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DOES CO-MORBID OBSTRUCTIVE SLEEP APNEA IMPAIR THE EFFECTIVENESS OF COGNITIVE AND BEHAVIORAL THERAPY FOR INSOMNIA?

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ABSTRACT

Aims: Co-morbid insomnia and obstructive sleep apnea (OSA) represents a highly prevalent and debilitating condition, however physicians and researchers are still uncertain as to the most effective treatment approach. Several research groups have suggested that these patients should initially receive treatment for their insomnia before the sleep apnea is targeted. The current study aims to determine whether cognitive and behavioral therapy for insomnia (CBT-i) can effectively treat insomnia in patients with co-morbid OSA, and whether its effectiveness is impaired by the presence of OSA.

Methods: A retrospective chart review was conducted to examine 455 insomnia patients entering a CBT-i treatment program in a hospital outpatient setting. 314 patients were diagnosed with insomnia-alone, and 141 with insomnia and co-morbid obstructive sleep apnea. Improvements in average sleep diary parameters, global insomnia severity, and several daytime functioning questionnaires from baseline, to post-treatment, to 3-month follow-up were compared between insomnia patients with- and without co-morbid sleep apnea.

Results: Insomnia patients with co-morbid OSA experienced significant improvements in insomnia symptoms, global insomnia severity, and other daytime functioning measures during and following treatment. Furthermore, improvements were no different between patients with or without co-morbid OSA. Sleep apnea presence and severity were not related to rates of insomnia-remission or treatment-resistance following treatment.

Conclusions: CBT-i is an effective treatment in the presence of co-morbid OSA. This information offers support for the suggestion that patients with co-morbid insomnia and obstructive sleep apnea should be treated with CBT-i prior to treatment of the OSA.

Keywords: insomnia, cognitive behavioral therapy for insomnia, co-morbid insomnia, secondary insomnia, obstructive sleep apnea.

Abbreviations

AHI – Apnea/Hypopnea Index

CBT-i – Cognitive Behavioral Therapy for Insomnia

COMISA – Co-Morbid Insomnia and Sleep Apnea

CPAP – Continuous Positive Airway Pressure Therapy

ESS – Epworth Sleepiness Scale

ISI – Insomnia Severity Index

OSA – Obstructive Sleep Apnea

RDI – Respiratory Disturbance Index

PSG – Polysomnography

1. INTRODUCTION

Insomnia and Obstructive Sleep Apnea (OSA) are the two most common sleep disorders, and frequently co-occur (1, 2). In fact, a recent review found that 27 to 85% of OSA patients in sleep disorder clinics report symptoms of co-morbid insomnia, and 17 to 69% of insomnia patients in sleep disorder clinics fulfil minimal diagnostic criteria for co-morbid OSA (3). These patients with Co-morbid Insomnia and Sleep Apnea (COMISA) not only experience difficulties initiating sleep, maintaining sleep, or waking too early and having difficulty returning to sleep, but when sleep is attained, it is marked by repetitive respiratory events, post-apneic arousals and fragmented sleep architecture (4). Furthermore, as both insomnia and OSA are independently associated with significant daytime functioning impairments and reduced quality of life, COMISA patients experience greater detriment in these domains, compared to groups of patients with either insomnia, or OSA alone (3, 5). Due to the increasing recognition of the prevalence and debilitating nature of COMISA, a growing amount of research has recently focused on treatment attempts in this population (3, 6-8).

Continuous Positive Airway Pressure (CPAP) therapy is the recommended treatment for moderate and severe OSA (9, 10). However, co-morbid insomnia symptoms are associated with reduced acceptance and use of CPAP therapy (11-15). The most common treatment recommendation for COMISA includes treatment of the insomnia with Cognitive and Behavioral Therapy for Insomnia (CBT-i), before initiating treatment of the OSA with CPAP therapy (3, 7, 16-18). It is thought that initially targeting the insomnia, and allowing patients to initiate and return to sleep quicker throughout the night, will also increase subsequent acceptance and use of CPAP therapy. Although this is a logical treatment suggestion, only a small handful of research has examined the suitability and effectiveness of CBT-i in the COMISA population.

CBT-i is the most effective treatment for insomnia, whether it presents as an isolated condition, or occurs in the presence of additional co-morbid disorders (19-22). CBT-i is a multi-component, non-pharmacological therapy which targets the underlying cognitive, behavioral and physiological process and factors which are thought to perpetuate the overall insomnia condition (23, 24). Trained sleep therapists or psychologists utilize several behavioral (e.g. stimulus control therapy, bedtime restriction therapy), cognitive (e.g. altering maladaptive sleep-related cognitions) and psycho-educational (e.g. basic sleep information, and sleep hygiene information) tools during weekly therapy sessions, to reduce anxiety and arousal associated with sleep, or the sleep environment (24-26). Because CBT-i targets the underlying processes believed to perpetuate the insomnia condition, rather than only the surface symptoms, improvements are sustained beyond the cessation of therapy (25).

