Treatment of Patients with Co-morbid Insomnia and Obstructive Sleep Apnea

by

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Abstract

Insomnia and Obstructive Sleep Apnea (OSA) are the two most common sleep disorders, occurring in 6-10%, and 23-50% of the general population, respectively (1-3). Furthermore, insomnia and OSA frequently co-occur within the same patient, resulting in increased impairments to sleep, daytime functioning, and quality of life (4, 5). Although Co-Morbid Insomnia and Sleep Apnea (COMISA) is a highly prevalent, and debilitating condition, only a small amount of research has investigated treatment approaches in this population.

Research examining treatment approaches in COMISA indicates that these patients are more difficult to treat, compared to patients with either insomnia- or OSA-alone (4). For example, COMISA patients show reduced acceptance and use of Continuous Positive Airway Pressure (CPAP) therapy, compared to patients with OSA-alone (6, 7). Alternatively, sedative and hypnotic medications commonly prescribed for insomnia symptoms can exacerbate manifestations of OSA, through depressant effects on the upper airway and controls of ventilation (4). Finally, Cognitive and Behavioral Therapy for Insomnia (CBT-i) is an effective treatment for primary, and co-occurring insomnia (8, 9), however has received little research attention in the COMISA population.

The current thesis aims to contribute to this field of sleep medicine, by investigating the characteristics, prevalence, and effectiveness of various discrete and combined treatment approaches in the COMISA population. Chapter 1 provides an overview of OSA and insomnia, where they occur independently. Chapter 2 includes a published review article documenting the characteristics, prevalence, and previous treatment attempts in COMISA patients (4). Chapter 3 includes an accepted manuscript, comparing the effectiveness of CBT-i in patients with insomnia-alone, and COMISA. It was found that patients with insomnia-alone (n = 314), and COMISA (n = 141) each experienced large improvements in sleep

parameters and daytime impairments during CBT-i. Furthermore, there were no significant differences in improvements between groups, indicating that the effectiveness of CBT-i is not reduced in patients with co-occurring OSA. Chapter 4 includes a manuscript describing a randomized controlled trial investigating the acute effectiveness of CBT-i (n = 72), versus a control condition (n = 73), in treating insomnia symptoms in participants with COMISA. It was found that CBT-i resulted in significantly greater improvements in sleep parameters, and global insomnia severity compared to the control condition. Chapter 5 includes a manuscript examining changes in daytime sleepiness, and subjective sleep parameters, before, during, and after CBT-i, in COMISA patients. This chapter indicated that CBT-i resulted in only a small transient increase in daytime sleepiness, and slight reduction of total sleep time during the first week of treatment, that rebounded to pre-treatment levels during each subsequent week. Chapter 6 reports a randomized controlled trial, investigating the impact of initial treatment with CBT-i (vs. no insomnia-treatment control), on subsequent acceptance and adherence to CPAP therapy, and long-term improvements in insomnia and OSA outcomes. It was found that initial treatment with CBT-i resulted in increased immediate acceptance and long-term use of CPAP therapy, compared to treatment with CPAP-alone. Furthermore, participants in the CBT-i condition reported greater improvements in global insomnia severity, and dysfunctional sleep-related cognitions, over the course of treatment. Finally, Chapter 7 includes an integrated discussion of the implications of the preceding chapters.

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Author Contributions to each Chapter

As this thesis includes several muti-author chapters, it is required by University policy that Alexander Sweetman specifically state where his contributions occurred. Co-authors' signatures of agreement with these statements may be found below.

Chapter 1. Introduction to Insomnia and Obstructive Sleep Apnea.

Alexander Sweetman authored this chapter.

Professor Leon Lack reviewed this chapter.

Chapter 2. Developing a Successful Treatment for Co-morbid Insomnia and Sleep Apnoea.

Alexander Sweetman was the primary author of this chapter; main contributor to text, compiling and reviewing references, constructing tables, in charge of submission and organising article review process, and wrote initial application to *Sleep Medicine Reviews* to consider this manuscript.

Prof. Leon Lack provided significant assistance with early drafts of manuscript, and initial application to *Sleep Medicine Reviews*.

Prof. Peter Catcheside assisted in drafting

Prof. Nick Antic assisted in drafting

Dr. Ching Li Chai-Coetzer assisted in drafting

Assoc. Prof. Simon Smith assisted in drafting

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Chapter 3. Does COMORBID Obstructive Sleep Apnea Impair the Effectiveness of Cognitive and Behavioral Therapy for Insomnia?

Alexander Sweetman was the primary contributor toward this chapter; tracked and reviewed hospital record data for all patients in study, undertook data entry, cleaning, formatting and analysis, primary contributor to text, in charge of submission and organising article review process.

Prof Leon Lack provided significant support with drafting, ethics approval, chief sleep Psychologist treating patients in the 'insomnia treatment program', and overseeing data collection from 2006 – present.

Sky Lambert assisted with data entry during research component of honours program.

Dr. Jodie Harris; drafting and sleep Psychologists involved in the 'insomnia treatment program'.

Prof. Michael Gradisar; drafting and sleep Psychologists involved in the 'insomnia treatment program'.

Chapters 4, 5, and 6 utilized data from a multi-site randomized controlled trial.

Title: Treating insomnia co-morbid with obstructive sleep apnoea: A randomized controlled clinical effectiveness trial.

National Health and Medical Research Council: 1049591.

Co-contributors to the trial included;

Prof. Doug McEvoy - Chief Investigator A, Physician

Assoc. Prof. Simon Smith- Chief Investigator B, trial Psychologist

Prof. Leon Lack – Chief Investigator C, Chief Psychologist

Dr. James Douglas- Chief Investigator D, Physician

Prof. Nick Antic – Chief Investigator E, Physician

Prof. Peter Catcheside- Chief Investigator F, Statistical advice

Dr. Ching Li Chai-Coetzer- Chief Investigator G, Physician

Amanda O'Grady - Research Co-ordinator

Nicola Dunn - Research Co-ordinator

Jan Robinson - Research Co-ordinator

Dr. Paul Williamson - Statistical Advice

Alexander Sweetman's contributions to Chapters 4, 5, and 6;

Alexander was the only PhD student involved in this AU $580K multi-site National Health and Medical Research Council-funded project. Alex commenced his PhD during the early design/planning stage of the project. He provided on-going significant contribution from the developmental stage, during the implementation of the project, through to the current data analysis and manuscript submission phase. His involvement has been core to this project's success, as he has played a significant role at all levels, and has been able to devote his entire workload to the project throughout the whole trial period.

Design;

- Introduced and justified use of several questionnaires for measurement of insomnia and OSA symptoms (Dysfunctional Beliefs and Attitudes about Sleep scale, Daytime Feelings and Functioning Scale, the Flinders Fatigue Scale), at key periods of trial.
- Amendment and construction of sleep diaries/overnight sleep diaries
- Assisted with amendments to original Ethics Approval.

- Co-wrote the CBT-i protocol (session content, slides, participant information; also drafted by Prof. Leon Lack and Assoc. Prof. Simon Smith), and accompanying CBT-i booklet (adapted from Prof. Leon Lack, and drafted by Prof. Doug McEvoy).

Sleep Technologist Duties;

- Setup ~100 patients for ambulatory PSG studies.
- Setup ~ 20 patients for ambulatory oximetry recording.

Research Coordinator assistance duties;

- Tracked patient progress through trial, speaking to patients during screening process (informed consent, etc.), conducting reminder phone calls prior to patient review appointments, and follow-up calls for overdue sleep diaries and questionnaire batteries.
- Data entry throughout trial, on-going communication with company managing online data storage system to ensure adequate data quality and import/export tools (Wappsystems Ltd.).
- Compiled monthly reports of patient recruitment, retention, and data quality, to present to group during steering committee meetings
- Presented interim patient safety indicators to 'data safety and management board'.
- Assisted in coordinating Psychologists during trial, training of Psychologist staff to ensure CBT-i treatment fidelity.
- Undertook detailed analysis of missing data, and compiled report for group.
- Undertook detailed analysis of objective sleep study data, reliability of objective sleep study measures, and compiled report for group.

Academic Duties;

- Main contributor to each Chapter (Chapters 4, 5, and 6). Wrote primary draft of each manuscript, and played central role in drafting process with group.
- Main contributor to 'Statistical Analysis Protocol' document (Appendix M). Wrote document and played central role in drafting and facilitating discussion of statistical concepts with group.
- Primary contributor to all statistical procedures including, exporting and formatting data, analyzing data, reporting outcomes to group, and constructing Tables and Figures for manuscripts.
- Presenting study data as poster and oral abstracts at APSS (Boston, 2017), ESRS (Bologna, 2016), and World Sleep (Prague, 2017).

Chapter 7. General Discussion

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Declaration

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed: [signature removed in uploaded version]

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Finally, thank you to my family and friends who have supported me throughout my PhD.

Glossary of Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea Hypopnea Index
APAP	Auto-titrating Positive Airway Pressure
CBT-i	Cognitive Behavioral Therapy for Insomnia
COMISA	Comorbid insomnia and Sleep Apnea
CPAP	Continuous Positive Airway Pressure
DBAS	Dysfunctional Beliefs and Attitudes about Sleep
EEG	Electroencephalography
ESS	Epworth Sleepiness Scale
HPA	Hypothalamic-Pituitary-Adrenal
ICSD	International Classification of Sleep Disorders
ISI	Insomnia Severity Index
NRS	Non-Restorative Sleep
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
PSG	Polysomnography
RDI	Respiratory Disturbance Index
UARS	Upper Airway Resistance Syndrome

List of Accepted Manuscripts, and Publications

Sweetman A, Lack LC, Catcheside PG, Antic NA, Chai-Coetzer CL, Smith SS, et al. Developing a successful treatment for co-morbid insomnia and sleep apnoea. *Sleep Med Rev*. 2017; 33: 28-38. DOI: http://dx.doi.org/10.1016/j.smrv.2016.04.004

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Sweetman A, Lack LC, Lambert S, Gradisar M, Harris J. Does co-morbid obstructive sleep apnea impair the effectiveness of cognitive and behavioral therapy for insomnia? *Sleep Med*. 2017; in press. DOI: https://doi.org/10.1016/j.sleep.2017.09.003

List of Published Abstracts, and Conference Presentations

Sweetman AM, Lack LC, Catcheside PG, Antic NA, Chai-Coetzer CL, Smith SS, et al. Examining insomnia subtypes in patients with comorbid insomnia and sleep apnea. 23rd Congress of the European Sleep Research Society Bologna, Italy, Sep 2016.

Sweetman AM, Lack LC, Antic NA, Chai-Coetzer CL, Smith SS, Douglas J, et al. Role of sleep misperceptions in relationship between co-morbid insomnia and obstructive sleep apnea. 23rd Congress of the European Sleep Research Society Bologna, Italy, Sep 2016.

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Sweetman AM, Lack LC, Catcheside PG, Antic NA, Chai-Coetzer CL, Smith SS, et al. Changes in sleep and sleep propensity during bedtime restriction therapy, in patients with co-morbid insomnia and sleep apnea. Sleep conference, Boston, USA. 2017.

Sweetman AM, Lack LC, Antic NA, Chai-Coetzer CL Smith SS, Douglas J, et al. Effectiveness of CBT-i in patients with co-morbid insomnia and sleep apnea - Oral Presentation. Sleep conference, Boston, USA. 2017.

Sweetman AM, Lack LC, Antic NA, Chai-Coetzer CL, Smith SS, Douglas J, et al. Effectiveness of CBT-i in patients with co-morbid insomnia and sleep apnea - Oral Presentation. World Sleep Congress, Prague, Czech Republic. 2017.

Sweetman A, Lack LC, Lambert S, Harris J, Gradisar M. Cognitive behavioural therapy for insomnia in patients with and without co-morbid sleep apnea - Oral Presentation. Adelaide Sleep Retreat, Adelaide, South Australia, Australia. 2016.

1 CHAPTER 1. Introduction to Obstructive Sleep Apnea and Insomnia.

As this thesis is concerned with the treatment of co-morbid insomnia and obstructive sleep apnea, it is important to briefly review each disorder independently. A thorough review of the aetiology, symptoms, diagnosis and treatment of both insomnia and obstructive sleep apnea is beyond the scope of the current thesis, so only a condensed summary of each is provided below.

1.1 Obstructive Sleep Apnea

1.1.1 Overview

Obstructive Sleep Apnea (OSA) is a disorder characterized by repetitive brief closure or narrowing of the upper airway during sleep (1). These respiratory events commonly terminate in transient arousals to lighter sleep or wakefulness, surges in blood pressure and sympathetic nervous system activation. OSA is also associated with acute and long-term consequences, including sleep fragmentation, daytime sleepiness and fatigue, reduced quality of life, and increased risk of traffic accidents and cardiovascular disease (2-6). OSA is diagnosed according to the average number of apneas and hypopneas experienced per hour of sleep (Apnea–Hypopnea Index; AHI) as assessed via polysomnography (PSG) (1, 7). According to minimal diagnostic criteria (1), obstructive sleep apnea hypopnea syndrome is prevalent in 2% of women and 4% of men aged 30 – 60 (8).

Continuous Positive Airway Pressure (CPAP) therapy is the recommended treatment for moderate and severe OSA (7, 9, 10). Patients treated with CPAP wear a pressurized nasal or oro-nasal mask throughout the night, which pneumatically splints open the upper airway (10). Although CPAP effectively controls both day- and night time manifestations of OSA, high rates of patient rejection and poor long-term use remain a significant barrier to its efficacy (11).

1.1.2 The Upper Airway and Upper Airway Obstruction

The human upper airway is a complicated component of the respiratory system, consisting of many muscles and structures which constantly interact to serve respiration, digestion and phonation (12). The upper airway can be divided into three separate regions; the *nasopharynx* is the uppermost section which connects the nasal cavity to the hard palate, the *oropharynx* extends from the hard palate to the epiglottis, and the *hypopharynx* extends from the base of the tongue to the larynx (13).

It is suggested that upper airway collapse results largely from a combination of reduced upper airway area, and reductions in compensatory muscle tone during sleep (12-16). The area of the upper airway is reduced in patients with OSA compared to normal sleepers (13, 17), due to increased size of surrounding soft tissue structures (e.g. tongue, lateral pharyngeal walls, etc.) (13, 17, 18), and craniofacial differences (13, 19-21). Breathing though a narrow airway creates greater negative intraluminal (suction) pressure, and therefore greater likelihood of upper airway collapse (14). As patients fall asleep, a reduction in muscle tone occurs (22), leaving individuals with reduced upper airway area vulnerable to airway collapse (23). Airway collapse is thought to occur when the increased negative airway pressure during inspiration outweighs the stabilizing force of these upper airway dilator muscles (14).

1.1.3 Definitions and Mechanisms of Respiratory Events

Respiratory events are categorized as *apneas* (cessation of breathing) or *hypopneas* (reduction in breathing), according to specific criteria (24, 25). Obstructive apneas are defined as a 90% decrease in airflow lasting for at least 10 seconds, with continued respiratory effort. The updated 2007 criteria define hypopneas as at least a 30% drop in airflow which lasts for at least 10 seconds, with an associated oxygen desaturation of at least 4% or subsequent arousal (25). The average number of apneas and hypopneas per hour of sleep are calculated to form the Apnea Hypopnea Index (AHI). The AHI is used as an indicator of OSA severity. Mild, moderate, and severe OSA is commonly diagnosed if AHI scores range from 5 - 15, 15 - 30, and > 30 respectively (7).

As the airway narrows or closes, patients continue attempting to inhale as indicated by continued or gradually increasing abdominal and thoracic movements (26). As airway flow decreases, patients experience a reduction in oxyhaemoglobin saturation, increased carbon dioxide retention, and subsequently experience a transient arousal from sleep (16). These

arousals are accompanied by activation of the sympathetic nervous system and upper airway dilator muscles to restore patency of the upper airway (27, 28). Although arousals are necessary to avoid asphyxiation, spikes in sympathetic nervous system activity, and surges in blood pressure throughout the night lead to significant sleep fragmentation, and have been linked to several long-term cardiovascular complications (28).

Post-apneic arousals do not always lead to full awakenings, but commonly present as a physiological arousal to lighter sleep (28, 29) As Lugaresi, Coccagna and Mantovani (pp. 87 – 88 (30)) comment, these "continuous somatic and autonomic arousals produced by the periodic apneas alter the whole pattern of sleep, as well as the course of the individual stages. In this sense, sleep is profoundly disturbed". Therefore, it is understandable that in severe cases of OSA, any facets of life which are dependent on the restorative properties of sleep are likely to be impacted. The frequency of respiratory events are also influenced by sleeping position and sleep stages throughout the night (31-36).

1.1.4 **Diagnosis, Prevalence, and Risk Factors**

Prevalence estimates for OSA vary widely depending on diagnostic tools, criteria, and the characteristics of different samples. According to the *International Classification of Sleep Disorders* (1), minimum diagnostic criteria for OSA include a AHI of at least five, with an associated complaint of one of the following; daytime sleepiness, unrefreshing sleep, fatigue, insomnia, night time choking/breath holding/gasping, loud snoring or breathing interruptions. Alternative criteria include an AHI of at least fifteen.

OSA, defined as an AHI ≥ 5 is found in 9% of women and 24% of men aged 30 – 60 years of age (8). However, after requiring a complaint of daytime sleepiness to satisfy minimal diagnostic criteria, this estimate is reduced to 2% of women and 4% of men (8). Davies and Stradling (37) conducted a review of the twelve major epidemiological studies undertaken prior to 1996, and found that the prevalence of sleep-disordered breathing varied

from .03 – 15%. In their own sample, population prevalence of OSA was estimated to be 3.6%; including 5.7% of males and 1.2% of females (37). Bearpark and colleagues (38) examined symptoms of snoring and sleep apnea in Australian males and found that 26% of the 294 adult participants had an AHI ≥ 5, and 3.1% also experienced daytime sleepiness. In 2002, Young, Peppard and Gottlieb (39) reviewed a larger pool of epidemiological meta-analytical studies and concluded that up to 5% of adults in Western countries have undiagnosed OSA.

Any physiological, anatomical or behavioral factors which further reduce upper airway area, or sleeping muscle tone are thought to increase a patient's risk of developing OSA (13, 40). Throughout the literature, the prevalence of OSA is commonly associated with the following risk factors; male gender (8, 40-42), increased body mass index (43-45), differences in upper airway size, craniofacial structure, and neck circumference (17, 18, 20), older age (46-48), and anatomical and craniofacial differences affecting the upper airway (19-21). Furthermore, manifestations of OSA may also be exacerbated by behavioral risk factors which reducing sleeping muscle tone, including; alcohol consumption (49, 50), sleep deprivation (51-55), and use of certain sedative/hypnotic medications (56-58).

1.1.5 Consequences of OSA

OSA is associated with several adverse consequences, not only to immediate sleep architecture and night time oxygen saturation (7, 13), but also with increased daytime impairments (29), risk of cardiovascular disease (4, 59), and reduced quality of life (2, 6). For example, excessive daytime sleepiness is a hallmark clinical symptom of OSA, and is in fact required among minimal diagnostic criteria (1, 60). However, other studies have also found that feelings of fatigue and lack of energy, are of equal importance to many OSA patients (3, 29). OSA is also associated with decreased neuropsychological functioning (61), increased

presence of co-morbid psychiatric symptoms (62, 63), occupational accidents (64), and a 2- to 7-fold increase in traffic accidents (5, 65).

The presence of OSA is also associated with an increased prevalence of other co-morbid disorders such as depression, anxiety and post-traumatic stress disorder (62, 66, 67). OSA also has a negative impact on wider society through increased healthcare treatment costs, absenteeism, and traffic accidents, and lost work productivity (68-70).

1.2 Continuous Positive Airway Pressure

1.2.1 Overview

Continuous Positive Airway Pressure (CPAP) therapy is the recommended treatment for moderate and severe OSA (7, 9, 10). Patients treated with CPAP wear a nasal, oronasal, or full-face mask for the duration of their sleep period, which administers a predetermined positive air pressure to act as a pneumatic splint (10), stabilizing the upper airway and preventing obstructive events from occurring (7, 10). Upper airway stability also leads to the reversal of many consequences of OSA; including daytime sleepiness, fragmented sleep architecture, and impaired daytime functioning, mood, and quality of life (71). However, despite the ability of CPAP to reverse many symptoms of OSA, poor acceptance and adherence present a major limitation to treatment effectiveness (11, 72).

1.2.2 Function and Efficacy of CPAP

CPAP pneumatically splints open the oropharyngeal airway by providing positive air pressure to counteract the closing forces of surrounding soft tissue structures (73-75). Different levels of pressure are needed to splint open the upper airway depending on the force of surrounding soft tissue structures and inspiratory suction, on upper airway closure (9).

The immediate effects of CPAP therapy include elimination of obstructive respiratory events and subsequent spikes in physiologic activity throughout the night (11, 75), reduced variation in blood pressure and heart rate, reduced electroencephalographic arousals,

stabilized oxygen saturation, perceptions of a more restorative sleep, and fewer episodes of nocturia throughout the night (32, 71, 76). Over time, CPAP also improves patients' sleep architecture by eliminating post-apneic arousals to lighter sleep; thereby allowing them a quicker progression to deep sleep (77-79). Long-term CPAP use also commonly leads to reductions in both subjective and objective sleepiness (80-82). CPAP also reduces risk of traffic accidents (83), and feelings of depression and anxiety (84, 85), and improves quality of life (71, 86).

1.2.3 CPAP Acceptance and Adherence

CPAP is an ongoing treatment which should be used each night to maintain these improvements (87, 88). Due to the long-term nature of treatment, difficulties adapting to using CPAP, and the side-effects of treatment, many patients have difficulty accepting and using CPAP for the duration of their sleep period each night (11, 83).

CPAP is associated with a range of side effects, which affect different patients to varying degrees (83, 89, 90). The most common side effects include nocturnal awakenings, claustrophobia and mask discomfort, machine noise, difficulty falling asleep with CPAP, and difficulty exhaling against positive air pressure (11, 89, 91, 92). Due to the side-effects, stigma, and cumbersome nature of treatment, many patients reject CPAP therapy immediately or soon after trialling CPAP during a titration study (11).

Technological developments including data cards and electronic information relaying within CPAP machines have allowed clinicians and researchers to measure objective patterns of CPAP adherence. Levels of patient acceptance and adherence vary widely between studies due to the specific CPAP equipment used, patients' level of education and support, sample characteristics, and differing definitions of 'adequate adherence'. For example, Weaver and Grunstein (11) reviewed research examining CPAP adherence in 12 studies and found that between 29 – 83% of patients use CPAP for fewer than four hours per night.

A large body of research has uncovered many possible predictors of CPAP rejection and low use (11). Importantly, co-morbid insomnia complaints also predict reduced CPAP adherence. Krakow and colleagues (93) first proposed that OSA patients with complaints of difficulties initiating and maintaining sleep require a three-fold increase in time and effort to successfully adapt to CPAP, compared to OSA patients without co-occurring insomnia. A growing body of evidence has recognized this pattern of poor CPAP adherence among patients with co-morbid insomnia. This research constitutes a core feature of the justification for the current thesis and will be discussed in the following sections.

1.3 Insomnia

1.3.1 Overview

Insomnia is a multifaceted disorder characterized by perceived difficulties falling asleep, remaining asleep, waking too early and being unable to return to sleep, or a combination of these difficulties. Diagnostic criteria also specify that these night time symptoms are associated with significant daytime functional or social impairments, including feelings of fatigue, poor mood, and impaired concentration (1). Insomnia can be defined as an acute symptom (e.g. in response to stressful life situations or medical issues), or as a chronic disorder which is maintained independently of those factors that instigated the poor sleep (94, 95). Chronic insomnia is prevalent in 6-12% of the population (96-99), however these estimates increase with age, female gender, and the presence of additional medical and psychiatric disorders (98, 100, 101). A gold-standard diagnosis of insomnia is established by a psychologist or trained sleep clinician, during a structured sleep interview, to interpret patients' self-reported sleep difficulties and daytime functioning information, and history of sleep, medical and psychiatric diagnoses (102).

Insomnia presents a great burden to patients' daytime functioning, mood and quality of life (97), and results in substantial costs to society through healthcare utilization, reduced

work productivity and absenteeism (68, 103). Insomnia can present as a *primary* sleep disorder, or be defined as '*co-morbid'* with other disorders (104). Both primary and co-morbid insomnia are effectively treated with Cognitive and Behavioral Therapy for Insomnia (CBT-i) (105), which unlike pharmacological treatments, commonly produces long-lasting benefits to patients' sleep and daytime functioning after the cessation of treatment (106).

1.3.2 Prevalence

Insomnia has been conceptualized as both a symptom (e.g. a general insomnia complaint; with or without daytime impairments, etc.) and a diagnosis (i.e. chronic insomnia; (98)). Epidemiological studies of the general population generally find that one third of the population suffer insomnia symptoms (e.g. difficulty falling asleep, difficulty remaining asleep, or waking too early) at any one time (97, 98, 107, 108). Alternatively, studies assessing complaints of sleeping difficulties accompanied by *daytime impairments*, report that between 9 – 19% of the population suffer from the disorder (98, 109). However, 'chronic insomnia' refers to a more enduring disorder which is associated with impaired sleep and daytime impairments on several occasions each week for a sustained period of months, or years. Studies employing these conservative diagnostic criteria have found that between 6 – 12% of the general population suffer from chronic insomnia at any one time (97, 98, 103, 107, 110, 111).

Insomnia is also associated with several risk factors that increase either the likelihood of sleep being disturbed, or an acute sleep complaint developing into a long-term insomnia diagnosis. Some of the most common risk factors for insomnia include; female gender, older age, lower education, unemployment or occupational status, symptoms of depression and anxiety, co-morbid medical diagnoses, and a history of smoking or substance use (96, 101, 104, 111-114).

1.3.3 **Insomnia Diagnosis**

The *International Classification of Sleep Disorders* (1) includes criteria to guide a diagnosis of insomnia, define specific insomnia subtypes, and differentiate insomnia from other sleep and medical disorders. According to these criteria, insomnia is commonly diagnosed according to frequent difficulties initiating or maintaining sleep, early morning awakenings, or chronically nonrestorative sleep, with associated daytime functional impairment, which have occurred for at least one month (115). Furthermore, co-morbid sleep disorders (e.g. narcolepsy, circadian rhythm disorders) must be ruled out for a diagnosis of primary insomnia (1, 115).

It is recommended that insomnia is diagnosed by an experienced psychologist or sleep clinician, who evaluates patients' sleep and daytime functioning complaints, history of medical and psychiatric diagnoses, and substance use, during a structured interview with the aid of questionnaires and sleep diary information (102). Multiple questionnaires measuring the presence, severity and history of insomnia symptoms are available. As the measurement of insomnia constitutes a core component of this thesis, these questionnaires are introduced in more detail in following sections.

1.3.4 **Insomnia Development**

Long-term insomnia is commonly conceptualized as a disorder of chronic hyperarousal (116, 117). 'Hyperarousal' reflects chronic activation of physiologic variables such as increased metabolic rate, heart rate, cortisol levels and core body temperature, and psychological factors including increased anxiety and distress, negative sleep-related ruminations, and worry over the consequences of sleep loss (95, 116-119). Together, these physiologic and cognitive symptoms are believed to drive patients into an alert, anxious and aroused state, which is incompatible with sleep initiation or resumption, and results in feelings of impaired daytime functioning (116, 118). In accordance with this theory, insomnia

is characterized by 24-hour activation of the sympathetic nervous system, conditioned physiological and cognitive arousal responses to the bedroom environment or sleep cues, and maladaptive behaviors and cognitions which can prevent sleep during the night and make patients feel fatigued and exhausted during the day (117).

Primary insomnia (also referred to as 'psychophysiological insomnia', or 'conditioned insomnia') occurs when insomnia symptoms are not attributable to other medical and psychiatric disorders (115). Several researchers have attempted to understand the development of insomnia with different models, including behavioral (120, 121), cognitive (119), physiological (117, 118, 122), and combined approaches (95, 123). Spielman's *3P* model is a versatile approach, which allows for inclusion of each of these different factors. Spielman's 3P model (94, 124), conceptualizes primary insomnia as a self-maintaining condition which results from *predisposing, precipitating,* and *perpetuating* factors.

Predisposing factors reduce the threshold necessary for sleep to be disturbed (124). Predisposing factors can include personality characteristics such as high anxiety, tension and a low arousal threshold, an irregular sleep-wake routine, or poor general health (101, 114, 124). Although predisposing factors may increase the likelihood of sleep being disturbed, they do not directly create an actual sleep disturbance.

Precipitating factors are transient events which trigger acute periods of sleep loss. Examples of events or circumstances leading to acute sleep loss may include psychological factors (e.g. stress or anxiety), medical problems (e.g. pain), poor sleep habits, or a mistimed circadian rhythm (e.g. due to travel through time-zones resulting in jet-lag). Although precipitating factors may be the initial trigger for disturbed sleep, Spielman's model proposes that they do not necessarily remain active at the time the patient is seeking treatment (125). It is suggested that chronic insomnia is maintained by a separate set of *perpetuating* factors (124).

Spielman's model proposes that *perpetuating* factors are any psychological, behavioral or physiological processes or patterns which maintain or exacerbate the insomnia, allowing it to exist independently of any initial *precipitating* factors (124). Many different perpetuating factors exist, and each individual patient may present with a different constellation of behaviors or cognitions which exacerbate the overall condition (124).

For example, in response to sleep loss and daytime impairments, patients with insomnia commonly engage in cognitive and behavioral 'coping strategies' (126). Although these coping strategies are intended to minimize the consequences of the insomnia, many of them instead serve to exacerbate the disorder (127). That is, these coping strategies commonly result in increased tension, arousal and anxiety, which create further impairments to sleep and daytime functioning. As these factors are believed to play a large role in the maintenance of insomnia, they also represent the main target of CBT-i.

1.3.4.1 Coping and Safety Behaviors

To reduce symptoms of sleep loss and associated daytime impairments, many patients engage in maladaptive safety behaviors or 'coping strategies'. For example, patients commonly extend the time that they spend in bed to increase their opportunity to acquire more sleep (94, 124). However, this attempt to 'catch up' on lost sleep is commonly counter-productive. In fact, extending time in bed is thought to primarily increase time spent *awake* in bed (94, 102). Extended time spent awake in bed is more likely to lead to tension and distress in the face of failed attempts at 'trying to fall asleep' or 'forcing oneself to sleep' (119, 128). After repeated pairing of time spent awake in bed and feelings of distress and anxiety, a conditioned relationship may begin to form (120). That is, the bedroom environment or routine may become a cue for arousal and wakefulness, rather than relaxation and sleep.

Other examples of maladaptive bedroom behaviors which are associated with increased physiological and cognitive arousal include; talking on the telephone, watching

television, long daytime naps, playing computer games, watching TV, smoking, excessive evening exercise, eating and 'clock watching' (119, 124). Therefore, the repetitive pairing of these arousing/stimulating behaviors with the bedroom environment may lead to a conditioned relationship, where the bedroom takes on the ability to provoke this arousal response.

1.3.4.2 Maladaptive Cognitions and Dysfunctional Beliefs about Sleep

Insomnia may also be maintained by negatively-toned cognitions or distorted beliefs and attitudes about sleep, which provoke feelings of anxiety and arousal, or lead to distorted perceptions of sleep and daytime impairments (119, 125). For example, many patients with insomnia lie in bed and worry about being unable to fall asleep and the consequences of their anticipated sleep loss (129, 130). It is also proposed that insomnia patients selectively attend to sleep related threats (119, 125). For example, as patients become more worried and distressed about their sleep, they begin attending more to internal physiological (e.g. bodily sensations) and environmental cues (e.g. noises in the bedroom), which lead to increased anxiety and arousal (119). These negatively toned cognitions are thought to lead to increased emotional and physiological arousal and activation of the 'fight of flight' response of the sympathetic nervous system, which further exacerbate sleep initiation and resumption difficulties, and result in daytime impairments (118).

It is also suggested that patients commonly hold specific unhelpful beliefs or unattainable goals, about sleep which perpetuate the overall condition (95). For example, patients are likely to believe that normal healthy sleep should be solid or unbroken for the total time in bed, and thus believe that sleep with even brief awakenings is indicative of abnormal sleep (167). Also, patients commonly ruminate over the impact of sleep on mood, energy, performance, general health and physical appearance. These beliefs or cognitions

may then lead to greater importance being placed on falling and remaining asleep, and therefore increased cognitive distress, anxiety and arousal (119).

After repeated occurrences of these maladaptive cognitive processes, behavioral routines, and states of elevated cognitive and physiological arousal, patients may find themselves 'trapped' in a circular and unrelenting pattern of hyperarousal, conditioned wakefulness, daytime fatigue, and impaired quality of life. Furthermore, what began as a perceived sleep disturbance of mild severity can become exacerbated into a more severe and debilitating chronic condition including actual deficits to sleep and daytime functioning.

1.3.5 **Consequences**

Diagnostic criteria for primary insomnia include some level of perceived daytime impairment (1). These include feelings of fatigue, poor mood, cognitive impairment, and impaired physical performance (97). In fact, it is reported that many insomnia patients are motivated to seek treatment primarily due to these daytime symptoms, rather than their disturbed sleep at night (97, 131). These daytime impairments are believed to lead to an increased rate of traffic accidents, decreased work productivity and high levels of absenteeism (68, 111, 132). Chronic insomnia is also associated with reduced quality of life, including reduced physical functioning, vitality, social functioning, emotional and mental health, and increased pain (114, 133-137). Insomnia also creates great economic costs to individuals and society through increased healthcare utilization for the diagnosis and treatment of the sleep complaint and associated medical complications, absenteeism and lost work productivity (103, 111, 132).

Chronic insomnia is also associated with symptoms of depression, anxiety and psychiatric disorders (138). Whether depression plays a contributing role to the development of insomnia, or results from insomnia symptoms such as sleep loss and reduced daytime functioning has been debated (139, 140). In fact, treatment of insomnia with cognitive and

behavioral methods has resulted in improvement in depressive symptomology in patients with co-morbid insomnia and depression (141).

1.4 Insomnia Treatments

1.4.1 Overview

Insomnia complaints are most commonly treated with medications (104, 142). Although medications can improve objective sleep parameters (143), they are associated with several side effects, and sleeping difficulties commonly re-emergence soon after medications are ceased (142). Furthermore, pharmaceutical therapies are generally not recommended for the treatment of insomnia in patients with co-morbid OSA, due to the depressant effects of sedative/hypnotic medications on upper airway muscles and arousal response, which can exacerbate the OSA (57). Therefore, further discussion of pharmaceutical treatments for insomnia are excluded from this thesis.

Alternatively, Cognitive and Behavioral Therapy for Insomnia (CBT-i) is now recommended as the first line treatment for insomnia (102, 143). CBT-i is a multi-component non-pharmacological therapy that targets the underlying psychological, behavioral and physiological factors believed to perpetuate the insomnia condition.

1.4.2 Cognitive Behavioral Therapy for Insomnia (CBT-i)

Currently, chronic insomnia is conceptualized as a disorder of chronic cognitive and physiological hyperarousal which results in perceptions of impaired sleep and daytime functioning (116-118). Rather than treating these night time and daytime symptoms directly (i.e. with medications), CBT-i focuses on the maladaptive patterns of behavior and dysfunctional cognitions which are believed to perpetuate the overall condition. In this way, CBT-i targets the root of the disorder, producing effective results that last well beyond the cessation of therapy (102, 106, 142). Dose-response data indicated that four individual sessions of CBT-i result in optimal response effect (144). Furthermore, CBT-i is equally

effective in group- or individual-based settings (145), and in the presence of several co-morbid medical and psychiatric diagnoses (105, 106). A brief description of the common components of CBT-i is provided below.

1.4.2.1 Sleep Education

CBT-i commonly begins with a session dedicated to discussing simple information about sleep. Providing patients with basic information about sleep in early sessions can reduce or alter common maladaptive or dysfunctional cognitions, and provides justification for other CBT-i components which are introduced in later sessions. This includes information about sleep architecture, sleep hygiene, variability in sleep need, natural variability in sleep occurring with age, and an introduction to the concept of sleep pressure. Patient should also be provided with information about insomnia (e.g. definitions, development, and common symptoms of insomnia) (125).

1.4.2.2 Bedtime Restriction Therapy

One of the most effective components of CBT-i is bedtime restriction therapy (also *sleep restriction therapy*) (146, 147). Bedtime restriction therapy aims to temporarily reduce the amount of time that patients spend in bed, to increase their sleep pressure, consolidate sleep periods throughout the night, and weaken the association between the bedroom environment and arousal-response (147, 148).

During the first week of bedtime restriction therapy, therapists examine patients' pre-completed sleep diaries to calculate the average time that they sleep each night (simple questionnaires assessing patients' perceptions of nightly sleep/bedtime parameters recorded over several days/weeks). As a general rule, patients are then instructed to restrict their bedtime hours to this average sleep time, but to no less than 5.5 hours. Over a consecutive number of nights, patients' arousal responses commonly result in some partial sleep loss and an acute increase in sleep propensity (148, 149). Patients are informed to expect these

feelings of sleepiness and it is explained that this increased sleep propensity will gradually overcome their conditioned arousal response and allow them to fall asleep and return to sleep quicker. Over the next 2-6 weeks, as patients begin to sleep for the large majority of the time that they spend in bed, their bedtime parameters are gradually titrated to longer times to allow them more sleep. As the therapist is titrating the patients' time in bed from week to week, the patient is provided with the information and tools to continue managing their own bedtime routine into the future to prevent insomnia relapse. Patients' total sleep time is commonly reduced during and immediately after CBT-i, however is significantly greater at later follow-up points, after patients titrate and gradually extend their bedtime parameters (106).

1.4.2.3 Stimulus Control Therapy

Stimulus control therapy is another effective behavioral component of CBT-i, aimed at reducing the association between the bedroom environment and feelings of arousal and alertness (106, 120). Patients are instructed to go to bed only when sleepy, and if unable to fall asleep within 15 minutes, to get out of bed and relax in another room until they feel sleepy. Like bedtime restriction therapy, patients are also instructed to keep a regular sleep-wake schedule (especially a fixed wake time regardless of sleep onset time), and avoid long naps during the day which can reduce the sleep pressure. Alongside bedtime restriction therapy, stimulus control therapy is the other component of CBT-i which best predicts improved sleep onset latency and reduced night time awakenings (146).

1.4.2.4 Cognitive Therapy

The cognitive component of CBT-i includes a range of strategies designed to assess, and restructure specific maladaptive or dysfunctional beliefs which can perpetuate the overall condition (125). During cognitive therapy, the therapist and patients focus on these specific maladaptive beliefs, addressing the supporting and contradictory evidence, and maladaptive consequences of each. The Dysfunctional Beliefs and Attitudes about Sleep (DBAS) scale

(150) is a helpful diagnostic tool which assesses patients' agreement with many commonly held maladaptive beliefs about sleep and insomnia.

It can also help to discuss associations between distorted or maladaptive negative cognitions, and cognitive arousal and anxiety. In some cases, 'thought diaries' can be completed by patients between sessions to record automatic sleep-related thoughts. Over time, and with sufficient prior training with the therapies, patients can independently assess the consequences of these thoughts and construct more realistic or helpful alternatives.

1.4.2.5 Paradoxical Intention Therapy

Paradoxical intention techniques are another cognitive approach which are recommended for the treatment of sleep onset insomnia (106). Paradoxical intention aims to have patients confront their fears and performance-anxieties associated with falling asleep, by having them attempt to remain awake for as long as possible (151). It has been found that paradoxical intention reduces sleep effort, and sleep performance anxiety among patients with sleep onset insomnia (128).

1.4.2.6 Relaxation Therapy

Relaxation therapy is another effective component of CBT-i which includes muscle relaxation, guided imagery and breathing exercises designed to directly lower patients' physiological and cognitive arousal before bed or whilst lying in bed attempting to fall back to sleep after an awakening (106, 152). Relaxation is thought to improve perceptions of sleep quality, while bedtime restriction/stimulus control therapies reduce perceived night time wakefulness (153, 154).

1.4.3 **Secondary and Co-morbid Insomnia**

Many cases of insomnia co-occur with additional medical or psychiatric diagnoses (107, 138, 155). Historically, the insomnia has been conceptualized as a secondary symptom of the co-occurring medical or psychiatric diagnosis (156). A diagnosis of secondary

insomnia implies that the insomnia is precipitated and maintained by the primary condition. If this is the case, the insomnia would be expected to improve or disappear when the primary disorder is treated, and remain stable whilst the primary disorder is invariant (157). Logically, the treatment provider would see little purpose in treating secondary insomnia directly, as the primary disorder would cause it to remain invariant or re-emerge soon after the cessation of therapy (139, 155).

