.6)	32.6 (8.9)	34.4 (9.6)	21.3 (6.7)	.664
Insomnia Severity Index	16.5 (1.1)[d]	18.7 (2.2)	19.5 (2.1)	21.6 (1.8)[a]	22.4 (4.7)	< .001
Epworth Sleepiness Scale	8.1 (0.8)[e]	11.2 (1.0)	9.1 (2.2)[e]	9.9 (1.9)[e]	16.6 (2.6)[a,c,d]	< .001
Dysfunctional Beliefs Scale	53.9 (3.8)[d,e]	63.3 (6.6)	61.5 (6.2)	69.2 (7.5)[a]	75.8 (22.0)[a]	< .001
Flinders Fatigue Scale	13.5 (1.5[b,d]	18.2 (2.7)[a]	17.5 (1.8)	19.3 (1.8)[a]	21.0 (7.1)	< .001
Sleep onset latency	47.1 (8.2)[d]	53.1 (14.0)	46.9 (19.1)	80.9 (29.8)[a]	51.4 (49.8)	.027
Wake time	92.7 (13.2)	108.6 (34.8)	81.4 (21.3)	113.0 (44.6)	110.4 (56.9)	.465
Total sleep time	364.2 (15.2)[d]	317.9 (33.4)	361.8 (34.3)	306.5 (44.6)[a]	364.2 (92.2)	.008
Sleep efficiency	69.6 (2.8)	61.9 (6.5)	70.6 (5.1)	61.5 (7.3)	69.0 (8.5)	.023

Pairwise comparisons: [a]significant difference vs "none", [b]significant difference vs "mild", [c]significant difference vs "moderate", [d]significant difference vs "severe", [e]significant difference vs "extremely severe".

attenuate the effect of CBTi vs control on reducing insomnia severity. Compared to the control group, patients in the CBTi group experienced a greater reduction in ISI scores pretreatment to posttreatment across levels of anxiety severity (interaction $P < .001$). A main effect of anxiety indicated greater ISI scores and diary-measured sleep onset latency (both $P \leq 0.04$) across intervention groups and repeated measurement occasions (eg, **Figure 3**).

Among patients in the CBTi group, there was no interaction effect between time and anxiety symptoms before treatment on the ISI ($P = .64$), any sleep diary parameters (all $P > .10$), sleepiness ($P = .80$), fatigue ($P = .49$), or the DBAS ($P = .38$). This pattern of results did not change after controlling for antidepressant prescriptions and benzodiazepine or after excluding the 27 patients in the CBTi group who used these medications in the 60-day period preceding randomization. Sensitivity analyses were conducted with pretreatment anxiety categories (instead of continuous predictor scores), which resulted in a similar pattern of results (supplemental material).

Effect of stress symptoms on response to cognitive behavioral therapy for insomnia

There were no 3-way interaction effects between stress symptoms before treatment (continuous score), intervention group, and time on the ISI ($P = .73$), any sleep diary measure of insomnia severity (all $P \geq .22$; see **Figure 4**), daytime sleepiness ($P = .67$), fatigue ($P = .39$), or the DBAS ($P = .32$), indicating that stress symptoms before treatment did not attenuate the effect of CBTi

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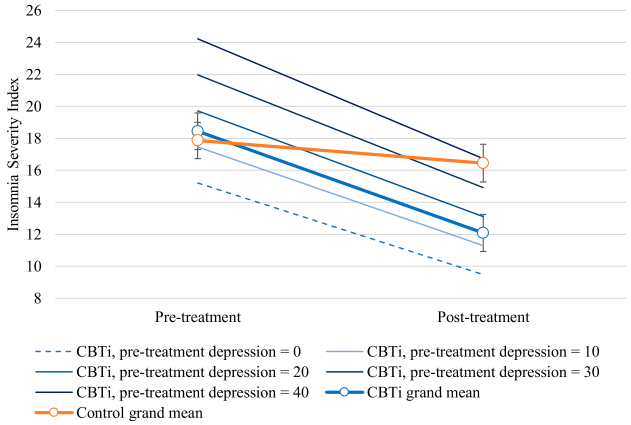
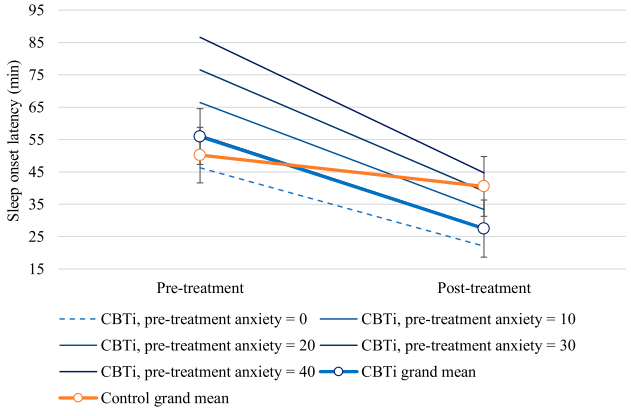
Figure 2—Changes in insomnia severity during treatment between intervention-group, time and depression severity before treatment (± confidence intervals).