Only a handful of case studies (27, 28), pilot studies (29-33), and one randomized controlled trial (8) have investigated the effectiveness of CBT-i in the COMISA population. Earlier case studies and pilot studies resulted in some disagreement over the impact of CBT-i in COMISA (3). However, in a recent randomized controlled trial, Fung and colleagues (8) found that patients with COMISA and patients with insomnia-alone experienced similar improvements in sleep parameters during CBT-i. The effect of CBT-i, versus a sleep education control condition, was examined in 39 older adult Veterans with insomnia-alone, and 95 older adult Veterans with insomnia and mild OSA. Participants completed a range of assessments at baseline, post-treatment, 6-month, and 12-month follow-up. CBT-i sessions were delivered by health educators under the supervision of a sleep psychologist, and included bedtime restriction therapy, stimulus control therapy, and cognitive therapy. At 6-months, COMISA participants treated with CBT-i displayed significantly greater improvements in sleep onset latency and overall sleep quality scores, compared to COMISA participants in the control condition. The authors also found that these insomnia

improvements resulting from CBT-i were similar for participants with insomnia-alone, and those with co-morbid mild OSA. Although these findings provide strong empirical evidence supporting the effectiveness of CBT-i in COMISA, more research is required in samples of different ages and different levels of OSA severity, to determine whether CBT-i is effective in insomnia patients with and without co-morbid OSA.

It is also possible that some COMISA patients experience insomnia which is secondary to their OSA (7, 27, 34). For example, during sleep periods marked by repetitive respiratory events and post-apneic arousals, some OSA patients may perceive periods of extended wakefulness or broken sleep, and present to sleep clinics with a complaint of insomnia (7, 35). If the insomnia complaint is a result of OSA manifestations, it is unlikely to improve with CBT-i (36). Some have suggested that such patients should be treated with CPAP therapy, which is more likely to improve both the insomnia and OSA (6, 7). One aim of the current study is to examine patterns of insomnia improvement and treatment-resistance following CBT-i, in COMISA patients and patients with insomnia-alone. It is expected that a greater number of COMISA patients will experience treatment-resistant insomnia due to possible casual relationships between the underlying OSA and secondary insomnia manifestations in a subset of COMISA patients.

COMISA is a highly prevalent and debilitating condition which is more difficult to treat compared to either disorder presenting alone. The most common treatment suggestion for COMISA includes initial treatment with CBT-i, to improve the insomnia condition, and increase subsequent acceptance and use of CPAP therapy. However, before implementing this treatment suggestion, it is essential to establish the effectiveness of CBT-i in the COMISA population. The current study aims to compare the effectiveness of CBT-i in patients with insomnia-alone, and patients with COMISA, in treating the daytime and night time symptoms of insomnia.

2. METHODS

2.1. Design

This study used a quasi-experimental design to examine the effectiveness of CBT-i in insomnia patients with- and without co-morbid OSA. These patients attended an out-patient insomnia treatment program at the Adelaide Institute for Sleep Health, The Repatriation General Hospital, Adelaide, South Australia, between February 2004, and November 2015. This research was approved by the Social and Behavioral Research Ethics Committee at Flinders University of South Australia. All participants gave consent for information to be used for research purposes.

2.2. Participants

Participants included 455 consecutive adult patients (Age *M* = 51.68, *SD* = 15.65; 33.1% Male) referred specifically to an insomnia treatment program at a multi-disciplinary sleep clinic, by a General Practitioner or another health professional. Inclusion criteria were: consent to have information used for research, aged 18 or over, an insomnia diagnosis according to DSM-IV criteria (and DSM-V from 2013-2015) performed by a registered psychologist (37), completion of baseline overnight polysomnographic sleep study, not currently admitted as hospital in-patient, and absence of CPAP therapy for duration of the follow-up period. Participants were initially divided into four groups based on OSA presence and severity; no OSA (*n* = 314, 69%), mild OSA (*n* = 103, 22.6%), moderate OSA (*n* = 25, 5.5%) and severe OSA (*n* = 13, 2.9%). However, because of the small number of patients in the 'moderate' and 'severe OSA' groups, the mild, moderate, and severe OSA groups were collapsed into one COMISA group (*n* = 141, 31%). Baseline demographic and descriptive data between these two groups appears in Table 1.

The insomnia treatment program cost patients $575 AUD, however upon referral with a Mental Health Care Plan from a General Practitioner, a Medicare rebate was applied which

reduced this cost to $50 AUD. Alternatively, Department of Veteran Affairs card holders were treated at no charge. These costs were thought to increase the generalizability of these findings to patients attending insomnia-treatment programs in 'real world' clinical settings.

2.3. Screening

2.3.1. ***Sleep Studies.*** Overnight Polysomnographic (PSG) sleep studies were routinely completed at baseline as part of the insomnia treatment program, to screen for additional sleep disorders and collect information about patients' objective sleep (Somté portable full PSG recorders, Compumedics, Melbourne, Australia). Electrodes were configured to record two electroencephalogram channels (C_3-A_2, C_4-A_1), two electrooculogram channels, one electromyogram channel, two respiratory effort channels, and two electromyogram channels to record leg movements. A finger oximeter was attached to continuously record oxyhemoglobin saturation. Nasal pressure and oro-nasal airflow were recorded with a nasal cannula, and an oro-nasal thermistor. All sleep studies were scored by experienced technicians according to AASM criteria (38-40).

These data were collected from February, 2004 to November, 2015. During this time, the study site's metric for defining OSA presence and severity changed from the Respiratory Disturbance Index (RDI), to the Apnea/Hypopnea Index (AHI). Participants entering the program prior to 2011 received an RDI (n=333) which included respiratory effort related arousals (40), whilst participants entering the program from 2011 onward received an AHI score (n=122), encompassing only apneas and hypopneas (41). As these indices represent different manifestations of OSA, different cut-offs were applied to indicate OSA severity; none, mild, moderate and severe OSA. For RDI, mild, moderate and severe cut-offs were indicated by scores of 15-29, 30-44, and > 45, respectively. Alternatively, for AHI, mild, moderate and severe cut-offs were indicated by scores of 11-20, 21-30, and > 30, respectively (39-41).