However, targeted treatments for co-occurring insomnia are effective (105, 141, 158-161). In some cases, treatment of the co-occurring insomnia has even had beneficial effects on what has historically been considered the primary disorder (e.g. Depression) (140, 141). Alternatively, research suggests that patients' insomnia commonly persists after treatment of the 'assumed' primary condition (138, 162, 163). Furthermore, it is difficult to distinguish secondary from co-morbid insomnia based on patients' baseline symptoms alone (139), resulting in a risk of clinicians misdiagnosing secondary insomnia, and withholding treatment that could be effective. For these reasons, more recent diagnostic schema have recommended a more general 'insomnia disorder' diagnosis, rather than specified diagnoses of 'secondary' or 'primary' insomnia (1).

The National Institutes of Health (104) has also acknowledged this growing body of research and suggest that the insomnia should be considered a 'co-morbid' disorder. Conceptualizations of secondary versus co-morbid insomnia are very important, as they influence diagnostic and treatment decisions, including clinicians' judgments to prescribe or withhold targeted insomnia treatment. From a psychological perspective, 'co-morbidity' simply implies that two or more disorders are co-occurring within the same patient (104).

It seems that whatever the initial cause; the insomnia which began as a secondary symptom of another disorder may gain functional independence, and a reciprocal relationship may emerge (139, 164). For example, although the co-occurring disorder may trigger the

transient sleep complaint (i.e. a precipitating factor), patients may begin engaging in maladaptive coping strategies and thinking styles, which will allow the insomnia to develop independently from the other disorder (i.e. perpetuating pathways). As the insomnia becomes independent of the primary diagnosis, it is better conceptualized as a 'co-morbid' condition, which requires an independent diagnosis, and is amendable to targeted insomnia-treatments.

Although the third edition of the *International Classification of Sleep Disorders* (1) recommends the diagnostic term 'insomnia disorder' (rather than 'secondary' or 'primary' insomnia), the field of co-occurring insomnia and OSA has continued attempting to distinguish cases of insomnia which are secondary to-, or functionally independent from the OSA. Therefore, this thesis has continued to use dated diagnostic terminology when reviewing research in the co-morbid insomnia/OSA field. In the case of insomnia co-occurring with OSA, the two disorders are currently conceptualized as 'co-morbid', as no cause-and-effect relationships in general have been consistently established (165, 166). Relationships between insomnia and OSA are introduced in the following chapter.

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2 CHAPTER 2. Developing a Successful Treatment for Co-morbid Insomnia and Sleep Apnea

This chapter includes a manuscript which was accepted for publication in *Sleep Medicine Reviews* in April, 2016. An additional brief introductory section has been added to give a background of the history of research into co-morbid insomnia and sleep apnea, and an additional section at the end of this chapter which provides a more detailed review of previous insomnia and OSA-treatments in the COMISA population.

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2.1 A Brief History of Research into Co-morbid Insomnia and OSA

The co-occurrence of insomnia and sleep apnea was first noted by Christian Guilleminault in 1973, in a paper published in *Nature* titled *Insomnia with sleep apnea: A new syndrome* (13). Following this recognition of COMISA, the field lay dormant for almost three decades (see Figure 2.1). This was possibly due to assumed differences in diagnostic schema associated with each disorder. For example, OSA has been typically recognized as a disorder primary affecting overweight males who present with symptoms of snoring and excessive daytime sleepiness. Alternatively, insomnia has been regarded as a disorder more commonly diagnosed in females, and those with nervous and anxious personality traits, and is associated with symptoms of night time wakefulness, increased stress, and hyperarousal. Because several of these characteristics of insomnia and OSA appear to perfectly oppose one-another (e.g. male vs. female, increased sleepiness vs. increased wakefulness, etc.), they have historically been conceptualized as two entirely independent disorders. It is possible that these distinct conceptualizations of insomnia and OSA led to the long period of dormancy in the field of research into their co-morbidity.

The field of COMISA research was re-ignited following the publication of two papers in close succession in 1999 and 2001, which documented a surprisingly high prevalence rate of co-morbid insomnia and sleep apnea (28, 32). Firstly, Lichstein and colleagues examined indices of sleep apnea among 80 older adults responding to advertisements for an insomnia treatment trial, who did not report common symptoms of OSA (e.g. absence of observed apneas, heavy snoring, excessive daytime sleepiness, etc.). It was found that 43% held sufficient diagnostic criteria for co-morbid OSA, and 29% held indications of moderate or severe OSA. Alternatively, Krakow and colleagues examined self-reported insomnia symptoms in a sample of OSA patients in a sleep disorder clinic. It was found that of 231 sleep apnea patients, 50% reported clinically meaningful complaints of insomnia.

These two studies challenged prior misconceptions of insomnia and OSA as distinct disorders occurring at opposite ends of an 'impaired sleep' continuum, and left little doubt of the need for further research to confirm the high prevalence, common characteristics, and examine the effectiveness of existing treatment approaches in the presence of this newly emerging 'co-morbid' disorder. Since this time, there has been a steadily growing number of publications investigating prevalence estimates, characteristics, and treatment approaches in COMISA patients (Figure 2.1).

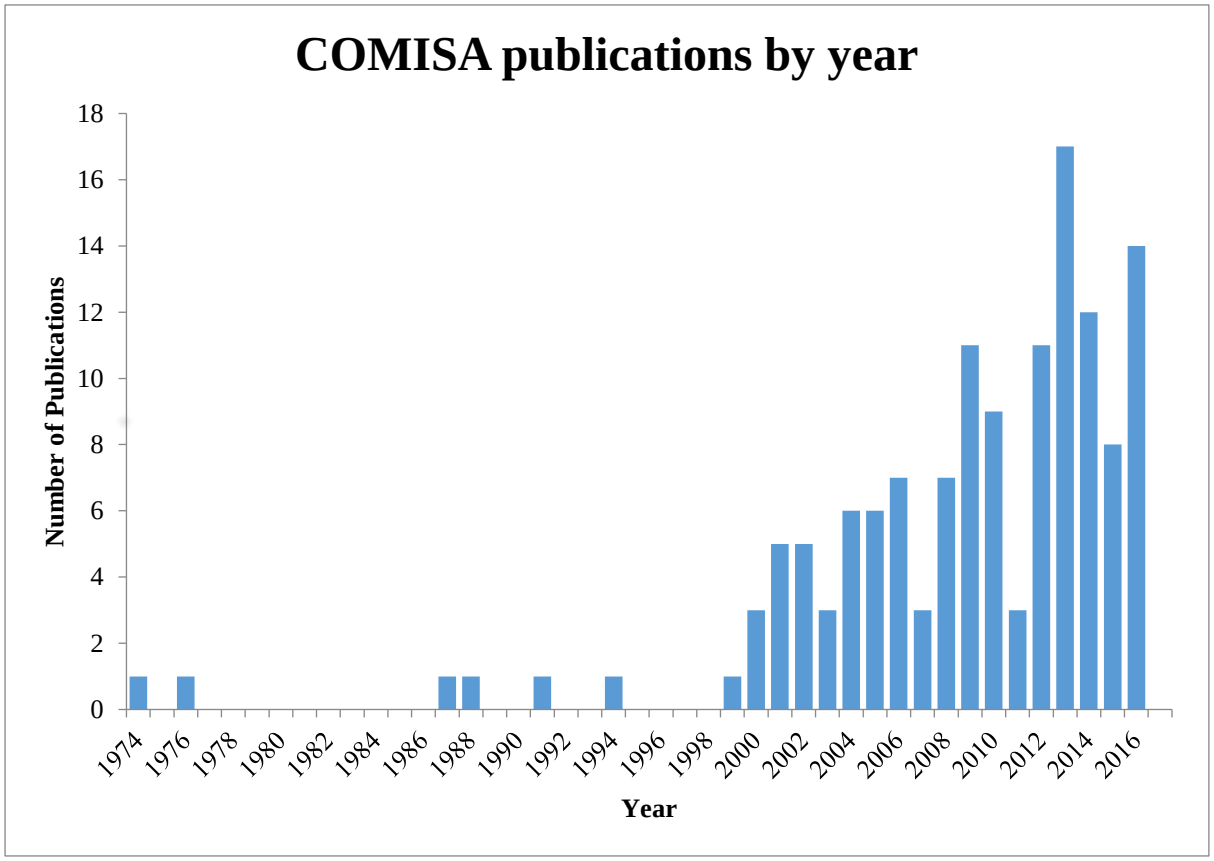

Figure 2.1 Publications in the area of co-morbid insomnia and sleep apnea by year.

3 CHAPTER 3. Does Co-morbid Obstructive Sleep Apnea Impair the Effectiveness of Cognitive and behavioral Therapy for Insomnia?

The Chapter includes a manuscript accepted for publication in *Sleep Medicine*, in September, 2017.

Chapter 3 has been removed due to copyright restrictions, but may be viewed at the following link.

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4 CHAPTER 4. The Effect of Cognitive Behavioral Therapy for Insomnia (CBT-i) in patients with Co-morbid Insomnia and Sleep Apnea

This chapter includes a manuscript intended for submission to the *Journal of Clinical Sleep Medicine*.

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Trial registration: Australian New Zealand Clinical Trials Registry: ACTRN12613001178730. Universal Trial Number: U1111-1149-4230.

Ethics Approval: Southern Adelaide Clinical Human Research Ethics Committee (428.12), Queensland University of Technology Research Ethics Unit (1300000302), and the External Request Evaluation Committee (Department of Human Services, Australia).

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4.1 Abstract

Aims: Although research has established that Cognitive and Behavioral Therapy for Insomnia (CBT-i) is an effective treatment for patients with primary insomnia and insomnia presenting with several co-morbidities, less is known about its effectiveness in patients with co-morbid Obstructive Sleep Apnea (OSA). The current study presents a randomized controlled trial, examining the short-term effectiveness of CBT-i, compared to a control condition, in insomnia patients with co-morbid OSA (AHI ≥ 15).

Methods: Participants included 145 individuals (55.2% Male, Age *y M* = 58.22, *SD* = 9.91) with physician/psychologist-diagnosed OSA and insomnia. Participants were randomly allocated to either 4-weekly 45-minute sessions of CBT-i or a no-treatment control condition. Insomnia symptoms including subjective and objective sleep parameters, global insomnia severity, dysfunctional cognitions, symptoms of depression, anxiety, stress, and daytime impairments were assessed with sleep diaries, overnight polysomnography, and self-report questionnaires.

Results: Improvements in subjective sleep onset latency, wake after sleep onset, and sleep efficiency, global insomnia severity, and dysfunctional sleep-related cognitions were significantly greater in the CBT-i than the control condition from pre- to post-treatment (all $p \leq .01$). Although there was a tendency for the CBT-i group to show greater improvements in symptoms of daytime fatigue, sleepiness, depression, anxiety and stress none of these reached statistical significance. By post-treatment, a significantly greater number of CBT-i treated participants were categorized as 'improved', compared to participants in the control condition (CBT-i = 63.8%; Control = 25.8%, $p < .001$). The CBT-i condition experienced significantly greater decrease in objective time spent awake after sleep onset, compared to the control condition. However, changes in other objective sleep parameters and sleep architecture were not significantly different between conditions.

Conclusions: CBT-i is an effective treatment for insomnia in the presence of co-morbid moderate and severe OSA. Although CBT-i improved sleep diary and global insomnia severity outcomes, some daytime symptoms did not show greater improvement when compared to a control condition. These daytime symptoms may result partly from the co-morbid OSA which remained untreated during CBT-i. Future research should examine the additional benefits and patterns of continuous positive airway pressure therapy use, following CBT-i in COMISA patients.

Keywords: Insomnia, Cognitive behavioral therapy for insomnia, co-morbid insomnia, obstructive sleep apnea.

4.2 Introduction

Insomnia and Obstructive Sleep Apnea (OSA) are the two most common sleep disorders, found in 6-10% and 2-4% of the general population respectively (1-3). Insomnia is characterized by a chronic complaint of difficulties initiating or maintaining sleep during the night, and associated daytime functioning impairments (4). Alternatively, OSA is characterized by repetitive brief closures (apnea) or narrowing (hypopnea) of the upper airway during sleep, which lead to intermittent hypoxemia, transient arousals, and surges in sympathetic nervous system activity (4). OSA is also associated with increased daytime fatigue, depression and sleepiness (5-7). OSA may be categorized as mild, moderate, or severe according to an average hourly apnea/hypopnea index (AHI) of 5-15, 15-30, and greater than 30, respectively (8).

A large body of evidence has found that co-morbid insomnia and sleep apnea (COMISA) is a highly prevalent condition. For example, Krakow and colleagues (9) conducted a chart review of 231 OSA patients, and found that 50% endorsed clinically significant insomnia complaints. Since this time, others have confirmed that 30-70% of patients with pre-diagnosed OSA also report clinically significant symptoms of insomnia (10-13). Alternatively, co-morbid OSA is also present in 29 – 67% of patients with pre-diagnosed insomnia (12, 14-16). These high prevalence estimates of COMISA have now been established in several samples, including sleep laboratory patients, U.S. military personnel, and patients with treatment-resistant insomnia (12). A handful of studies have also examined indicators of both insomnia and sleep apnea in the general population, finding that 7-58% of sleep apnea-positive respondents also reported symptoms of insomnia, and 6-16% of insomnia-positive respondents also held symptoms indicative of sleep apnea (12).

As both disorders are independently associated with impairments to sleep and daytime functioning, it appears that COMISA patients experience the additive effects of each (12).

For example, COMISA patients experience more severe sleep disruption (9, 17, 18), and daytime impairments (6, 9, 15, 19, 20), increased symptoms of depression and psychiatric disorders (9, 11, 20-24), and reduced quality of life (25), compared to patients with one disorder-alone.

Although COMISA is a common and highly debilitating condition, it is also more difficult to treat compared to either disorder in isolation. Effective treatments for both insomnia and OSA exist, however appear to be impaired in the presence of the co-morbid diagnosis. For example, the recommended treatment for moderate-severe OSA is Continuous Positive Airway Pressure (CPAP) therapy (8, 26). However, OSA patients with co-morbid insomnia, despite the presence of more severe sleep disruption and daytime impairments, are less likely to accept and use CPAP therapy, compared to those with OSA-alone (9, 27-32). This finding has led several groups of researchers to suggest that COMISA patients should receive treatment for their insomnia prior to the initiation of CPAP therapy (12, 13, 33, 34). It is thought that initially treating these patients' insomnia, will reduce their time spent awake during the night, and result in increased acceptance and use of CPAP therapy. Although this is a logical suggestion, very little is known about the effectiveness of insomnia-treatments in patients with overlapping OSA.

Cognitive and Behavioral Therapy for Insomnia (CBT-i) is the recommended treatment for insomnia (35, 36). CBT-i is a multi-component, non-pharmacological therapy delivered during individual or small-group sessions (37). CBT-i aims to modify cognitive, behavioral and physiological processes and factors which are believed to perpetuate the insomnia condition (35, 38). Components used in CBT-i generally fall within three categories. *Cognitive strategies* focus on challenging dysfunctional or maladaptive beliefs about sleep, and altering patterns of anxiety, stress, and sleep-preventing thoughts (39). *Behavioral strategies* aim to decrease time spent awake in bed during the night through

manipulation of bedtime routines during the day/evening, and ameliorating conditioned arousal responses to the bedroom environment and routine (40, 41). Finally, *Educational strategies* aim to provide patients with basic information about sleep to dispel common misconceptions which can lead to anxiety and distress (39, 42). CBT-i is effective for patients with primary insomnia (35), and in the presence of multiple medical and psychiatric co-morbidities (43-45). A handful of case studies (32, 46), pilot studies (47-52), small experimental studies (53, 54), a quasi-experimental study (55), and a recent randomized controlled trial (56) have resulted in some disagreement over the effectiveness of CBT-i in COMISA patients. Therefore, a high quality randomized controlled trial investigating the effectiveness of CBT-i in a sample of patients with moderate and severe co-morbid OSA is needed.

Melendrez, Krakow, Johnston, Sisley and Warner (51) reported in an abstract, that CBT-i effectively improved insomnia symptoms among seven female crime victims with COMISA and Post-Traumatic Stress Disorder (PTSD). Insomnia symptoms showed significant improvement from pre- to post-treatment, with marked improvement in six of the seven patients. However, participants still reported clinically significant levels of insomnia at post-treatment.

The same group of researchers later examined the effectiveness of CBT-i in 17 COMISA patients with histories of failed insomnia-treatment (50). Of these 17 patients, 8 experienced non-clinical levels of insomnia following CBT-i. However, these patients were also trauma survivors who may have held additional psychiatric diagnoses (such as PTSD), which may impact the effectiveness of CBT-i, and generalizability of these findings to other COMISA patients.

Guilleminault, Palombini, Poyares and Chowdhuri (52) also reported their attempts to treat 32 patients with co-morbid insomnia and upper airway resistance syndrome (a sub-

clinical form of OSA), with CBT-i. The treatment included six 90-minute sessions involving sleep hygiene information, stimulus control therapy, sleep restriction therapy, and cognitive therapy. Participants showed significant improvements in *objective* sleep onset latency, total sleep time and wake after sleep onset, and *subjective* daytime fatigue from pre-treatment to 6-month follow-up. As these patients were diagnosed with sub-clinical OSA, the generalizability of these findings to patients with co-morbid OSA is unknown.

Later, Guilleminault, Davis and Huynh (53) used a cross-over design to compare the effects of CBT-i and surgical treatment for OSA, among 30 patients with co-morbid insomnia and mild-OSA. Although CBT-i improved patients' sleep parameters, symptoms of daytime fatigue persisted, and none of the patients initially receiving CBT-i felt that their sleep disorder was fully improved. Surgical treatment was reported to be more effective at improving symptoms of both disorders.

Sweetman and colleagues (54) recently compared the effectiveness of CBT-i in patients with insomnia-alone, and co-morbid insomnia and OSA. Both groups showed significant improvement in subjective sleep parameters, and measures of fatigue, depression and anxiety during treatment. Improvements for each of these symptoms were not significantly different among the groups. Although no control condition was used, these results indicate that co-morbid mild, moderate and severe OSA does not reduce the effectiveness of CBT-i in treating insomnia symptoms.

Finally, Fung and colleagues (56) recently documented a randomized controlled trial, examining the effectiveness of CBT-i, compared to a sleep education control condition, in older adult Veterans (aged 60 years and older) with insomnia-alone, and insomnia with co-morbid mild sleep apnea. 39 patients with insomnia-alone, and 95 patients with COMISA completed a range of assessments at pre-treatment, post-treatment, long-term follow-up. After 6-months, COMISA patients treated with CBT-i displayed significantly greater

improvements in sleep onset latency and overall sleep quality scores, compared to COMISA patients in the control condition. Furthermore, the authors found that the insomnia improvements resulting from CBT-i were similar for patients with insomnia-alone, and those with COMISA. It is unknown whether these results are generalizable to younger COMISA patients, or patients who hold a diagnosis of moderate or severe OSA.

Taken together, these studies suggest that CBT-i may be an effective treatment for insomnia in the presence of co-morbid sleep apnea. However, of these studies, the only randomized controlled trial was undertaken on a highly selected sample of COMISA patients. There remains a need for a high quality randomized controlled trial investigating the effectiveness of CBT-i in a sample of COMISA patients of different ages, with diagnoses of moderate and severe co-morbid OSA.

4.3 Methods

4.3.1 Design

This study used a 2 (treatment condition: CBT-i, Control) x 2 (time: pre-treatment, post-treatment) mixed factorial design to evaluate the effectiveness of CBT-i in treating multiple night time and daytime symptoms of insomnia in COMISA patients. Participants included in the current study were enrolled in a larger randomized controlled trial investigating the impact of CBT-i, versus a no-treatment control condition, on subsequent CPAP acceptance and long-term adherence (57). Following the post-CBT-i outcome period, all participants commenced CPAP; therefore, only the immediate effects of CBT-i on insomnia symptoms are reported here. This research was approved by the South Australian Human Research Ethics Committee, Flinders University multi-Institutional agreement for NHMRC funding schemes (APP1049591), and the Prince Charles Hospital ethics committee (National Ethics Application HREC/13/QPCH/52).

4.3.2 **Participants**

Participants included 145 adults (Age *y M* = 58.22, *SD* = 9.91, 55.17% Male) with psychologist-diagnosed insomnia, and sleep physician-diagnosed OSA, who were recommended for treatment with CPAP therapy. Participants were recruited through sleep physicians working at two sites in Australia; the Adelaide Institute for Sleep Health, in Adelaide, South Australia, and The Prince Charles Hospital, in Brisbane, Queensland.

Inclusion criteria were; AHI ≥ 15 according to full night Polysomnographic (PSG) recording, a clinical diagnosis of OSA and recommendation of CPAP by a sleep physician, and a psychologist diagnosis of insomnia according to sleep diary and daytime impairment criteria (see below) , appropriate age range (18 – 75 years), absence of any additional co-morbid sleep disorders, or medical disorders which required immediate treatment, absence of; any significant memory, perceptual or behavioral disorder, neurological deficits which prevented self-administration of CPAP equipment, significant language barriers, current employment as a commercial driver, episodes of falling asleep while driving in the past six months, or participants who resided significantly remotely from the clinic to preclude follow-up visits. Any prospective participants who elected an initial OSA treatment approach other than CPAP (e.g. surgery, mandibular advancement splint, etc.) were excluded (*n* = 15). Information relating to serious adverse events (hospitalizations, motor vehicle accidents, new diagnoses, etc.) occurring during the BRT (or waitlist) period were collected and compared between conditions.

4.3.3 **Screening**

Figure 4.1 illustrates screening numbers, and retention of participants during the study protocol. Participants were recruited through two screening arms at each site. The first screening arm targeted clinical patients attending sleep laboratories for overnight sleep studies, who had an AHI of 15 or greater (*n* = 2,131). Participants who also reported

insomnia symptoms (according to a total score of at least 14, and a composite score of at least 4 on the first three 'sleep' items of the ISI) proceeded for further screening (n = 707; 33.2% of participants with AHI ≥ 15). The second screening arm included advertisements placed in local print, radio, and television media, to direct potential participants to an online screening platform to register interest in the trial (*n* = 739). These potential participants then completed two brief online questionnaires screening for symptoms of insomnia and OSA. Insomnia symptoms were indicated according to the above ISI criteria. Risk factors of OSA were assessed with the OSA50 Questionnaire (Appendix G). Individuals who indicated symptoms of both insomnia and OSA were invited to undergo an overnight oximetry study to further screen for physiological indicators of OSA (88). Participants with at least 10 oxygen desaturations per hour of sleep during the overnight oximetry study were further screened with a full-night diagnostic sleep study. Sleep Physicians reviewed all prospective laboratory and website-screened participants with AHI scores of 15 or greater who also indicated insomnia symptoms. Following a sleep physician diagnosis of OSA and recommendation for CPAP therapy, participants were referred to research staff for information and consent for the trial and collection of pre-treatment demographic data. Participants who remained eligible completed one-week sleep diaries and a questionnaire battery. Psychologists with experience in diagnosing and treating insomnia disorders then used this material to inform a diagnosis of insomnia, according to ICSD-2 diagnostic criteria (4). Insomnia diagnostic criteria included; average sleep onset latency of ≥ 30 minutes, *or* average wake after sleep onset of ≥ 45 minutes, *or* sleep efficiency of ≤ 75%, *and* self-reported significant daytime impairment. Participants were required to hold an insomnia complaint for at least 6 months. Following a diagnosis of insomnia, participants were randomized to one condition and entered the trial. Table 4.1 displays demographic, sleep and daytime impairment information for participants

in each condition. Independent t-tests revealed that no sleep, daytime impairment, or demographic variables differed significantly between conditions.

Table 4.1 Demographic and Pre-Treatment Descriptive Data.

	CBT- i **M (SD)**	**Control** **M (SD)**	***t***	***p***
Male *n* (%)	40 (55.6)	40 (54.8)	.008^	.927
Age	59.12 (9.92)	57.33 (9.89)	-1.086	.279
Apnea/Hypopnea Index	33.17 (19.83)	35.83 (23.87)	0.722	.471
Body Mass Index	34.45 (6.34)	36.19 (6.46)	1.623	.107
Arousal Index	32.72 (16.98)	35.65 (22.25)	.886	.377
Diary Total Sleep Time	346.10 (76.97)	353.02 (79.44)	.539	.590
Diary Sleep Onset Latency	56.09 (49.36)	48.39 (33.81)	-1.097	.274
Diary Wake After Sleep Onset	95.02 (60.92)	102.90 (74.33)	.698	.486
Diary Time in Bed	516.54 (73.48)	520.41 (77.48)	.309	.758
Diary Sleep efficiency	67.21 (12.18)	68.46 (14.32)	.564	.573
Insomnia Severity Index	18.49 (5.35)	17.92 (4.68)	-0.681	.497
Daytime Functioning Scale	16.94 (8.03)	17.77 (8.52)	.598	.551
Flinders Fatigue Scale	15.96 (6.83)	15.92 (5.79)	-0.39	.969
Epworth Sleepiness Scale	8.92 (5.00)	9.68 (4.55)	.968	.335
DBAS	6.03 (1.85)	5.86 (1.54)	-0.601	.549
Depression	14.53 (11.39)	14.63 (12.77)	.051	.959
Anxiety	10.22 (8.75)	8.93 (7.87)	-0.934	.352
Stress	15.14 (9.51)	15.56 (9.81)	.264	.792

^ Chi-square statistic, CBT-i = Cognitive and Behavioral Therapy for Insomnia, DBAS = Dysfunctional Beliefs and Attitudes about Sleep scale.

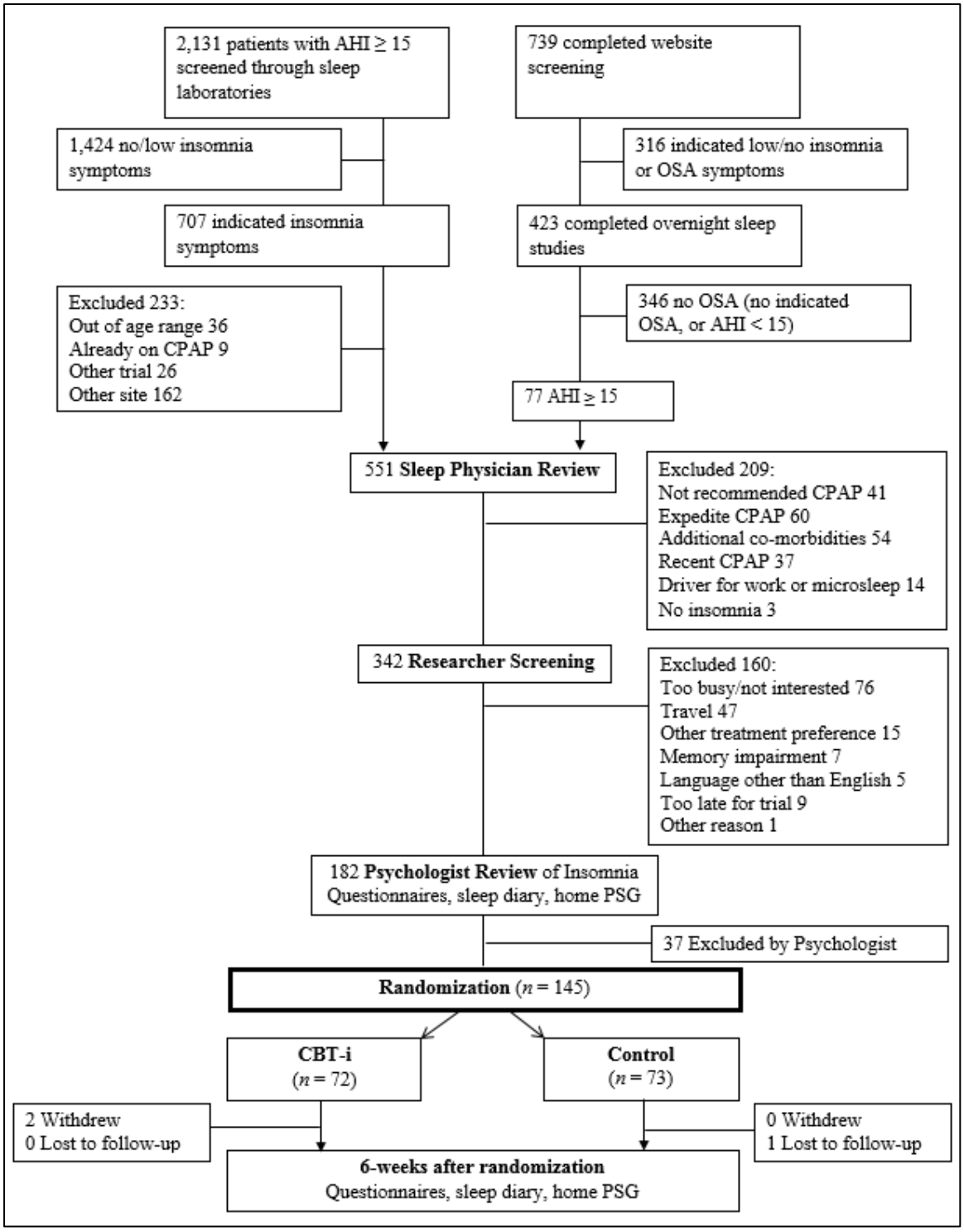

Figure 4.1 Screening and flow diagram. AHI = Apnea/Hypopnea Index, CBT-I = Cognitive and behavioral Therapy for Insomnia, CPAP = Continuous Positive Airway pressure, OSA = Obstructive Sleep Apnea, PSG = Polysomnography.

4.3.4 **Outcome Measures Completed at Pre- and Post-Treatment.**

4.3.4.1 One-Week Sleep Diaries.

Sleep diaries (Appendix I) are the recommended outcome measure of sleep in insomnia treatment research (58). Sleep diaries were used to assess participants' average weekly subjective sleep parameters before and after treatment. Participants indicated their nightly; time in bed, 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.

4.3.4.2 Sleep Studies

In addition to the laboratory sleep study to diagnose OSA, home-based overnight Polysomnographic (PSG) sleep studies were completed at pre- and post-treatment (Somté portable full PSG recorders, Compumedics, Melbourne, Australia). Electrodes were attached by trained sleep technicians 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 oxyhaemoglobin saturation. Nasal pressure and oro-nasal airflow were recorded with a nasal cannula, and an oro-nasal thermistor. Experienced technicians at each site scored all sleep studies according to American Academy of Sleep Medicine criteria (59). PSG outcomes included objective total sleep time, sleep onset latency, wake after sleep onset, sleep efficiency, AHI, Arousal Index, and percentage time spent in each sleep stage (stage 1, stage 2, slow wave sleep, and rapid eye movement sleep). Technicians were blind to participants' treatment condition.

4.3.4.3 The Insomnia Severity Index (ISI).

The ISI (60) (Appendix A) is a 7-item questionnaire which has been widely used as an outcome measure of insomnia severity in treatment studies (61). 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 (60), and has been used in the COMISA population (62-64). Because the ISI measures some daytime/psychological symptoms which are shared with OSA, a sub-score derived from the first three 'sleep' impairment items of the ISI was also calculated to measure the symptoms which are unique to insomnia (12, 62). This score ranged from 0 – 12, with higher scores representing greater difficulties initiating or maintaining sleep, or waking too early and being unable to return to sleep. A cut-off of 14 on post-treatment ISI scores has commonly been used to indicate improvements in insomnia complaints following treatment, and a cut-off of less than 8 has been used to indicate remission of insomnia symptoms (61). A cut-off of less than 4 was also used on the ISI sub-score at post-treatment, to measure improvements specifically in night time symptoms of insomnia. Finally, 'improved insomnia' was also defined as at least an 8-point decrease in the ISI (91).

4.3.4.4 The Flinders Fatigue Scale.

The Flinders Fatigue Scale (65) (Appendix B) is a 7-item self-report questionnaire which measures feelings of fatigue experienced over the previous fortnight. Participants answer six questions such as "was fatigue a problem for you?" on a scale of 0 (not at all) to 4 (extremely). One additional item asks about experiences of fatigue at seven possible times during the day, with one point awarded for each time. Possible scores on the Flinders Fatigue Scale range from 0 to 31, with higher scores indicating greater daytime fatigue. The Flinders Fatigue Scale has adequate reliability and validity in insomnia and OSA patients and good discriminant validity against the Epworth Sleepiness Scale (65-67)).

4.3.4.5 The Daytime Feelings and Functioning Scale.

The Daytime Feelings and Functioning Scale (Appendix C) is a 12-item self-report measure of daytime feelings and functioning over the previous fortnight (66). 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 daytime functioning (66, 68).

4.3.4.6 The Epworth Sleepiness Scale (ESS).

The ESS (69) (Appendix E) is an 8-item self-report scale measuring daytime sleepiness in various situations. 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 (70)), and convergent validity when compared to objective measures of daytime sleepiness (71). A cut-off of 10 or less has been used to indicate normal levels of sleepiness on the ESS.

4.3.4.7 The Dysfunctional Attitudes and Beliefs about Sleep scale (DBAS-16).

The DBAS-16 (72) (Appendix F) is a 16-item self-report questionnaire which assesses participants’ agreement with dysfunctional or maladaptive beliefs, appraisals, attributions and attitudes about sleep (73). Participants indicate their agreement with each item on a scale of 0 – 10, with possible responses ranging from “strongly disagree” to “strongly agree”. A total DBAS score is calculated by finding the average score of all 16 items. Scores range from 0 – 10, with higher scores representing greater agreement with dysfunctional attitudes and beliefs about sleep. Morin and colleagues (72) report adequate internal consistency as measured by Cronbach’s alpha (.77).

4.3.4.8 The Depression, Anxiety and Stress Scale.

The Depression, Anxiety and Stress Scale (74) (Appendix D) is a 21-item self-report questionnaire which measures feelings of depression, anxiety and stress. The three sub-scale scores range from 0 – 42, with higher scores indicated more depression, anxiety or stress. The

subscales of the Depression, Anxiety and Stress 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 (75, 76).

4.3.5 Cognitive Behavior Therapy for Insomnia (CBT-i)

Participants were randomly allocated to receive either four-weekly, 45-minute sessions of CBT-i, or a control condition. CBT-i was administered by registered or provisional psychologists with previous CBT-i experience. Each therapy session was delivered to small-groups or individual participants. Previous research has found that both group-based, and individual CBT-i result in comparable improvements in sleep and daytime symptoms (37), and dose-response data indicate that four individual sessions result in the optimum response to CBT-I (89). During CBT-i, participants were not provided with any information about OSA or CPAP therapy. Components of CBT-i included; basic sleep and sleep hygiene information, bedtime restriction therapy, PSG and sleep misperception feedback, cognitive therapy, and relapse prevention. Bedtime restriction was introduced in the first session, and reviewed in each subsequent session. Daytime symptoms were targeted during the third session with education (explanation of the 'hyperarousal' model of insomnia; relationships between arousal, anxiety, stress and daytime fatigue), and cognitive therapy (providing examples of maladaptive thoughts/processes, and more realistic alternatives).

4.3.5.1 Materials accompanying CBT-i.

To ensure treatment fidelity, therapists were provided with a structured manual, session checklist and power-point slides, and underwent additional training before delivering the CBT-i program. Sessions were recorded with small handheld digital audio recorders, and a randomly selected 10% of sessions were selected for assessment by an independent psychologist to measure treatment fidelity (Appendix K and L). Each participant undergoing

CBT-i was provided with a booklet which reviewed concepts discussed during each week of treatment. Participants completed 7-day sleep diaries and an ESS after each week of CBT-i, to be used by the therapist during the following week's session to instruct bedtime restriction therapy decisions.

4.3.5.2 Protocol for Bedtime Restriction Therapy.

As increased sleepiness is a common symptom of OSA (4), it was believed that the COMISA sample would have greater levels of pre-existing sleepiness compared to patients with insomnia-alone (54). For this reason, sleepiness was taken into account when setting the bedtime parameters to avoid any risk of accidents or dangerous levels of sleepiness. Therefore, the degree of restriction depended on participants' levels of subjective sleepiness at pre-treatment and during each CBT-i session.

Psychologists questioned participants about feelings of sleepiness and reviewed ESS responses during each weekly session of therapy. Psychologists were instructed to modify the bedtime restriction protocol based on clinical judgements of participants' sleepiness and sleep parameters from week-to-week. As a guide; if a participant scored from 0 – 9 on the pre-treatment ESS, bedtime restriction was undertaken as normal (e.g. participants' time in bed was restricted to diary-measured sleep time, with a minimum of 5.5 hours). If a participant scored from 10 – 14 on the ESS, bedtime restriction was modified, so minimum restriction would equal the participant's total sleep time during their overnight PSG study if that was greater than their reported average diary total sleep time. It was thought that because many insomnia (and COMISA) patients underestimate their sleep prior to treatment, this would result in slightly less bedtime restriction, than if restriction was based off diary sleep parameters. Finally, if a participant scored 15 or greater on the ESS at pre-treatment, their bed- and rise-times were regularized, and daytime napping was discouraged, but no bedtime restriction was employed.

4.3.6 **Procedure**

The protocol for the current study can be seen in Figure 4.1. Following a diagnosis of insomnia, participants were randomized to either the CBT-i or control condition. Randomization was independently conducted at the Pharmacy Department of the Repatriation General Hospital in South Australia. Participants were stratified according to; site (Adelaide, or Queensland), gender (M or F), age (>, or < 50 years), OSA severity (AHI >, or < 30), insomnia severity (ISI >, or < 22), and prior CPAP use (yes, or no).

Following four weeks of CBT-i (vs. control), participants completed another home-based overnight sleep study, one-week sleep diary, and outcome questionnaires. As participants commenced with CPAP immediately after the post-CBT-i outcome period, no long-term effects of CBT-i on insomnia symptoms are reported here.

4.3.7 **Data Analysis**

Data were analyzed with IBM SPSS (version 22) software using intention to treat analyses. Linear Mixed Model analyses were used to examine improvements in sleep diary, PSG, and questionnaire outcomes from pre- to post-treatment between CBT-i and control conditions. Repeated measures (pre- and post-treatment) were nested within individual participants, who were nested within conditions (CBT-i and control). Auto-regressive co-variance structures were used as it was expected that variability in outcomes would remain constant between times, but correlations between repeated measures would become weaker over successive follow-up points. Fixed effects included condition and time, while individuals were entered as a random factor. In addition, chi-square analyses were used to compare rates of normalized sleepiness scores, and insomnia-improvement, response, and remission between conditions. A Fischer's Exact test was used to compare rates of adverse events between conditions.

All diary, and PSG outcomes were inspected for outliers and normality. Positive skewness (≥1) were observed at pre- and post-treatment for diary-measured sleep onset latency and wake after sleep onset, and PSG-measured sleep onset latency, and wake after sleep onset. Negative skewness was observed for PSG-measured sleep efficiency. Logarithmic transformations resulted in normally distributed data on these outcomes. Linear Mixed Model analyses were repeated for untransformed and logarithmic-transformed outcomes. Inferential outcomes remained unchanged between transformed and untransformed data for each outcome. Therefore, untransformed data were reported to facilitate understanding of descriptive statistics. Single positive outliers were also observed for PSG-measured sleep onset latency and wake after sleep onset. Group comparison analyses were re-run after assigning these participants the next highest value. Inferential statistics remained unchanged for each outcome, so observed data were retained.

4.3.8 Outcome Measure Completion and Participant Retention

Missing data at pre-treatment were observed in 0% of sleep diaries and questionnaire batteries, and 1.4% of PSG sleep studies (one participant from the CBT-i condition who withdrew before completing the pre-treatment PSG). In the CBT-i and control conditions missing post-treatment data were observed for 7.1% and 2.7% of overnight sleep studies, 4.2% and 9.6% of questionnaire batteries, and 6.9% and 20.6% of sleep diaries, respectively. Participants failing to complete post-treatment sleep diaries were more likely to be in the control than the CBT-i condition ($\chi^2(1) = 6.56$, $p = .01$). This was primarily due to participants in the control condition beginning CPAP therapy before post-treatment sleep diaries could be collected. Furthermore, participants in the CBT-i condition were more routinely completing sleep diaries during bedtime restriction therapy, and were more likely to complete diaries at post-treatment. No other differences in missing data were observed for other outcomes at pre- or post-treatment between conditions. Three participants withdrew

from the trial before the post-treatment assessment. One participant in the control condition withdrew due to time commitments, and two in the CBT-i condition withdrew immediately after being randomized due to un-related illness, and loss of interest.