The depression subscale was scored on a scale of 0 (lowest severity) to 42 (highest severity). Different insomnia severity change scores are modeled on pretreatment depression severity scores in increments of 10 (ie, 0, 10, 20, 30, and 40). CBTi = cognitive behavior therapy for insomnia.

Figure 3—Changes in sleep onset latency during treatment between intervention-group, time and anxiety severity before treatment (± confidence intervals).

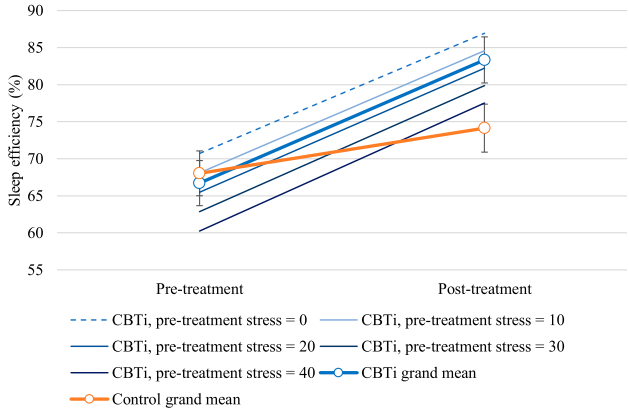


The anxiety subscale was scored on a scale of 0 (lowest severity) to 42 (highest severity). CBTi = cognitive behavior therapy for insomnia.

vs control on reducing insomnia severity. A group by time interaction in ISI indicated greater insomnia improvement in the CBTi group by posttreatment (P =.001), while a main effect of stress indicated greater ISI scores (P <.001) across intervention groups and repeated measurement occasions.

Among patients in the CBTi group, there was no interaction effect between time and stress symptoms before treatment on the ISI (P =.45), any sleep diary parameters (all P >.33), sleepiness (P =.65), fatigue (P =.39), or the DBAS (P =.15). This pattern of results did not change after controlling for antidepressant prescriptions and benzodiazepine or after excluding the 27 patients in the CBTi group who used these medications in the 60-day period preceding randomization. Sensitivity analyses were conducted with pretreatment stress categories (instead of

Figure 4—Changes in sleep efficiency during treatment between intervention-group, time and stress severity before treatment (± confidence intervals).



The stress subscale was scored on a scale of 0 (lowest severity) to 42 (highest severity). CBTi = cognitive behavior therapy for insomnia.

continuous predictor scores), which resulted in a similar pattern of results (supplemental material).

Treatment attendance, adherence, and satisfaction

Among patients in the CBTi group, treatment sessions 1–4 were attended by 97%, 96%, 94%, and 90% of patients, respectively. Binary logistic regression analyses indicated no association between severity of depression, anxiety, or stress symptoms before treatment and attendance of any treatment sessions (all $P \geq .14$).

We also investigated "adherence to psychologist-prescribed time in bed" during each CBTi session (ie, by calculating the difference between psychologist-prescribed time in bed and diary-measured time in bed during the subsequent week). Bedtime restriction was initiated during the first treatment session and titrated over the subsequent 3 sessions.[19] Among those in the CBTi group, diary-measured time in bed was greater than the prescribed time in bed during sessions 2 (mean difference = 35.6 minutes; CI = 13.5, P < .001), 3 (mean difference = 21.9 minutes; CI = 11.3, P < .001), 4 (mean difference = 12.4 minutes; CI = 8.6, P = .006), and posttreatment (mean difference = 15.2 minutes; CI = 9.7, P < .003). There were no significant correlations between severity of depression, anxiety, or stress symptoms before treatment, and adherence to bedtime restriction recommendations during session 2 (all correlation $P \geq .24$), session 3 (all $P \geq .42$), or by posttreatment (all $P \geq .27$). During treatment week 4, significant correlations between adherence to bedtime restriction with pretreatment depression (r [63] = −.277, P = .027) and anxiety symptoms (r[63] = −.251, P = .045) were observed. These negative correlations indicated that patients commencing treatment with more severe depression/anxiety symptoms were more likely to stay in bed for the recommended time, while patients commencing treatment with less depression/anxiety symptoms were more likely to stay in bed for longer than the recommended time. No relationship between stress symptoms and adherence to bedtime restriction recommendations were observed during session 4 (P =.26).