2.4. Outcome Measures collected at baseline, post-treatment, and three-month follow-up.

2.4.1. ***One-Week Sleep/Wake Diaries.*** Sleep diaries are the recommended outcome measure for insomnia-treatment research (42). Sleep diaries were used to assess participants' average weekly subjective sleep parameters at baseline and during each follow-up period. Participants indicated their nightly; sleep onset latency, wake after sleep onset, and total sleep time for one week. Average sleep efficiency was also calculated by dividing average weekly total sleep time by time in bed, and multiplying by 100.

2.4.2. ***The Insomnia Severity Index (ISI).*** The ISI was used to measure improvements in insomnia severity during treatment. The ISI is a 7-item questionnaire which has been widely used as an outcome measure of insomnia severity in treatment studies (43). Scores range from 0 – 28, with higher scores representing more severe insomnia. The ISI is a valid measure of insomnia severity in populations of primary insomnia patients, and has been used in the COMISA population (6, 14, 44). ISI scores were also used to categorize insomnia remission (ISI<8), and patterns of treatment resistant insomnia (ISI improvement <4) at post-treatment and 3-month follow-up.

2.4.3. Daytime Functioning and Impairment Scales. The Epworth Sleepiness Scale (ESS) (45) is an 8-item self-report scale which was used to measure changes in subjective daytime sleepiness during treatment. Scores range from 0-24 with greater scores indicating more daytime sleepiness. The ESS has been reported to have adequate test-retest reliability (.82) and internal consistency as measured by Cronbach's alpha (.88) (45).

The Flinders Fatigue Scale (46) is a 7-item self-report questionnaire which was used to measure changes in feelings of fatigue during treatment. Patients answered answer six questions such as "was fatigue a problem for you?" on a five-point scale ranging from 0 (not at all) to 4 (extremely). One additional question relates to experiencing fatigue at seven

possible times during the day, with one point given for each time that is indicated. Possible scores on the scale range from 0 to 31, with higher scores indicating more daytime fatigue. The scale has adequate reliability and validity (46-48).

The Daytime Feelings and Functioning Scale is a 12-item self-report measure which was used to assess changes in daytime feelings and functioning during treatment (47). Responses to 12 items such as “lacked motivation”, “Had difficulty accomplishing daytime tasks”, and “felt lethargic” are added to form an overall score ranging from 0 to 36, with higher scores indicating greater daytime impairment. This measure has adequate internal consistency, discriminant validity and is sensitive to treatment-related changes in reported daytime functioning (47).

2.4.4. The *Dysfunctional Attitudes and Beliefs about Sleep scale*. The Dysfunctional Attitudes and Beliefs about Sleep-12 scale is a 12-item self-report questionnaire which assesses participants’ agreement with dysfunctional or maladaptive beliefs, appraisals, attributions and attitudes about sleep (49). Participants indicate their agreement with each item on a scale of 0 – 100, with possible responses ranging from “strongly disagree” to “strongly agree”. A total score is calculated by finding the average score of all 12 items. Total scores range from 0 – 100, with higher scores representing greater agreement with dysfunctional attitudes and beliefs about sleep. Morin and colleagues (49) report adequate internal consistency as measured by Cronbach’s alpha (.77).

2.4.5. The *Depression, Anxiety and Stress Scale.* The Depression, Anxiety and Stress Scale (50) is a 42-item self-report questionnaire which was used to measure symptoms of depression, anxiety and stress before and after CBT-i. The three sub-scale scores range from 0 – 42, with higher scores indicated more depression, anxiety or stress. The subscales of this scale have been found to have adequate internal consistency as measured by Cronbach’s

alpha (.87 - .94), as well as the overall scale (.93) and good convergent and discriminant validity when compared to other measures of depression, anxiety, and stress (51, 52).

2.5. Procedure for Insomnia Treatment Program

Following a diagnosis of insomnia, performed by a registered psychologist (Psychologists had 5 – 35 years of experience diagnosing and treating insomnia disorders), patients completed the baseline assessment (sleep diary and questionnaires), before an overnight home-based PSG sleep study was undertaken to screen for the presence of any additional sleep disorders. Patients then attended a group sleep education session (group sizes of 6-10 patients) which lasted two hours. These education sessions included information about the definitions and nature of insomnia, basic sleep information such as 90 min sleep cycles of deep and light sleep (53), positive sleep hygiene, the interplay between cognitions, behavior and sleep, and the effect of sleep medications. Patients then attended 4-6 personalized treatment consultations with an experienced sleep psychologist. During these sessions, psychologists used a range of cognitive, behavioral, and educational components to target specific mechanisms underlying each patients' insomnia condition (54). Follow-up assessments (sleep diaries and questionnaires) were completed again at post-treatment, and three-months after the baseline assessment.

Table 1. Demographic and Baseline Descriptive Data.