4.4 Results

4.4.1 CBT-i Compliance and Credibility

Of the 72 participants randomized to receive CBT-i, 8 (11.4%) did not complete all four CBT-i sessions. Two participants withdrew immediately after randomization, one participant was lost to follow-up after the first session, two participants cancelled sessions due to sickness, one participant did not attend the final session due to discontinuation of bedtime restriction therapy, and two participants cancelled the fourth session and did not wish to re-book.

The main behavioral component of CBT-i was bedtime restriction therapy. Bedtime restriction therapy was formally discontinued in five participants during the CBT-i protocol; two participants had to remain lying down in bed for extended periods due to health reasons, one participant found it unhelpful and refused to comply, one participant was responsible for caring for their partner and was required to stay in bed, and one was experiencing increased anxiety about sleep due to the bedtime restriction protocol. Bedtime restriction therapy techniques were also occasionally modified, according to psychologists' clinical judgements of participants' pre-treatment self-reported sleepiness, and changes in sleepiness and sleep parameters occurring during CBT-i. These modifications to bedtime restriction therapy were thought to reflect clinical practice, and hence increase the generalizability of these results to COMISA patients in clinical settings.

During the third CBT-i session, participants also completed a brief questionnaire (Appendix J) which assessed perceptions of treatment credibility. On average, participants perceived that CBT-i was a highly logical treatment (84.9%), and reported high levels of

confidence (91.5%), and expectations that CBT-i would result in improvement in their symptoms (72.0%).

4.4.2 Treatment Purity

All CBT-i sessions were audio recorded and a randomly selected 10% of sessions were reviewed by an independent psychologist with extensive experience working with insomnia patients, who determined adequate treatment fidelity (Appendix K and L).

4.4.3 Treatment Comparisons

The effectiveness of CBT-i, versus the control condition, on sleep diary, questionnaire, and PSG outcomes of insomnia was examined on an intention to treat basis with Linear Mixed Model analyses. Tables 4.2, 4.3 and 4.4 display descriptive and inferential statistics for the independent effects of time and interactions between time and condition for sleep diary, questionnaire, and PSG outcomes, respectively. Figures 4.2 and 4.3 display graphical representations of interactions between condition and time on sleep diary and questionnaire outcomes, respectively.

Table 4.2 Between-group changes in sleep diary parameters from pre- treatment to post-treatment.

	CBT-i	**Control**	**Interaction**		
	Mean (95%CI)	**Mean (95%CI)**	***F***	***df***	***p***
Total Sleep Time (min)					
Pre-Treatment	346.17 (18.74)	350.64 (18.62)	0.09	126.10	.760
Post-Treatment	371.32 (19.01)	372.89 (19.51)			
Per Group Change	25.15 (12.82)**	22.25 (13.67)**			
Sleep Onset Latency (min)					
Pre-Treatment	56.58 (8.71)	49.55 (8.65)	12.08	107.84	.001
Post-Treatment	27.90 (8.90)	40.47 (9.28)			
Per Group Change	-28.69 (7.67)**	-9.08 (8.14)*			
Wake After Sleep Onset (min)					
Pre-Treatment	94.51 (13.80)	99.31 (13.71)	7.69	130.24	.006
Post-Treatment	43.24 (14.21)	79.07 (15.08)			
Per Group Change	-51.27 (15.24)**	-20.24 (16.04)*			
Sleep Efficiency (%)					
Pre-Treatment	66.75 (3.06)	67.98 (3.04)	29.15	127.25	<.001
Post-Treatment	83.37 (3.12)	74.09 (3.25)			
Per Group Change	16.62 (2.64)**	6.11 (2.80)**			
Time In Bed (min)					
Pre-Treatment	522.03 (18.92)	520.49 (18.79)	23.25	126.21	<.001
Post-Treatment	446.48 (19.37)	507.74 (20.30)			
Per Group Change	-75.55 (17.70)**	-12.75 (18.74)			

CBT-i = Cognitive and Behavioral Therapy for Insomnia.
* change per condition $p < .05$, ** change per condition $p < .01$

Table 4.3 Changes in questionnaire outcomes during treatment between conditions.

	CBT-i	**Control**	**Interaction**		
	Mean (95%CI)	**Mean (95%CI)**	***F***	***df***	***p***
Insomnia Severity Index					
Pre-Treatment	18.49 (1.24)	17.92 (1.23)	34.43	137.39	<.001
Post-Treatment	12.10 (1.25)	16.49 (1.27)			
Per Group Change	-6.38 (1.17)**	-1.43 (1.19)*			
Insomnia Severity Index sub-score					
Pre-Treatment	7.29 (0.58)	6.84 (0.58)	27.71	136.74	<.001
Post-Treatment	4.45 (0.59)	6.14 (0.60)			
Per Group Change	-2.85 (0.57)**	-0.69 (0.58)*			
Daytime Feelings and Functioning Scale					
Pre-Treatment	16.94 (1.88)	17.77 (1.87)	0.51	134.89	.478
Post-Treatment	14.45 (1.90)	15.89 (1.90)			
Per Group Change	-2.49 (1.20)**	-1.88 (1.22)**			
Flinders Fatigue Scale					
Pre-Treatment	15.96 (1.47)	15.92 (1.46)	2.78	135.42	.098
Post-Treatment	13.57 (1.49)	15.00 (1.50)			
Per Group Change	-2.39 (1.22)**	-0.92 (1.24)			
Epworth Sleepiness Scale					
Pre-Treatment	8.92 (1.09)	9.68 (1.09)	3.50	134.59	.064
Post-Treatment	7.24 (1.11)	9.16 (1.12)			
Per Group Change	-1.68 (0.86)**	-0.52 (0.87)			
Dysfunctional Beliefs and Attitudes about Sleep scale					
Pre-Treatment	60.28 (4.02)	58.58 (3.99)	22.07	135.27	<.001
Post-Treatment	48.52 (4.09)	58.37 (4.11)			
Per Group Change	-11.76 (3.41)**	-0.21 (3.47)			
Depression					
Pre-Treatment	14.53 (2.76)	14.63 (2.74)	0.34	132.84	.563
Post-Treatment	12.94 (2.78)	13.78 (2.80)			
Per Group Change	-1.59 (1.74)	-0.85 (1.79)			
Anxiety					
Pre-Treatment	10.22 (1.92)	8.93 (1.91)	3.21	134.66	.076
Post-Treatment	8.65 (1.94)	8.97 (1.95)			
Per Group Change	-1.57 (1.25)*	0.04 (1.28)			
Stress					
Pre-Treatment	15.15 (2.22)	15.56 (2.21)	3.82	135.68	.053
Post-Treatment	12.68 (2.25)	15.48 (2.27)			
Per Group Change	-2.46 (1.68)**	-0.08 (1.72)			

CBT-i = Cognitive Behavioral Therapy for Insomnia.
* change per condition $p < .05$, ** change per condition $p < .01$

Table 4.4 Changes in objective sleep outcomes during treatment between conditions.

	CBT-i	**Control**	**Interaction**		
	Mean (95%CI)	**Mean (95%CI)**	***F***	***df***	***p***
Apnea/Hypopnea Index					
Pre-Treatment	33.04 (5.28)	35.83 (5.19)	3.26	137.42	.073
Post-Treatment	29.60 (5.34)	37.37 (5.23)			
Per Group Change	-3.44 (3.92)	1.54 (3.79)			
Stage 1 Sleep (%)					
Pre-Treatment	22.67 (3.47)	24.23 (3.42)	0.30	138.49	.585
Post-Treatment	21.92 (3.51)	24.45 (3.44)			
Per Group Change	-0.75 (2.50)	0.22 (2.43)			
Stage 2 Sleep (%)					
Pre-Treatment	48.13 (2.60)	45.91 (2.57)	0.02	138.27	.886
Post-Treatment	47.03 (2.64)	45.03 (2.58)			
Per Group Change	-1.09 (2.13)	-0.88 (2.07)			
Slow Wave Sleep (%)					
Pre-Treatment	12.97 (2.29)	15.34 (2.26)	1.26	137.95	.264
Post-Treatment	13.22 (2.32)	14.29 (2.27)			
Per Group Change	0.25 (1.63)	-1.05 (1.59)			
Rapid Eye Movement Sleep (%)					
Pre-Treatment	16.24 (1.65)	15.20 (1.63)	0.18	138.38	.675
Post-Treatment	17.79 (1.69)	16.25 (1.64)			
Per Group Change	1.55 (1.70)	1.05 (1.65)			
Total Sleep Time (min)					
Pre-Treatment	375.21 (20.53)	358.36 (20.25)	2.41	137.24	.123
Post-Treatment	355.43 (21.04)	363.79 (20.49)			
Per Group Change	-19.78 (22.98)	5.42 (22.42)			
Sleep Onset Latency (min)					
Pre-Treatment	32.46 (9.43)	29.17 (9.30)	0.36	136.85	.550
Post-Treatment	21.24 (9.70)	23.32 (9.43)			
Per Group Change	-11.22 (21.65)	-5.85 (12.36)			
Wake After Sleep Onset (min)					
Pre-Treatment	95.66 (13.60)	82.07 (13.41)	4.74	139.70	.031
Post-Treatment	69.67 (13.89)	77.19 (13.55)			
Per Group Change	-25.99 (13.72)**	-4.88 (13.38)			
Sleep Efficiency (%)					
Pre-Treatment	74.32 (2.92)	74.99 (2.88)	2.52	136.24	.115
Post-Treatment	79.25 (2.99)	76.43 (2.92)			
Per Group Change	4.93 (3.11)**	1.44 (3.04)			

AHI = Apnea Hypopnea Index, CBT-i = Cognitive Behavioral Therapy for Insomnia, SaO2 = Oxygen Saturation.

* change per condition $p < .05$, ** change per condition $p < .01$

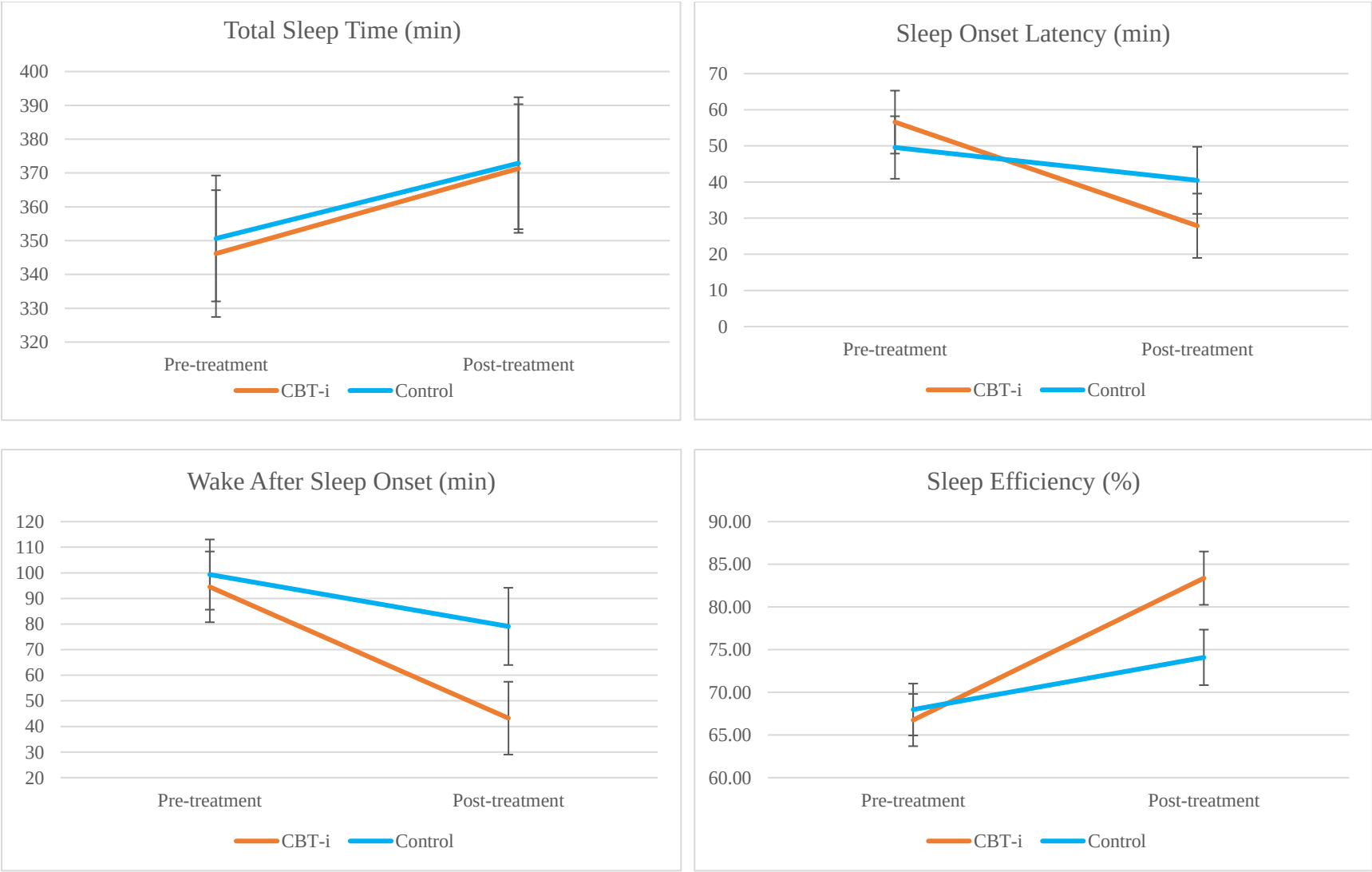

Figure 4.2 Changes in sleep diary outcomes between conditions during treatment. Error bars represent ±95% Confidence Intervals.

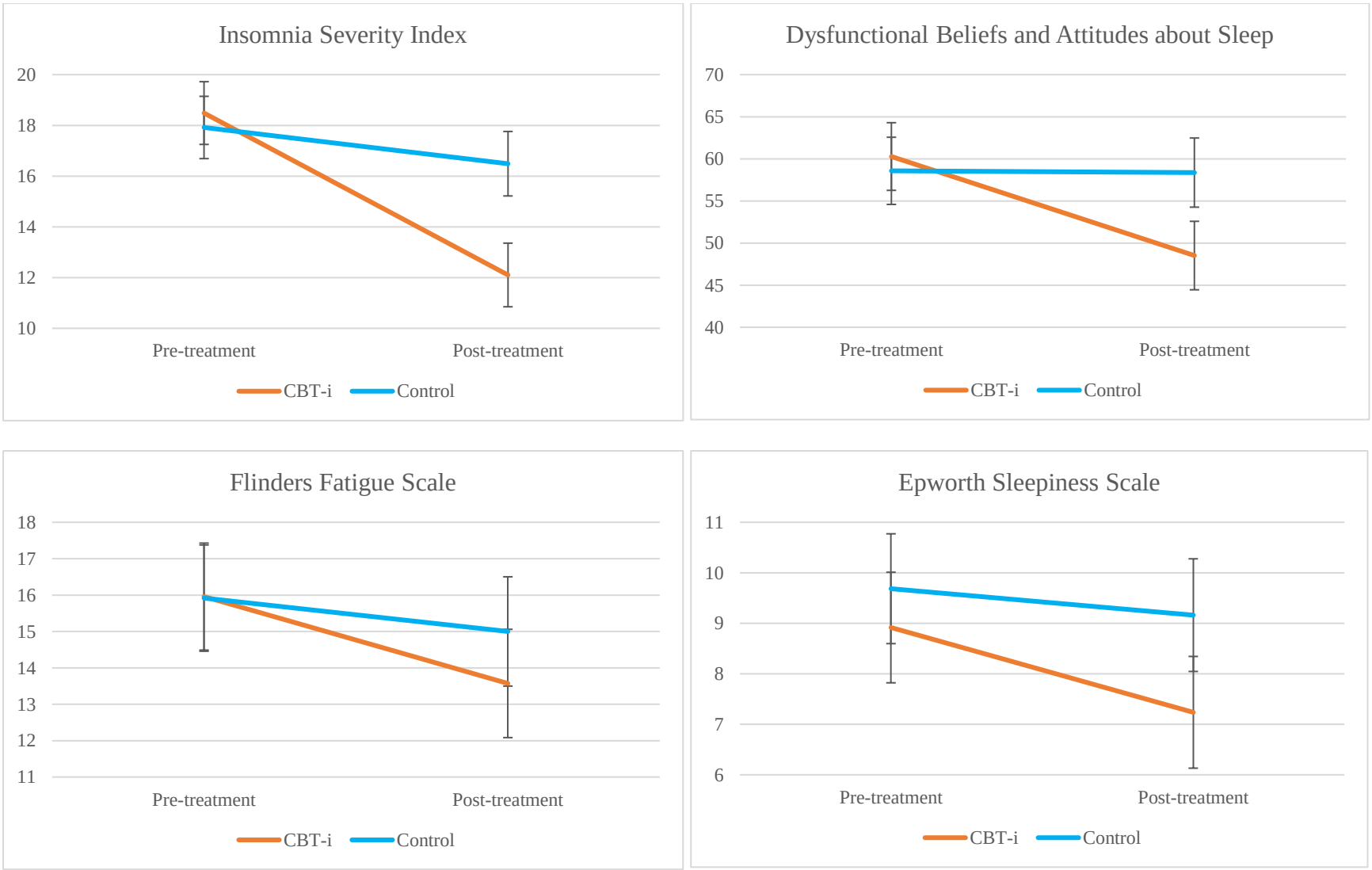

Figure 4.3 Changes in questionnaire outcomes between conditions during treatment. Error bars represent ±95% Confidence Intervals.

It was predicted that participants treated with CBT-i would experience greater improvements in sleep-diary parameters and global insomnia severity from pre- to post-treatment compared to participants in the control condition. Participants in the CBT-i condition experienced significantly greater improvements in diary measured sleep onset latency, wake after sleep onset, and sleep efficiency. However, no significant interactions were observed in improvements in diary total sleep time (Table 4.2, Figure 4.2). Participants in the CBT-i condition experienced significantly greater improvements in global insomnia severity, and the ISI sub-score, from pre- to post-treatment, compared to participants in the control condition (Table 4.3, Figure 4.3).

It was also predicted that participants in the CBT-i condition would experience significantly greater improvements in symptoms of daytime impairments, depression, anxiety and stress, and dysfunctional sleep-related cognitions, compared to participants in the control condition. The CBT-i group did show significantly greater improvements in dysfunctional sleep-related cognitions, and each sub-scale of the DBAS. Although the CBT-i group did show significant reductions in reported fatigue, daytime sleepiness, and daytime feelings and functioning scales, the improvement comparison with the control group did not reach statistical significance (Table 4.3, Figure 4.3). Likewise, although the CBT-i group did experience significant reductions in anxiety and stress during treatment (Table 4.3), the interaction effect with the control group did not reach significance.

It was also predicted that participants in the CBT-i condition would experience significantly greater improvement in objective sleep parameters and sleep architecture, compared to participants in the control condition. As seen in Table 4.4, participants in the CBT-i condition experienced significantly greater reduction in objective wake after sleep onset during treatment, compared to the control group. However, the trends for greater

improvements in sleep onset latency and sleep efficiency were not significant. No other objective sleep parameters, indices of sleep architecture, or manifestations of OSA severity differed significantly between groups during treatment. There was a trend for slightly greater AHI reduction in the CBT-i condition, however this effect was of negligible clinical significance.

4.4.4 Treatment-Responders, Remitters, and Adverse Events

It was predicted that participants in the CBT-i condition would display significantly greater rates of insomnia improvement, compared to participants in the control condition. Insomnia improvements were operationalized in three ways. Firstly, the sleep-diary criteria used by the psychologist when performing a diagnosis of insomnia were re-applied to post-treatment sleep diaries (i.e. SOL ≥ 30, WASO ≥ 45, and SE < 75%), to examine the number of participants in each group no longer meeting these criteria. It was found that significantly more participants in the CBT-i condition (48%) than the control condition (23%) no longer met these sleep diary criteria ($\chi^2(1) = 8.30$, $p = .005$).

Secondly, a cut-off of less than 14, on the post-treatment ISI was used to determine the proportion of participants in each condition who no longer indicated clinically significant insomnia symptoms (61). It was found that significantly more participants in the CBT-i condition (63.8%) than the control condition (25.8%) no longer indicated clinically significant insomnia symptoms ($\chi^2(1) = 19.68$, $p < .001$).

In addition, a cut-off of less than 8 on the post-treatment ISI was used to determine the proportion of participants in each condition who were in ‘remission’ of insomnia symptoms (61). It was also found that significantly more participants in the CBT-i condition (30.4%) than the control condition (3%) were categorised as insomnia remitters at 6-weeks ($\chi^2(1) = 17.92$, $p < .001$).

Insomnia responders were defined as any participants who showed at least an 8-point reduction in the ISI during treatment (91). It was found that significantly more participants in the CBT-i condition (46.4%) than the control condition (6.1%) showed a pattern of insomnia response from baseline to 6-weeks ($\chi^2(1) = 28.04$, $p < .001$).

A cut-off of less than 4, on the ISI sub-score was used to determine the proportion of participants in each condition with clinically significant reductions in these 'sleep' symptoms. It was found that significantly more participants in the CBT-i condition (47.8%) than the control condition (13.6%) no longer indicated clinically significant night time insomnia symptoms ($\chi^2(1) = 18.40$, $p < .001$).

Finally, a cut-off of 10 or less on the 6-week ESS was used to indicate normalized levels of sleepiness. There was no significant difference in the proportion of participants in the CBT-i (75.4%) or control (60.6%) condition who experienced normal levels of sleepiness by 6-weeks ($\chi^2(1) = 3.38$, $p = .06$).

One participants in each condition experienced an adverse event during the BRT phase (or equivalent waitlist time) of the trial. These included; admission to hospital with weakness and ataxia of left upper and lower limbs, and chest pain on exertion resulting in cardiology review, possible coronary artery disease and on-going management. Adverse events were deemed to be unrelated to the BRT protocol. No additional falls or motor vehicle accidents were recorded during the BRT period of the trial.

4.4.5 **Impact of OSA severity on CBT-i**

Finally, it was predicted that greater OSA severity would be associated with reduced effectiveness of CBT-i. Participants receiving CBT-i were categorized into moderate, or severe levels of OSA severity according to pre-treatment AHI cut-offs of < 30, and ≥30, respectively (as all participants had previously satisfied AHI ≥ 15 inclusion criteria, no 'mild' severity group was available). Among participants in the CBT-i condition, moderate and

severe OSA was observed in 36 (51.4%), and 34 (48.6%) participants, respectively. Linear Mixed Model analyses were undertaken to examine the effect of OSA severity groupings on improvements in sleep diary outcomes, and total ISI scores from pre- to post-treatment in these participants. The only significant interaction ($F(67.65) = 5.22$, $p = .025$) indicated that participants with moderate OSA experienced greater improvements in diary sleep onset latency (36.3 minutes improvement, ±95%CI = 12.0) compared to participants with severe OSA (16.6 minutes improvement, ±95%CI = 12.3). No other significant interactions were observed (all $p > .30$). Overall, these results indicate that COMISA participants with moderate and severe OSA experienced similar levels of improvement in the majority of the sleep diary outcomes, and global insomnia severity during treatment.

4.5 Discussion

COMISA participants receiving CBT-i experienced significantly greater improvements in several insomnia symptoms from pre- to post-treatment, compared to participants in the control condition. This effect was found when comparing improvements in sleep diary parameters, global insomnia severity, and dysfunctional beliefs and attitudes about sleep. CBT-i also led to significantly greater rates of insomnia-remission, according to commonly used cut-offs on the ISI (61), and sleep-diary insomnia-diagnostic criteria, compared to the control condition. Furthermore, among participants receiving CBT-i, levels of OSA severity were not related to the degree of change in global insomnia severity, or the majority of the diary outcomes during treatment. However, CBT-i did not lead to significantly greater improvements in some daytime impairments including fatigue, sleepiness, general daytime functioning, depression, anxiety or stress, compared to the control condition. Overall, these results suggest that CBT-i effectively treats night time symptoms, maladaptive sleep-related cognitions, and global insomnia severity in patients with COMISA, however some daytime impairments persist immediately after treatment.

4.5.1 **Group Comparisons**

Although the CBT-i condition experienced significantly greater improvements in diary sleep efficiency, sleep onset latency, and wake after sleep onset compared to the control condition, no significant interactions were observed for diary total sleep time. Indeed, part of the CBT-i protocol included bedtime restriction therapy, which operates via temporary reduction of time in bed, to increase sleep pressure, consolidate sleep periods and change conditioned relationships between the bedroom environment and states of arousal and wakefulness (38, 41). Although bedtime restriction is one of the most effective components of CBT-i (77), one side effect is temporarily reduced time spent asleep while the therapeutic effects are taking place (78). It is probable that many participants in the CBT-i condition continued to utilize bedtime restriction therapy during the post-treatment assessment phase, thus explaining why there was no difference in changes in total sleep time between conditions, but significant differences in time spent awake and sleep efficiency outcomes. Other randomized controlled trials examining the effectiveness of CBT-i have also observed that CBT-i has less of an effect on post-treatment total sleep time, compared to other sleep parameters such as sleep onset latency, or wake after sleep onset (35, 79). Compared to a recent meta-analysis of the effect of CBT-i in patients with co-morbid insomnia, participants in the current study appeared to experience similar, if not greater, improvements in sleep diary outcomes following CBT-i (80).

As expected, participants in the CBT-i condition experienced greater reduction in global insomnia severity, compared to participants in the control condition (80). The ISI includes three ‘sleep impairment’ symptoms, and four items which measure daytime sequelae. A sub-scale including only the first three items of the ISI also showed that CBT-i participants experienced greater improvement in ‘night time’ insomnia symptoms, compared

to participants in the control condition. These results indicate the effectiveness of CBT-i in targeting both the night time and daytime components of insomnia in COMISA patients.

Insomnia patients are more commonly motivated to seek treatment because of the functional impairments experienced during the day, rather than their reduced sleep at night (81, 82). Regarding daytime impairments, CBT-i did not result in significantly greater improvements in symptoms of fatigue, sleepiness, general daytime functioning, depression, anxiety, or stress in the immediate post-treatment week compared to the control condition. One explanation for this unpredicted result may arise from the necessity of evaluating the treatment effect too soon after the start of bedtime restriction therapy. As this study was a part of a larger COMISA project to evaluate the effects of treating insomnia before the administration of CPAP and the desire not to delay CPAP any longer than necessary, the only post-treatment evaluation was the week immediately following the last treatment session of a brief 4-week CBT-i program. It is likely that at this stage participants had not been titrated out to their final amount of time in bed. This is evidenced by the much greater decrease of time in bed at the post-treatment evaluation of the CBT-i group (76 min) than the control group (13 min). If the CBT-i participants had been titrated out to a greater time in bed as would normally occur with more weekly sessions, it may have been the case that they would have should greater decreases in daytime sleepiness, fatigue, and the other daytime impairments.

Another explanation for less improvement of daytime impairments than the sleep parameters may be that these symptoms were resulting partly from the un-treated OSA. Like insomnia, OSA is also associated with feelings of daytime sleepiness, fatigue, depression and impaired concentration (5, 6, 12). In the current sample, it is possible that these daytime impairment domains were partly a manifestation of the OSA, and therefore did not show any greater improvements in the CBT-i condition, as the insomnia improved with treatment. In

fact, the persistence of some daytime impairments following CBT-i may increase future CPAP outcomes among these patients. For example, perceived improvements in symptomology during CPAP can increase subsequent CPAP adherence (83-85). Hypothetically, if CBT-i ameliorated all daytime impairments, it may create a perceived floor-effect in these impairments, and reduce motivation to continue using CPAP during subsequent treatment phases. It will be important to examine reductions in daytime symptomology among COMISA patients after they begin CPAP therapy. Although no interaction effects were observed when comparing improvements in daytime impairments between conditions, the CBT-i condition did experience significant improvement in the majority of these outcomes from pre- to post-treatment, and trended towards greater improvements than the control condition. The only exception being depression scores which were in the moderate range at pre-treatment, but showed no significant improvement in either condition.

To examine the effect of OSA-severity on the effectiveness of CBT-i, participants in the CBT-i condition were categorized into moderate, and severe co-morbid OSA groups. It was found that participants with moderate OSA experienced slightly greater improvement in diary-measured sleep onset latency during treatment, compared to patients with severe OSA. This effect may have been due to greater sleep onset estimates in the moderate group at pre-treatment. No other significant interactions between OSA-severity and time were observed for diary outcomes or ISI scores, indicating that the effectiveness of CBT-i is largely unrelated to the severity of COMISA patients' OSA. These results can be taken in conjunction with Fung and colleagues' data (56), to suggest that CBT-i is an effective treatment for insomnia in the presence of co-occurring mild, moderate, and severe OSA.

4.5.2 **Responder Analyses**

Rates of insomnia improvement were analyzed in several ways. Firstly, the sleep diary criteria initially used by psychologists to diagnose insomnia were re-applied to post-treatment diaries. Although this operationalization does not equate to a psychologist determination of insomnia presence or severity, diary criteria have been suggested to indicate insomnia improvements following treatment (61). By post-treatment, a significantly greater number of participants in the CBT-i condition no longer held diary insomnia-diagnostic criteria, compared to participants in the control condition. However, 52% of CBT-i-treated participants still had at least one sleep diary impairment criterion following treatment. It is possible that the presence of co-morbid OSA prevented some patients from achieving these quantitative insomnia improvements. For example, respiratory events terminate in post-apneic arousals, which can result in awakenings from sleep. It is possible that some participants' increased night time wakefulness was due to multiple post-apneic arousals and awakenings, and misperceived wakefulness between multiple awakenings. If this was the case, CBT-i would have little effect on perceived wake after sleep onset if OSA manifestations remain unchanged. Future research may wish to examine the nature and severity of these post-apneic events more specifically among COMISA patients who show reduced insomnia improvements with CBT-i.

Participants in the CBT-i condition were significantly more likely to experience improved global insomnia severity by follow-up, compared to participants in the control condition. This was found when examining rates of insomnia improvement, remission and response, between conditions. According to an ISI cut-off of 14, 64% of participants in the CBT-i condition were categorized as 'improved'. However, four items of the ISI assess symptoms which are shared by both insomnia and OSA (12). Therefore, a cut-off of lower than four points on the ISI subscale (measuring only night time symptoms of insomnia) was

also used to define insomnia-improvements. It was found that 48% of CBT-i participants experienced insomnia improvements according to the ISI subscale, following CBT-i. In a recent study examining changes in insomnia symptoms in COMISA participants treated with CPAP therapy, it was found that 45% of participants no longer experienced insomnia (according to the same ISI subscale criteria) (62). Although these rates of improvement are similar, participants in the current study satisfied more conservative insomnia diagnostic criteria, and were likely more resistant to improvement.

4.5.3 Limitations

This research should be interpreted in light of several limitations. Firstly, no placebo control condition was used to equate therapist attention, or participants' expectations, between conditions. As previous placebo-controlled trials have demonstrated that CBT-i is consistently more effective than placebo conditions, it was thought that employing a placebo condition would result in great cost for little or no scientific gain. Furthermore, these data were drawn from a larger randomized controlled trial, which prevented use of a placebo-control condition. This larger trial aimed to compare the combination of CBT-i and CPAP, to the current 'treatment as usual' approach of CPAP-alone (i.e. without any placebo-control treatment prior to the initiation of CPAP therapy). All participants attended one pre-treatment psychologist review session prior to randomization, and several review appointments with sleep physicians, technicians, and researchers throughout the current protocol period. Therefore, different conditions received a similar amount of time with specialist and research staff.

Secondly, only a brief four-session CBT-i protocol was employed which may have limited the effectiveness of CBT-i in treating some insomnia domains. Other researchers have previously used up to 17-session CBT-i protocols (90), which allow therapists to allocate more time to the cognitive processes believed to maintain insomnia. It is possible that had an

extended CBT-i protocol been used in the current study, participants treated with CBT-i may have shown greater improvement of their daytime symptoms. A four-session protocol was chosen in the current study, to reduce patients' delay in progressing to CPAP, and because of support from previous dose-response data (89).

A small amount of missing data at post-treatment was unavoidable due to participant withdrawal, and participants progressing to CPAP therapy which precluded utilizable post-CBT-i data. There were significantly fewer sleep diaries collected from the control condition at post-treatment, primarily for these study design reasons. Linear mixed model analyses were chosen over the more common 'analysis of variance' approach, due to their ability to accommodate missing data (86, 87).

Finally, only the immediate effects of CBT-i on insomnia symptoms were examined in the current trial. All participants in the current study attended sleep laboratories for a CPAP titration study, and were subsequently set up with their own CPAP equipment to use at home for the following 4-6 months. Therefore, any long-term follow-up of CBT-i would have been confounded by the use of CPAP therapy. It seems probable that greater improvements may have been shown by the CBT-i group had more treatment sessions and a relaxation of the time in bed been possible. Other research suggests that CBT-i results in enduring improvements in insomnia symptoms among patients with co-morbid mild OSA (56). Results from this larger randomized controlled trial will be published elsewhere.

4.5.4 Future Research

It will now be important to establish whether these improvements among CBT-i-treated COMISA patients translate into grater CPAP acceptance and adherence. As discussed, it is thought that OSA patients with co-morbid insomnia spend more time awake in bed wearing pressurized masks, thereby leading to poor CPAP acceptance and adherence (12). Several groups have suggested that these patients' insomnia be treated first to remove this

barrier to CPAP acceptance. These results show that CBT-i improves subjective sleep parameters, objective time spent awake after sleep onset, and global insomnia severity among COMISA patients. Future research should now determine whether insomnia improvements resulting for CBT-i will also translate to increased subsequent CPAP acceptance and long-term use.

Depending on definitions used, 36-52% of participants in the CBT-i condition did not experience insomnia-improvement during treatment. Future research should also examine predictors of 'insomnia-improvements' in COMISA patients treated with CBT-i, to predict which patients are likely to require additional or varied treatment approaches. It is possible that some COMISA patients will show little improvement during CBT-i, but large improvements in both the insomnia and OSA when treated with CPAP therapy (e.g. (62)). Predicting patterns of treatment responses such as this will improve knowledge of tailored treatment approaches for future COMISA patients.

4.5.5 **Conclusions**

CBT-i is an effective treatment for insomnia patients with co-morbid moderate and severe OSA. Compared to a control condition, CBT-i resulted in significantly greater improvements in the majority of sleep diary outcomes, global insomnia severity, and dysfunctional sleep-related cognitions. Daytime impairments did not show significantly greater improvements in the CBT-i condition, which may be due to their secondary association to the co-morbid OSA or insufficient time to titrate participants' amount of time in bed before evaluating the full post-treatment effects. Future research should examine the impact of CBT-i on subsequent acceptance and adherence to CPAP therapy among patients with co-morbid insomnia and sleep apnea.

4.6 Chapter 4 Reference List

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5 CHAPTER 5. Changes in Sleepiness and Sleep Parameters before, during, and after Cognitive and Behavioral Therapy for Insomnia, in Patients with Co-Morbid Insomnia and Sleep Apnea.

This Chapter includes a manuscript intended for submission to *Sleep Medicine*.

The description of the *Participant inclusion criteria*, *Screening,* and *CBT-i treatment components* included in the Methods section of the current Chapter is largely re-produced from Chapter 4. These repeated sections are included to present a cohesive chapter, however attention is drawn to each of these sections, so examiners may overlook them where necessary.

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5.1 Abstract

Aims: Co-occurring insomnia and Obstructive Sleep Apnea (OSA) represents a frequent and debilitating condition which is difficult to treat. Cognitive and Behavioral Therapy for Insomnia (CBT-i) is currently recommended as the initial treatment in these patients. One of the most effective components of CBT-i is Bedtime Restriction Therapy (BRT), which results in acutely increased daytime sleepiness, as the therapeutic effects take place. Because untreated OSA is also associated with increased daytime sleepiness, it is important to monitor any further increases in sleepiness during BRT, to ensure that these patients can be safely treated with CBT-i.

Methods: 72 participants with insomnia (psychologist-diagnosis), and OSA (AHI≥15) completed sleep diaries and daytime sleepiness questionnaires, at pre-treatment, and during 4-weekly sessions of CBT-i. BRT was introduced in the first session and modified by psychologists over the subsequent three sessions. Changes in subjective sleepiness and sleep parameters were investigated with linear mixed model analyses.

Results: Compared to pre-treatment, participants experienced a small (1.2-point) increase in daytime sleepiness in the first week of BRT. However, daytime sleepiness returned to pre-treatment levels at weeks 2, 3, and 4. Total sleep time was reduced by 25 minutes following the initiation of BRT, however rebounded during the course of therapy until week 4 total sleep time was 29-minutes greater than pre-treatment estimates. Finally, other sleep diary outcomes showed gradual improvement during the course of therapy, and were significantly greater by the later sessions of CBT-i.

Conclusions: BRT is associated with an immediate small increase in daytime sleepiness in COMISA patients. However, following the first week, daytime sleepiness returns to pre-treatment levels. BRT is an effective and safe component of CBT-i in the presence of moderate and severe co-morbid OSA. Psychologists and therapists should continue to

monitor future patients' subjective sleep propensity closely, especially during the initial sessions of CBT-i.

Keywords: Insomnia, Cognitive behavioral therapy for insomnia, bedtime restriction therapy, sleep restriction therapy, co-morbid insomnia, obstructive sleep apnea.

5.2 Introduction

Insomnia and Obstructive Sleep Apnea (OSA) are the two most common sleep disorders, and frequently co-occur (1). Insomnia is conceptualized as a disorder of chronic hyperarousal (2), which is characterized by difficulties initiating, or maintaining sleep, or early morning awakenings from sleep, and associated daytime impairments (3). Insomnia is found in 6-10% of the general population (3-5). Alternatively, OSA is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) reduction of breathing through the night, commonly leading to fragmented sleep architecture, perceptions of non-restorative sleep, and impaired daytime functioning (3). Daytime sleepiness is a common symptom of OSA, and is used as a clinical indicator of OSA in diagnostic schema (3). Possibly due to this increased sleepiness, OSA is also associated with a 2 – 7-fold increase in traffic accidents (6). OSA with daytime sleepiness occurs in 2-4% of the general population (7).

Recent research has found that 17-69% of insomnia patients also fulfil diagnostic criteria for Obstructive Sleep Apnea (OSA), when assessed with polysomnography (PSG) (1). A large amount of research now suggests that Co-Morbid Insomnia and Sleep Apnea (COMISA) is a highly prevalent disorder, which is associated with great impairments to sleep, daytime functioning, and quality of life, and is more difficult to treat compared to each disorder presenting independently (1).

The most effective treatment for moderate-severe OSA is continuous positive airway pressure (CPAP) therapy (8). However, when co-morbid insomnia symptoms are also present, patients experience greater difficulty adapting to CPAP devices, and are therefore more likely to reject treatment or use CPAP for fewer hours each night (9-12). This has led to the suggestion that COMISA patients' insomnia should be initially treated, to improve subsequent CPAP acceptance and use (1, 13, 14). The most effective treatment for primary and co-morbid insomnia is Cognitive and Behavioral Therapy for Insomnia (CBT-i) (15, 16).

However, the effectiveness and mechanisms of CBT-i in the COMISA population has received little research.

Bedtime Restriction Therapy (BRT) is one of the most effective components of CBT-i (also called *sleep restriction therapy*) (17). BRT is a behavioral component of CBT-i which aims to reduce conditioned relationships between the bedroom environment or routine, and a state of arousal and alertness, and thereby decrease night time wakefulness (18). To achieve this, therapists guide patients to temporarily reduce the time that they spend in bed over several consecutive nights, to gradually increase sleep pressure, to reduce the length of night time awakenings, and consolidate sleep periods. After patients begin sleeping for the majority of the time that they spend in bed (e.g. >85%), therapists guide them to gradually extend the time they spend in bed, from week-to-week, until a comfortable and satisfying equilibrium between time in bed, sleep time, and sleepiness is achieved.