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Finally, there were no significant correlations between severity of depression, anxiety, or stress symptoms before treatment with ratings of treatment credibility (all correlation $P \geq .51$) or expectations (all $P \geq .91$) during the third CBTi session.

DISCUSSION

We found no evidence that symptoms of depression, anxiety, or stress are associated with a reduced response to CBTi in patients with COMISA. Furthermore, among patients in the CBTi group, symptoms of depression, anxiety, and stress before treatment were not associated with reduced attendance of CBTi sessions, reduced adherence to weekly bedtime restriction therapy recommendations, or any difference in treatment credibility or expectations during CBTi. These findings have important implications for the treatment of patients with COMISA with comorbid mental health symptoms who experience greater levels of insomnia severity, daytime fatigue, and sleepiness before treatment.[8] Patient with COMISA with symptoms of depression, anxiety, and stress should be referred for CBTi, which improves insomnia and may improve subsequent management of the OSA.[4,20,23]

Before treatment, approximately half of this sleep clinic COMISA sample reported at least mild symptoms of depression, anxiety, and stress, while approximately one-quarter reported severe/extremely severe depression, anxiety, and stress symptoms (**Table 1**). These prevalence and severity estimates are similar to those reported in previous COMISA samples recruited from sleep clinics[9,48] and the general population.[8,34,49] We also observed that patients commencing treatment with higher levels of depression, anxiety, and stress also reported increased severity of insomnia (questionnaire and quantitative sleep diary measures), daytime sleepiness and fatigue, and more dysfunctional beliefs and attitudes about their sleep. Hence, this study adds to the literature suggesting a high prevalence of depression, anxiety, and stress symptoms among patients with COMISA and the potential bidirectional interplay between sleep and mental health symptoms before treatment.[33,50]

Although previous research has reported that comorbid depression,[25] anxiety,[27] distress,[26] and overall psychiatric symptoms[24,25] may predict reduced response to CBTi in patients with insomnia, we found no evidence of this relationship among 145 patients with COMISA after a 4-session CBTi program vs no-treatment control. In fact, the severity of depression, anxiety, and stress symptoms before treatment did not significantly attenuate changes in any questionnaire or diary-measured marker of nocturnal or daytime insomnia symptoms resulting from treatment in these patients (eg, **Figure 2**, **Figure 3**, and **Figure 4**). This pattern of results remained unchanged after controlling for prescriptions of antidepressant and benzodiazepine medicines. We also observed that severity of depression, anxiety, and stress were not associated with reduced attendance of CBTi sessions or any reduction in adherence to weekly bedtime restriction therapy recommendations. This implies that sleep clinic patients with COMISA should be considered for CBTi as the first line treatment, even when comorbid depression, anxiety, and stress symptoms in the moderate and severe range are reported.

Although depression, anxiety, and stress symptoms did not attenuate overall change in insomnia severity during CBTi, main effects of each psychiatric symptom on insomnia severity across repeated measures were observed. As illustrated in **Figure 2**, this resulted in insomnia severity remaining elevated at the pretreatment and posttreatment assessment periods in patients with more severe psychiatric symptoms. Theoretically, to achieve similar levels of insomnia severity posttreatment, patients commencing treatment with severe comorbid depression symptoms would require a substantially greater overall ISI reduction between pretreatment and posttreatment (eg a ~15-point ISI reduction) compared to patients commencing treatment with lower/no psychiatric symptoms (eg a ~6-point ISI reduction). Future research should examine whether additional sessions of CBTi, or combined interventions targeting insomnia, psychiatric symptoms, and OSA, promote greater improvement of insomnia in patients with COMISA and psychiatric symptoms. For example, although the brief 4-session CBTi intervention improved insomnia symptoms in this study, future research should assess whether longer 6–10 session CBTi programs promote greater insomnia improvements among patients with COMISA and psychiatric symptoms. Alternatively, it is possible that interactions between the untreated OSA and psychiatric symptoms reduced improvement of insomnia symptoms during CBTi in some patients. Indeed, untreated OSA is associated with greater depression symptoms,[51] and CPAP therapy may reduce depression and improve quality of life.[52] Future studies may wish to investigate combination treatment approaches, including CBTi and targeted treatment of psychiatric symptoms (behavioral activation and/or pharmacotherapy) and OSA (CPAP and non-CPAP therapies) in patients with COMISA and psychiatric symptoms.