	All M (SD)	**Insomnia-only M (SD)**	**COMISA M (SD)**	***t***	***p***
Gender (male %)	33.1%	10.6%	40.4%	χ^2 = 5.86	.053
Age	51.68 (15.65)	48.97 (15.27)	57.73 (14.83)	-5.67	< .001*
Body Mass Index	26.27 (4.93)	25.55 (4.77)	27.89 (4.93)	-4.51	< .001*
Arousal Index	14.25 (8.02)	12.45 (6.72)	18.10 (9.16)	-6.36	< .001*
Diary Total Sleep Time	323.74 (92.10)	332.74 (91.35)	305.12 (91.23)	2.66	.008*
Diary Sleep Onset Latency	63.36 (55.54)	62.97 (49.70)	64.16 (66.21)	-0.17	.866
Diary Wake After Sleep Onset	106.10 (73.87)	102.46 (70.56)	113.85 (80.25)	-1.34	.181
Diary Sleep Efficiency	66.30 (16.80)	67.18 (16.14)	64.47 (18.03)	1.40	.163
Insomnia Severity Index	19.35 (4.30)	19.87 (4.21)	17.92 (4.23)	3.50	.001*
Daytime Functioning Scale	17.78 (7.30)	17.97 (7.21)	17.36 (7.50)	0.76	.447
Fatigue Severity Scale	18.48 (6.50)	18.91 (6.38)	17.50 (6.66)	2.01	.045*
Epworth Sleepiness Scale	5.75 (4.61)	5.32 (4.60)	6.58 (4.54)	-2.47	.014*
Dysfunctional Beliefs and Attitudes about Sleep scale	39.47 (9.34)	40.24 (9.35)	37.73 (9.28)	2.55	.011*
Depressive symptoms	12.16 (10.09)	12.00 (9.66)	12.48 (10.95)	-0.42	.267
Anxiety Symptoms	7.61 (7.78)	7.95 (8.02)	6.94 (7.26)	1.17	.245
Stress	16.32 (9.65)	17.10 (9.50)	14.80 (9.80)	2.16	.032*

COMISA – Co-morbid Insomnia and Sleep Apnea

2.6. Overview of Data Analysis

All data were analyzed with IBM SPSS (Version 22). Linear Mixed Models analyses were undertaken to examine differences in insomnia improvements during treatment between patients with insomnia-alone, and COMISA. As age and gender differed between groups at baseline, significant interactions were re-analyzed while controlling for these variables. Chi-

square analyses were used to examine rates of insomnia remission and treatment-resistance during therapy.

2.7. Missing Data

Of the 455 participants beginning treatment, missing sleep diary data were observed at baseline, post-treatment, and 3-months in 24%, 33%, and 49%, respectively. Missing ISI data were observed in 35%, 60%, and 61%, at each subsequent follow-up, respectively. Finally, missing data on other outcome questionnaires were observed in 13%, 44%, and 47% at each subsequent follow-up, respectively. Pearson Chi-Square tests revealed that rates of missing ISI data at baseline differed significantly between patients with COMISA (45% missing) and those with insomnia-alone (31% missing; $\chi^2(1) = 8.12$, $p = .004$). There were no other significant differences in rates of missing data between groups, for any other outcomes at any follow-up. Patterns of missing data were considered to be missing at random, according to pre-defined criteria (55). Missing data occurred primarily because of lack of systematic collection of each outcome from each patient, and the modification and delayed introduction of some questionnaires (e.g., the ISI) to the questionnaire battery over the 12-year period. Therefore, patterns of missing data were thought to be unrelated to patients' study group or disease severity. Linear Mixed Models analyses were chosen over the ANOVA approach due to the ability to handle randomly missing data (55, 56).

3. RESULTS

3.1. Effect of CBT-i

It was predicted that patients with co-morbid insomnia and sleep apnea (COMISA) would experience significant improvements in insomnia symptoms during CBT-i. COMISA patients showed statistically significant improvement in all sleep diary (Table 2) and questionnaire measures (Table 3) from baseline to 3-month follow-up. Similarly, as expected, the group with insomnia-alone showed robust improvements in all sleep parameters, as well

as the majority of questionnaire measures during treatment. The only exception to this was the Epworth Sleepiness Scale which showed no significant difference from baseline to post-treatment (p = .12), and a small significant decrease between post-treatment and 3-month follow-up (p = .002), however no overall significant effect of time.

3.2. Group Comparisons

It was expected that patients with COMISA might show smaller improvement of outcome measures than the patients with insomnia-alone. However, there were no statistically significant interactions in improvements in the majority of sleep diary parameters or questionnaire outcomes (See Tables 2 and 3, and Figures 1 and 2). The only significant sleep diary interaction showed that COMISA patients experienced slightly greater improvements in total sleep time than patients with insomnia-alone during treatment (As seen in Table 2, Figure 1). As age and gender differed between groups at baseline, significant interactions were repeated while controlling for these variables. After controlling for age and gender, the interaction between group and time on total sleep time was no longer statistically significant (F(569.17) = 0.49, p = 0.61).

COMISA patients showed slightly less improvement in the ISI, and the DBAS scale during treatment, compared to patients with insomnia-alone (Table 3, Figure 2). After controlling for gender and age, interaction terms were no longer statistically significant for ISI (F(463.53) = 2.63, p = .07), or DBAS outcomes (F(568.89) = 1.28, p = .28). Finally, COMISA patients experienced significantly greater reductions in the Epworth Sleepiness Scale (ESS) compared to patients with insomnia-alone (Table 3, Figure 2). This interaction remained significant after controlling for age and gender. There were no statistically significant interactions in improvements in the remaining questionnaire measures during treatment, between patients with insomnia-alone, and COMISA patients (Table 3).

To further investigate the association of OSA severity and insomnia improvements during CBT-i, change scores were computed for each sleep diary sleep parameter from baseline to post-treatment, and baseline to three-month follow-up (e.g. change in total sleep time from baseline to post-treatment, change in total sleep time from baseline to three-month follow-up, etc.). Correlational analyses revealed that OSA severity (AHI/RDI) was not related to changes in any sleep parameter during treatment (all $r < .1$, all $p > .05$).