However, while these effects are taking place, patients commonly experience mild partial sleep deprivation, and increased levels of daytime sleepiness (19, 20). These side effects are especially common during the first weeks of BRT, while conditioned arousal responses remain strong (20). For example, Kyle and colleagues (20) examined changes in daytime sleepiness, and objective sleep parameters before, during, and after 4-weekly sessions of BRT in 16 insomnia patients. It was found that patients' sleepiness scores were increased during the first three weeks of BRT, however returned to pre-treatment levels by 3-month follow-up. This change in sleepiness was associated with a large decrease in objective total sleep time during the early stages of BRT, which began to rebound by the third session. Improvements were observed in sleep onset latency, wake after sleep onset, sleep efficiency, and global insomnia severity during BRT. Patients with primary insomnia are thought to suffer from a disorder of chronic hyperarousal, which results in prologued night time wakefulness, and daytime fatigue, poor mood, and impaired concentration (2). By definition,

insomnia is a disorder of increased *sleeplessness* rather than increased *sleepiness*. Therefore, acutely increased sleepiness during the early stages of BRT has been of marginal concern to clinicians and most patients.

However, because OSA is associated with increased daytime sleepiness before treatment, it is thought that restricting these patients' sleep, and further increasing their daytime sleepiness during BRT may put them at increased risk of traffic or occupational accidents (6, 21, 22). For example, Vakulin and colleagues (6) examined the effect of partial sleep restriction on simulated driving performance in 38 OSA patients and 20 normal sleepers. OSA patients experienced a significantly greater number of steering deviations, and crashes following a single night of partial sleep deprivation, compared to a night of normal sleep. Furthermore, OSA patients also displayed significantly greater detriments to driving performance between the normal night and sleep-restricted night, compared to the normal sleepers. It was concluded not only that OSA patients are vulnerable to the effects of partial sleep restriction, but that they may also be more vulnerable than normal sleepers.

CBT-i is recommended as the initial treatment for patients with COMISA. However, the most effective component of CBT-i, BRT, is associated with temporarily reduced sleep time, and increased daytime sleepiness. Because OSA and COMISA patients experience increased daytime sleepiness before treatment, further increases in sleepiness during BRT may place them at an increased risk of vehicular or occupational accidents. It is important to examine the acute effects of BRT on daytime sleepiness in COMISA patients, to ensure the safety of this highly recommended treatment approach.

5.3 Methods

5.3.1 Design

This study used a single-group design to examine changes in daytime sleepiness, and sleep parameters over 5 occasions (Time: pre-treatment, week 1, week 2, week 3, and week 4). BRT was initiated during the first week of CBT-i.

5.3.2 Participants

Participants included 72 adults (Age *y M* = 59.12, *SD* = 9.92, 55.6% Male) with psychologist-diagnosed insomnia, and sleep physician-diagnosed OSA (AHI *M* = 33.17, *SD* = 19.83; BMI *M* = 34.45, *SD* = 6.34). These participants were drawn from a larger randomized controlled trial, including two sites, investigating the effects of CBT-i (vs. No insomnia treatment) on insomnia symptoms, and subsequent acceptance and use of CPAP therapy (23). Only data from participants in the CBT-i condition are included in the current study.

NB: This section is largely repeated from Chapter 4.

Inclusion criteria were; AHI ≥ 15 according to full night PSG recording, a clinical diagnosis of OSA and recommendation of CPAP by a sleep physician, and a psychologist diagnosis of insomnia according to sleep diary and daytime impairment criteria (see below), appropriate age range (18 – 75 years), absence of any additional co-morbid sleep disorders, or medical disorders which required immediate treatment, absence of; any significant memory, perceptual or behavioral disorder, neurological deficits which prevented self-administration of CPAP equipment, significant language barriers, current employment as a commercial driver, episodes of falling asleep while driving in the past six months, or participants who resided significantly remotely from the clinic to preclude follow-up visits. Participants who immediately rejected the physician's recommendation for a trial of CPAP were excluded.

5.3.3 **Screening**

NB: This section is largely repeated from Chapter 4.

Screening numbers can be found in Figure 5.1. Participants were recruited through two screening arms at each site. The first screening arm targeted clinical patients attending sleep laboratories for overnight sleep studies, who had an AHI of 15 or greater (n = 2,131). Participants who also reported insomnia symptoms, according to a total Insomnia Severity Index (ISI) score of at least 14, and a composite score of at least 4 on the first three 'sleep' items (24) proceeded for further screening. The second screening arm included advertisements placed in local print, radio, and television media, to direct potential participants to an online screening platform to register interest in the trial (n = 739). These potential participants then completed the ISI and OSA50 (29) to screen for symptoms of insomnia and OSA. Individuals who indicated symptoms of both insomnia and OSA were invited to undergo an overnight oximetry study to further screen for physiological indicators of OSA. Participants with at least 10 oxygen desaturations per hour of sleep during the overnight oximetry study were further screened with a full-night diagnostic sleep study (Somte, Compumedics, Melbourne, Australia). Sleep Physicians reviewed all prospective laboratory and website-screened participants with AHI scores of 15 or greater. Following a sleep physician diagnosis of OSA and recommendation for CPAP therapy, participants were referred to research staff for information and consent for the trial and collection of pre-treatment demographic data. Participants who remained eligible completed one-week sleep diaries and a questionnaire battery. Provisional and qualified psychologists with experience in diagnosing and treating insomnia disorders then used this material to inform a diagnosis of insomnia, according to ICSD-2 diagnostic criteria (3). Insomnia diagnostic criteria included; average sleep onset latency of ≥ 30 minutes, *or* average wake after sleep onset of ≥ 45 minutes, *or* sleep efficiency of ≤ 75%, *and* self-reported significant daytime impairment.

Participants were required to hold an insomnia complaint for at least 6 months to fulfil diagnostic criteria. Following a diagnosis of insomnia, participants were randomized to the CBT-i (n = 72) or control (n = 73) condition.

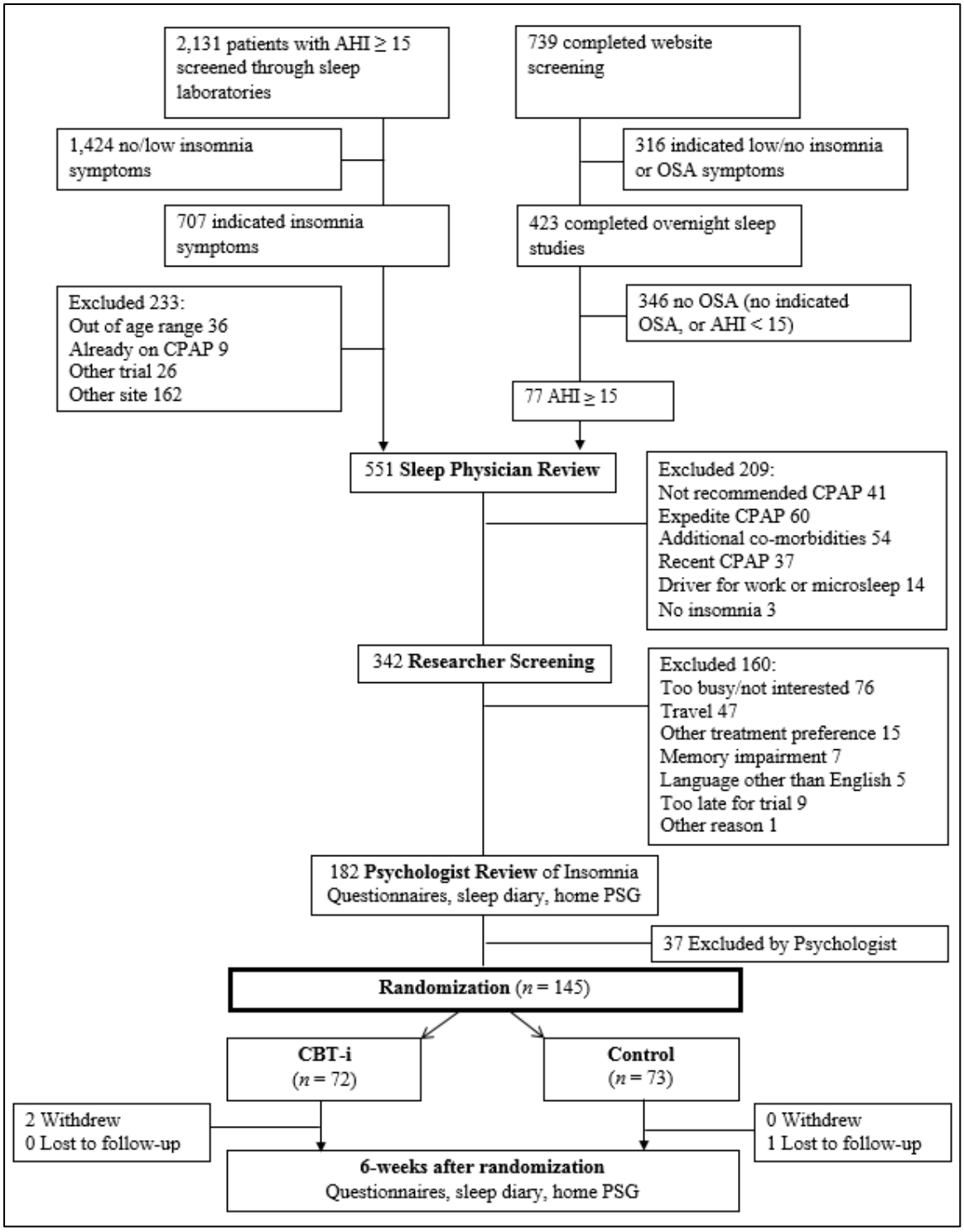


Figure 5.1 Screening and flow diagram. AHI = Apnea/Hypopnea Index, CBT-I = Cognitive and behavioral Therapy for Insomnia, CPAP = Continuous Positive Airway pressure, OSA = Obstructive Sleep Apnea, PSG = Polysomnography.

5.3.4 **Outcome Measures**

Sleep diaries (Appendix I) and subjective sleepiness scales (Appendix e) were completed the week before beginning CBT-i (pre-treatment), and for each of the four weeks of CBT-i. Sleep diaries are the recommended outcome measure of sleep in insomnia treatment research (25). Sleep diaries were used to assess participants' average weekly subjective sleep parameters. Participants indicated their nightly; time in bed, 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. The Epworth Sleepiness Scale (ESS) (26) is an 8-item self-report scale measuring perceived likelihood of falling asleep in various situations. Scores range from 0-24 with greater scores indicating more daytime sleepiness. The ESS has been reported to have adequate test-retest reliability and internal consistency (26). A cut-off of at least 10 has previously been used to indicate significant daytime sleepiness (30).

5.3.5 **Cognitive Behavior Therapy for Insomnia (CBT-i)**

NB: This section is largely repeated from Chapter 4.

Participants were treated with four-weekly, 45-minute sessions of CBT-i, administered by registered or provisional psychologists with previous CBT-i experience. Components of CBT-i included; basic sleep education, sleep hygiene information, bedtime restriction therapy, PSG and sleep misperception feedback, cognitive therapy, and relapse prevention. BRT was introduced during the first session, and was a primary component of each subsequent session.

5.3.5.1 Materials accompanying CBT-i.

To ensure treatment fidelity, therapists were provided with a structured manual, session checklist and power-point slides, and underwent additional training before delivering the CBT-i program. Each participant undergoing CBT-i was provided with a booklet which

reviewed concepts which were discussed during each week of treatment. Participants completed diaries before, and the ESS during each week of CBT-i, to be used by therapists to instruct BRT titration decisions.

5.3.5.2 Protocol for Bedtime Restriction Therapy.

As increased sleepiness is a common symptom of OSA (3), psychologists considered participants' ESS scores, and verbally-reported sleepiness when setting the bedtime parameters, to avoid any risk of accidents or dangerous levels of sleepiness. Based on elevated or increasing levels of subjective sleepiness, clinical judgments were made to either discontinue, or modify the standard BRT protocol. Psychologists were also provided with a set of suggestions to indicate when to consider modifying BRT techniques. For example, if a participant scored from 0 – 9 on the pre-treatment ESS, it was suggested that bedtime restriction was undertaken as 'normal' (e.g. participants' time in bed was restricted to diary-measured sleep time, with a minimum of 5.5 hours). If a participant scored from 10 – 14, it was suggested that bedtime restriction was 'modified', so minimum restriction would equal whichever was greater of; the participant's objective total sleep time during their overnight PSG study, or their subjective total sleep time from their pre-treatment sleep diary. It was thought that because many insomnia (and COMISA) patients underestimate their sleep prior to treatment (27), restricting their time in bed to their objective total sleep time would result in a less bedtime restriction, than if restriction was based on diary-measured sleep parameters. Finally, if a participant scored 15 or greater on the ESS at pre-treatment, it was suggested that psychologists consider regularizing their bed- and rise-times, discourage daytime napping, and withhold BRT. These suggested modifications and psychologists' clinical judgements were thought to replicate clinical practice, and hence increase the generalizability of the current findings to future COMISA patients.

5.3.6 **Data Analysis**

Data were analyzed with IBM SPSS (version 22) software using intention to treat analyses. Linear Mixed Model analyses were used to examine changes in ESS and diary-measured sleep parameters before, and during CBT-i. Repeated measures were nested within individual participants. Auto-regressive co-variance structures were used, and time was entered as a fixed effect.

Visual inspections revealed that sleep efficiency scores were negatively skewed, and sleep onset latency and wake after sleep onset estimates were positive skewed throughout treatment. Logarithmic transformations resulted in normally distributed data on these outcomes. Analyses were run on untransformed and logarithmic-transformed variables. Inferential outcomes remained unchanged between transformed and untransformed data. Therefore, untransformed data were reported to facilitate understanding of descriptive statistics.

5.3.7 **Missing Data**

Missing sleep diary and ESS data were observed in 13.9, and 4.2% of participants at pre-treatment, respectively. Missing sleep diary data were observed in 6.9, 5.6, 9.7, and 6.9% of participants during weeks 1-4, respectively. Missing ESS data were observed in 5.6, 5.6, 11.1, and 4.2% of participants during weeks 1-4, respectively. Missing data primarily occurred because of; participants forgetting to bring sleep diaries to appointments, missed appointments, and early withdrawal from the study in two participants due to unrelated health issues, and loss of interest. Therefore, missing data were considered to be ‘missing at random’, according to pre-defined criteria (28).

5.4 Results

5.4.1 CBT-i Compliance

Of the 72 participants randomized to receive CBT-i, 8 (11.4%) did not complete all four CBT-i sessions. Two participants withdrew immediately after randomization, one participant was lost to follow-up after the first session, two participants cancelled sessions due to sickness, one participant did not attend the final session (due to discontinuation of BRT), and two participants cancelled the fourth session and did wish to re-book.

BRT was formally discontinued in four participants during the CBT-i protocol; one participant had to remain lying down in bed for extended periods due to health reasons (psychologist restricted 'lights out' time rather than 'time in bed'), one participant found it unhelpful and refused to comply, one participant was responsible for caring for their partner and was required to stay in bed, and one was experiencing increased anxiety about sleep due to the BRT protocol. All analyses were re-run without these four participants. Descriptive and inferential statistics remained unchanged, so original analyses were reported for intention to treat purposes.

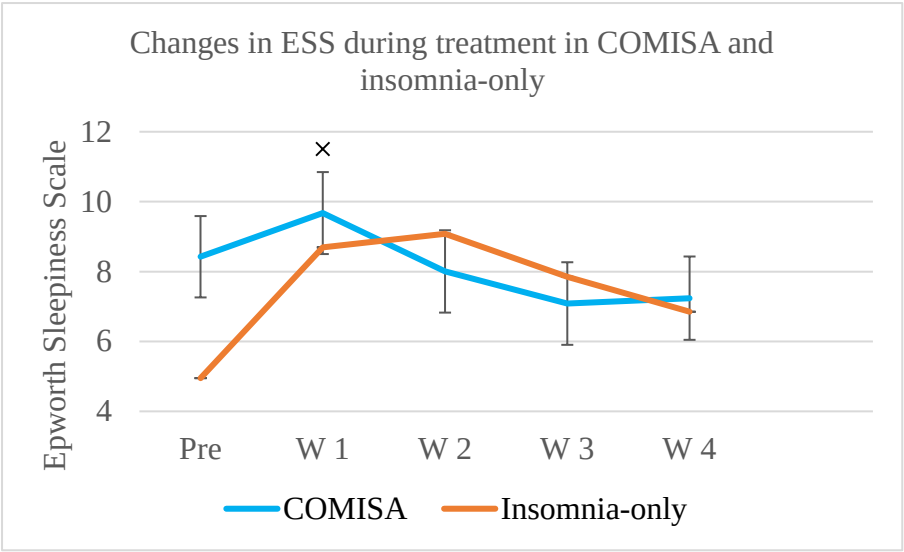
5.4.2 Changes in Sleep and Sleep Propensity during CBT-i

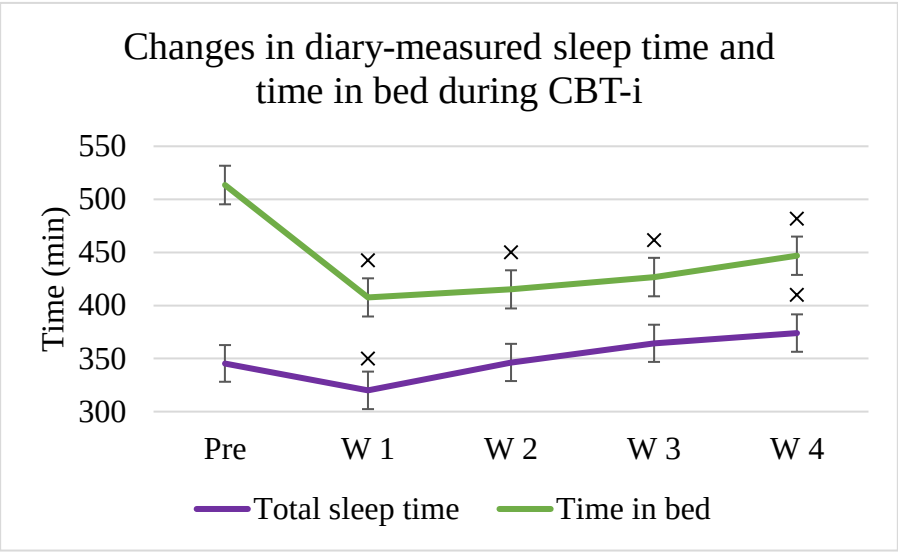
Compared to pre-treatment, ESS scores were increased following the first week of CBT-i, but returned to pre-treatment levels during sessions 2, 3, and 4 (Table 5.1, Figure 5.2). Figure 5.2 also displays average ESS scores observed during bedtime restriction therapy in a group of patients with insomnia-alone, drawn from a previous publication (20). An ESS cut-off of 10 has previously been used to indicate significant daytime sleepiness (30). According to this cut-off, significant daytime sleepiness was observed in 38% of participants at pre-treatment, and 50, 32, 28, and 30% of participants during sessions 1-4, respectively.

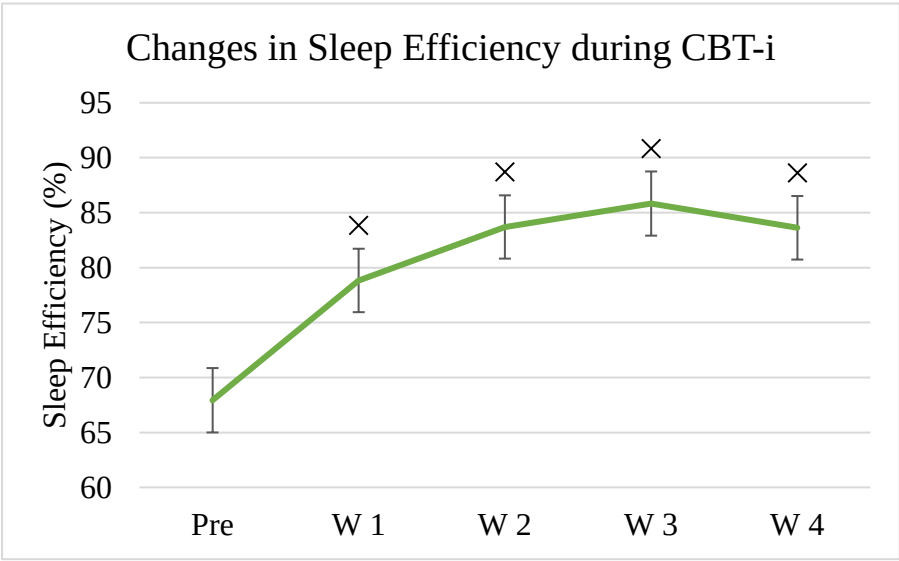
Total sleep time (Table 5.1, Figure 5.2) showed a significant reduction compared to pre-treatment, by week 1 (25.4-minute decrease, $p = .001$), and gradually increased over the

subsequent weeks until a significant improvement was seen by week 4 (28.6-minutes greater than pre-treatment, $p = .004$). Time in bed (Table 5.1, Figure 5.2) was significantly reduced over the course of treatment, with significantly lower estimates observed at weeks 1-4, compared to pre-treatment (all $p < .001$). Sleep Efficiency estimates (Table 5.1, Figure 5.2) increased steadily over the course of treatment, with significantly greater scores observed at weeks; 1 (10.9% improvement), 2 (15.8% improvement), 3 (17.9% improvement) and 4 (15.7% improvement), compared to pre-treatment (all $p < .001$).

Changes in sleep onset latency, and wake after sleep onset were also examined during treatment (Table 5.1, Figure 5.2). Wake after sleep onset estimates showed significant improvement at weeks; 1 (46.1-minutes), 2 (51.7-minutes), 3 (53.4-minutes) and 4 (45.4-minutes), compared to pre-treatment (all $p < .001$). Alternatively, sleep onset latency estimates showed significant improvement by weeks 2 (27.5-minutes), 3 (29.0-minutes) and 4 (29.9-minutes), compared to pre-treatment (all $p \leq .001$).







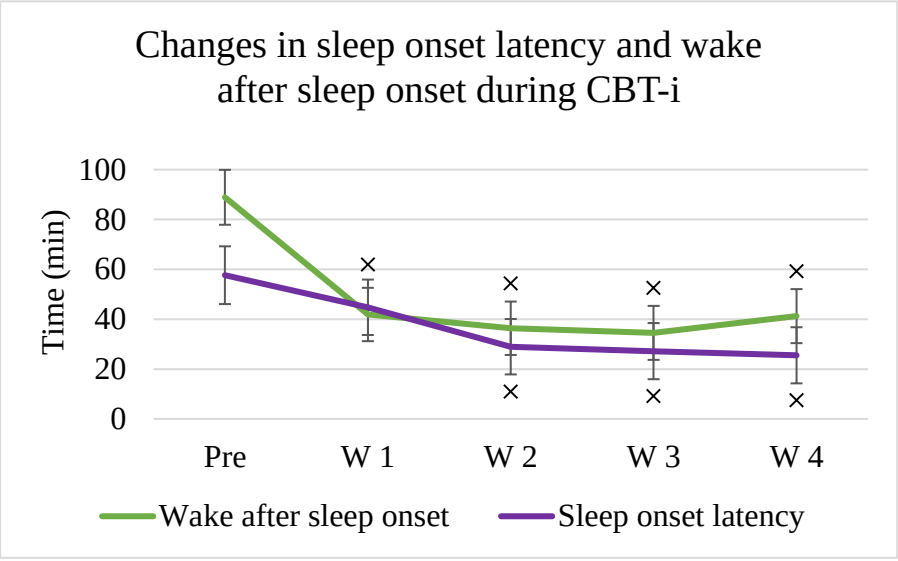


Figure 5.2 Changes in Sleepiness and Sleep Parameters during Treatment. 'Insomnia-only' data were drawn from Kyle and colleagues (20). Significant change from pre-treatment indicated by x ($p < .05$).

Table 5.1 Average (±CI) sleepiness and sleep parameters before, during, and after CBT-i.

	Pre-CBT-i	**Bedtime Restriction Therapy**			
		Week 1	**Week 2**	**Week 3**	**Week 4**
Epworth Sleepiness Scales					
	8.42	9.67*	8.00	7.09	7.24
	(1.17)	(1.18)	(1.18)	(1.19)	(1.18)
Total Sleep Time (min)					
	345.41	320.04**	346.38	364.38	374.01*
	(17.68)	(17.53)	(17.52)	(17.64)	(17.58)
Time in Bed (min)					
	513.52	407.61**	415.21**	426.78**	446.88**
	(18.17)	(17.98)	(7.97)	(18.12)	(18.05)
Sleep Efficiency (%)					
	67.93	78.83**	83.70**	85.83**	83.62**
	(2.93)	(2.89)	(2.88)	(2.92)	(2.89)
Wake After Sleep Onset (min)					
	89.03	42.98**	37.29**	35.67**	43.59**
	(10.68)	(10.44)	(10.41)	(10.56)	(10.47)
Sleep Onset Latency (min)					
	56.26	44.35	28.78**	29.37**	26.35**
	(11.12)	(10.76)	(10.70)	(10.90)	(10.76)

ESS = Epworth Sleepiness Scale, CBT-i = Cognitive and Behavioral Therapy for Insomnia, *p* values indicate significant difference vs. Pre-treatment, *= $p \leq .05$, **= $p \leq .001$.

5.5 Discussion

Levels of daytime sleepiness showed a small significant increase following the first week of BRT, however were not significantly different from pre-treatment during any subsequent week of treatment, in a large sample of participants with co-morbid insomnia and OSA. During the first week of BRT, participants also experienced a 25-minute reduction in total sleep time, which rebounded throughout the course of treatment, until total sleep time was 29 minutes greater than pre-treatment estimates by week 4. Sleep efficiency, sleep onset latency, and wake after sleep onset all showed gradual improvement during each week of CBT-i and were significantly more improved than pre-treatment levels by the later sessions. These results suggest that when monitored and managed closely, BRT is a safe and effective component of CBT-i in patients with moderate and severe co-morbid OSA.

Kyle and colleagues (20) observed that among participants with primary insomnia, BRT was associated with an immediate 3.7-point increase in ESS scores, which remained elevated over the following three weeks of BRT. COMISA participants also experienced a significant increase in sleepiness during the first session of CBT-i, however by an average of only 1.2-points. Furthermore, COMISA participants experienced an immediate reduction in daytime sleepiness after the first week of CBT-i, indicating that BRT resulted in lower, and shorter-lasting increases in sleepiness in COMISA participants, compared to the previous sample of participants with insomnia-alone. However, Kyle and colleagues also employed slightly greater restriction of time in bed during their BRT protocol as evidenced by a 130-minute decrease in time in bed during the first week, compared to the 106-minute decrease observed in the current COMISA participants. This resulted in faster reductions in night time wakefulness, and greater increases in daytime sleepiness in the insomnia-only sample (20). The participants with primary insomnia also began treatment with slightly lower ESS scores

compared to the current COMISA participants, however both groups reported similar levels of daytime sleepiness by the final treatment session.

This study included several limitations. Firstly, although there was a protocol for the delivery and weekly-modification of BRT, psychologists were instructed to use their clinical discretion to modify BRT practices according to changes in participants' reported daytime sleepiness and sleep parameters from week-to-week. In a small handful of participants, psychologists decided to relax the amount of restriction in order to balance participant satisfaction and safety, with improvements to sleep. However, this methodology also reflects clinical practices, and therefore increase generalizability of this research. Secondly, no long-term follow-up of changes to sleep and sleepiness was reported because all participants began using CPAP therapy immediately after CBT-i, which would have confounded the effect of BRT on sleepiness and sleep parameters. Finally, the BRT protocol was delivered alongside other common components of CBT-i, including basic sleep education, sleep hygiene, cognitive therapy, and PSG feedback. Therefore, we are unable to confirm the unique contribution of BRT to changes in sleep and sleepiness in the current sample. However, these results still demonstrate that BRT does not lead to concerning increases in sleepiness during CBT-i in COMISA patients. Furthermore, as BRT is rarely delivered independently of other CBT-i components, the delivery of a full CBT-i package increases the generalizability of these findings to future COMISA patients treated in clinical settings.

Future research should aim to confirm these changes in daytime sleepiness during CBT-i in COMISA patients. This could be expanded with a wider range of outcomes, including simulated driving performance measures, and multiple sleep latency testing measured at key points before, during, and after therapy. Future research may also wish to examine the independent effect of BRT on insomnia symptoms and future CPAP compliance in COMISA, rather than administering a full CBT-i package. If BRT improves sleep

parameters, independently of other CBT-i components, it may also increase subsequent CPAP acceptance and use. The combination of BRT and CPAP may be a more economical treatment strategy, when compared to the administration of a full CBT-i package before CPAP in each COMISA patient.

5.5.1 **Conclusions**

In this study, CBT-i was an effective and safe treatment in the presence of co-morbid moderate and severe OSA. BRT was associated with only slightly increased daytime sleepiness during the first week of treatment, however participants' daytime sleepiness returned to pre-treatment levels for each of the remaining sessions. These results suggest that when therapists pay careful attention to changes in patients' sleepiness and sleep parameters, COMISA patients' insomnia can be effectively and safely treated with CBT-i. It is recommended that future research also examine changes in objective sleepiness, and simulated driving performance, during BRT in COMISA patients.

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6 Chapter 6. Impact of Cognitive and Behavioral Therapy for Insomnia on subsequent Acceptance and Use of Continuous Positive Airway Pressure Therapy in Patients with Co-morbid Insomnia and Obstructive Sleep Apnea: A Randomized Controlled Trial.

This chapter is not intended for submission. However, these data will later be written for submission to the *Journal of the American Medical Association* as a Randomized Controlled Trial. This chapter includes additional analyses which will not be included in this manuscript.

The description of the *Participants*, *Measures*, and *CBT-i treatment components* included in the Methods section of the current Chapter is largely re-produced from Chapter 4. These repeated sections are included to present a cohesive chapter, however attention is drawn to each of these sections, so examiners may overlook them where necessary.

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Trial registration: Australian New Zealand Clinical Trials Registry: ACTRN12613001178730. Universal Trial Number: U1111-1149-4230.

Ethics Approval: Southern Adelaide Clinical Human Research Ethics Committee (428.12), Queensland University of Technology Research Ethics Unit (1300000302), and the External Request Evaluation Committee (Department of Human Services, Australia).

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6.1 Abstract

Context: Co-morbid insomnia and Obstructive Sleep Apnea (OSA) is a common and debilitating condition which is difficult to treat.

Objectives: To evaluate the effect of initial Cognitive and Behavioral Therapy for insomnia (CBT-i), versus a no insomnia-treatment control, on subsequent acceptance and long-term use of Continuous Positive Airway Pressure (CPAP) therapy, and improvements in insomnia and OSA symptoms.

Design, setting, and Patients: Prospective, parallel-arm, multi-site randomized controlled trial including 145 participants (55.2% Male, Age M = 58.22, SD = 9.91) with co-morbid insomnia and OSA. Participants were followed from baseline to 6-months post-randomization.

Interventions: Participants were randomized to initially receive either 4 weekly CBT-i sessions, or no insomnia-treatment control, before beginning CPAP therapy. This treatment protocol was also split into two phases to examine the independent effects of each treatment; the CBT-i, and the CPAP phase.

Main outcome measures: The primary between-group outcome was objective average nightly CPAP adherence from CPAP-setup to 6-month follow-up. Improvements in additional outcomes were examined between-groups from baseline to 6-months, and during the two treatment phases (CBT-i and CPAP phases). These included; improvements in objective sleep parameters, diary-measured sleep parameters, global insomnia severity, subjective sleepiness, fatigue, dysfunctional sleep-related cognitions, depressive symptoms, anxiety symptoms and stress. Rates of immediate CPAP acceptance/rejection, and differences in objective nightly CPAP adherence among participants who accepted CPAP, were also examined between conditions.

Results: During the CBT-i phase, the CBT-i condition experienced significantly greater improvement of diary-measured sleep parameters, global insomnia severity, daytime sleepiness, dysfunctional sleep-related cognitions, stress, and objective wake after sleep onset, compared to the control group (all $p < .05$). Following the CBT-i phase, initial CPAP acceptance was higher in the CBT-i (98.6%), compared to the control (89.0%) condition ($p = .034$). Furthermore, participants in the CBT-i condition showed 58.5-minutes (*CI* = 52.8) greater average nightly objective CPAP adherence over the first 4-months of use compared to participants in the control condition ($p = .03$). The CPAP phase was associated with further improvements in diary-measured sleep parameters and daytime impairments in each group. Unexpectedly, the control condition experienced greater improvement of diary-measured wake after sleep onset and sleep efficiency, and global insomnia severity during the CPAP phase, compared to the CBT-i condition. Finally, during the total protocol period, the CBT-i group showed greater improvement of global insomnia severity, and dysfunctional sleep-related cognitions (both $p \leq .001$). However, both conditions showed similar improvements in other diary-measured, and objective sleep, and daytime functioning outcomes from baseline to 6-months.

Conclusion: In patients with co-morbid insomnia and OSA, the combination of CBT-i and CPAP results in greater initial acceptance and long-term use of CPAP therapy, and greater improvements in global insomnia severity compared to treatment with CPAP-alone. However, there were similar (all $p > .05$) improvements in diary-measured and objective sleep parameters, and daytime functioning outcomes by 6-months follow-up. Initial treatment with CBT-i was associated with greater immediate improvement of sleep-diary and questionnaire measures of insomnia. However, during the CPAP phase of the study, the control condition experienced greater improvements in diary-measured wakefulness, objective wake after sleep onset, and global insomnia severity than the CBT-i condition. This

was likely due to the CBT-i condition experiencing a floor effect in these symptoms following CBT-i. It is recommended that patients with this co-morbid disorder should be treated with a combination of CBT-i and CPAP therapy to more rapidly improve insomnia symptoms and increase CPAP acceptance and long-term adherence.

Keywords: Insomnia, Obstructive Sleep Apnea, Cognitive and Behavioral Therapy for Insomnia, Co-morbid, Continuous Positive Airway Pressure Therapy, Adherence.

6.2 Introduction

Obstructive Sleep Apnea (OSA) and insomnia are the two most common sleep disorders, found in 2-4, and 6-10% of the general population, respectively (1-3). OSA is characterized by repetitive brief obstruction (apnea) or narrowing (hypopnea) of the upper airway during sleep (4). These respiratory events lead to temporary reduction of oxygen saturation, and terminate in post-apneic transient arousals, surges in sympathetic nervous system activity, and the resumption of breathing. The primary index of OSA presence and severity is the Apnea/Hypopnea Index (AHI), which reflects the average number of respiratory events experienced per hour of sleep. Diagnostic criteria for OSA include either; an AHI of at least 5, with additional day/night time symptoms, or an AHI of at least 15 (4). OSA is associated with feelings of non-restorative sleep, daytime sleepiness and fatigue, reduced quality of life, and increased risk for cardiovascular disease and motor vehicle accidents (5-8).

Alternatively, insomnia is characterized by a chronic complaint of difficulties initiating sleep, maintaining sleep, or waking too early and being unable to return to sleep (4). Like OSA, insomnia is also associated with reduced quality of life, and significant daytime functional, social, and occupational impairments (9). However, rather than being associated with increased sleep propensity, insomnia is more commonly conceptualized as a disorder of chronic hyper-arousal; characterized by increased psychological anxiety, distress and fatigue, 24-hour activation of the sympathetic nervous system, and conditioned arousal responses to the bedroom environment or routine (10, 11). Insomnia can present as an independent primary condition, however commonly presents as a co-morbid condition with a range of other disorders (12, 13).

Insomnia and OSA present together more commonly than would be expected, given the general population prevalence estimates of each disorder (14). For example, between 27-

85% of OSA patients presenting to sleep disorder clinics hold a clinically significant complaint of co-morbid insomnia (14). Alternatively, 17-69% of insomnia patients hold sufficient diagnostic criteria for co-morbid OSA (14). Patients suffering from Co-Morbid Insomnia and Sleep Apnea (COMISA) experience the additive detrimental night time and daytime symptoms of each disorder. Furthermore, medical specialists are faced with difficult diagnostic and treatment decisions, and typically effective treatments for each disorder are impaired (14).

The recommended treatment for moderate and severe OSA is Continuous Positive Airway Pressure (CPAP) therapy (15, 16). Although CPAP effectively stabilizes the upper airway and improves other manifestations of OSA (17), patient acceptance and long-term adherence to CPAP remains a significant barrier to treatment. For example, a review of 12 studies found that 29-83% of OSA patients use CPAP for fewer than the minimum recommended four hours per night (18). Importantly, recent research indicates that OSA patients with symptoms of co-morbid insomnia are less likely to accept and use CPAP therapy (19-24), compared to OSA patients without insomnia symptoms. Therefore, several research groups have suggested that COMISA patients' insomnia should be treated initially, to increase subsequent acceptance and use of CPAP therapy (14, 19, 25-27).

The recommended treatment for insomnia is Cognitive and Behavioral Therapy for Insomnia (CBT-i) (28, 29). CBT-i is a non-pharmacological, multi-component therapy which aims to reduce and modify the psychological, behavioral and physiological processes and factors that are believed to perpetuate the insomnia condition, thereby resulting in improvements which persist beyond the cessation of therapy (29-31). Preliminary evidence suggests that CBT-i is an effective treatment for insomnia in the presence of co-morbid OSA (32-34). It is expected that initially treating COMISA patients with CBT-i will result in

durable improvements in insomnia symptoms and sleep parameters, which will increase subsequent CPAP acceptance and long-term use.

Although COMISA is a prevalent and debilitating condition, little is known about how the disorder develops or is most effectively treated. Currently, the most highly recommended treatment involves a combination of CBT-i to improve night time sleep parameters before CPAP is initiated to treat the OSA. To the current researchers' knowledge, this is the first high quality randomized controlled trial comparing the effectiveness of CPAP-alone, to combined CBT-i and CPAP in the COMISA population.

The primary hypothesis predicted that compared to treatment with CPAP-alone, the sequential delivery of CBT-i and CPAP therapy would result in increased average nightly objective CPAP adherence. Furthermore, an additional primary hypothesis predicted that treatment with CBT-i and CPAP therapy would lead to greater improvements in objective sleep efficiency from baseline to 6-month follow-up, compared to treatment with CPAP-alone. Secondary hypotheses predicted that compared to treatment with CPAP-alone, the combination of CBT-i and CPAP therapy would lead to greater improvements in insomnia symptoms (sleep diary and questionnaire outcomes) and additional objective sleep parameters (sleep onset latency, wake after sleep onset, and total sleep time) by 6-week follow-up, and the final 6-month follow-up. A secondary CPAP hypothesis predicted that participants in the CBT-i condition would show greater rates of immediate CPAP acceptance (i.e. would begin using CPAP at home), compared to the control condition. Finally, a per-protocol hypothesis predicted that among these participants who immediately accepted CPAP therapy, objective nightly CPAP adherence would be significantly higher in the CBT-i than the control condition.

6.3 Methods

6.3.1 Participants

NB: This section is largely repeated from Chapter 4.

Participants included 145 adults (Age *y M* = 58.22, *SD* = 9.91; 55.2% Male) with psychologist-diagnosed insomnia, and sleep physician-diagnosed OSA (AHI ≥ 15), who were recommended for a trial of CPAP therapy. Participants were recruited through sleep and respiratory specialists working at two sites in Australia: the Adelaide Institute for Sleep Health, Flinders Medical Centre, Adelaide, South Australia, and The Prince Charles Hospital, Brisbane, Queensland, Australia, between November 2013 and April 2016 (Figure 6.1). Participants were recruited through sleep laboratories, and an online screening platform, at each site. Clinical patients attending sleep laboratories who indicated insomnia symptoms, and had OSA (AHI ≥ 15) were considered for the trial. The online screening arm included three tiers of screening (questionnaires, simple home-based apnea link study, and home-based diagnostic sleep study) before prospective participants attended an appointment with a sleep physician for consideration for the trial.

Inclusion criteria were; appropriate age range (18 – 75 years), a diagnosis of insomnia performed by a registered psychologist (see below), AHI ≥ 15 according to full night Polysomnographic (PSG) recording, a clinical diagnosis of OSA and recommendation of CPAP therapy by a sleep physician, patient willingness to trial CPAP, and absence of any of the following; any additional sleep disorder (e.g. rapid eye movement behavior disorder, restless leg syndrome, delayed sleep/wake phase disorder, etc.) or medical disorder which required immediate treatment, any significant memory, perceptual or behavioral disorder, any neurological deficits which prevented self-administration of the CPAP equipment, any significant language barriers, or any participants who resided so remotely from the clinic to preclude follow-up visits.

Following a physician diagnosis of OSA and recommendation of CPAP therapy, prospective participants attended a session with a registered psychologist who assessed sleep diary and questionnaire data, to perform a diagnosis of insomnia. Sleep diary diagnostic criteria included one of the following; average weekly sleep onset latency of > 30 minutes, *or* wake after sleep onset of > 45 minutes, *or* sleep efficiency of < 75%, *and* at least one associated daytime impairment (e.g. sleepiness, fatigue, poor concentration, etc.). Participants were required to have held these insomnia symptoms for at least 6 months to fulfil diagnostic criteria.