Given the high prevalence of depression, anxiety, and stress symptoms in COMISA[8,9] and the complexities involved in its diagnosis and treatment,[3,4,49] this information is of high importance for clinicians when deciding on the most suitable treatment approach for these patients. CBTi is an effective and appropriate treatment for patients with COMISA,[18,19] which improves insomnia and reduces OSA severity[18,21] and may increase subsequent CPAP use.[20,22,23] The current study also suggests that CBTi is suitable and effective for the many patients with COMISA who report co-occurring symptoms of depression, anxiety, and stress before commencing treatment.

Treatment of insomnia with CBTi has previously been shown to reduce depressive symptoms among patients reporting comorbid insomnia and depression.[33,53] It is possible that improvement in symptoms of depression, anxiety, and stress in COMISA patients may depend on the "chief" complaint of patients (ie, whether patients are motivated to seek treatment primarily because of insomnia symptoms or probable OSA symptoms). Indeed, we previously reported that CBTi was associated with improved depression, anxiety, and stress symptoms among a sample of 141 patients referred for treatment of insomnia symptoms who were later found to have co-occurring OSA.[18] In contrast, we previously reported that CBTi

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did not improve symptoms of depression, anxiety, or stress compared to no-treatment control in the current COMISA sample who were primarily referred for investigation/treatment of OSA rather than insomnia.[22] As symptoms of depression, anxiety, and stress may result from a wide range of comorbid conditions and lifestyle, environmental, and contextual factors, it is possible that they were independent of insomnia symptoms in these patients and therefore showed little improvement as the insomnia was treated with CBTi. Alternatively, it is also possible that improvement in these mental health symptoms occurred at a slower rate during CBTi and were not detected at the immediate posttreatment measurement period in this study. More research is required to understand the interplay between insomnia, OSA, and mental health symptoms during different single and combined treatment approaches in COMISA.

Limitations

Several limitations should be considered when interpreting this study. Firstly, these results may not be generalizable to individuals recruited outside of sleep clinic settings. Although several studies have examined the impact of depression, anxiety, and stress symptoms on response to CBTi in patients with insomnia, we are not aware of any other studies examining this association in patients with COMISA. Therefore, future research is required to examine the impact of depression, anxiety, and stress symptoms on the response to CBTi in patients with COMISA recruited from different primary care and community settings.

Secondly, although we measured depression, anxiety, and stress symptoms with a well-established questionnaire with good psychometric properties,[38,40,41] this measure does not directly reflect diagnostic criteria for depressive or anxiety disorders. It is possible that these results may not generalize to patients with COMISA who also meet diagnostic criteria for major depressive disorder/generalized anxiety disorder. Although the present results do not show a diminished CBTi response in the most severe depression/anxiety levels, future research should investigate the effect of diagnosed depression/anxiety on response to CBTi in patients with COMISA to confirm the current results.

Finally, this study did not utilize long-term follow-up measures of insomnia symptoms following CBTi or control, which would be helpful in establishing whether insomnia improvements are sustained following CBTi among patients with COMISA and mental health symptoms. As all patients commenced CPAP therapy immediately after the posttreatment assessment period, longer-term follow-up of the effect of depression, anxiety, and stress symptoms on improvement of insomnia following CBTi vs control was not possible.[22]

CONCLUSIONS

Among patients with COMISA, we found no evidence that depression, anxiety, or stress symptoms before treatment attenuate the effectiveness of CBTi in treating insomnia. Furthermore, depression, anxiety, and stress symptoms before treatment did not reduce adherence to bedtime restriction therapy recommendations or perceived credibility and expected benefits of CBTi. Therefore, patients with COMISA should be referred for CBTi to treat insomnia and potentially improve subsequent acceptance and use of CPAP therapy, even in the presence of comorbid symptoms of depression, anxiety, and stress.

ABBREVIATIONS

AHI, apnea-hypopnea index
CBTi, cognitive behavioral therapy for insomnia
CI, confidence interval
COMISA, comorbid insomnia and sleep apnea
CPAP, continuous positive airway pressure
DASS, depression, anxiety, and stress scale
DBAS, dysfunctional beliefs and attitudes about sleep scale
ISI, insomnia severity index
OSA, obstructive sleep apnea

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