Table 2. Changes in sleep diary measures during treatment for patients with insomnia-alone, and COMISA.

	Insomnia-Alone M (95%CI)	**COMISA M (95%CI)**	**Interaction**		
			F	***df***	***p***
Total Sleep Time (min)					
Baseline	331.7 (10.3)	306.8 (15.0)	4.33	570.70	.014^
Post-Treatment	366.3 (10.5)	330.8 (15.8)			
3-Months	373.3 (11.0)	365.1 (17.0)			
Change by 3-Months	41.7 (12.4)*	58.4 (19.0)*			
Sleep Onset Latency (min)					
Baseline	62.59 (5.02)	64.41 (7.27)	0.12	512.26	.889
Post-Treatment	27.42 (5.12)	29.78 (7.87)			
3-Months	24.66 (5.47)	24.37 (8.56)			
Change by 3-Months	-37.94 (7.44)*	-40.03 (11.33)*			
Wake After Sleep Onset (min)					
Baseline	102.56 (6.93)	113.73 (10.18)	0.49	543.56	.614
Post-Treatment	42.03 (7.17)	52.36 (10.84)			
3-Months	43.58 (7.67)	47.39 (12.18)			
Change by 3-Months	-58.98 (10.40)*	-66.35 (16.05)*			
Sleep Efficiency (%)					
Baseline	67.28 (1.72)	64.53 (2.53)	1.87	551.47	.156
Post-Treatment	83.84 (1.77)	79.39 (2.69)			
3-Months	84.41 (1.88)	83.48 (2.97)			
Change by 3-Months	17.13 (2.40)*	18.94 (3.68)*			

COMISA = Co-morbid insomnia and sleep apnea
* $p < .001$ main effect of time per group
^no longer significant after adjusting for baseline differences in age and gender, between groups.

Table 3. Changes in daytime/psychological measures during treatment.

	Insomnia-alone M (±95%CI)	COMISA M (±95%CI)	Interaction		
			F	*Df*	*p*
Insomnia Severity Index					
Baseline	19.9 (0.6)	18.0 (1.1)	4.56	449.67	.011^
Post-Treatment	9.5 (0.8)	9.6 (1.3)			
3-Months	7.6 (0.8)	8.2 (1.3)			
Change by 3-Months	-12.2 (1.10)**	-9.8 (1.80)**			
Epworth Sleepiness Scale					
Baseline	5.3 (0.5)	6.5 (0.7)	3.42	507.97	.034
Post-Treatment	5.9 (0.6)	5.8 (0.8)			
3-Months	4.9 (0.6)	5.2 (0.9)			
Change by 3-Months	-0.4 (0.67)	-1.3 (0.97)*			
Flinders Fatigue Scale					
Baseline	18.9 (0.7)	17.5 (1.1)	1.59	565.30	.205
Post-Treatment	12.3 (0.9)	11.2 (1.3)			
3-Months	10.0 (0.9)	10.2 (1.3)			
Change by 3-Months	-8.8 (1.19)**	-7.3 (1.78)**			
Daytime Functioning					
Baseline	17.9 (0.8)	17.2 (1.2)	1.49	509.59	.227
Post-Treatment	10.9 (0.9)	11.4 (1.4)			
3-Months	9.4 (1.0)	9.9 (1.5)			
Change by 3-Months	-8.5 (1.13)**	-7.3 (1.71)**			
Dysfunctional Beliefs and Attitudes about Sleep					
Baseline	40.2 (1.0)	37.7 (1.5)	5.38	561.00	.005^
Post-Treatment	28.2 (1.2)	27.7 (1.9)			
3-Months	25.1 (1.3)	26.5 (1.9)			
Change by 3-Months	-15.1 (1.56)**	-11.2 (2.36)**			
Depressive Symptoms					
Baseline	12.07 (1.14)	12.67 (1.64)	0.26	477.16	.975
Post-Treatment	7.98 (1.26)	8.82 (1.91)			
3-Months	6.81 (1.31)	7.56 (1.91)			
Change by 3-Months	-5.26 (1.51)**	-5.11 (2.17)**			
Anxiety Symptoms					
Baseline	7.78 (0.84)	7.02 (1.20)	0.87	462.77	.419
Post-Treatment	5.01 (0.95)	5.02 (1.40)			
3-Months	4.86 (0.99)	3.93 (1.39)			
Change by 3-Months	-3.12 (1.12)**	-3.09 (1.56)**			
Stress					
Baseline	17.10 (1.06)	14.77 (1.51)	2.34	500.73	.098
Post-Treatment	10.94 (1.17)	10.13 (1.77)			
3-Months	9.26 (1.21)	9.19 (1.80)			
Change by 3-Months	-7.84 (1.48)**	-5.59 (2.15)**			

COMISA = Co-morbid insomnia and sleep apnea,
*p < .01 main effect of time per group
** p < .001 main effect of time per group
^no longer significant after adjusting for baseline differences in age and gender, between groups.