6.3.2 **Design**

A graphical representation of the study protocol is presented in Figure 6.1. This study used an experimental 2 (treatment condition: CBT-i + CPAP, Control + CPAP) x 4 (time: baseline, 6-weeks, 3-months, and 6-months post-randomization) mixed factorial design to evaluate the efficacy of a combination of CBT-i and CPAP for the treatment of COMISA patients, compared with CPAP treatment alone. All participants started CPAP therapy following the 6-week follow-up, and objective adherence data were downloaded after 1-week of use, and at 3- and 6-months follow-up.

Changes in multiple night time and daytime symptoms of insomnia and OSA were assessed during the two treatment phases (CBT-i phase: baseline to 6-weeks, CPAP phase: 6-weeks to 6-months) and compared between the two treatment conditions (treatment condition: CBT-i + CPAP, Control + CPAP). Changes in multiple night time and daytime symptoms were also assessed during the whole study protocol (Baseline to 6-months) and compared between the two conditions. As this study aimed to compare the novel CBT-i + CPAP treatment approach, to the current treatment as approach (i.e. short waiting period before initiating CPAP), no placebo control was utilized. 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), and the External Request Evaluation Committee (Department of Human Services, Australia).

6.3.3 **Measures**

NB: With exception of the 'CPAP adherence' outcome, this section is largely repeated from Chapter 4.

6.3.3.1 The OSA50

The OSA50 (Appendix g) is a 4-item self-report questionnaire (assessing waist circumference, snoring behavior, witnessed apneas, and age) used to predict a diagnosis of OSA, which was used as an online screening questionnaire (35, 36). Scores range from 0 – 10, with higher scores indicating greater likelihood of OSA. Participants scoring 5 or above proceeded to the next stage of screening.

6.3.3.2 The Insomnia Severity Index (ISI)

The ISI (Appendix A) is a 7-item self-report scale used to assess global insomnia severity (37), which was used as a screening and secondary outcome measure. 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 (37), and has been widely used in the COMISA population (14). To be considered for the trial, participants were required to indicate a total score of at least 14, and a composite score of at least 4 on the first three 'sleeping difficulty' items of the ISI. The sum of these first three items was also calculated at each follow-up, to create a ISI sub-score, to examine changes in 'sleeping difficulty' insomnia symptoms. Rates of insomnia response and remission were also analysed following the completion of each treatment phase. Insomnia responders were defined as participants who experienced at least an 8-point reduction in ISI from baseline to 6-weeks,

and baseline to 6-months. Insomnia remitters were defined as participants who scored less than 8 by 6-weeks or 6-months.

6.3.3.3 Overnight Apnea Link

Eligible website-screened participants were further screened with an overnight apnea link device. The Apnea link (ResMed Corporation, Australia) continuously measures blood oxygen saturation and nasal pressure throughout the night, and has adequate psychometric properties in predicting OSA (35, 38). A total oxygen desaturation index of 10 or greater (indicating probable OSA) was used as a cut-off to progress to further screening.

6.3.3.4 7-Day Sleep/Wake Diaries

Sleep diaries (Appendix I) were used as an insomnia diagnostic tool, and a secondary outcome measure. Participants indicated their bed time, sleep onset latency, wake after initial sleep onset, and total sleep time each night for one week. Sleep efficiency was also calculated by dividing average weekly total sleep time by time in bed, and multiplying by 100. Participants completed 7-day sleep diaries at baseline, during CBT-i, and at 6-week, 3-month, and 6-month follow-ups.

6.3.3.5 Polysomnographic (PSG) Sleep Studies

All participants completed a full-night PSG study (Compumedics, Melbourne, Australia) before randomization to confirm a diagnosis of OSA. Participants also completed PSG studies at home during baseline, 6-weeks, and at 6-months, and in sleep laboratories for CPAP titration studies. During each sleep study, 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 (chest and abdomen), and two channels to record leg movements. A finger oximeter was attached to continuously record oxyhaemoglobin saturation, a nasal cannula for nasal pressure, and an oro-nasal thermistor to record oro-nasal airflow. Trained sleep technicians and scorers (blind to participants'

condition) scored studies according to AASM 2007 criteria with additional 2009 ASTA commentary (39, 40). Participants also completed sleep diaries during their laboratory and home-based PSG studies to indicate time in bed and final rise times, and perceived sleep onset, total sleep, and wake after sleep onset parameters. Technicians used a combination of these self-reported bed/rise times and objective physiological data (finger oximeter, artefact, position, nasal cannula attachment) to estimate 'time in bed' parameters.

6.3.3.6 The Epworth Sleepiness Scale (ESS)

The ESS (Appendix E) is an 8-item self-report scale measuring daytime sleepiness (41), which was completed during each follow-up. Participants are asked to report their likelihood of falling asleep in 8 situations (e.g. "sitting and reading", "as a passenger in a car for an hour without a break"). Scores range from 0-24 with greater scores indicating more daytime sleepiness. The ESS has adequate reliability, internal consistency (42), and some discriminability of the excessive daytime sleepiness associated with narcolepsy (43). A cut-off of 10 or less was used to indicate a normalized level of daytime sleepiness at 6-week, and 6-month follow-up.

6.3.3.7 The Flinders Fatigue Scale

The Flinders Fatigue Scale (Appendix B) is a 7-item self-report questionnaire which measures feelings of fatigue (44), which was completed during each follow-up. Participants answer 6 questions such as "was fatigue a problem for you?" on a scale of 0 (not at all) to 4 (extremely). One additional item asks about the experience of fatigue at 7 possible times throughout the day, with 1 point awarded for each indicated time. Possible scores on the flinders fatigue scale range from 0 to 31, with higher scores indicating more daytime fatigue. The flinders fatigue scale has adequate internal consistency, ability to discriminate between good and poor sleepers, and discriminant validity in comparison to a measure of sleepiness (44-46).

6.3.3.8 The Daytime Feelings and Functioning Scale

The Daytime Feelings and Functioning Scale (Appendix C) is a 12-item self-report measure of impaired daytime feelings and functioning experienced over the past two weeks (45), which was completed during each follow-up. Items such as "*had a reduced quality of life"*, and *"felt irritable"* are summed 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 daytime functioning (45, 47).

6.3.3.9 The Depression, Anxiety and Stress Scale

The Depression, Anxiety and Stress Scale (Appendix D) is a 21-item self-report questionnaire which measures feelings of depression, anxiety and stress (48), which was completed during each follow-up. Three sub-scales range from 0 – 42, with higher scores indicating greater depression, anxiety and stress. These sub-scales have been found to have adequate internal consistency, convergent and discriminant validity when compared to other measures of depression, anxiety, and stress (49, 50).

6.3.3.10 CPAP Adherence Outcomes.

All participants were provided with CPAP equipment free of charge, from the CPAP-setup appointment to the 6-month review appointment. In-built modems were used to automatically upload daily adherence data to a password-protected online cloud (encore anywhere, and encore pro, Philips Respironics, USA). CPAP adherence data were downloaded in two ways. For the primary analysis of average CPAP adherence between conditions, objective CPAP adherence data were downloaded at the final 6-month review, and average nightly use was calculated for each participant. Secondly, CPAP data were also downloaded at several repeated time points throughout the trial to examine temporal changes in average CPAP adherence. These included CPAP follow-ups after one-week of use, at 3-

months follow-up, and 6-months follow-up (representing immediate, short-term, and long-term use, respectively).

6.3.4 Treatment Interventions

Participants were randomly allocated to initially receive either CBT-i, or a no insomnia treatment control condition. Following this, each participant began treatment with CPAP therapy.

6.3.4.1 Cognitive Behavior Therapy for Insomnia (CBT-i).

NB: This section is largely repeated from Chapter 4.

CBT-i was administered by registered, experienced psychologists, over the course of four-weekly 45-minute individual or small-group sessions (Appendix k and l include the fidelity checklists, and a Table detailing the components, setting, and fidelity checks related to CBT-i). Group treatment sessions were received by 11.4% of participants, 71.4% received individualized treatment sessions, and 17.1% received a combination of group and individualized sessions. Group treatment sessions were arranged where possible to economize on treatment expense, but this was not practical in many cases. Change in the ISI scores from baseline to 6-week follow-up did not differ between these delivery types (F (2, 65.71) = 0.451, p = .639). Previous research has also found that group-based and individually administered CBT-i leads to comparable insomnia improvements (51). CBT-i components included bedtime restriction therapy, basic information about sleep, sleep hygiene information, cognitive therapy, and relapse prevention.

6.3.4.2 Materials accompanying CBT-i.

NB: This section is largely repeated from Chapter 4.

To ensure treatment fidelity, therapists were provided with a structured manual, session checklist, and power-point slides, and initially underwent additional training from a highly experienced sleep psychologist. Each participant undergoing CBT-i was provided with

a booklet which reviewed concepts which were discussed during each week of therapy. Participants completed 7-day sleep diaries and an ESS after each week of CBT-i. This information was used by the therapist during the following week's session to titrate the amount of bedtime restriction applied during the subsequent week.

6.3.4.3 Protocol for Bedtime Restriction Therapy

NB: This section is largely repeated from Chapter 4.

Bedtime parameters were restricted to match participants' baseline total sleep time measured via 7-day sleep diaries. However, psychologists were also instructed to modify these normal bedtime restriction techniques based on observations of excessive daytime sleepiness, to avoid any dangerous levels of sleepiness or increased risk of accidents. These modifications were thought to ensure participants' safety, and more adequately reflect 'real world' CBT-i practices suitable for COMISA patients. Participants' bedtime parameters were extended by 15 – 30 minutes on subsequent weeks if their previous week's sleep efficiency scores were greater than 85%. If their sleep efficiency scores were lower than 85%, current bedtime parameters continued for the following week.

6.3.4.4 Therapists

NB: This section is largely repeated from Chapter 4.

Therapists included 7 registered Psychologists with experience in CBT-i. Therapists attended a training meeting in Adelaide, South Australia prior to the commencement of the trial, and maintained contact throughout the trial to preserve treatment fidelity. Participants completed treatment credibility and satisfaction questionnaires during the third week of therapy (Appendix j). A one-way analysis of variance indicated that treatment credibility and satisfaction did not differ between therapists (p = .371).

6.3.4.5 CBT-i compliance and Credibility

NB: This section is largely repeated from Chapter 4.

Of the 72 participants randomized to receive CBT-i, 7 (9.7%) did not complete all four CBT-i sessions. Two participants withdrew during the baseline assessment and randomization process, two participants cancelled sessions due to sickness, one participant did not attend the final session due to discontinuation of bedtime restriction therapy, and two participants cancelled the fourth session and did wish to re-book.

The main behavioral component of CBT-i was bedtime restriction therapy. Bedtime restriction therapy was formally discontinued in five participants during the CBT-i protocol; two participants had to remain lying down in bed for extended periods due to health reasons, one participant found it unhelpful and refused to comply, one participant was responsible for caring for their partner and was required to stay in bed, and one was experiencing increased anxiety about sleep due to the bedtime restriction protocol.

During the third CBT-i session, participants also completed a brief questionnaire which assessed perceptions of treatment credibility. On average, participants perceived that CBT-i was a highly logical treatment (84.9%), and reported high levels of confidence (91.5%), and expectations that CBT-i would result in improvement in their insomnia symptoms (72.0%).

All CBT-i sessions were audio recorded and a randomly selected 10% of sessions were reviewed by an independent psychologist with extensive experience working with insomnia patients, to perform fidelity checks. Checklists were completed by the independent psychologist to confirm adequate treatment fidelity (see Appendix k).

6.3.4.6 Continuous Positive Airway Pressure (CPAP) Therapy

CPAP was introduced during laboratory CPAP titration studies immediately after the 6-week follow-up, by experienced sleep technicians (blind to participants' study condition). Following the CPAP titration study, participants returned to sleep clinics or CPAP suppliers (Air Liquide, Australia) for appointments with sleep physicians and CPAP nurses/technicians

to be coached and instructed on the use of their CPAP equipment. Participants returned to clinics 1-week, and 4-weeks after starting CPAP, to discuss and overcome any side-effects/acute issues with CPAP equipment. All CPAP nurses/technicians associated with CPAP treatment in the second phase of the trial were blind to participants' treatment condition.

6.3.5 Procedure

Following completion of baseline questionnaires, sleep diaries, overnight sleep studies, and a psychologist-diagnosis of insomnia, participants were randomized to either the CBT-i or control condition. Randomization was undertaken using minimization (MinimPy (52)) to ensure balance between groups in potential confounders. Randomization was independently conducted by the Pharmacy Department of the Repatriation General Hospital in South Australia. Participants were stratified according to; site (Adelaide, or Queensland), gender (M or F), age (>, or < 50 years), OSA severity (AHI >, or < 30), insomnia severity (ISI >, or < 22), and prior CPAP use (yes, or no). Following the four-weekly CBT-i sessions (or equivalent waiting period), participants completed the questionnaire battery, 7-day sleep diary, and home-based PSG at 6-week follow-up. All participants then returned to sleep laboratories to undergo overnight CPAP titration studies, and subsequent review appointments with sleep physicians. Following these appointments, participants were set up with their own CPAP devices by CPAP nurses/technicians. Participants' objective average CPAP use was downloaded after 1-week of CPAP use, and 3- and 6-months. The primary outcome was average CPAP use from CPAP-setup to 6-month review. However, to examine the effect of time on CPAP use, three repeated CPAP adherence measures were also calculated for average use after 1-week (M = 7.3 days included), from 1-week to the 3-month review (M = 24.1 days included), and from the 3-month to the 6-month review (M = 93.3 days included). The average number of days of CPAP use, were not significantly different

between conditions during any follow-up (all $p > .05$). Questionnaires, and sleep diaries were completed at 3- and 6-month post-randomization. During the final 6-month follow-up, participants also completed a home-based PSG (while wearing CPAP devices if they were habitually using CPAP at this time). Rates of CPAP use during the 6-month PSG did not differ between the CBT-i (86.89%) and control (76.27%) participants ($\chi^2(1) = 2.26$, $p = .133$). Participants attended review appointments with sleep physicians, and returned CPAP equipment, before returning to standard clinical treatment protocols. Participants in the control condition were subsequently offered CBT-i, however their follow-up data were not recorded.

6.3.6 Participant Screening, Flow, and Attrition

Participant retention and flow numbers are presented in Figure 6.1. In total 16 participants (11.03% of those randomized) withdrew/were lost to follow-up during the study, including 7 from the CBT-i condition and 9 from the control condition (Fisher's Exact Test $p = .792$).

6.3.7 Treatment Sample Characteristics

Demographic and disease characteristics of each condition are presented in Table 6.1. There were no significant differences in any demographic, disease severity, or outcome measures, between conditions at baseline.

6.3.8 Overview of Data Analysis

An independent statistical analysis plan (Appendix M) detailing the primary and secondary outcomes, hypotheses, and analytical methods was signed by the chief investigator and statistician, prior to unmasking and analysis of the data. All data were analysed with SPSS version 22 (IBM Statistics, USA). The primary outcome, average nightly CPAP adherence between groups, was analysed with an independent samples t-test. The secondary outcomes, including; changes in diary-measured and objective sleep parameters, and

questionnaire outcomes were analysed with linear mixed models analyses on an intention to treat basis. Changes in these outcomes were assessed during the whole study period, and during each independent treatment phase of the study (i.e. the CBT-i, and CPAP phases). Finally, changes in CPAP adherence over time (immediate, short-term, long-term) were analysed with linear mixed model analyses. Bonferroni corrections were built into each model, to control for the multiple planned comparisons (e.g. change in ISI during CBT-i, change in ISI during control, interaction between conditions and time on ISI during CBT-i phase, etc.). Differences in rates of immediate CPAP rejection between conditions was also analysed with a Fischer's Exact Test. Differences in rates of insomnia response, and remission, and normalized sleepiness were analysed with chi-squared analyses.

Missing data were categorized as missing at random, and missing completely at random according to pre-defined criteria (53). Rates of missing questionnaire, CPAP adherence and objective sleep study outcomes were not significantly different between groups at any outcomes (all $p \geq .3$). Missing 7-day sleep diaries were more likely to occur in the control group (20.5% missing) at 6-week follow-up, as participants in the CBT-i condition (6.9% missing) were habitually completing sleep diaries during each week of CBT-i, and diary data from the fourth week of CBT-i was imputed for a small number of participants who missed the 6-week diary outcome ($\chi^2(1) = 5.641$, $p = .018$). Rates of missing diary data at the remaining follow-ups did not differ significantly between conditions (all $p \geq .10$).

Data were inspected for normality and outliers, and primary and secondary analyses were performed on transformed and un-transformed data. A small handful of single positive outliers were observed for diary-measured sleep onset latency, and wake after sleep onset, objective sleep onset latency, and AHI. These single outliers were assigned the next highest score. Positively skewed distributions (skewness ≥ 1) were observed for objective wake after

sleep onset and sleep onset latency, diary-measured wake after sleep onset and sleep onset latency, AHI, and anxiety. Negatively skewed distributions were observed for objective sleep efficiency. Logarithmic transformations were undertaken, which resulted in normally distributed data (Skewness < 1) for each of these variables. Following correction of outliers and logarithmic transformations, all Linear Mixed Model analyses were re-run and interaction terms examined. As inferential statistics of the main outcomes of interest remained largely unchanged between the corrected and uncorrected data, the initially observed data were reported to facilitate understanding of descriptive statistics. CPAP adherence outcomes revealed bi-modal distributions when including the participants who immediately rejected CPAP therapy (and received an average adherence score of zero at each subsequent follow-up). Therefore, a secondary per-protocol analysis of CPAP adherence among only participants who began using CPAP at home was also undertaken.

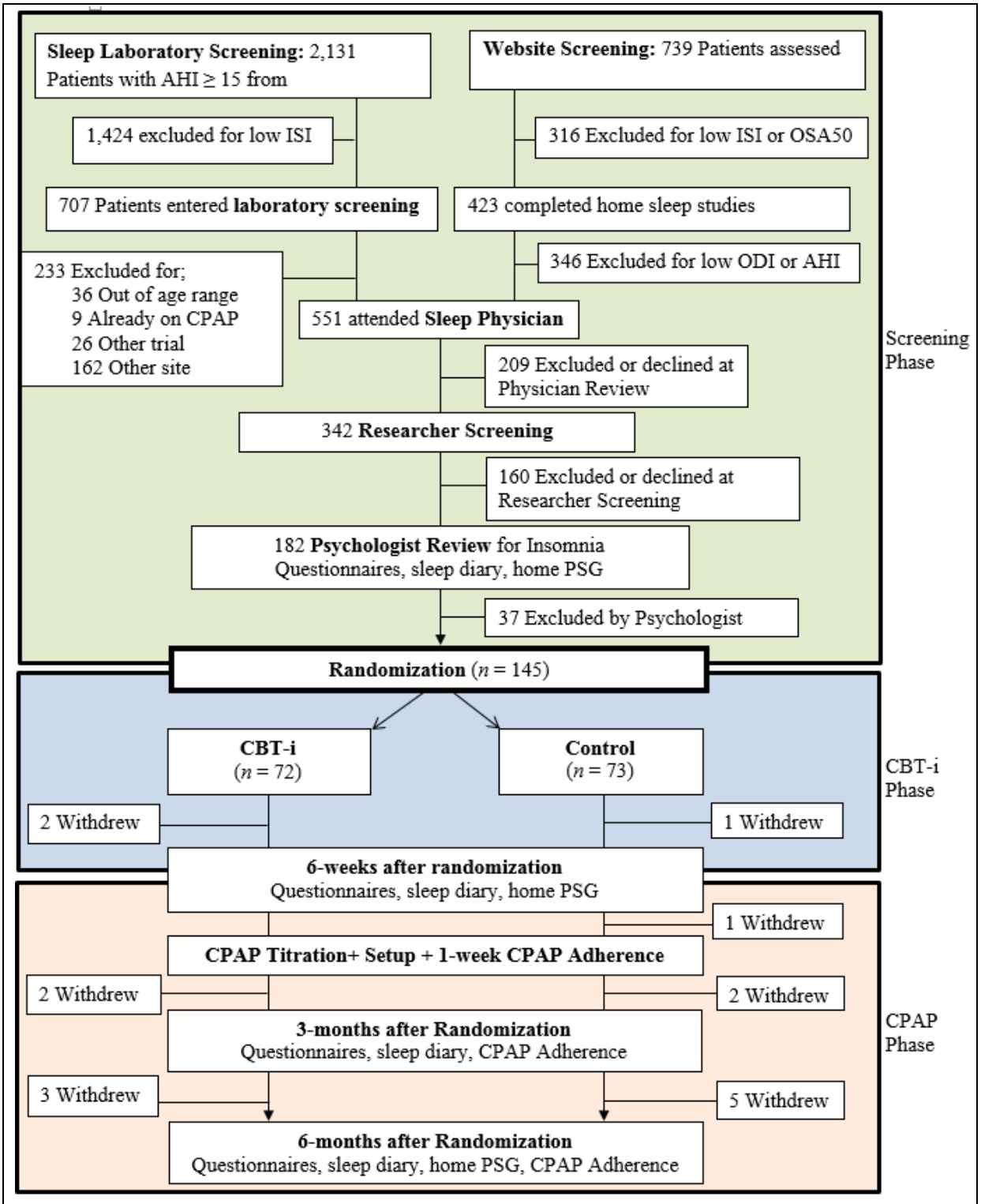

Figure 6.1 Participants screening and study protocol diagram. AHI = Apnea/Hypopnea Index, CPAP = Continuous Positive Airway Pressure, CBT-i = Cognitive and Behavioral Therapy for Insomnia, PSG = Polysomnography, ISI = Insomnia Severity Index.

Table 6.1 Baseline Characteristics of Participants

Characteristic/Outcome	CBT-i M (SD)	Control M (SD)	t / χ^2	p
Age, y	59.12 (9.92)	57.33 (9.89)	-1.086	.279
Sex, No. (%), Male	40 (55.6)	40 (54.8)	.008^	.927
Site, No. (%) Adelaide	47 (65.28)	48 (65.75)	.004^	.952
Body Mass Index	34.45 (6.34)	36.19 (6.46)	1.623	.107
Questionnaire Outcomes				
Insomnia Severity Index	18.49 (5.35)	17.92 (4.68)	-.681	.497
Epworth Sleepiness Scale	8.92 (5.00)	9.68 (4.55)	.968	.335
Flinders Fatigue Scale	15.96 (6.83)	15.92 (5.79)	-.39	.969
Depression	14.53 (11.39)	14.63 (12.77)	.051	.959
Anxiety	10.22 (8.75)	8.93 (7.87)	-.934	.352
Stress	14.81 (9.36)	15.10 (9.57)	.185	.854
Overnight Sleep Study				
Total Sleep Time, min	375.21 (86.09)	358.36 (87.06)	-1.167	.245
Wake after sleep onset, min	95.66 (63.28)	82.07 (49.51)	-1.438	.153
Sleep Onset Latency, min	32.46 (63.71)	29.17 (33.22)	-.390	.697
Sleep Efficiency, %	74.32 (14.06)	74.99 (11.88)	.310	.757
Apnea/Hypopnea Index	33.17 (19.83)	35.83 (23.87)	.722	.471
Arousal Index	32.72 (16.98)	35.65 (22.25)	.886	.377
Sleep Diary				
Total sleep time, min	346.10 (76.97)	353.02 (79.44)	.539	.590
Time in bed, min				
Sleep onset latency, min	56.09 (49.36)	48.39 (33.81)	-1.097	.274
Wake after sleep onset, min	95.02 (60.92)	102.90 (74.33)	.698	.486
Sleep efficiency, %	67.21 (12.18)	68.46 (14.32)	.564	.573

^ Chi-square statistic, CBT-i = Cognitive and Behavioral Therapy for Insomnia, TAU = Treatment as Usual.

6.4 Results

6.4.1 CPAP adherence

The effect of condition on average nightly CPAP use from CPAP-setup to 6-months was analysed with an independent samples t-test. Two participants from the CBT-i condition withdrew during baseline measures/randomization, and were excluded from the analysis. Average nightly CPAP use from CPAP-setup to 6-months was 58.5-minutes higher (*CI* = 52.8) in the CBT-i (*M* = 263.6 *SD* = 166.2) than the control (*M* = 205.1, *SD* = 153.4) condition ($t(141) = -2.19$, $p = .03$).

No significant condition by time interaction on average CPAP adherence was observed (Table 6.2, Figure 6.2). This interaction was analysed with a linear mixed model analysis, with 1-week, 3-month, and 6-month adherence intervals for each participant. Participants in both conditions showed gradually decreasing average CPAP adherence over the three CPAP follow-up periods (both $p < .01$). Although no interaction was observed, the average difference in adherence between conditions was successively greater during each follow-up period (32.3-minute difference at 1-week, 57.3-minute difference at 3-months, and 63.9-minute difference at 6-months).

Participants in the CBT-i condition were more likely to begin using CPAP therapy at home following the laboratory titration night (98.6%), compared to participants in the control condition (89.0%; Fischer's $p = .034$). In fact, only one participant in the CBT-i condition immediately rejected CPAP, after instruction to do so by their sleep physician, based on a decreased AHI during two diagnostic sleep studies after the initial randomization sleep study. An additional independent samples t-test revealed that among these participants who began using CPAP therapy at home, there was no significant difference in average CPAP use from CPAP setup to 6-months between the CBT-i (*M* = 267.45, *SD* = 164.29), and control (*M* = 230.34, *SD* = 143.35) conditions ($t(132) = -1.39$, $p = .167$). When examining only the

participants who initially accepted CPAP, both conditions also showed decreasing CPAP adherence over time (both $p \leq .01$, Table 6.2), however no overall significant interaction effect was observed.

To examine rates of CPAP rejection over time in each condition, a Kaplan-Meier survival analysis was also undertaken (Figure 6.3). It was found that participants in the CBT-i condition showed a trend for significantly greater rates of CPAP use survival over time, compared to participants in the control condition ($\chi^2(1) = 2.93$, $p = .087$). In total, 76.4% of CBT-i participants, and 63% of control participants continued with CPAP therapy to the end of the study protocol. This difference approached statistical significance ($\chi^2(1) = 3.07$, $p = .08$).

Finally, an additional factorial ANOVA was undertaken to examine the effect of study site on average CPAP adherence, and the effect of site on differences in adherence between conditions (Figure 6.4). The interaction term revealed a trend, indicating that the difference between CBT-i and control conditions was greater at the Queensland site (M = 131.61 minutes greater in the CBT-i condition) compared to the South Australian site (M = 22.94 minutes greater in the CBT-i condition; $F(1,143) = 3.86$, $p = .051$). The main effect of site revealed that CPAP adherence was significantly greater among participants at the Queensland (M = 276.38 minutes) than the South Australian site (M = 213.72 minutes; $F(1,143) = 5.13$, $p = .025$).

An additional chi-square analysis was conducted to compare the proportion of participants in each condition who used CPAP for at least 4 hours per night on at least 70% of nights. There was no significant difference between rates of adequate CPAP use in the CBT-i (50%) and control (35.6%) conditions ($\chi^2(1) = 3.02$, $p = 0.082$).

Table 6.2 Changes in average (±CI) CPAP adherence, and objective sleep parameters between groups, during treatment.

CPAP Outcomes	**Cognitive and Behavioral Therapy for Insomnia**				**Control**				**1-week to 6-month Interaction**		**1-week to 3-month Interaction**		**3-month to 6-month Interaction**	
	1-week	3-months	6-months	Change	1-week	3-months	6-months	Change	*t*	*p*	*t*	*p*	*t*	*p*
Intention to Treat; CPAP Adherence (min)	294.53 (38.64)	295.06 (39.88)	255.28 (38.74)	-39.24*	262.19 (38.01)	237.77 (39.44)	191.36 (37.91)	-70.83^	1.81	.072	1.32	.189	0.35	.726
CPAP Acceptors; CPAP Adherence (min)	298.80 (37.08)	299.64 (38.48)	258.97 (37.19)	-39.82*	294.89 (38.43)	268.61 (40.38)	214.87 (38.31)	-80.02^	2.16	.032	1.36	.183	0.64	.520
Objective Sleep Outcomes									**Baseline to 6-month Interaction**		**Baseline to 6-week (CBT-i Phase)**		**6-week to 6-month (CPAP Phase)**	
	Baseline	6-weeks	6-month	Change	Baseline	6-weeks	6-month	Change	*t*	*p*	*t*	*p*	*t*	*p*
Sleep Efficiency (%)	74.32 (2.77)	79.27 (2.83)	81.33 (2.96)	7.01^	74.99 (2.73)	76.43 (2.76)	79.20 (2.99)	4.21*	1.17	.243	1.68	.094	-0.32	.750
Total Sleep Time (min)	375.21 (20.71)	355.15 (21.20)	380.92 (22.24)	5.71	358.36 (20.42)	363.79 (20.66)	355.41 (22.49)	-2.95	0.46	.644	-1.56	.121	1.96	.051
Sleep Onset Latency (min)	32.46 (8.14)	21.22 (8.37)	17.99 (8.83)	-14.47*	29.17 (8.02)	23.32 (8.13)	18.70 (8.98)	-10.47	-0.49	.628	-0.70	.486	0.17	.865
Wake After Sleep Onset (min)	95.66 (13.18)	69.69 (13.48)	63.77 (14.06)	-31.89^	82.07 (13.00)	77.18 (13.14)	69.31 (14.19)	-12.76	1.77	.078	-2.10	.037	0.18	.855

CPAP, Continuous Positive Airway Pressure, main effect of time in each condition * $p \leq .05$, ^ $p \leq .001$.

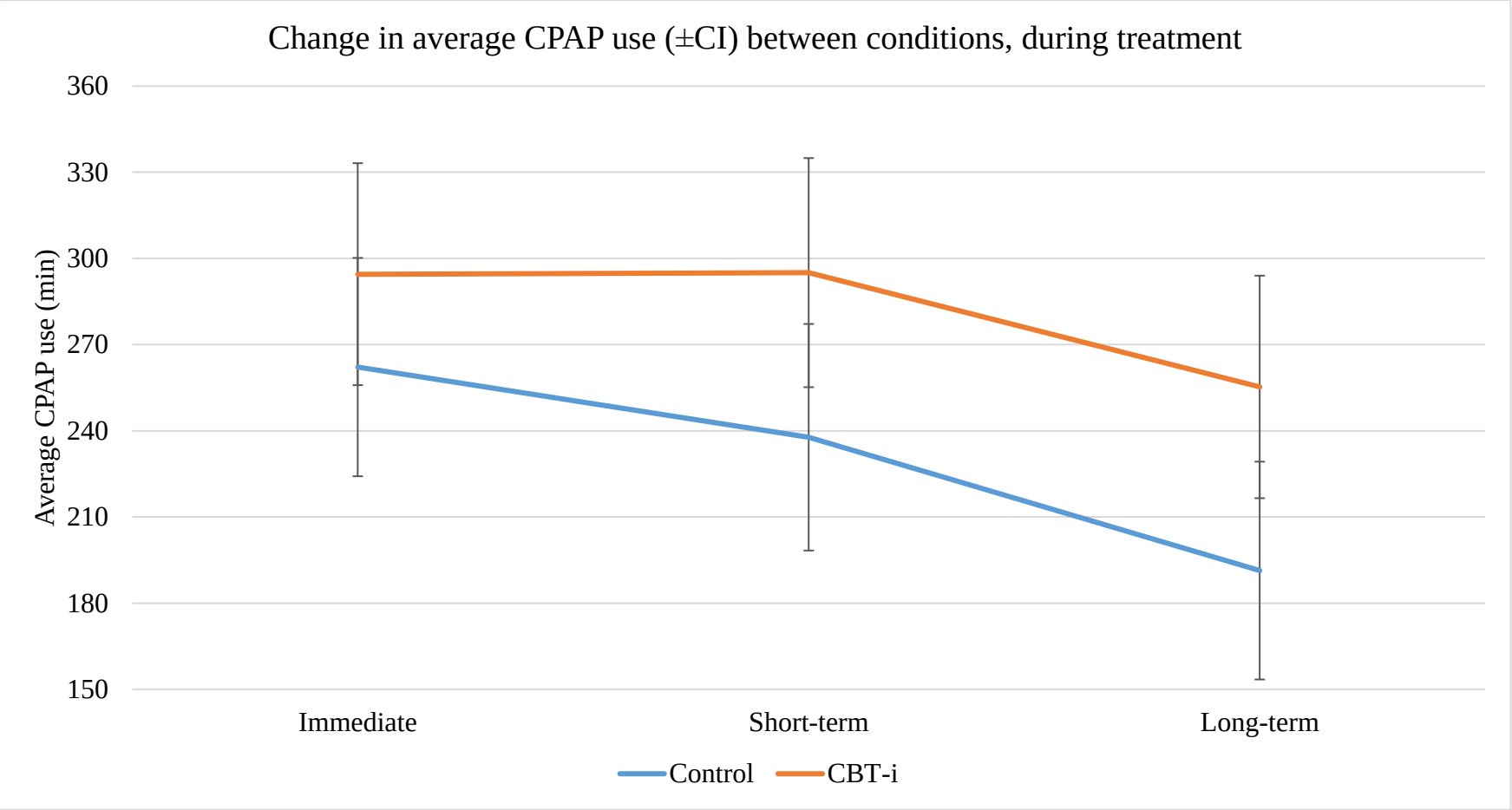

Figure 6.2 Changes in CPAP adherence, between groups during treatment (±95% CI).

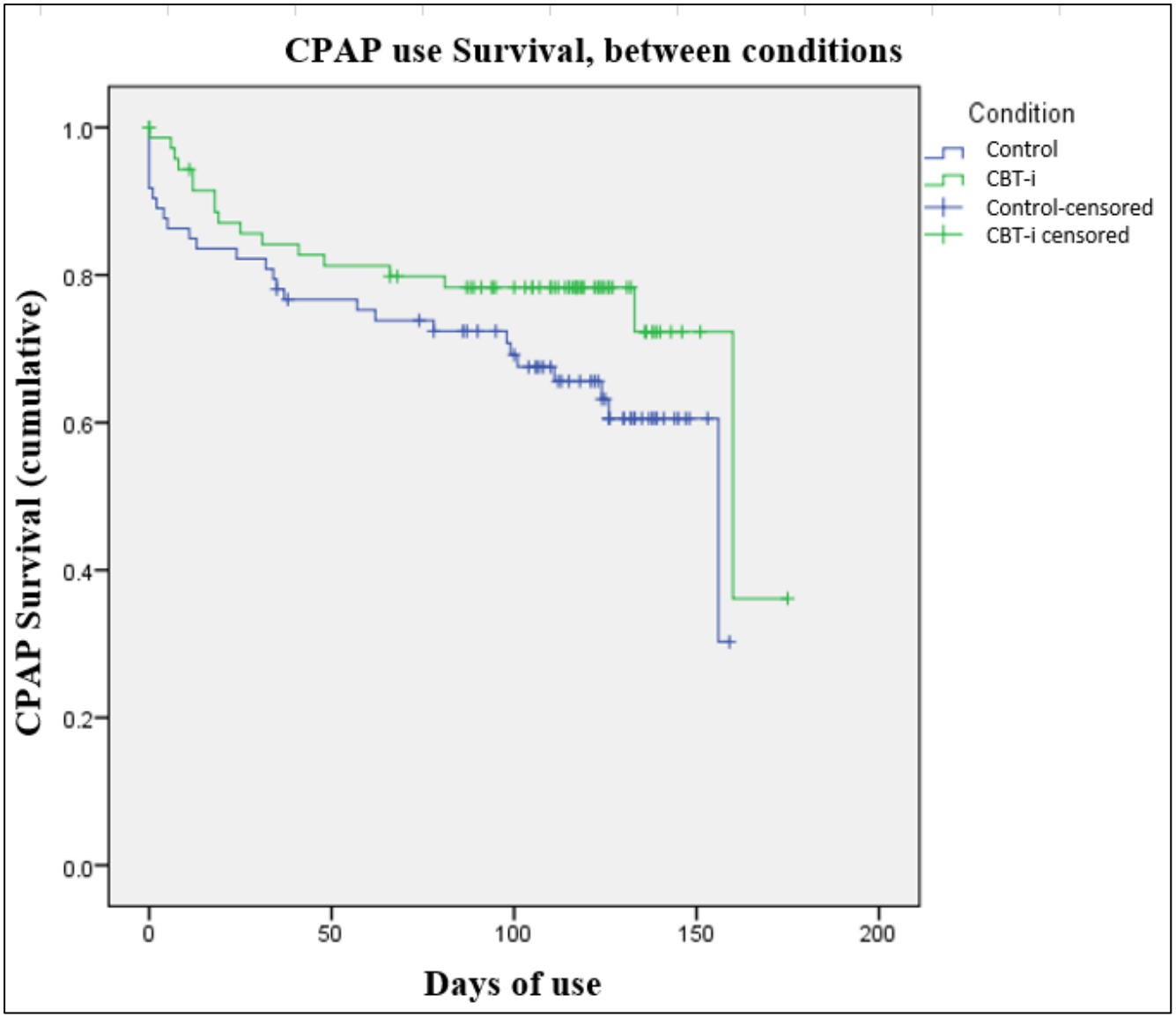

Figure 6.3 Survival analysis indicating rates of CPAP rejection over time, between conditions.

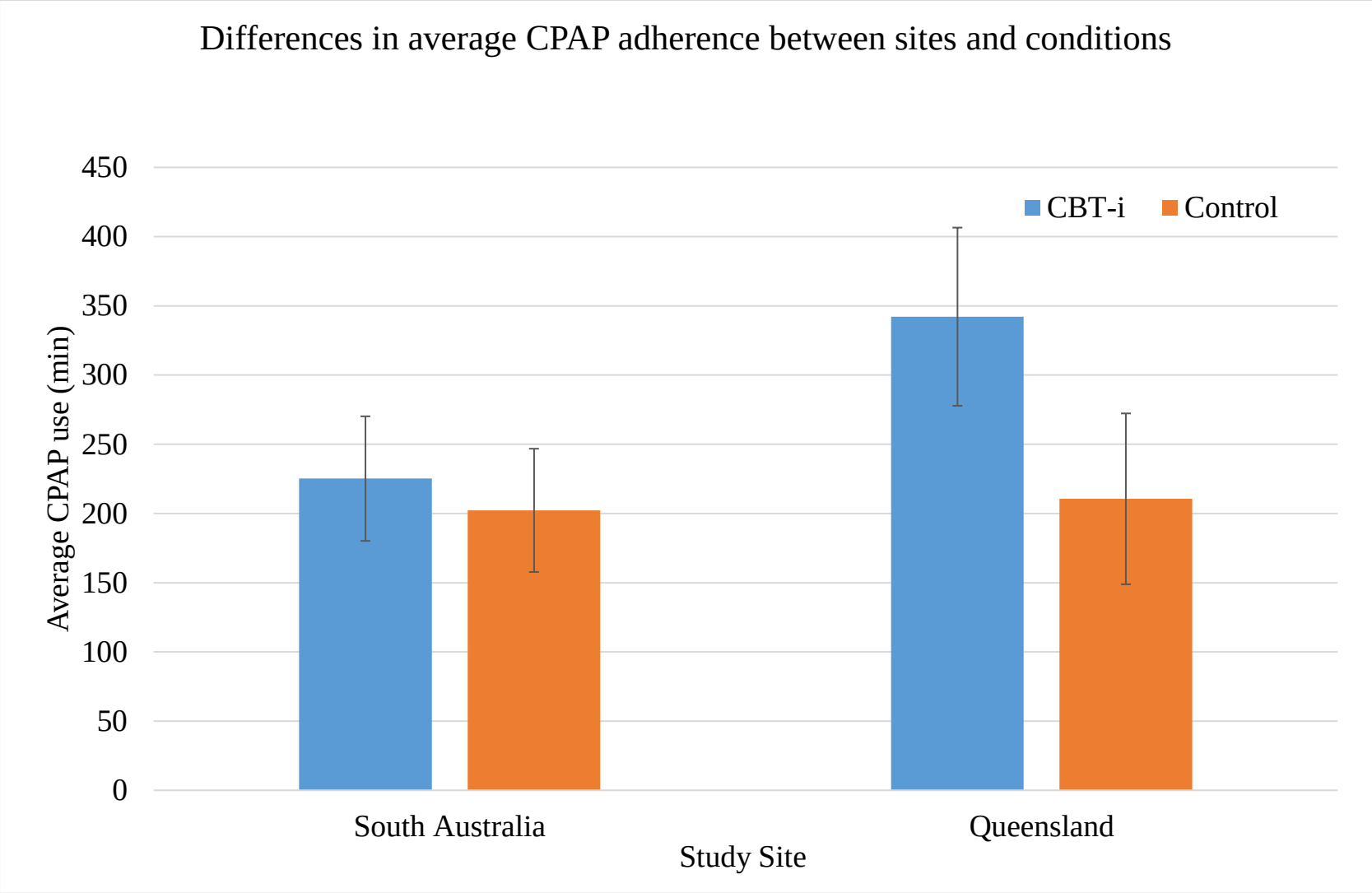

Figure 6.4 Effect of study site and condition on average CPAP adherence.