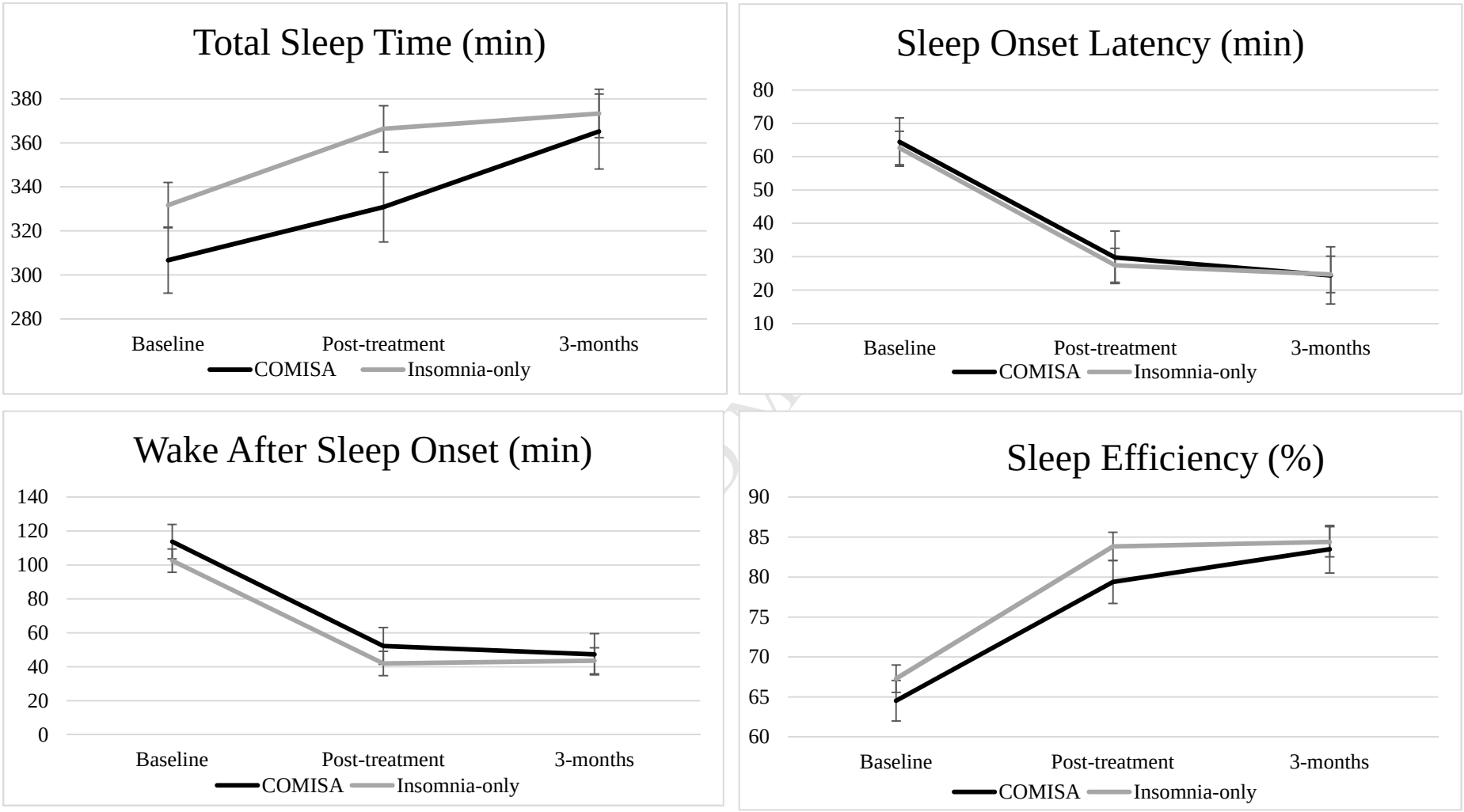

Figure 1. Changes in sleep parameters during treatment between groups, during treatment (±95% CI).