6.4.2 Effect of CPAP use on secondary symptoms

In this study, it is also possible to examine the effect of CPAP use on several secondary outcome measures during the CPAP phase of the trial. It would be presumed that those who used CPAP more, would show greater improvements of sleep and daytime measures. To examine the relationship between CPAP use and improvements in other sleep and daytime functioning outcomes among the whole sample, additional correlational analyses were undertaken. 'Change' variables were calculated for each sleep diary, questionnaire, and PSG outcome by subtracting 6-week data from 6-month data (i.e. change in symptoms during the CPAP phase of the study). Greater average CPAP use was weakly but significantly associated with greater improvement in diary-measured wake after sleep onset ($r(103) = -.271$, $p = .005$), and sleep efficiency ($r(103) = .267$, $p = .006$), the ISI ($r(115) = -.216$, $p = .02$), fatigue scale ($r(115) = -.344$, $p < .001$), sleepiness scale ($r(115) = -.226$, $p = .015$), dysfunctional beliefs and attitudes about sleep scale ($r(115) = -.269$, $p = .004$), and AHI ($r(113) = -.308$, $p < .001$). Trends for associations between greater CPAP use, and greater improvements in daytime feelings and functioning ($r(115) = -.167$, $p = .073$), and diary-measured total sleep time ($r(103) = .173$, $p = .08$) were also observed.

6.4.3 Objective Sleep Study Comparisons

6.4.3.1 Treatment Phase 1: CBT-i

Participants in the CBT-i condition experienced significantly greater improvement of objective wake after sleep onset from baseline to 6-week follow-up compared to the control condition (Table 6.2, Figure 6.8). Furthermore, a trend indicated that CBT-i participants experienced greater improvement of objective sleep efficiency during this treatment phase. The CBT-i condition did not show significantly greater improvements in any other objective sleep outcome during CBT-i (Table 6.2). After applying a Bonferroni correction to account for the 12 tests of interaction effects, probability levels of < .004 were required for objective

sleep outcomes to be considered statistically significant. At this corrected probability level, changes in objective wake after sleep onset no longer showed greater improvement among the CBT-i condition during the CBT-i phase of the trial.

6.4.3.2 Treatment Phase 2: CPAP therapy

From 6-weeks to 6-months, a trend for a significant interaction indicated that participants in the CBT-i condition experienced greater improvement of objective total sleep time, compared to participants in the control condition (Table 6.2, Figure 6.6). No other objective sleep outcomes showed a significant interaction during the CPAP treatment phase.

6.4.3.3 Full Protocol Analysis

The effect of combined CBT-i and CPAP, versus CPAP-only, on changes in objective sleep parameters from baseline to 6-month follow-up was analysed with linear mixed model analyses. Although participants in the CBT-i condition experienced significant improvement in objective sleep efficiency during treatment, these improvements were not significantly different to those observed in the control condition (interaction $p = .243$, Table 6.2, Figure 6.5). Participants in the CBT-i condition also experienced significant improvement in objective wake after sleep onset, and sleep onset latency from baseline to 6-month follow-up. However, these improvements were not significantly different from those observed in the control condition (Table 6.2, Figures 6.7 and 6.8). Objective total sleep time showed no significant change during treatment in either condition (Table 6.2, Figure 6.6).

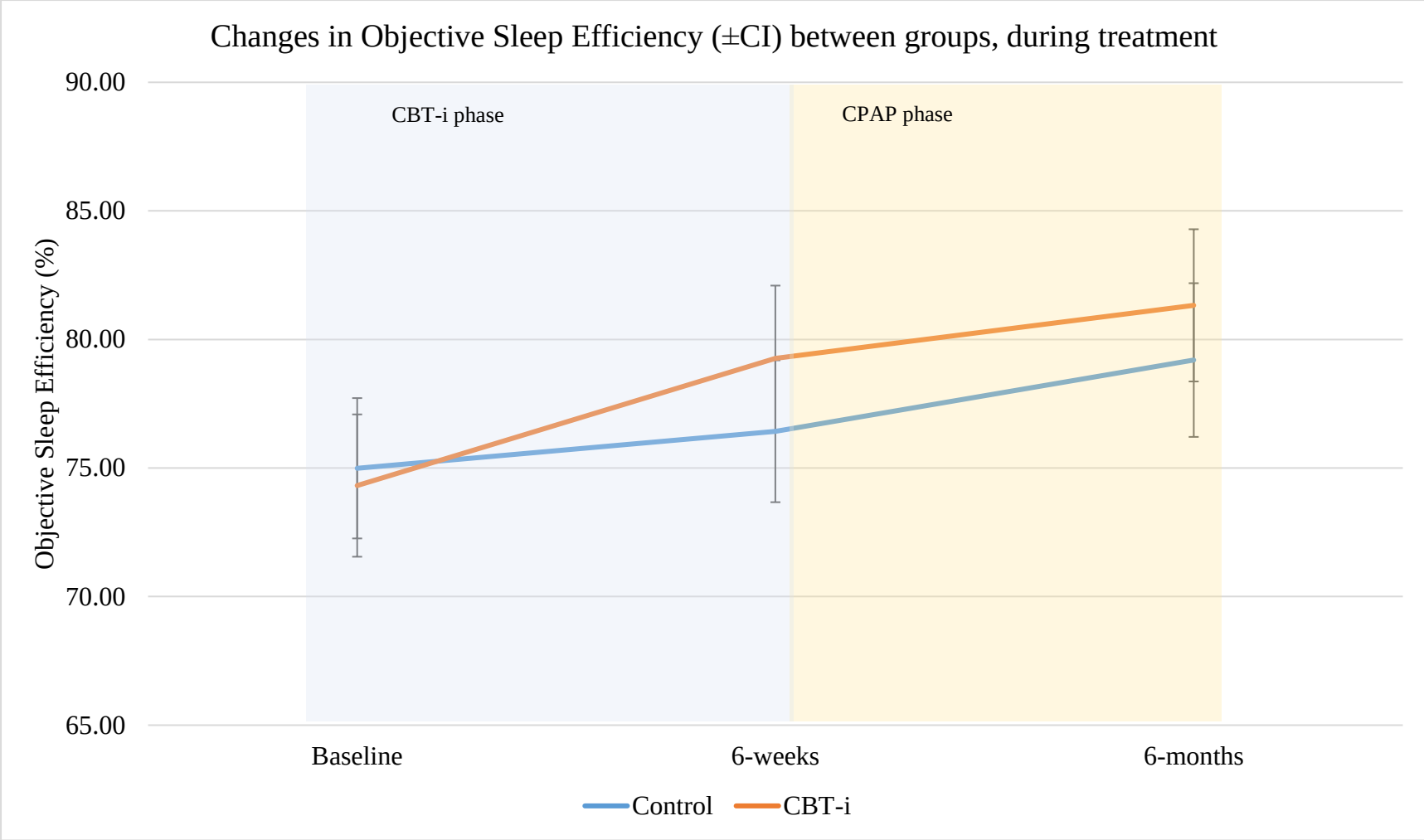

Figure 6.5 Changes in Objective Sleep Efficiency, between groups during treatment (±95% CI).

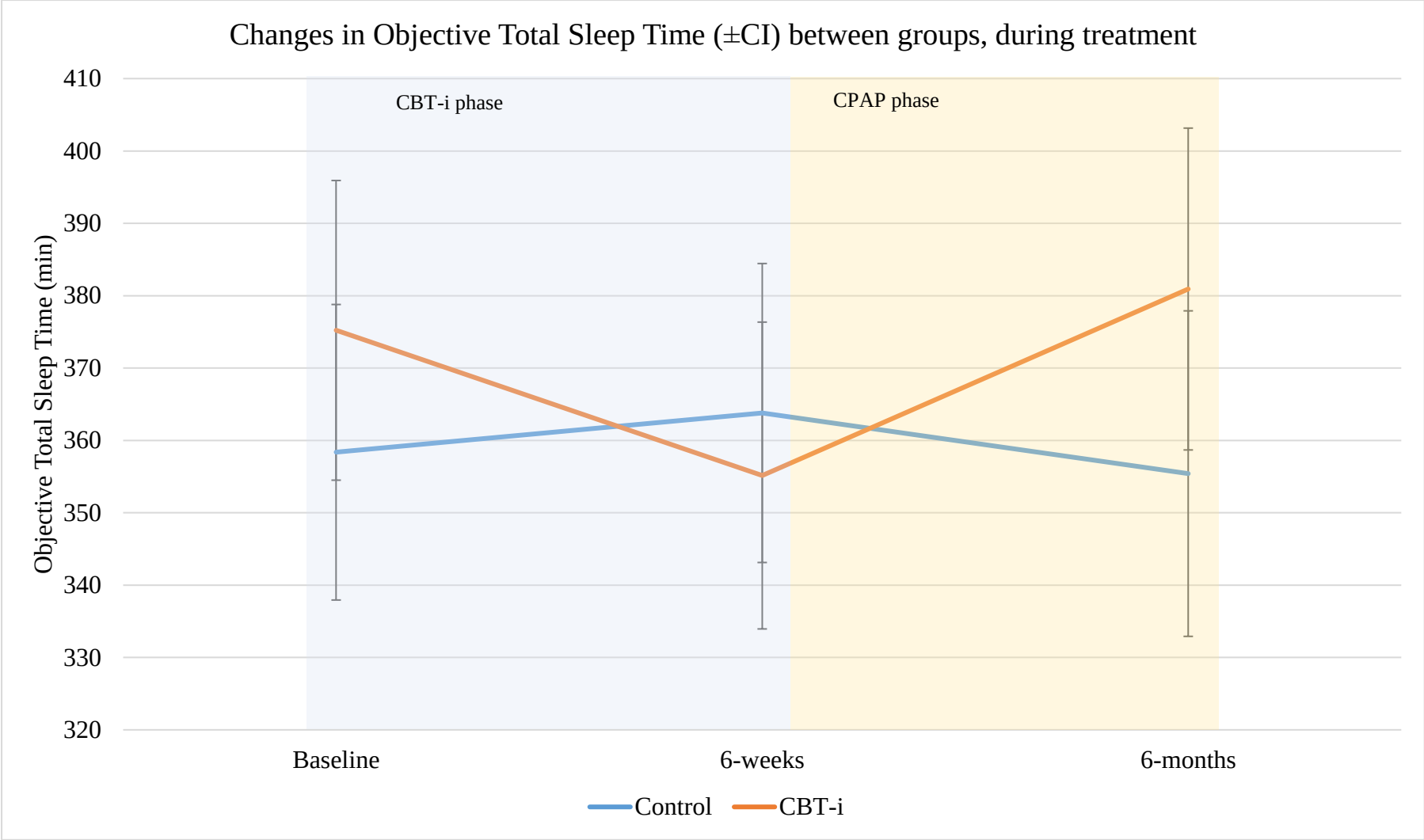

Figure 6.6 Changes in Objective Total Sleep Time, between groups during treatment (±95% CI).

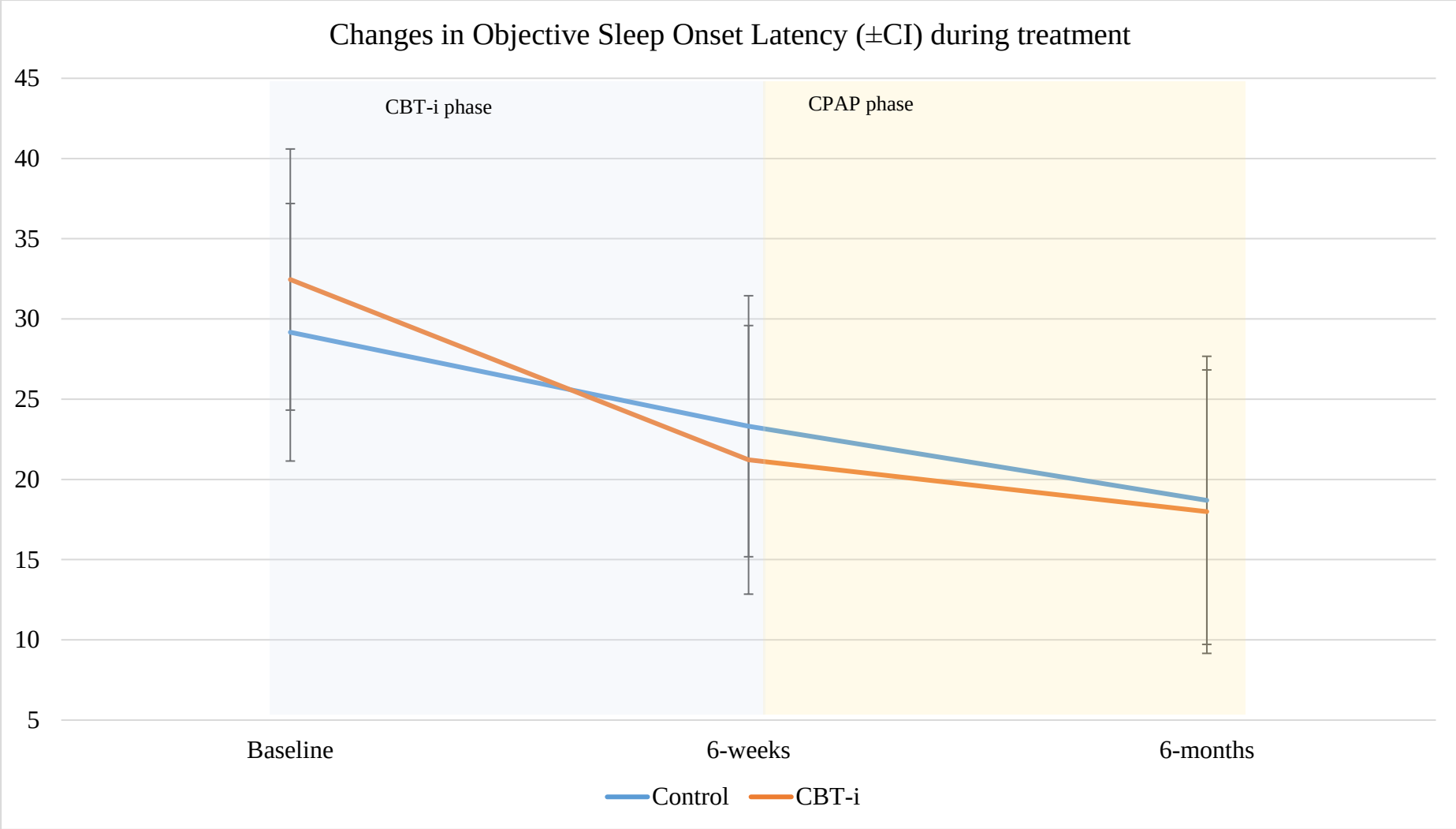

Figure 6.7 Changes in Objective Sleep Onset Latency, between groups during treatment (±95% CI).

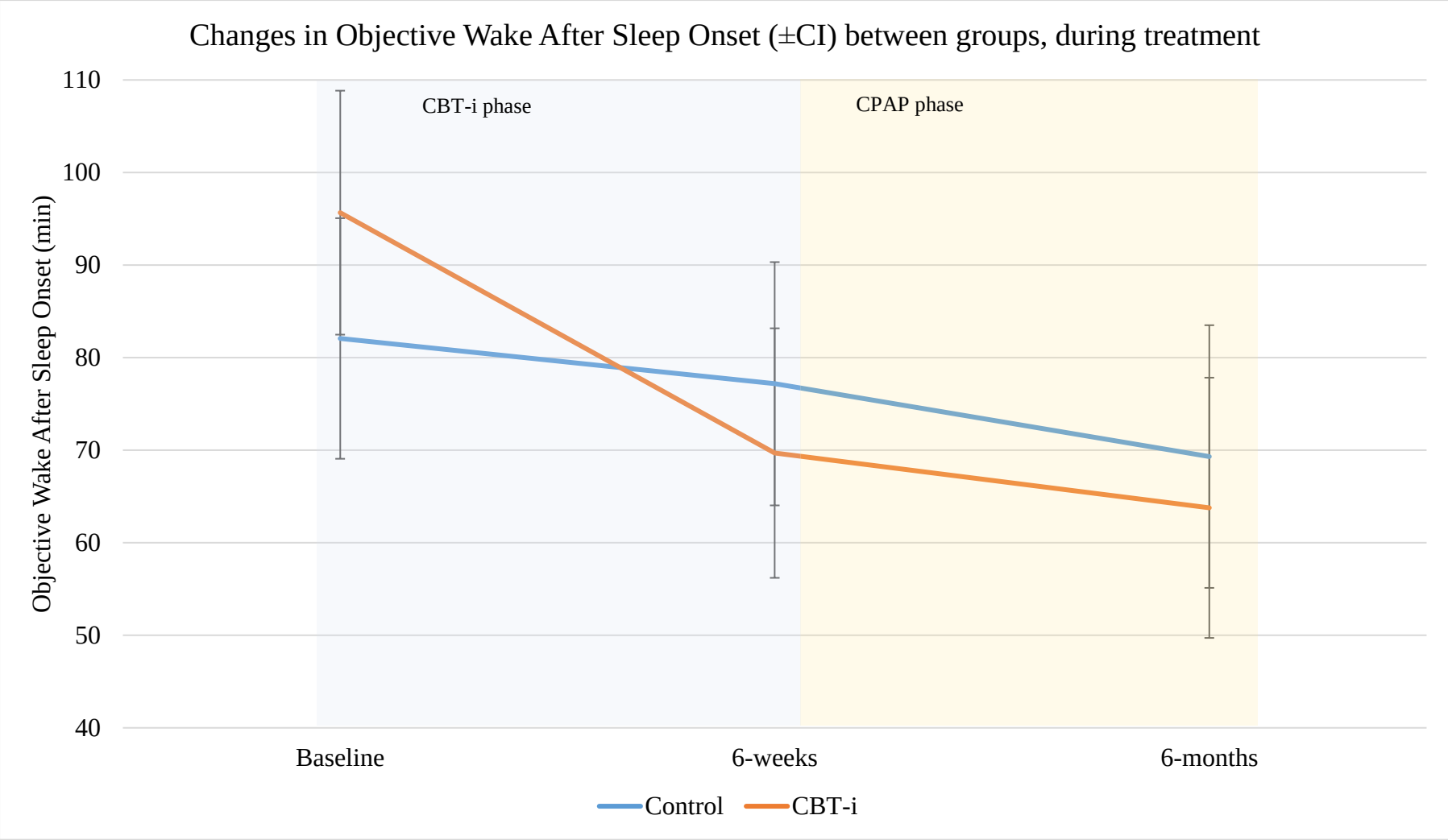

Figure 6.8 Changes in Objective Wake After Sleep Onset, between groups during treatment (±95% CI).

6.4.4 **Insomnia improvements following CBT-i and CPAP therapy**

6.4.4.1 Treatment Phase 1: CBT-i

It was predicted that the CBT-i condition would experience significantly greater improvement in symptoms of insomnia from baseline to 6-weeks, compared to the control condition. Participants in the CBT-i condition experienced significantly greater improvements in diary-measured sleep onset latency, wake after sleep onset, and sleep efficiency from baseline to 6-weeks, compared to participants in the control condition (all $p \leq .002$; Table 6.3, Figures 6.10 – 6.12). Alternatively, diary-measured total sleep time showed significant improvement by 6-weeks in the CBT-i condition, however no significant interaction between condition and time was observed (Table 6.3). The CBT-i condition also experienced significantly greater improvement in the ISI and ISI sub-scale from baseline to 6-weeks, compared to the control condition (both $p < .001$; Table 6.4, Figures 6.14 and 6.15).

6.4.4.2 Treatment Phase 2: CPAP therapy

During the subsequent CPAP treatment phase, participants in the control condition experienced significantly greater improvement of diary-measured wake after sleep onset, and sleep efficiency (Table 6.3, Figures 6.10 and 6.12). The control condition also experienced significantly greater reduction of the global insomnia severity sub-scale, and a trend for greater improvement in global insomnia severity from 6-weeks to 6-months, compared to the CBT-i condition (Table 6.4, Figures 6.14 and 6.15). During the CPAP phase, the CBT-i condition showed a small significant increase in diary-measured total sleep time, however no significant change in diary-measured sleep onset latency, wake after sleep onset, or sleep efficiency.

6.4.4.3 Full Protocol Analysis

It was also predicted that the CBT-i condition would show significantly greater improvement of insomnia symptoms from baseline to 6-months. The ISI and ISI sub-scale

showed significantly greater improvement during treatment in the CBT-i, compared to the control condition during the full study protocol (Table 6.4, Figures 6.14 and 6.15). However, no significant difference in improvements in diary-measured sleep onset latency, wake after sleep onset, total sleep time or sleep efficiency, were observed, between conditions (Table 6.3). Although, a trend was observed for greater improvements in sleep onset latency (*M* difference = 12.48 minutes, *CI* = 14.39, *p* = .089) and sleep efficiency (*M* difference = 3.88 percent, *CI* = 4.37, *p* = .081) in the CBT-i condition during treatment. Participants in the CBT-i condition experienced significantly greater decrease of diary-measured time in bed from baseline to 6-month follow-up (Table 6.3, Figure 6.13).

6.4.4.4 Bonferroni Correction for Sleep Diary Outcomes

After applying a Bonferroni correction based on 15 tests of interaction effects, probability levels of < .003 were required for sleep diary outcomes to be considered statistically significant. During the CBT-i phase of the trial, sleep onset time, wake after sleep onset, sleep efficiency each showed significantly greater improvement in the CBT-i condition. For the full-protocol, and CPAP phase, no statistically significant differences in improvements between conditions was observed after applying the Bonferroni correction.

Table 6.3 Changes in mean (±CI) diary-measured sleep parameters between groups, during treatment.

	Cognitive and Behavioral Therapy for Insomnia					**Control**					**Baseline to 6-month Interaction**		**Baseline to 6-week (CBT-i Phase)**		**6-week to 6-month (CPAP Phase)**	
	Baseline	6-weeks	3-month	6-month	Change	Baseline	6-week	3-month	6-month	Change	*t*	*p*	*t*	*p*	*t*	*p*
Total Sleep Time (min)	346.17 (18.58)	371.72 (18.89)	399.98 (19.53)	394.67 (19.29)	48.50^	350.64 (18.45)	375.01 (19.43)	389.78 (19.33)	403.25 (19.83)	52.61^	-0.33	.739	0.124	.902	-0.433	.665
Time in Bed (min)	522.03 (18.45)	446.25 (18.81)	477.25 (19.58)	472.35 (19.32)	-49.69	520.49 (18.32)	507.48 (19.47)	508.25 (19.37)	500.42 (20.00)	-20.07	-2.14	.034	-5.177	< .001	2.350	.019
Sleep Onset Latency (min)	56.59 (7.97)	26.77 (8.17)	27.17 (8.61)	26.13 (8.47)	-30.45^	49.55 (7.92)	38.80 (8.57)	37.54 (8.51)	31.58 (8.88)	-17.97**	-1.71	.089	-3.111	.002	0.898	.370
Wake After Sleep Onset (min)	94.51 (12.73)	44.75 (13.01)	40.05 (13.60)	44.07 (13.46)	-50.44^	99.32 (12.65)	78.24 (13.51)	60.46 (13.47)	51.84 (14.04)	-47.47^	-0.265	.792	-3.232	.001	2.335	.020
Sleep Efficiency (%)	66.75 (2.99)	83.46 (3.05)	84.14 (3.18)	83.98 (3.13)	17.23^	67.98 (2.97)	74.61 (3.16)	76.80 (3.14)	81.32 (3.24)	13.34^	1.75	.081	5.018	< .001	-2.719	.007

Main effect of time in each condition: * $p \leq .05$, ** $p \leq .01$, ^ $p \leq .001$.

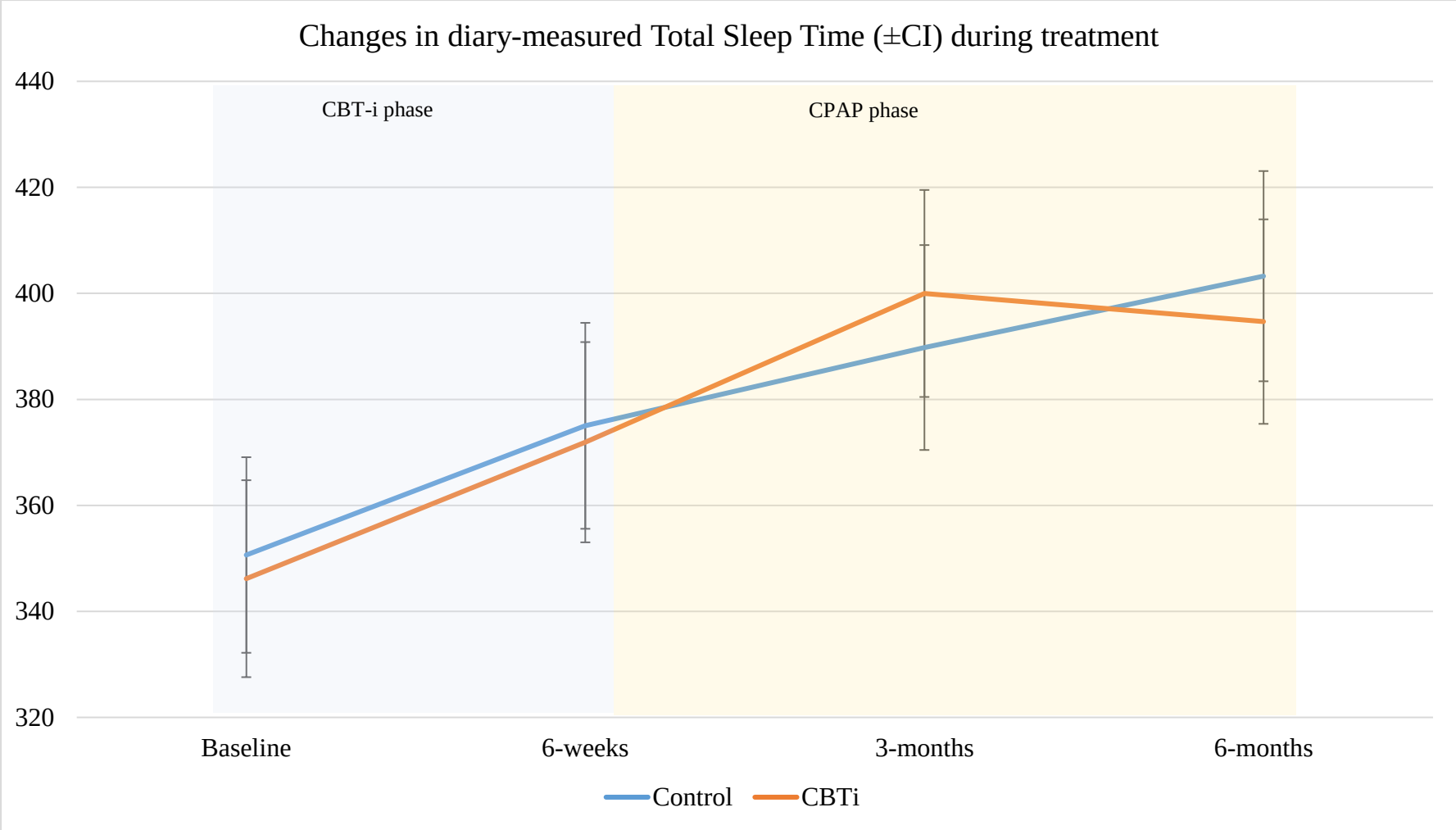

Figure 6.9 Changes in Diary-measured Total Sleep Time, between groups during treatment (±95% CI).

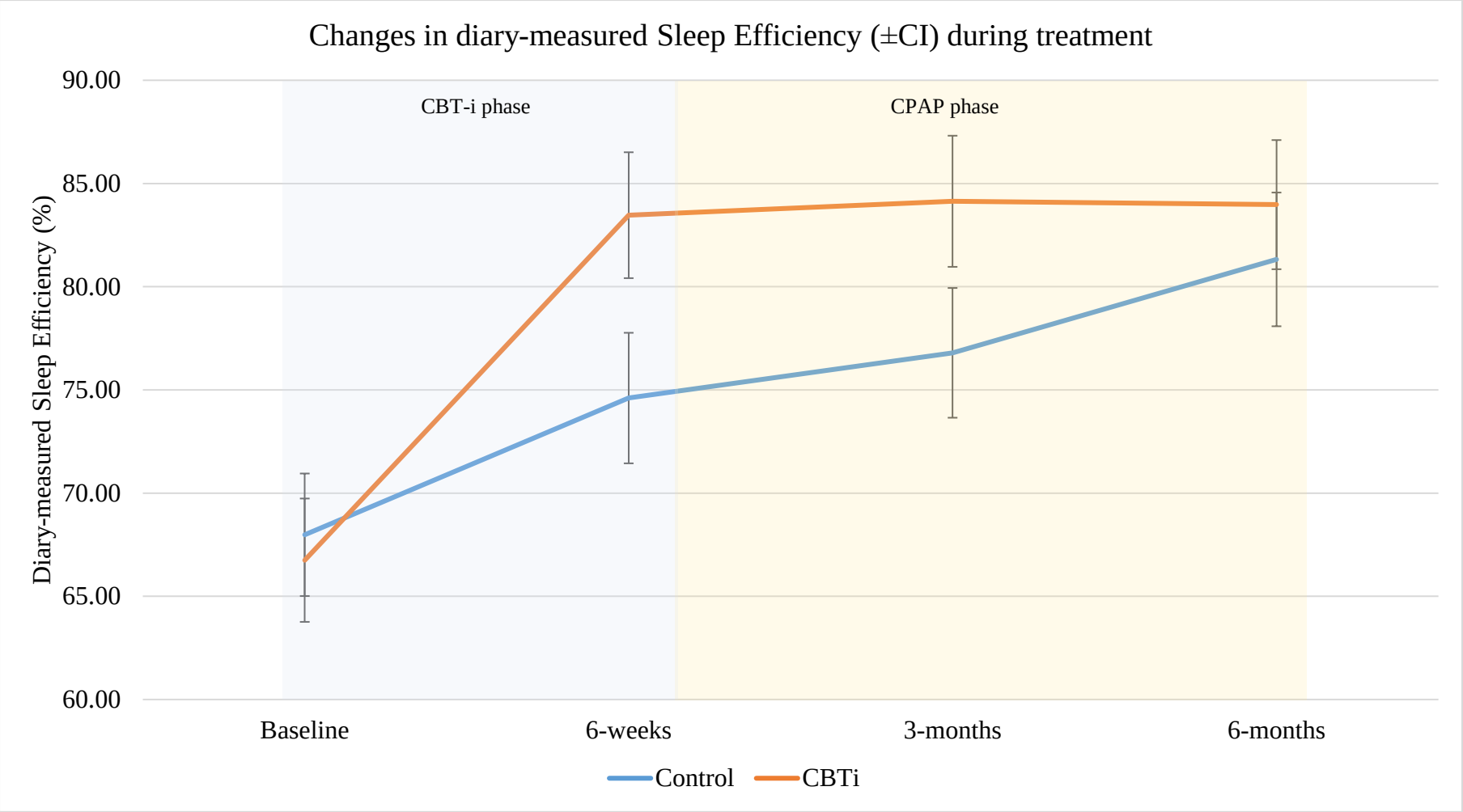

Figure 6.10 Changes in Diary-measured Sleep Efficiency, between groups during treatment (±95% CI).

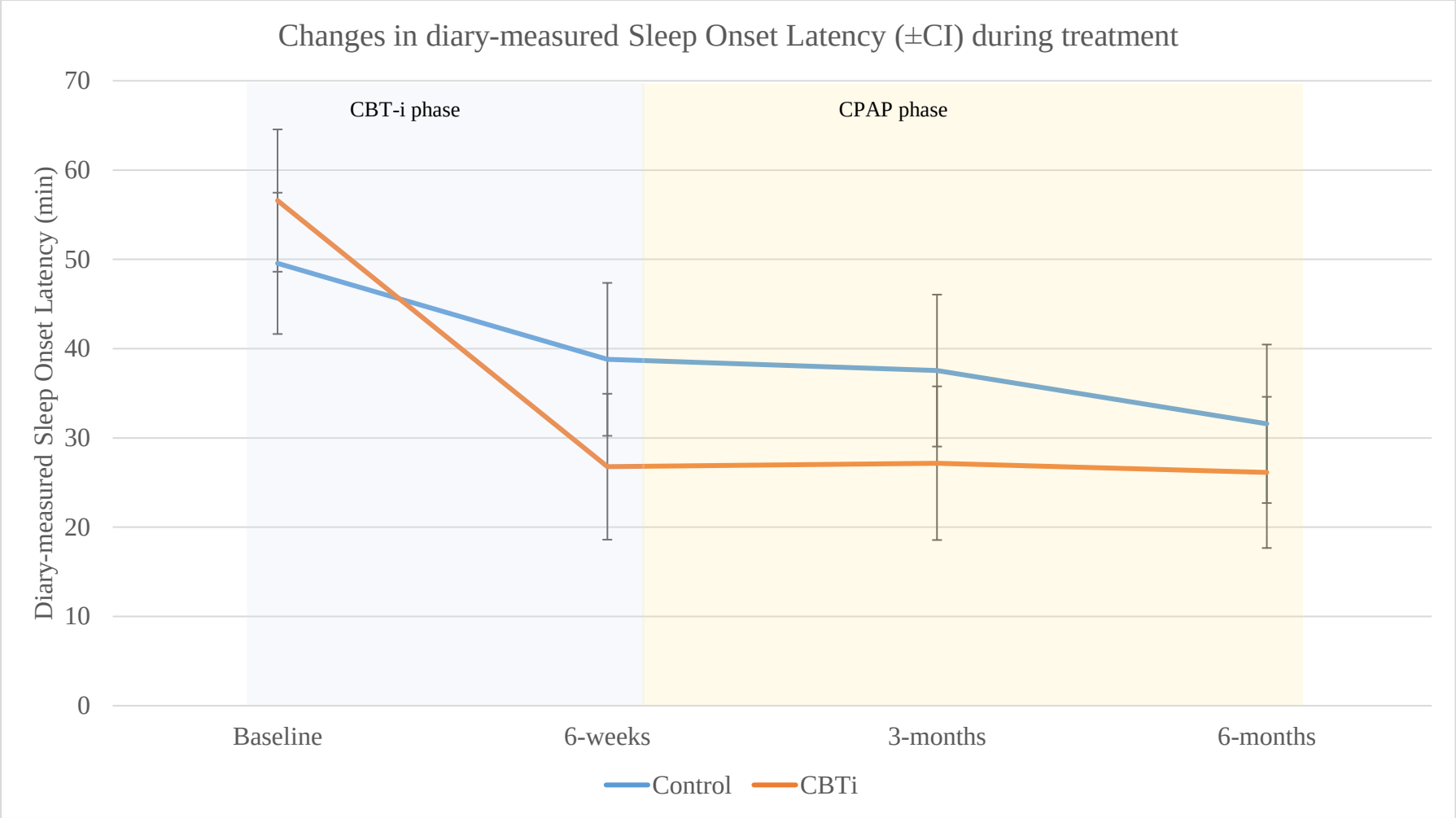

Figure 6.11 Changes in Diary-measured Sleep Onset Latency, between groups during treatment (±95% CI).

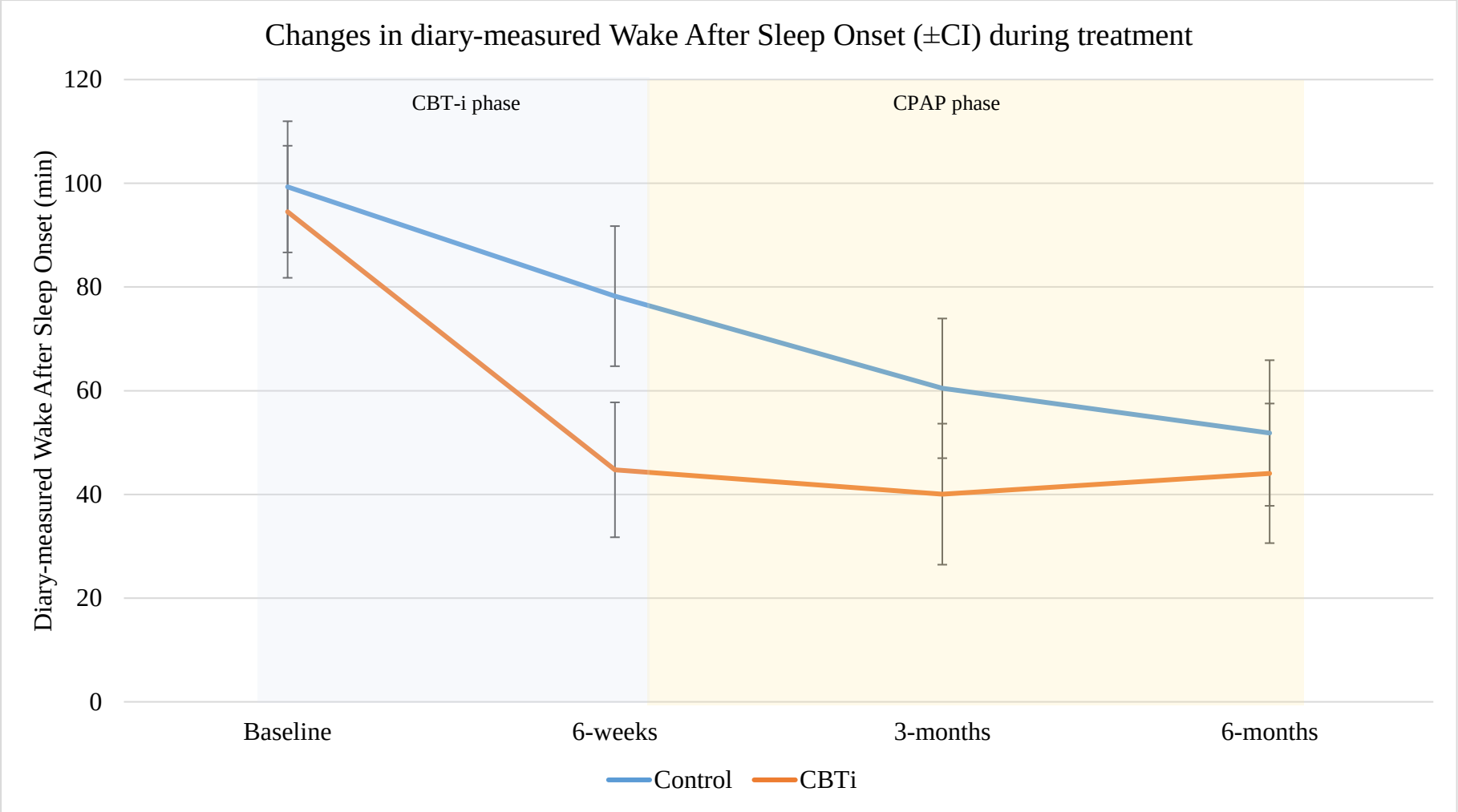

Figure 6.12 Changes in Diary-measured Wake After Sleep Onset, between groups during treatment (±95% CI).

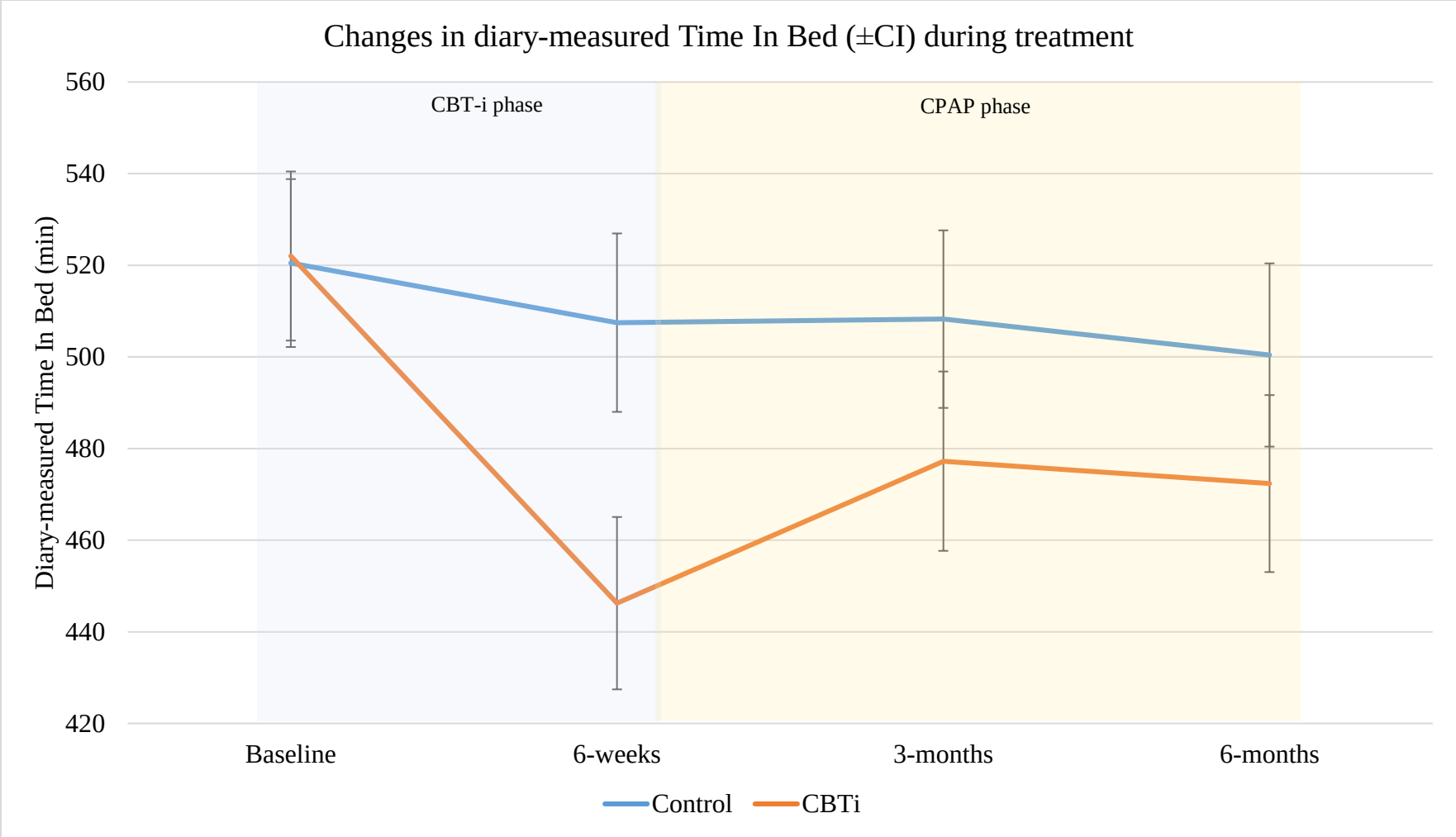

Figure 6.13 Changes in Diary-measured Time In Bed, between groups during treatment (±95% CI).

Table 6.4 Changes in mean (±CI) questionnaire outcomes between groups, during treatment.

	Cognitive and Behavioral Therapy for Insomnia					**Control**					**Baseline to 6-month Interaction**		**Baseline to 6-week (CBT-i Phase)**		**6-week to 6-month (CPAP Phase)**	
	Baseline	6-weeks	3-month	6-month	Change	Baseline	6-week	3-month	6-month	Change	*t*	*p*	*t*	*p*	*t*	*p*
Insomnia Severity Index	18.49 (1.33)	12.21 (1.35)	9.83 (1.38)	8.95 (1.40)	-9.54^	17.92 (1.32)	16.56 (1.36)	13.10 (1.39)	11.61 (1.41)	-6.31^	-3.27	.001	-5.985	<.001	1.722	.086
Insomnia sub-scale	7.29 (0.59)	4.49 (0.60)	4.03 (0.61)	3.79 (0.62)	-3.51^	6.84 (0.59)	6.18 (0.60)	5.14 (0.62)	4.52 (0.63)	2.32^	-2.60	.010	-5.760	<.001	2.146	.033
Flinders Fatigue Scale	15.96 (1.54)	13.69 (1.55)	10.33 (1.58)	9.84 (1.60)	-6.12^	15.92 (1.52)	15.02 (1.56)	11.98 (1.59)	11.84 (1.61)	-4.07^	-1.89	.060	-1.556	.121	-0.631	.528
Daytime Feelings and Functioning Scale	16.94 (1.89)	14.45 (1.88)	11.92 (1.91)	10.96 (1.92)	-5.99^	17.77 (1.85)	15.96 (1.89)	12.90 (1.92)	12.85 (1.93)	-4.92^	-0.97	.333	-0.706	.481	-0.350	.727
Epworth Sleepiness Scale	8.92 (1.02)	7.24 (1.03)	6.09 (1.05)	5.82 (1.06)	-3.09^	9.69 (1.01)	9.20 (1.03)	7.71 (1.05)	6.76 (1.06)	-2.93^	-0.23	.820	-2.117	.035	1.452	.148
Dysfunctional Beliefs about Sleep scale	60.28 (4.25)	48.68 (4.28)	43.12 (4.36)	42.31 (4.39)	-17.97^	58.58 (4.22)	58.33 (4.30)	53.95 (4.37)	52.70 (4.41)	-5.88*	-4.59	<.001	-5.154	<.001	-0.285	.776
Depressive Symptoms	14.53 (2.65)	12.98 (2.67)	10.69 (2.71)	10.14 (2.72)	-4.38^	14.63 (2.63)	13.74 (2.68)	11.19 (2.71)	11.65 (2.74)	-2.98*	-0.93	.355	-0.540	.589	-0.508	.612
Anxiety Symptoms	10.22 (1.85)	8.78 (1.86)	8.34 (1.89)	8.11 (1.90)	-2.11	8.93 (1.83)	9.09 (1.87)	7.42 (1.90)	6.90 (1.91)	-2.04	-0.07	.942	-1.794	.074	1.459	.146
Stress	15.14 (2.16)	12.76 (2.18)	11.10 (2.22)	11.44 (2.23)	-3.70^	15.56 (2.15)	15.62 (2.20)	13.10 (2.23)	12.73 (2.25)	-2.84*	-0.65	.514	-2.097	.037	1.190	.235

Main effect of time in each condition: * $p \leq .05$, ** $p \leq .01$, ^ $p \leq .001$.

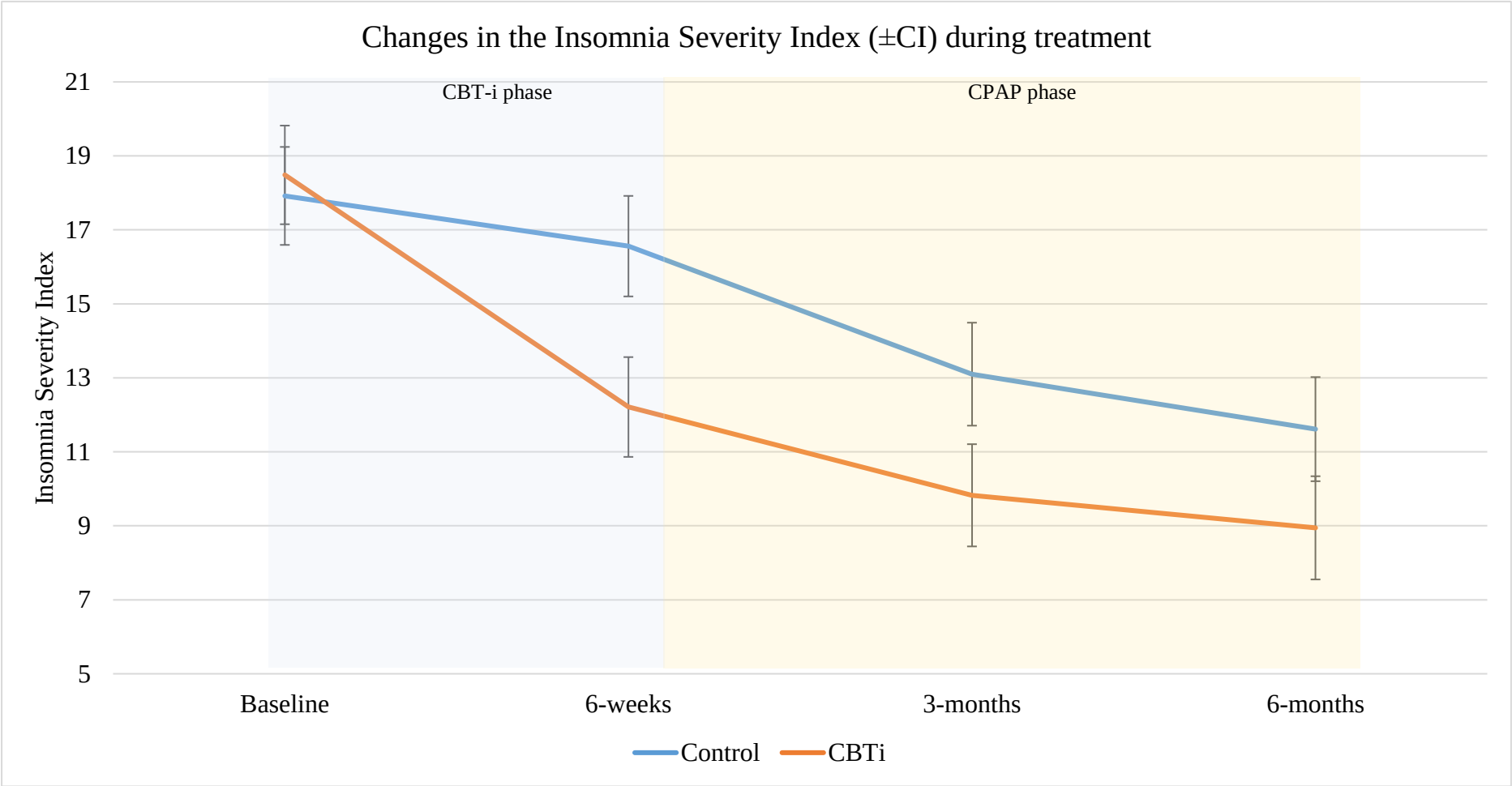

Figure 6.14 Changes in the Insomnia Severity Index, between groups during treatment (±95% CI).

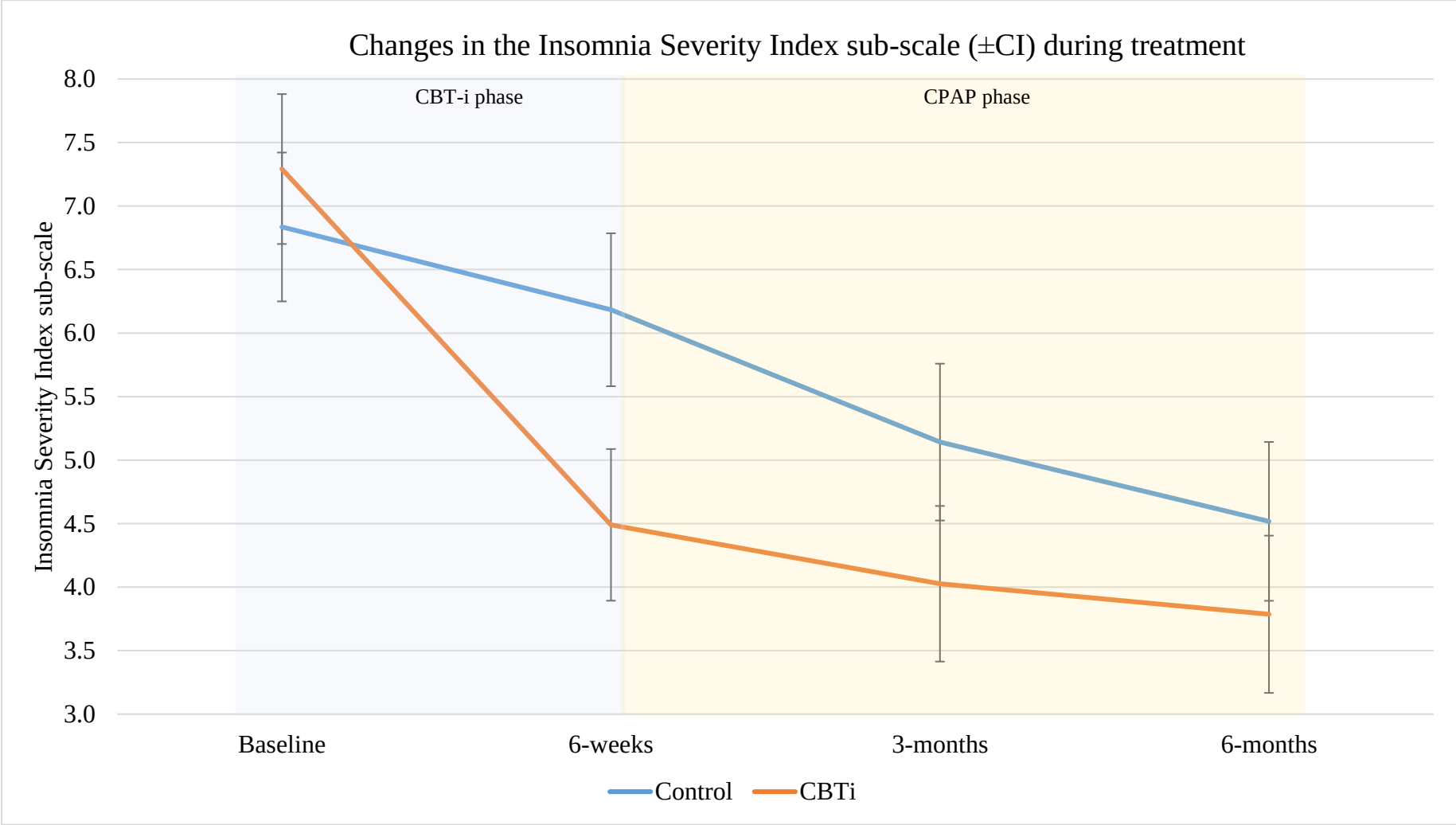

Figure 6.15 Changes in the Insomnia Severity Index sub-scale, between groups during treatment (±95% CI).

6.4.5 **Daytime Functioning Improvements**

6.4.5.1 Treatment Phase 1: CBT-i

It was predicted that participants in the CBT-i condition would experience greater improvements in daytime functioning questionnaire outcomes from baseline to 6-week follow-up. The CBT-i condition experienced significantly greater improvements in daytime sleepiness, dysfunctional sleep-related cognitions, and stress by 6-weeks, compared to the control condition (Table 6.4, Figures 6.18 and 6.19). A trend indicated that the CBT-i condition also experienced greater improvement of daytime fatigue, however this did not reach statistical significance (Table 6.4). No significant differences in improvements in general daytime feelings and functioning, anxiety symptoms, or depressive symptoms were observed between conditions during the CBT-i phase (Table 6.4).

6.4.5.2 Treatment Phase 2: CPAP therapy

During the CPAP phase, no significant interactions were observed between condition and time on any daytime functioning outcomes (Table 6.4). Following the initiation of CPAP therapy, both conditions continued to experience improvement of daytime sleepiness, fatigue, general daytime functioning, dysfunctional sleep-related cognitions, and depression over time (all $p < .05$). Only the control condition experienced a small improvement in stress and anxiety symptoms during the CPAP phase of the protocol.

6.4.5.3 Full Protocol Analysis

It was also predicted that the CBT-i + CPAP condition would experience significantly greater improvements in daytime impairments from baseline to 6-months, compared to the CPAP-only condition. Although the CBT-i condition experienced significant improvements in daytime sleepiness, fatigue, general daytime functioning, (all $p < .001$), and depression, anxiety and stress (all $p < .03$) by 6-months, no significant condition by time interactions were observed for these outcomes (Table 6.4, Figures 6.16 – 6.19). A trend indicated greater

improvements in the fatigue scale among participants in the CBT-i condition from baseline to 6-months (p = .06). Furthermore, the difference between conditions in fatigue scores was slightly greater at each successive follow-up (1.34-points at 6-weeks, 1.65-points at 3-months, 2.00-points at 6-months; Figure 6.16).

Alternatively, the CBT-i participants did experience a significantly greater reduction of dysfunctional beliefs and attitudes about sleep by 6-months, compared to control participants (Table 6.4, Figure 6.19). This pattern was also true for the four subscales of the dysfunctional beliefs and attitudes about sleep scale (i.e. the expectations, effects, worry, and medication-related beliefs subscales). In fact, the CBT-i condition experienced significantly greater reduction of dysfunctional cognitions by 6-weeks, 3-months, and 6-months compared to the control condition (all $p \leq .006$).

6.4.5.4 Bonferroni Correction for questionnaire outcomes

After applying a Bonferroni correction based on 27 tests of interaction effects, probability levels of < .001 were required for questionnaire outcomes (Table 6.4) to be considered statistically significant. From baseline to 6-months, only the ISI total score, and dysfunctional sleep-related cognitions showed significantly greater improvements in the CBT-i condition. During the CBT-i phase, the ISI, ISI sub-score, and dysfunctional sleep-related cognitions scores showed significantly greater improvement in the CBT-i condition. No questionnaires showed significantly different responses during the CPAP-phase of the trial after applying the Bonferroni correction

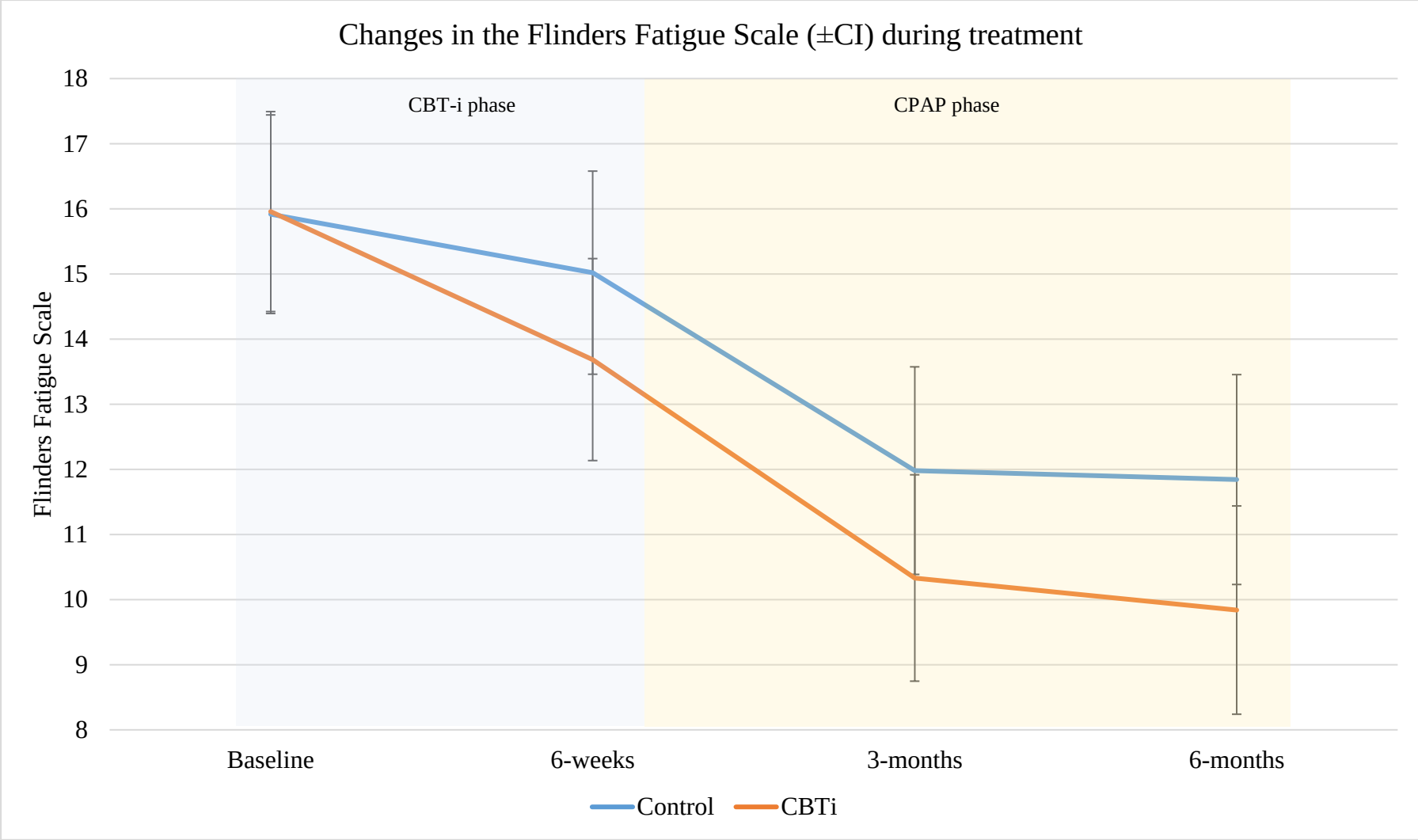

Figure 6.16 Changes in the Flinders Fatigue Scale, between groups during treatment (±95% CI).

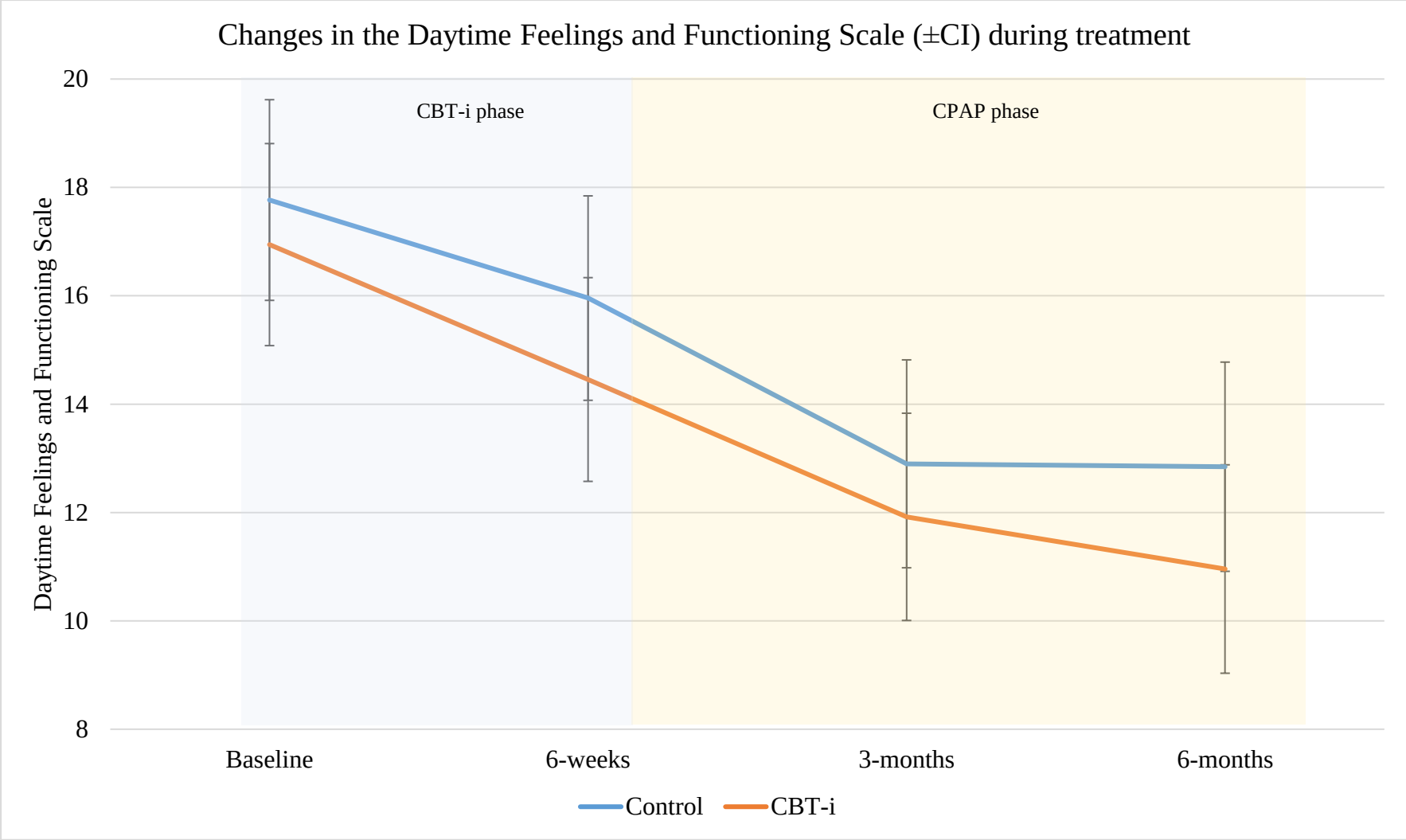

Figure 6.17 Changes in Daytime Feelings and Functioning Scale, between groups during treatment (±95% CI).

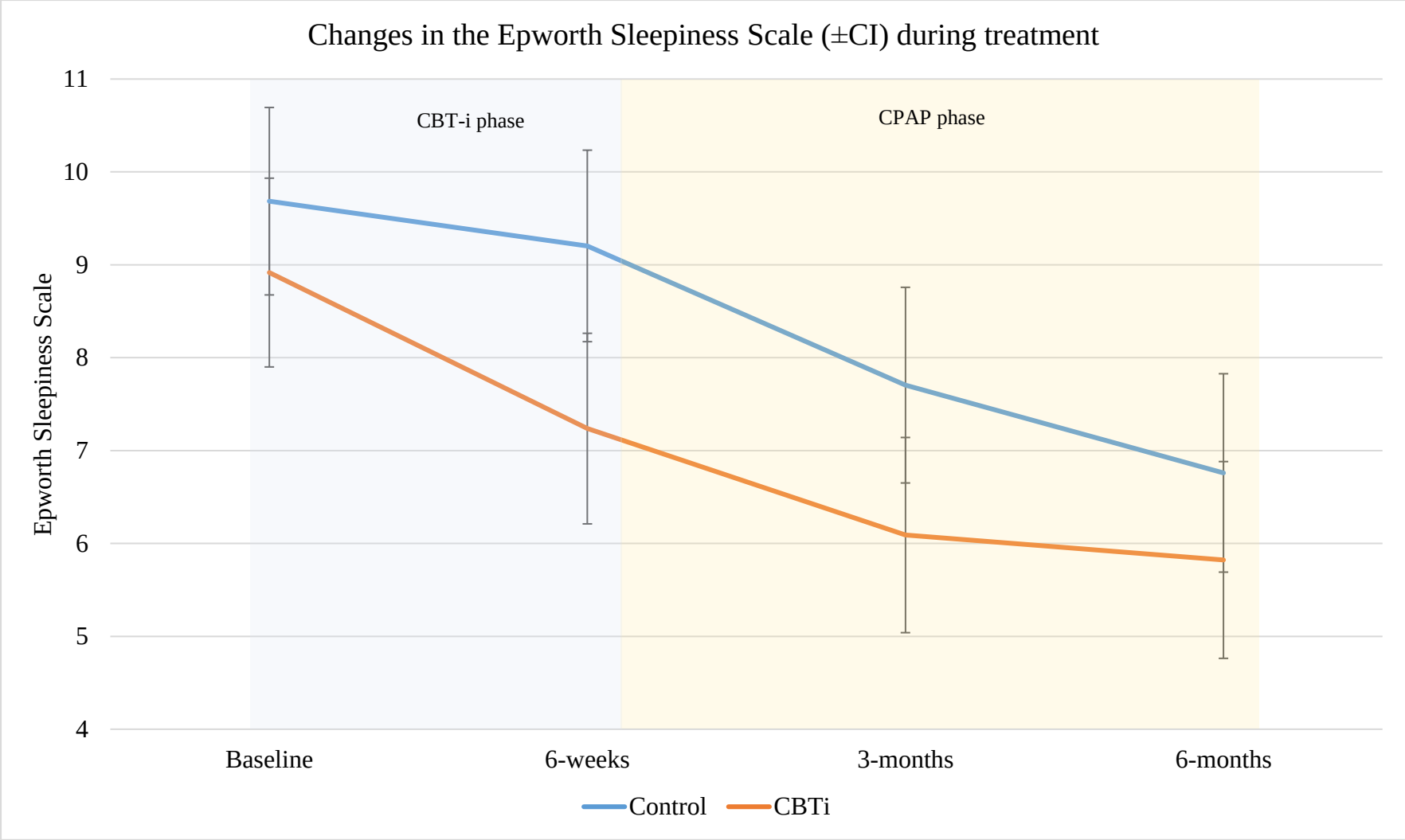

Figure 6.18 Changes in the Epworth Sleepiness Scale, between groups during treatment (±95% CI).

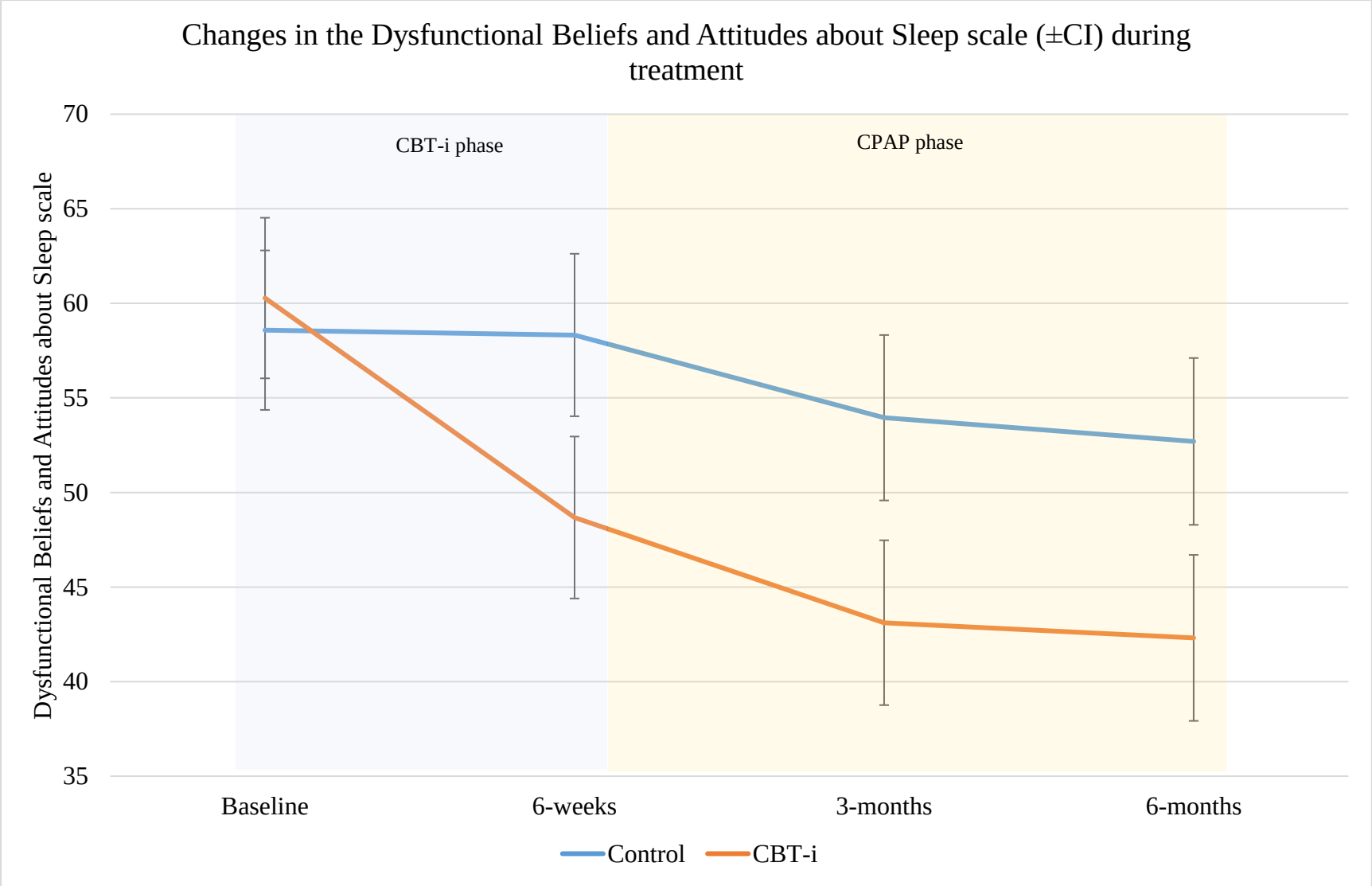

Figure 6.19 Changes in the Dysfunctional Beliefs and Attitudes about Sleep scale, between groups during treatment (±95% CI).

6.4.6 **Early CPAP Side Effects**

Following the first week of CPAP use, all participants who began using CPAP returned to sleep clinics for a review appointment with a CPAP nurse to address any acute problems with CPAP effectiveness and CPAP side-effects. Participants responded to a brief questionnaire assessing their experience of several CPAP side effects (listed in Figure 6.20). Fischer's Exact tests revealed that participants in the control condition were more likely to report the presence of at least one side effect associated with CPAP, compared to participants in the CBT-i condition (p = .008). Furthermore, participants in the control condition were more likely to report difficulties keeping masks in place during the night, compared to participants in the CBT-i condition (p = .019). It was also expected that the CBT-i condition would be less likely to report difficulties resuming and initiating sleep with CPAP, however this was not the case (p-values of .191, and .178, respectively). No other side-effects differed between conditions.

Multiple independent samples t-tests were also undertaken to examine differences in average nightly minutes of CPAP adherence from CPAP-setup to 6-months, between participants who did/did not report each of these side effects. It was found that CPAP adherence was significantly lower among participants who reported any side effect (M = 233.38, SD = 154.76), compared to those who did not report any side effects (M = 304.06, SD = 148.71; $t(128) = 2.264$, p = .025). Furthermore, CPAP adherence was also significantly lower among participants reporting difficulties exhaling ($t(128) = 2.855$, p = .005), claustrophobia ($t(128) = 3.363$, p = .001), involuntary removal of CPAP equipment ($t(7.09) = 5.279$, p = .001), difficulties resuming sleep ($t(128) = 3.223$, p = .002), and difficulties initiating sleep ($t(128) = 2.026$, p = .045), and anxiety related to CPAP therapy ($t(128) = 3.644$, $p < .001$). Finally, a trend indicated that irritation due to air leaks was associated with lower CPAP adherence ($t(128) = 1.967$, p = .051). Claustrophobia, involuntary removal of

CPAP equipment, difficulties resuming sleep, and anxiety remained significantly related to CPAP use at a corrected probability level of <.003, after applying a Bonferroni correction to account for multiple significance tests.

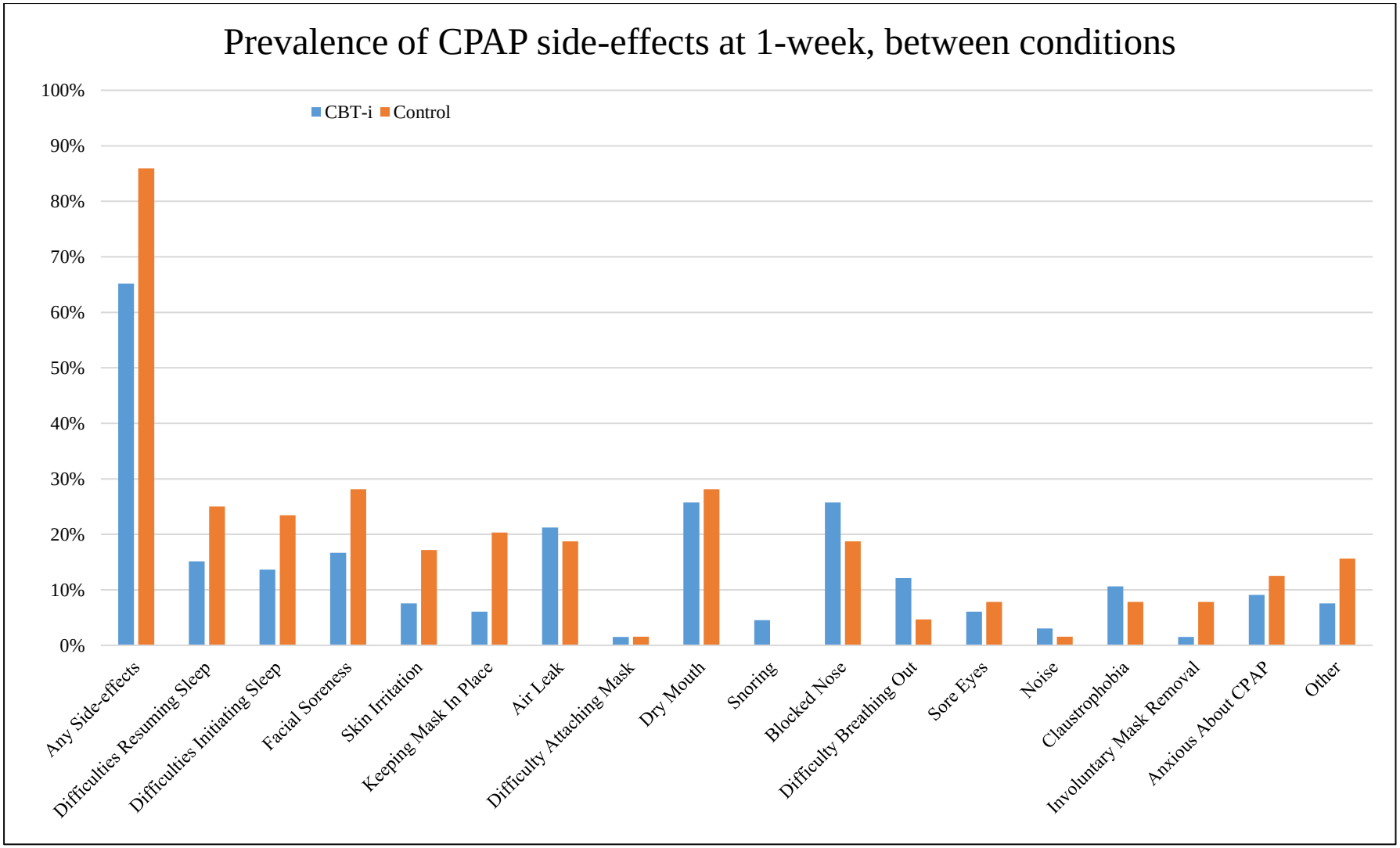

Figure 6.20 Differences in prevalence of CPAP side effects between conditions.

6.4.7 Treatment Responders and Remitters

Rates of insomnia response, and remission were also examined during each treatment phase. A ISI cut-off of less than 8 was used to determine the proportion of participants in each condition who achieved insomnia remission at 6-weeks and 6-months. At both 6-weeks participants in the CBT-i condition (30.4%) were significantly more likely than participants in the control condition (3%) to achieve insomnia remission ($\chi^2(1) = 17.92$, $p < .001$). Participants in the CBT-i condition (53.2%) were also more likely to achieve insomnia remission at 6-months compared to participants in the control condition (31.7%;($\chi^2(1) = 5.80$, $p = .02$).

Insomnia responders were also defined as any participants who experienced at least an 8-point improvement in the ISI from baseline to 6-weeks, and baseline to 6-months. Participants in the CBT-i condition were more likely to show a clinically significant insomnia response at both 6-weeks (46.4%) and 6-months (62.9%), compared to participants in the control condition (6-week insomnia responders: 6.1%; 6-month insomnia responders: 38.3%; both $p < .01$).

Finally, the proportion of participants in each condition achieving normalized sleepiness scores (ESS of 10 or below) were also compared at both 6-weeks and 6-months. At 6-weeks, 75% of the CBT-i participants and 60% of the control participants reported normal levels of sleepiness, while at 6-months, 87% of the CBT-i participants and 90% of the control participants reported normal levels of sleepiness. In each case, no significant difference in the proportion of participants achieving normalized sleepiness was observed between conditions.

6.5 Discussion

6.5.1 Overview

An initial 4-week CBT-i program resulted in significantly greater immediate acceptance and long-term objective use of CPAP therapy in patients with co-occurring

insomnia and OSA, compared to the current 'treatment as usual' approach including CPAP alone. The combination of CBT-i and CPAP therapy was also associated with significantly greater improvements in global insomnia severity, night time insomnia complaints, dysfunctional beliefs and attitudes about sleep, and a trend for greater improvements in daytime fatigue, diary-measured sleep onset latency and sleep efficiency by 6-month follow-up. However, several measures of daytime impairment and objective sleep parameters showed no statistically significant differences of improvements between conditions during treatment.