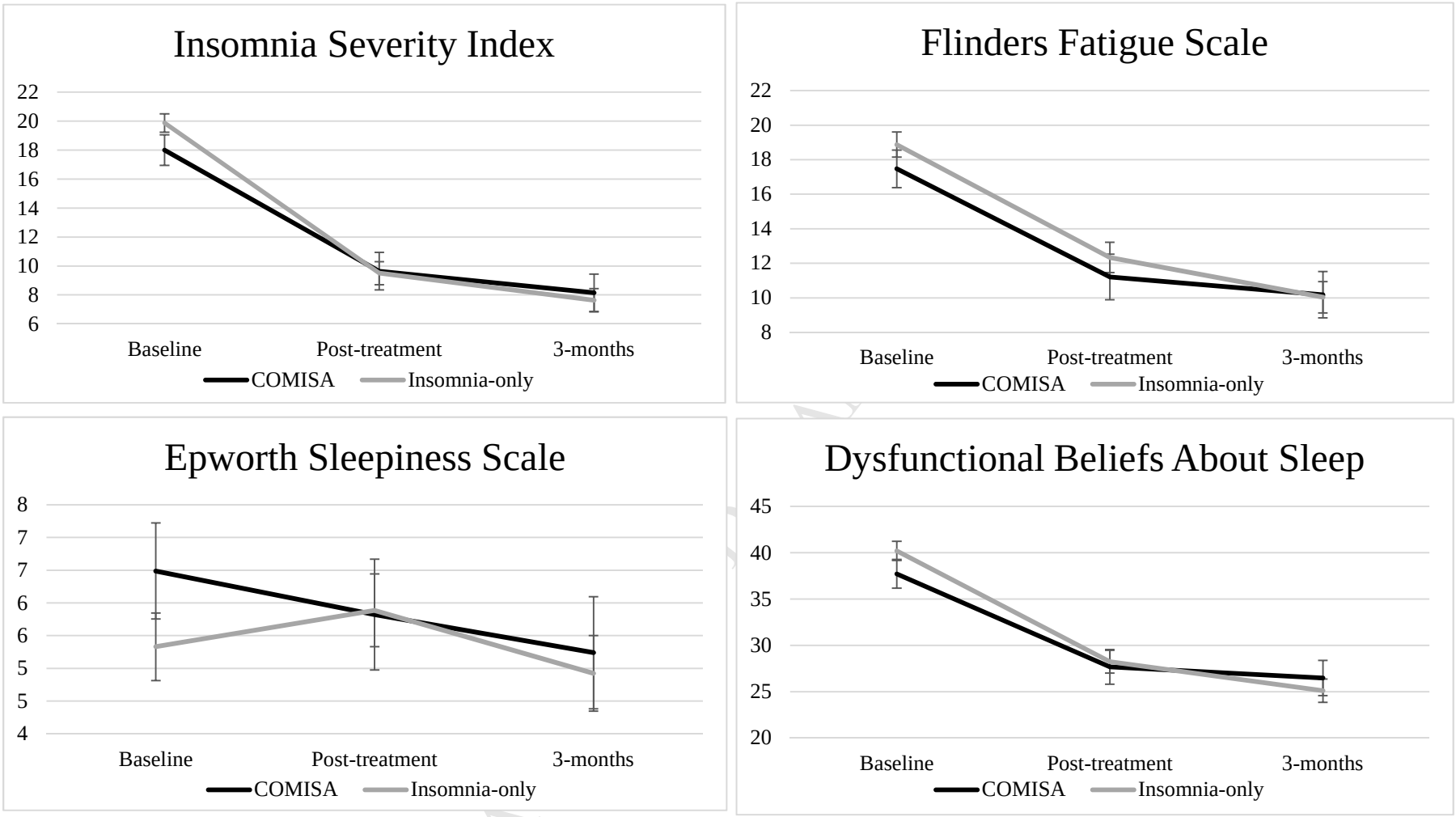

Figure 2. Changes in Insomnia Severity, and daytime impairments in patients between groups, during treatment (±95% CI).

3.3. Responder Analyses

The responder analysis compared the rates of insomnia remission (ISI<8) between the two groups. At post-treatment, rates of insomnia remission were not statistically different ($\chi^2(1) = 1.35$, $p = .25$) for patients with COMISA (36.0%) and insomnia-alone (45.5%). At 3-month follow-up, rates of insomnia remission were also not statistically different, ($\chi^2(1) = 1.16$, $p = .28$), for patients with COMISA (52.9%) and insomnia-alone (61.7%).

Finally, to investigate the proportion of patients who experienced a pattern of 'treatment-resistant insomnia' during treatment, participants with less than 4-points improvement in the ISI from baseline to post-treatment and baseline to three-month follow-up were compared between groups. From baseline to post-treatment, rates of insomnia non-response were not significantly different ($\chi^2(1) = 0.05$, $p = .83$) between patients with COMISA (18.6%) and insomnia-alone (20.2%). From baseline to three-month follow-up, rates of treatment-resistant insomnia were also not significantly different ($\chi^2(1) = 0.89$, $p = .35$) between patients with COMISA (17.1%) and insomnia-alone (11.4%). Furthermore, among only patients with COMISA, levels of OSA severity (mild, moderate and severe) were not significantly related to treatment-resistant insomnia ($\chi^2(2) = 0.68$, $p = .71$), indicating that OSA severity did not influence rates of non-improvement.

4. DISCUSSION

The current results suggest that CBT-i is an effective insomnia treatment in the presence of OSA. Specifically, COMISA patients experienced significant robust improvement in all sleep and daytime functioning variables during CBT-i. Furthermore, the effectiveness of CBT-i was not decreased by the presence or severity of co-morbid OSA, when compared to patients with insomnia-alone. These findings offer support for an important aspect of the current popular treatment suggestion; that COMISA patients can be treated with CBT-i to improve insomnia symptoms prior to the initiation of CPAP therapy

(17, 18). Research investigating the impact of sequential CBT-i and CPAP therapy is currently being conducted (17, 57, 58).

In the current study, COMISA patients experienced significant improvements in subjective sleep parameters, symptoms of fatigue, sleepiness, daytime functioning, dysfunctional sleep-related thinking patterns, and global insomnia severity, from baseline to follow-up periods. For example, among COMISA patients, reported total sleep time increased by 24.1 minutes, sleep onset latency estimates decreased by 34.6 minutes, wake after sleep onset decreased by 61 minutes, and sleep efficiency increased by 14.9% by post-treatment. These improvements are also comparable to those observed in a recent meta-analysis of CBT-i in patients with insomnia-alone (19), which found that CBT-i resulted in improvements compared to non-treatment control groups in total sleep time of 7.6 minutes, sleep onset latency of 19 minutes, wake after sleep onset of 26 minutes, and sleep efficiency of 10% by post-treatment. Thus, the improvements from CBT-i in the COMISA patients of the present study were as great, if not greater than, those with insomnia-alone from the recent meta-analysis.

COMISA patients experienced significantly greater improvements in ESS scores during treatment. This interaction remained significant after controlling for age and gender. This difference was due to COMISA patients beginning treatment with significantly greater daytime sleepiness which was reduced to similar levels to patients with insomnia-alone, by 3-month follow-up. ‘Excessive daytime sleepiness’ is a central symptom of OSA, and it is unsurprising that COMISA patients had increased sleep propensity at baseline (59). Importantly, COMISA patients did not experience significantly elevated sleepiness at post-treatment with the use of bedtime restriction therapy. One concern over the use of bedtime restriction therapy in COMISA relates to the effect of bedtime restriction therapy on increased sleep propensity (60), in OSA patients with pre-existing elevated sleepiness. These

data indicate that the use of bedtime restriction therapy in COMISA patients with mild, moderate and severe OSA, does not lead to significantly increased levels of sleepiness by post-treatment. However, levels of sleepiness should be closely monitored from week-to-week of CBT-i in COMISA patients, and bedtime parameters modified accordingly to ensure patients' safety. Future studies may wish to replicate this analysis with a range of additional outcome measures (e.g., objective driving performance, and reaction time tasks) administered before, during, and after CBT-i in patients with and without co-morbid OSA.

These results suggest that the effectiveness of CBT-i is not impaired by the presence of co-morbid OSA. Some researchers have indirectly cast doubt on the effectiveness of CBT-i for patients with COMISA, by suggesting that a significant number of COMISA patients experience insomnia as a secondary symptom of their OSA (6, 7, 35). For example, OSA is associated with repetitive post-apneic arousals from sleep, and it is possible that some patients perceive periods of wakefulness following these arousals, and present to sleep clinics with a complaint of insomnia (27). While their OSA diagnosis remains stable, these 'secondary insomnia' patients would be expected to show very little response to CBT-i, and consequently, would create a pattern of reduced improvements observed for the COMISA group as a whole. However, in the current study, as COMISA patients and those with insomnia-alone experienced comparable improvements in both night time and daytime symptoms of insomnia during CBT-i, regardless of OSA severity, it is unlikely that a large proportion of COMISA patients were suffering from insomnia which was secondary to their OSA.

To examine patients in each condition who showed little response to CBT-i, 'treatment-resistant insomnia' was defined as less than 4-points improvement in the Insomnia Severity Index during treatment. From baseline to three-month follow-up, 17.1% of COMISA patients failed to experience insomnia improvements, versus 11.4% of patients with

insomnia-alone. This difference was not statistically significant, suggesting that co-morbid OSA does not increase rates of insomnia non-response during CBT-i. Furthermore, no significant differences were observed in rates of insomnia remission between groups at either follow-up, suggesting that co-morbid OSA does not reduce rates of insomnia-remission following CBT-i. As rates of treatment-resistant insomnia were similar between COMISA and insomnia-only groups, it is unlikely that a large proportion of the COMISA group were suffering from insomnia as a secondary symptom of their OSA. However, it is possible that some of the COMISA non-responders will experience further insomnia improvements after starting CPAP (7).

The current results should be interpreted in light of several limitations. Firstly, these data were collected from clinical patients seen over a 12-year period at an out-patient insomnia treatment clinic. Although great care was taken to collect and record sleep diary and questionnaire data at each follow-up period, some loss of data is inevitable due to patient non-compliance and withdrawal, changes in the questionnaire battery, and non-systematic recording of outcome data. Although missing data were defined as missing at random, according to pre-defined criteria (55), it is possible that some patients who experienced less insomnia-improvement were also more likely to have missing follow-up data, thereby resulting in a small increase in estimates of insomnia-improvements during treatment. However, as rates of missing data were similar between the insomnia-only, and COMISA groups, this pattern of missing data is very unlikely to effect the primary conclusions of the study. Unfortunately, no control condition was used. As these data reflect clinical patients who commonly paid for treatment, it was unfeasible to employ a placebo control condition. Previous research has documented the benefits of CBT-i over a placebo control condition in COMISA patients (8). Furthermore, CBT-i is already a well-established treatment, and the primary aim of current study was to compare the effect of CBT-i among patients with

COMISA and insomnia-alone, which should not necessarily require a control condition against an established treatment. Finally, these were patients who specifically sought insomnia treatment with a primary complaint of insomnia, rather than more general sleep laboratory patients, or community-dwelling individuals suffering from insomnia or COMISA. It is possible that COMISA patients who seek insomnia treatment are more likely to experience improvement with CBT-i, compared to patients who seek treatment primarily for symptoms of OSA who are later found to have co-morbid insomnia, or those who do not seek treatment. For example, if COMISA patients with a primary complaint of OSA were offered CBT-i, it is possible that they would be more likely to reject treatment or become disinterested over time. It will be important for future research to determine whether a 'chief complaint' of insomnia vs. OSA is associated with the effectiveness of different treatment options in the COMISA population (61).

4.1. Conclusion

Co-morbid insomnia and sleep apnea is a highly prevalent and debilitating condition, which is associated with a unique set of complexities that can limit effective treatment options. The most common treatment suggestion for COMISA patients is to use CBT-i to improve the insomnia symptoms, before initiating CPAP therapy to treat the OSA (3, 18, 62). The current results suggest that CBT-i is an effective treatment in the COMISA population, and that the effectiveness of CBT-i is not impaired by the presence or severity of co-morbid OSA. In fact, COMISA patients may experience slightly greater reduction of daytime sleepiness during CBT-i, compared to patients with insomnia-alone. Therefore, CBT-i should be considered as an initial treatment option among COMISA patients, which not only improves insomnia symptoms, but may improve subsequent acceptance and use of CPAP therapy when treating the OSA.

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Highlights

1. Co-morbid insomnia and obstructive sleep apnea commonly co-occur.
2. The effectiveness of CBT-i is not reduced in patients with co-morbid sleep apnea.
3. CBT-i may also improve subsequent CPAP use in patients with co-morbid insomnia and sleep apnea.