As CBT-i is a brief and effective treatment, it will be possible to administer this therapy to future COMISA patients between the diagnostic and CPAP titration appointments. This is expected to provide rapid relief from insomnia symptoms and improve subsequent CPAP outcomes, without delaying patients' progression to CPAP therapy for treatment of their OSA. These results therefore suggest a change in focus of many sleep clinics around the world. Currently, the vast majority of sleep clinics specialize in OSA diagnosis and treatment, and lack the resources to diagnose and treat cases of insomnia with CBT-i. However, these results indicate that targeted insomnia diagnosis and treatment resources would greatly benefit future patients presenting with both primary and co-morbid insomnia disorders. This would require a change of health service delivery in the sleep medicine area to devote greater resources and importance to sleep psychologist and CBT-i experts.

6.5.2 **CPAP Outcomes**

Participants in the CBT-i condition showed a 58.5-minute increase in average nightly CPAP adherence over the first four months of use, compared to participants in the control condition. The secondary CPAP analyses indicated that this difference was largely a result of the CBT-i condition experiencing greater rates of initial CPAP acceptance (98.6%), compared to the control condition (89.0%). In fact, after eliminating any participants who

rejected CPAP therapy during or immediately after the CPAP titration night, there were no significant differences in objective average adherence between the two conditions for those who began using CPAP. Furthermore, mixed model analyses of immediate (1-week), short-term (3-months), and long-term (6-months) average CPAP adherence, indicated that average CPAP use showed similar rates of gradual decline over time in each condition, with only a trend for slightly less decline in the CBT-i condition. Finally, a survival analysis indicated that rates of CPAP rejection were similar between the two conditions during the total trial period. Therefore, initial treatment with CBT-i appears to increase the rate of immediate acceptance of CPAP therapy in participants with COMISA, however after patterns of early acceptance and use are established, CBT-i appears to have little on-going effect on patterns of CPAP use.

Past research has shown that greater time spent using CPAP is associated with greater improvement of secondary manifestations of OSA, including sleepiness and quality of life (54). However, in the current study, although the CBT-i group showed significantly greater CPAP use (mean of 58.5 minutes), no differences in improvements in daytime sleepiness, general daytime functioning, depression, anxiety, or stress between conditions were observed. Therefore, one may conclude that because the addition of CBT-i has a limited effect on COMISA patients' daytime impairments and quality of life, it is not a valuable addition to the current treatment approach of CPAP-alone in this co-morbid population. However, the addition of CBT-i did lead to significantly greater long-term improvements in global insomnia severity, night time insomnia complaints, and dysfunctional sleep-related cognitions, compared to treatment with CPAP-alone. A trend also indicated that CBT-i participants reported greater reduction of daytime fatigue during the treatment protocol, compared to the control participants. Participants in the CBT-i condition also experienced a rapid improvement of several diary-measured sleep parameters, which the control group only

experienced following several months of CPAP use. Furthermore, a 58.5-minute increase in CPAP adherence may also lead to improvements in other cardiovascular and neurocognitive outcomes which were not assessed in the current study. Finally, although no significant interaction effect between condition and time on CPAP adherence was observed, the CBT-i condition appeared to show gradually greater CPAP adherence during each subsequent CPAP follow-up, compared to the control condition (Figure 6.2). For example, during the first CPAP follow-up, the CBT-i group showed 32.3 minutes' greater adherence, whereas a 63.9-minute difference was observed between conditions by 6-months. It is possible that given an additional follow-up period, 12-months after randomization, a significant interaction favoring greater maintenance of CPAP use in the CBT-i condition would be found.

The effect of CBT-i on CPAP outcomes should also be interpreted with consideration of the strength of the CBT-i manipulation. Whilst the CBT-i manipulation was very brief (four 50-minute sessions), cost-effective (55), and safe (56), it also resulted in increased CPAP adherence for the following 4-months of use. Furthermore, the CBT-i participants showed gradually greater CPAP use over time, indicating that their nightly adherence would continue to be greater for several additional months into the future. Thus, although the conditions showed only a moderate difference in average adherence, the difference resulted from a very small manipulation, compared to the longevity of its influence.

Correlational analyses were undertaken to examine associations between CPAP use, and improvements in secondary symptoms of each disorder from 6-weeks to 6-months (i.e. during the CPAP phase). In agreement with previous research, greater average CPAP use was associated with greater AHI reduction, and greater improvement in daytime fatigue, sleepiness, and a trend for greater reduction of daytime impairments (17, 54). Interestingly, greater CPAP use was also moderately associated with greater improvements in global insomnia severity, and improved diary-measured total sleep time, wake after sleep onset, and

sleep efficiency. Although the correlational nature of this analysis does not allow for causal conclusions, these results raise the possibility that either; greater CPAP use resulted in greater improvement of insomnia symptoms, or greater sustained improvement of insomnia symptoms (following the CBT-i phase) allowed patients to more readily accept and continue using CPAP therapy.

6.5.2.1 CPAP Side-Effects

Among participants who began using CPAP therapy, it was found that those in the CBT-i condition were more likely to report that they had not experienced any CPAP side-effects following the first week of CPAP use, compared to participants in the control condition. It is possible that the improvements in perceptions of sleep onset latency and night time wakefulness occurring with CBT-i led to this difference in perceptions of acute CPAP side-effects. However, of the item-by-item analyses of CPAP side-effects, the only significant difference indicated that the CBT-i condition reported fewer difficulties keeping the masks in place throughout the night, compared to the control condition. It was expected that the CBT-i participants would also be significantly less likely to report difficulties initiating and maintaining sleep with CPAP therapy, however this was not the case.

It was also found that participants who reported no CPAP side-effect after the first week of use, showed a 29-minute increase in CPAP adherence over the first 4 months, compared to participants who experienced at least one side-effect. It appears that a general reduction in CPAP side-effects may have partly mediated the relationship between CBT-i and increased CPAP adherence. Focusing on decreasing these early negative experiences with CPAP in COMISA patients may be one additional way to increase their long-term adherence. In fact, it may be possible to integrate an additional component into the standard CBT-i protocol when used in COMISA patients, which focuses on overcoming symptoms of anxiety, claustrophobia, and sleep initiation and resumption difficulties associated with CPAP

therapy. Integrated multidisciplinary treatment models such as this may lead to additional increases in CPAP outcomes in the COMISA population (57), compared to the discrete delivery of standardized CBT-i and CPAP therapy, as investigated in this study.

6.5.3 Objective Sleep Outcomes

It was also expected that CBT-i would improve immediate, and long-term objective sleep parameters, thereby allowing participants to more readily accept and continue using their CPAP equipment. CBT-i has previously been found to improve objective sleep outcomes in insomnia patients (31). The CBT-i condition experienced 21.1-minutes greater decrease of objective wake after sleep onset during the CBT-i phase, compared to the control condition, however no other objective sleep parameters showed a significant interaction during this first treatment phase. It is possible that these immediate reductions of night time wakefulness continued into the CPAP phase of the trial, allowing the CBT-i participants to return to sleep quicker while wearing CPAP equipment, and subsequently experience fewer night time side-effects of CPAP. In turn, this difference in improvement of objective wakefulness may be partly responsible for the increased rates of immediate CPAP acceptance and use in the CBT-i condition.

When examining the subsequent effect of CPAP therapy during the second treatment phase, it was found that neither condition experienced significant improvement in any objective sleep parameters. These data indicate that the initial improvements in night time wakefulness experienced in the CBT-i condition were sustained throughout the CPAP phase of the protocol. However, CPAP therapy had little impact on these participants' objective sleep parameters. It should also be noted that insomnia patients experience significant night-to-night variability in sleep parameters, and the use of a single-night PSG recording at each follow-up should be interpreted alongside the more reliable sleep-diary measures (58, 59).

6.5.4 **Sleep Diary and Insomnia Outcomes**

Participants in the CBT-i condition experienced large improvements in diary-measured sleep onset latency, wake after sleep onset, and sleep efficiency during the CBT-i phase of the study. However, following these improvements, it appears that a floor effect may have truncated any additional improvement in sleep parameters among the CBT-i participants during the subsequent CPAP phase of the trial. Therefore, during this CPAP phase, the control condition continued to experience gradual improvement of sleep parameters, while the CBT-i condition showed little change. The full protocol analyses revealed that both conditions experienced similar improvement of diary-measured sleep parameters during the trial period, with the CBT-i group trending toward greater improvement of sleep onset latency and sleep efficiency. Overall, it appears that administering CBT-i prior to CPAP therapy results in a more immediate improvement of sleep diary parameters, which are sustained following the initiation of CPAP therapy. Alternatively, when treated with CPAP-alone, these improvements occurred at a much slower rate, until both groups experienced similar levels of sleep diary improvement by 6-month follow-up. It is likely that the immediate reductions of perceived sleep onset latency and night time wakefulness experienced by the CBT-i condition were also an important factor which influenced the increased rate of CPAP acceptance, and long-term use.

Compared to the control condition, the CBT-i condition also showed greater improvement of global insomnia severity, the ‘sleeping difficulties’ insomnia sub-scale, and dysfunctional sleep-related cognitions during the CBT-i phase. Furthermore, participants in the CBT-i condition were more likely to achieve the ‘insomnia responder’ and ‘insomnia remission’ cut-offs, compared to those in the control condition. It is possible that these improvements in night time/daytime insomnia symptoms experienced shortly before beginning CPAP therapy were also partly responsible for the increased rates of immediate

CPAP acceptance in the CBT-i condition. During the subsequent CPAP phase of the trial, both conditions continued to experience similar rates of improvement to global insomnia severity, and dysfunctional sleep-related cognitions. Interestingly, the control condition experienced a greater reduction of the 'sleeping difficulties' sub-scale during the CPAP phase, although this may be partly due to a floor effect in improvements in the CBT-i condition (who experienced no significant change in the insomnia sub-scale during the CPAP phase). It appears that while CBT-i is associated with a more immediate and robust improvement of insomnia severity, CPAP therapy is also associated with gradual improvement of night-time insomnia symptoms in these COMISA patients. Indeed, Björnsdóttir and colleagues previously reported that two years of CPAP therapy was associated with improvements in frequent awakenings, but not sleep onset, or early morning awakening complaints among COMISA patients (60).

6.5.5 **Daytime Functioning Outcomes**

It was expected that the CBT-i condition would experience significantly greater improvements in all daytime functioning outcomes than the control condition, during each phase of the study. During the CBT-i phase, participants in the CBT-i condition experienced slightly greater reduction of daytime sleepiness and stress compared to the control condition. However, when examining the proportion of participants who experienced normalized sleepiness scores following the CBT-i phase, no difference between conditions was observed. Furthermore, mixed model analyses indicated that no other differences in improvement of daytime fatigue, depression or anxiety, or general daytime functioning were observed between conditions. It is possible that these symptoms of fatigue and impaired daytime functioning were largely a manifestation of the co-morbid OSA in these COMISA patients (5), and therefore showed little improvement when the night time insomnia symptoms were treated during CBT-i.

During the CPAP phase, both conditions continued to experience similar levels of improvement in all daytime functioning outcomes. Furthermore, during the full protocol, both conditions experienced similar, significant improvement of daytime sleepiness, daytime functioning, depressive symptoms, and stress. Only the daytime fatigue scale showed a trend (p = .06), indicating progressively greater improvement in the CBT-i condition over the full protocol period. Correlational analyses also indicated that the degree of improvement in sleepiness, fatigue, and stress from 6-weeks to 6-months were each significantly positively related to average CPAP adherence. Although the combination of CBT-i and CPAP therapy resulted in greater insomnia improvement and CPAP use, these differences did not translate into greater improvements in any secondary daytime functioning outcomes. However, as differences in CPAP adherence between conditions became gradually more pronounced during the later follow-ups, the CBT-i condition also continued to experience greater improvement of several daytime impairments (e.g. fatigue, and general daytime functioning). If an additional longer-term follow-up were conducted, it is possible that the CBT-i condition would show greater adherence to CPAP therapy, and additional greater improvement of these daytime impairments, compared to the control condition.

6.5.6 Future research

As this study represents the first high-quality trial examining the effectiveness of CBT-i and CPAP in the COMISA population, it is important that future research confirm these findings in different settings, and different COMISA samples. Several ongoing trials of a similar nature are currently being conducted (26, 60-63). Furthermore, it is recommended that future research also manipulate the components, and timing of the CBT-i sessions, to maximize the efficiency of CBT-i, in treating the insomnia and improving CPAP outcomes. For example, it may be possible to also increase immediate CPAP acceptance (and therefore long-term use) with bedtime restriction therapy-alone, rather than the full CBT-i protocol.

Although previous research (20, 60) has linked 'insomnia symptoms' to reduced CPAP outcomes, participants in the current study were required to hold formal diagnoses of insomnia performed by registered psychologists. It is likely that this resulted in a sample of participants with more severe insomnia symptoms, compared to those included in previous COMISA research studies (60). Future research may wish to examine this combined treatment approach in COMISA patients with moderate complaints of 'insomnia symptoms' (e.g. on the ISI), rather than formal psychologist-diagnoses of insomnia. It may also be possible to use electronic or online CBT-i platforms (64) to support the increased number of participants entering research trials as these inclusion criteria are modified.

One limitation of the current study was the short time available for CPAP therapy. The linear mixed model analyses indicated a trend for greater maintenance of CPAP use in the CBT-i, but not the control condition. An additional longer-term follow-up period may have confirmed this pattern of results, and provided additional support for the combined treatment approach in treating other secondary night time/daytime symptoms. For example, other research in the COMISA field has included follow-up assessments after two years of CPAP therapy (60, 65).

Future COMISA treatment research should also examine the effect of an integrated psychologist-led intervention including CBT-i and specific CPAP-related sleep restriction/hygiene advice continuing into the CPAP phase of the trial. In the current study, the CBT-i intervention did not include any information related to OSA or CPAP therapy (in fact, any questions pertaining to CPAP therapy were deferred to future sleep physician review appointments). It was decided that all CPAP/OSA information should be omitted from the CBT-i protocol in order to examine the discrete influence of 'standardized' CBT-i on insomnia severity and CPAP outcomes. However, future research aiming to maximize treatment outcomes in COMISA patients should also consider prescribing tailored bedtime

restriction therapy advice during the CPAP phase of the trial; to enable patients to manage their own daytime sleepiness, sleep time, and length of night time awakenings while beginning CPAP therapy. Furthermore, motivational interviewing techniques may be integrated into the CBT-i program to prepare patients to overcome common side-effects of CPAP therapy, and encourage CPAP use (e.g. (66)). If patients continue employing some slight degree of sleep restriction during the CPAP phase, they may experience shorter night time awakenings, and be less likely to remove CPAP equipment half way through the night. For example, the CBT-i condition used CPAP for an average of 264-minutes each night, however spent an average of 472-minutes in bed at 6-months. Presumably, many participants used CPAP therapy for the first half of the night, however removed CPAP equipment following night time awakenings part-way through the night, and experienced repetitive hypoxic events for the remaining sleep time. Continued use of bedtime restriction may decrease the length of night time awakenings, and improve participants' ability to resume sleep with CPAP. Furthermore, if CPAP equipment were removed following several hours of sleep time, a continued bedtime restriction protocol would decrease the remaining time available for hypoxic-sleep without CPAP in place.

Finally, insomnia and OSA occur together more commonly than what would be expected, given the general population prevalence estimates of each disorder (1-3, 14). Therefore, it is also suggested that future research investigate the proposed causal mechanisms linking insomnia and OSA, to develop a better understanding of the aetiology of this disorder. This would require experimental studies which manipulate or measure these proposed mediating factors, including frequency and timing of post-apneic arousals and awakenings (67), patients' misperceptions of multiple post-apneic arousals as prolonged wakefulness and insomnia symptoms (68), patterns of nocturia and changes during treatment (69), and depression of upper airway muscle activation following sleep restriction in

COMISA and OSA patients (70). Developing a more comprehensive understanding of the aetiology of COMISA may lead to more specific treatment approaches which are tailored to precise patient profiles and symptom clusters. For example, in some COMISA patients the insomnia symptoms may be largely maintained by the post-apneic awakenings and sleep fragmentation associated with the OSA and would show little response to CBT-i. Alternatively, other COMISA patients' insomnia symptoms may have developed functional independence from the OSA and would require targeted treatment with CBT-i to improve.

6.5.7 **Limitations**

This study should be interpreted in light of several limitations. Firstly, a small amount of missing data were observed due to participant withdrawal, non-compliance, and faults with CPAP equipment. Of all questionnaire, sleep diary, sleep study, and CPAP outcomes, both conditions experienced a similar amount of missing data at each follow-up, with only one exception. Sleep diaries collected at 6-weeks were more likely to be missing in the control condition than the CBT-i condition. This was caused by CBT-i participants habitually completing sleep diaries prior to this time, and continuing during the 6-week follow-up. In some cases, CBT-i participants' diaries from the final CBT-i session were imputed to the 6-week data (which represented the week immediately following CBT-i). Rates of missing diary data were not believed to be related to disease severity or improvements in either condition. In fact, all data were defined as missing at random/missing completely at random according to pre-defined criteria (53). Furthermore, linear mixed model analyses were chosen as the primary analytical test of the repeated measures outcomes, due to the ability to handle randomly missing data, and conform to intention-to-treat criteria.

Secondly, no placebo control condition was utilized in participants not receiving CBT-i. Although this would have been a helpful addition to aid interpretation of the immediate effectiveness of CBT-i, the current study primarily aimed to compare the novel

‘CBT-i and CPAP’ treatment approach to the current ‘treatment as usual’ approach of CPAP-alone. Furthermore, previous studies have found the CBT-i produces significantly greater insomnia-improvements than a placebo-control condition (30). Therefore, the addition of a placebo control condition was thought to incur great cost for little scientific gain.

Finally, objective sleep efficiency was measured via home-based PSG studies at three time points throughout the protocol. Although time spent asleep was calculated and scored via objective methods (39), sleep efficiency was also partly dependent on self-reported time in bed. It is possible that participants mis-reported their bed/rise times in several cases, which would have impacted sleep efficiency estimates. However, scoring technicians are aware of this mis-reporting effect, and routinely use physiologic traces to guide bed/rise time estimations (e.g. oximeter and nasal cannula attachment, change in position sensor from upright to horizontal, artefact, etc.). Furthermore, it is unlikely that one condition was systematically more accurate in their reporting of their time in bed during PSG studies than the other condition, and scorers were blind to participants’ condition when estimating these bed/rise times. Future studies may also wish to employ actigraphic measures of sleep, which provide an ‘objective’ measure, collected over a number of consecutive nights to reduce the influence of night-to-night variability.

6.5.8 **Conclusion**

Co-morbid insomnia and OSA is a highly prevalent and debilitation condition, which is more difficult to treat, compared to either disorder presenting in isolation. The current study found that initial treatment with CBT-i rapidly improves perceived insomnia symptoms, and increases subsequent acceptance, and adherence to CPAP therapy among these patients. However, there were few differences of improvements in objective sleep parameters, or daytime functioning outcomes observed between conditions. On balance, it is recommended that sleep physicians refer COMISA patients for an initial brief course of

CBT-i, during the standard period that patients spend waiting for CPAP titration and CPAP setup bookings. It is expected that this combined treatment approach will rapidly improve the insomnia symptoms and increase long-term subsequent CPAP outcomes in this co-morbid population.

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7 CHAPTER 7. General Discussion

This Chapter is not written for submission to an academic journal.

This chapter is not intended for publication.

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7.1 Summary of Aims

The aim of this thesis was to introduce readers to insomnia, OSA and COMISA, review literature documenting the prevalence, characteristics, and previous treatment attempts in the COMISA population, and present a detailed report of the findings of two treatment studies in COMISA patients. Although COMISA is a highly prevalent condition which results in great impairment to sleep, daytime functioning, and quality of life, only a small amount of research has previously examined the effectiveness of various discrete and combined treatment approaches in this population. Therefore, it is important to undertake and report research such as this to improve understanding of the effectiveness of different treatment approaches in this population. The overall findings, limitations, and implications of the research undertaken in this thesis are discussed below.

7.2 Summary of Findings

7.2.1 COMISA Prevalence

The research included in this thesis suggests that co-morbid insomnia occurs in one third of OSA patients, and co-morbid OSA occurs in one third of insomnia patients in sleep disorder clinics. For example, Chapter 3 examined a consecutive group of treatment-seeking insomnia patients who routinely underwent a home-based PSG during their intake to the program. It was found that 31% (out of a total 455 patients) held sufficient diagnostic criteria for co-morbid OSA. Alternatively, Chapters 4, 5, and 6 used data collected from consecutive

patients referred to two sleep laboratories in Australia for suspected OSA. Of the 2,131 patients with OSA (according to an AHI of at least 15), clinically significant insomnia symptoms were present in 33.2% (707 patients). These data are in agreement with previous COMISA prevalence estimates drawn from sleep clinic populations (1, 2). Although prevalence rates appear to be increased in more specific samples including US military personnel/Veterans (3-5), and patients with treatment-resistant insomnia (6).

As the prevalence of COMISA is so high, it is suggested that patients presenting to sleep clinics with a chief-complaint of OSA also be tested for insomnia symptoms via easily administered questionnaires (e.g. the ISI). Alternatively, patients presenting with a chief-complaint of insomnia should be assessed for co-morbid OSA symptoms via either basic ambulatory studies (e.g. oximetry and nasal cannula to indicate OSA presence), or an overnight sleep study. Better detection of co-morbid insomnia and OSA will allow treating Physicians to prescribe more appropriate treatment approaches, resulting in greater treatment adherence, and better outcomes for each disorder. Alternatively, failure to detect co-morbid OSA among insomnia patients may result in inappropriate treatment of insomnia symptoms (e.g. with sedative medications), and failure to detect and manage insomnia symptoms among OSA patients may result in poor CPAP outcomes.

7.2.2 Effectiveness of CBT-i in COMISA

Two studies were conducted to examine the effectiveness of CBT-i in the COMISA population, and one additional study to examine changes in sleep parameters and daytime sleepiness during CBT-i. Chapter 3 compared insomnia improvements during CBT-i in patients with COMISA and patients with insomnia-only. It was assumed that the co-morbid group would be more difficult to treat because of the overlapping OSA symptoms, and therefore experience less insomnia improvement compared to patients with insomnia-only. However, similar improvements were observed in all sleep and daytime functioning

outcomes from baseline to 3-month follow-up. In fact, after controlling for baseline differences in age and gender, the only significant interaction indicated that COMISA patients experienced *greater* reduction of daytime sleepiness during treatment compared to the insomnia group. This effect was largely due to COMISA patients experiencing greater levels of daytime sleepiness at baseline, which was reduced to a similar level as the insomnia-only patients during treatment.

Chapter 4 indicated that COMISA patients treated with CBT-i show greater improvements in global insomnia severity, specific complaints of nocturnal insomnia symptoms, diary-measured sleep parameters, objectively measured night time wakefulness, and dysfunctional thinking patterns during treatment, compared to patients in a no-treatment control condition. Although the CBT-i condition showed significant improvement of daytime fatigue and functioning during treatment, these improvements were not significantly greater than those observed in the control condition. It is possible that these daytime symptoms were a manifestation of both the insomnia and OSA before treatment, and therefore showed a smaller response when only one disorder (i.e. the insomnia) was treated and the other remained invariant. Indeed, there were no changes in AHI from pre- to post-treatment in either condition, indicating that these patients' OSA severity remained unchanged during CBT-i.

As bedtime restriction therapy has been linked to increased sleepiness and performance deficits in OSA (7), Chapter 5 included an analysis of changes in sleep parameters and daytime sleepiness occurring with the bedtime restriction therapy component of CBT-i. It was found that levels of daytime sleepiness were slightly increased during the first week of bedtime restriction therapy, however returned to pre-treatment levels during the subsequent weeks. Alternatively, all sleep parameters were significantly improved at post-

treatment. These results indicate that CBT-i is a safe treatment in the presence of co-morbid OSA, when participants' subjective sleepiness is monitored from week-to-week.

Several research groups have suggested that COMISA patients should be treated with a combination of CBT-i and CPAP therapy to improve insomnia symptoms and facilitate improved acceptance and use of CPAP therapy. Previous research including a handful of case studies, pilot studies, and one randomized controlled trial have resulted in some disagreement over the effectiveness and appropriateness of CBT-i in the COMISA population. Furthermore, the only randomized controlled trial included only COMISA patients with mild OSA (8). The above chapters have extended these findings to indicate that the effectiveness of CBT-i is not impaired in the presence of co-morbid mild – severe OSA, CBT-i is more effective than a non-treatment control condition in COMISA patients, and CBT-i is also a safe and effective insomnia treatment in the presence of moderate and severe OSA. Furthermore, these findings have now been established in COMISA samples both with a chief-complaint of insomnia, and in those referred primarily for suspected OSA.

7.2.3 **Effect of CBT-i on CPAP outcomes in COMSIA**

Chapter 6 presented the findings of a multi-site randomized controlled trial, investigating the impact of CBT-i, versus a no-insomnia treatment control, on subsequent acceptance and use of CPAP therapy, and improvements in symptoms of insomnia and OSA. To the current authors' knowledge, this is the first high-quality randomized controlled trial investigating this 'combined' treatment approach in the COMSIA population. It was expected that improvements in sleep parameters occurring with CBT-i would result in greater acceptance and long-term adherence to CPAP therapy compared to the current 'treatment as usual' approach including CPAP-alone. Indeed, the participants initially receiving CBT-i were more likely to initially accept CPAP therapy, and displayed significantly greater rates of CPAP adherence over the first 4-months of treatment. A large body of research has now

found that COMISA patients display reduced CPAP adherence, compared to patients with OSA-alone. The present study indicates that initially treating the insomnia with CBT-i increases subsequent CPAP adherence in these COMISA patients.

Although the combination of CBT-i and CPAP therapy was associated with greater improvement of global insomnia severity, and improved CPAP outcomes, no differences in objective sleep, or daytime functioning outcomes were observed between conditions throughout the trial protocol. There are several possible reasons that similar patterns of sleep and daytime functioning improvement were observed in each condition. It appears that some COMISA patients' daytime impairments are resistant to change, even with treatment of each disorder. Although the CBT-i condition experienced greater CPAP adherence, it is possible that this difference in adherence was not large enough to result in greater improvements in daytime functioning measures compared to the control condition. It is also possible that these daytime impairments were also partly a result of additional un-controlled medical or psychiatric diagnoses (e.g. depression and anxiety which are also associated with daytime sleepiness and fatigue). Therefore, future research examining additional psychiatric and medical co-morbidities in these COMISA patients who experience residual daytime functioning impairments should be undertaken.

7.3 Secondary Insomnia

Some researchers have discussed the possibility that COMISA patients' insomnia is a secondary manifestation of their OSA (9-11). Indeed, previous research has found that treating the OSA can improve insomnia symptoms in COMISA patients (10, 12-14). Lichstein (15) suggests that in cases of secondary insomnia, the insomnia should show no response to targeted insomnia treatment (e.g. CBT-i) but show large improvement with treatment of the (assumed) primary disorder (e.g. treatment of OSA with CPAP therapy). Hypothetically, if COMISA patients' insomnia represents a secondary manifestation of their

OSA it would be expected that; a) COMISA patients would experience less insomnia-improvement during CBT-i compared to patients with insomnia-only, b) COMISA patients treated with CBT-i would experience similar changes in insomnia compared to COMISA patients in a control condition, and c) COMISA patients with more severe OSA would experience less insomnia improvement with CBT-i than COMISA patients with mild or moderate OSA. As each of these hypotheses were rejected, the suggestion that the majority of COMISA patients experience secondary insomnia is not supported.

Firstly, COMISA patients showed an adequate treatment response when treated with CBT-i. Not only did COMISA patients experience similar insomnia improvements during CBT-i compared to patients with insomnia-alone (Chapter 3), but also experienced greater insomnia improvement following CBT-i compared to a no-treatment control (Chapter 4). Furthermore, the severity of patients' OSA also had no impact on the effectiveness of CBT-i in either of these above studies, suggesting that greater presence or severity of OSA does not impair the effectiveness of CBT-i in treating insomnia symptoms.

Finally, if COMISA patients' insomnia symptoms were secondary to their OSA, CPAP therapy would treat both the insomnia and OSA. However, previous research has found that insomnia symptoms reduce CPAP adherence in COMISA (16-20) and can even cause new-onset insomnia in some cases (21). Furthermore, Chapter 6 demonstrates that treating insomnia symptoms prior to starting CPAP results in greater acceptance and long-term use of CPAP therapy. These data indicate that untreated insomnia symptoms are associated with worse CPAP outcomes, which would not be expected if the insomnia was secondary and improved with CPAP therapy.

Alternatively, (in Chapter 6) some participants receiving CPAP-alone did show significant improvement of insomnia symptoms after beginning CPAP therapy. For example, from 6-weeks to 6-months, control participants experienced a significant 5-point decrease in

global insomnia severity, 6.7% increase in diary-measured sleep efficiency, 28-minute improvement in diary-measured total sleep time, and 26-minute reduction in diary-measured wake after sleep onset. Furthermore, while 74% of these control patients experienced clinically significant insomnia before beginning CPAP, this number was reduced to 30% by the 6-month follow-up. This supports the notion that some insomnia secondary to OSA may be present since treatment with CPAP was associated with decreases in insomnia symptoms.

Taken together, these findings suggest that the insomnia symptoms of COMISA patients are a combination of factors independent of the OSA and secondary to the OSA. If the insomnia complaint is conceptualized as being mostly or entirely secondary to the OSA, effective treatment with CBT-i is likely not to be considered, and patients would then have reduced CPAP outcomes when treated with CPAP-alone. Although some COMISA patients appear to experience improvement of insomnia symptoms with CPAP therapy, previous attempts to distinguish these patients according to presenting symptoms/phenotypes at baseline have been contradictory (10, 12, 16, 21). Therefore, until further phenotyping/tailored-treatment research is undertaken, it is recommended that the insomnia continue to be conceptualized as a functionally independent disorder, and COMISA patients receive targeted treatments for each diagnosis (22). Recent diagnostic schema also recommends a diagnosis of 'insomnia disorder' (28), and 'co-morbid insomnia' (22), rather than the historical 'secondary insomnia' in cases of co-occurring insomnia.

7.4 Limitations and Generalizability

This thesis includes several chapter-specific limitations sections, however more general limitations of the thesis, and the generalizability of these results also warrants consideration. Firstly, the only treatments which were considered in the preceding chapters were CBT-i, and CPAP therapy. Although these are the most effective treatments for insomnia and OSA, respectively, not all COMISA patients will wish to undertake CBT-i, and

many patients immediately reject or discontinue CPAP therapy over time. Therefore, future research investigating the effectiveness and adherence to other insomnia- and OSA-treatments in these COMISA patients who reject CBT-i and CPAP therapy is recommended. For example, upper-airway surgery and mandibular advancement devices are commonly considered when CPAP therapy is rejected. Alternatively, alongside CBT-i, sedative/hypnotic medication are the most commonly studied and prescribed insomnia treatment (23). Although there has been great reluctance to prescribe insomnia-medications in the presence of co-morbid OSA (24), more recent research suggests that some medications may be more suitable in specific OSA populations (25).

The timing and sequence of the 'combined' CBT-i and CPAP therapy approach may also play an important role in acceptance and use of CPAP therapy. For example, the current study considered only the impact of sequential treatment with CBT-i and CPAP therapy versus CPAP-alone, whilst on-going research by another group aims to compare these two treatment approaches with simultaneous delivery of CBT-i and CPAP therapy (27). It is possible that simultaneous treatment of both the insomnia and OSA will result in more robust and rapid improvements to each disorder, and increased CPAP adherence. However, the sequential treatment approach was chosen in the study reported above, because it enabled an interim measure of insomnia- and OSA-severity between the CBT-i and CPAP phases.

The two samples examined in the experimental chapters of this thesis were patients recruited from sleep disorder units, and their treatment-responses may not generalize to other samples. For example, these participants were motivated to seek treatment, and may have been more likely to adhere to CBT-i protocols, and CPAP therapy, compared to COMISA patients recruited from primary care settings, or the general population. Furthermore, the participants examined in chapters 4 – 6, included patients with at least moderate insomnia *and* OSA (although many were in the severe range of each disorder). For example, insomnia

was diagnosed by psychologists according to strict questionnaire, sleep diary, and self-report criteria, whilst OSA was diagnosed by sleep physicians, according to an overnight sleep study and a AHI of at least 15. Therefore, each of these participants indicated at least moderate symptoms of insomnia and OSA at baseline, and their treatment-responses may be different to participants in other research samples. Figure 7.1 presents different diagnostic severity ratings and symptoms for insomnia and OSA, with the shaded red sections indicating the minimum severity of each disorder required for inclusion to the treatment program examined in chapters 4 – 6. Other COMISA research has also examined patients with more severe insomnia but less severe OSA (8), and more severe OSA but less severe insomnia (10). The characteristics of these COMISA samples should be considered when comparing samples from different studies, or clinical patients in sleep units.

Finally, symptoms of additional co-morbid psychiatric and medical disorders were common in these samples and may have impacted the patterns of improvements in each disorder. However, these co-morbidities are very common in the COMISA population (in fact, co-morbid psychiatric co-morbidities appear to be more common among COMISA patients, compared to patients with OSA-alone) (1, 26), and a choice was made to include patients with various medical and psychiatric symptoms, to increase the external validity of the findings.

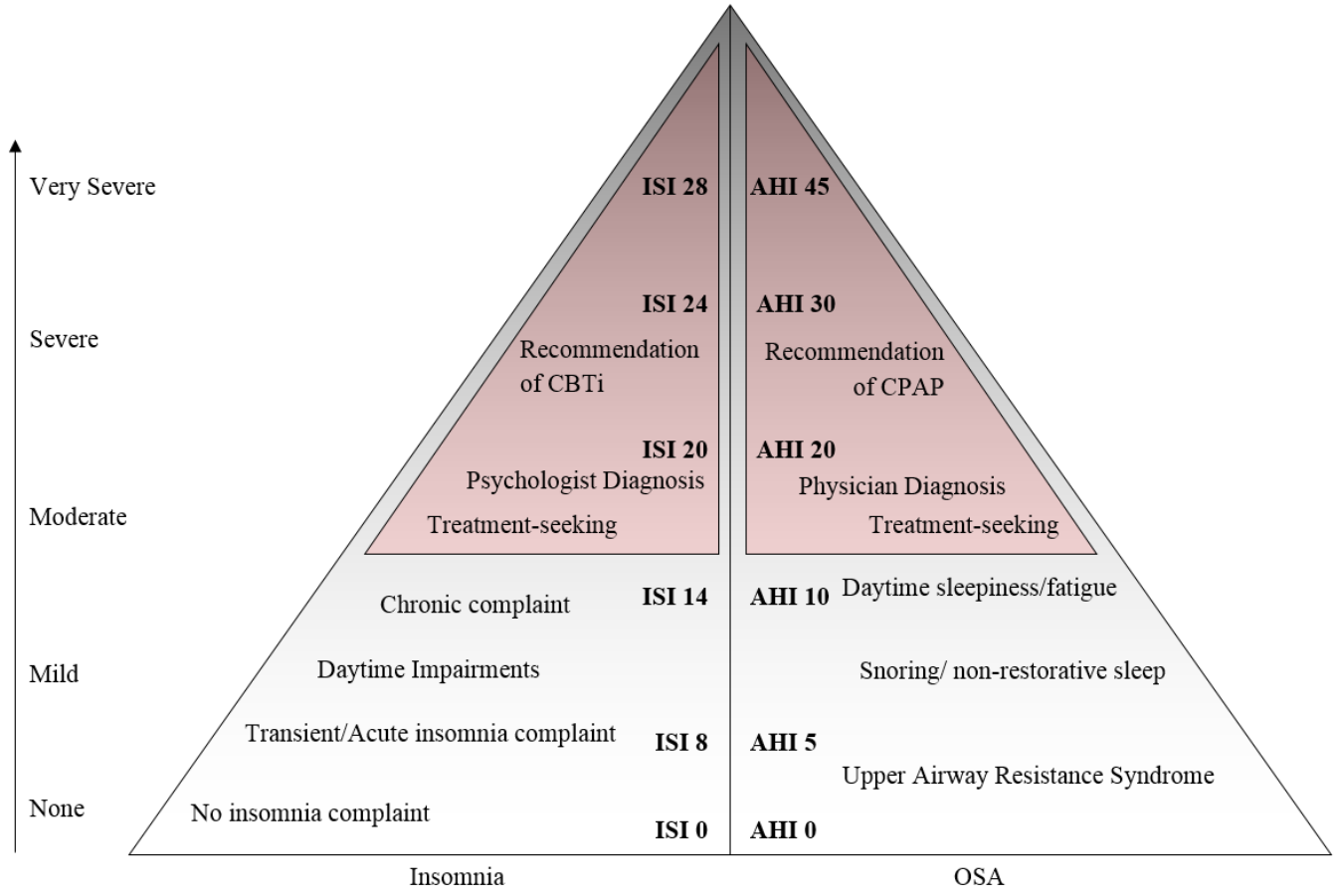

Figure 7.1. Severity Triangle indicating possible 'severity' cut-offs in COMISA research, with the darker triangles indicating the cut-off utilized in chapters 4 – 6.

7.5 Conclusions

Co-morbid insomnia and OSA is a highly prevalent and debilitating condition. Only a small amount of research has previously examined the effectiveness of different treatment approaches in this population, and has resulted in contradictory evidence. The above chapters indicate, in two samples of COMISA patients, that these patients' insomnia can be effectively treated with existing cognitive and behavioral techniques. This thesis has also documented the results of this long-awaited randomized controlled trial, investigating the effectiveness of combined CBT-i and CPAP therapy, versus CPAP therapy-alone, in the treatment of COMISA. As combined CBT-i and CPAP therapy results in greater improvements in insomnia severity, and increased CPAP outcomes, it is recommended that this treatment approach is considered for future COMISA patients in sleep clinic settings. More research is needed to confirm the findings of this thesis in other samples, and further refine treatment approaches for this common and complex disorder.

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8 APPENDICES

8.1 APPENDIX A - Insomnia Severity Index

Please circle the appropriate response for ALL QUESTIONS.

Please rate the current severity of your insomnia problem(s).

Difficulty falling asleep

none mild moderate severe very severe

Difficulty staying asleep

none mild moderate severe very severe

Problem waking up too early

none mild moderate severe very severe

2. How satisfied/dissatisfied are you with your current sleep pattern?

Very satisfied Satisfied Neutral Dissatisfied Very dissatisfied

0 1 2 3 4

3. To what extent do you consider your sleep problem to INTERFERE with your daily functioning?

(eg daytime fatigue, ability to function at work/daily chores, concentration, memory, mood etc)

Not at all A little Somewhat Much Very much

Interfering interfering

0 1 2 3 4

4. How noticeable to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not noticeable A little Somewhat Much Very much

at all noticeable

0 1 2 3 4

5. How worried/distressed are you about your current sleep problem?

Not at all A little Somewhat Much Very much

worried worried

0 1 2 3 4

8.2 APPENDIX B - Flinders Fatigue Scale

We are interested in the extent that you have felt **fatigued** (tired, weary, exhausted) over the last **two weeks**.
We **do not** mean feelings of **sleepiness** (the likelihood of falling asleep).
Please circle the appropriate response in accordance with your average feelings over this two-week period.

Was fatigue a problem for you?

0	1	2	3	4
Not at all		moderately		extremely

Did fatigue cause problems with your everyday functioning (eg: work, social, family)?

0	1	2	3	4
Not at all		moderately		extremely

Did fatigue cause you stress?

0	1	2	3	4
Not at all		moderately		extremely

How often did you suffer from fatigue?

0	1	2	3	4
0 days/week	1-2 days/week	3-4 days/week	5-6 days/week	7 days/week

At what time(s) of the day did you typically experience fatigue? ***Please tick box(es)***

Early morning	☐	Late afternoon	☐
Mid morning	☐	Early evening	☐
Midday	☐	late evening	☐
Mid afternoon	☐		

How severe was the fatigue you experienced?

0	1	2	3	4
Not at all		moderately		extremely

How much was your fatigue caused by poor sleep?

0	1	2	3	4
Not at all		moderately		entirely

8.3 APPENDIX C - Daytime Feelings and Functioning Scale

We would like to know how you are feeling and functioning during the day.
Please indicate how frequently across the past two weeks you have:
(tick one box for each statement)

	Never or seldom	**Occasionally**	**Often**	**Frequently or almost all the time**
Felt lethargic	☐	☐	☐	☐
Felt irritable	☐	☐	☐	☐
Lacked motivation	☐	☐	☐	☐
Been unable to concentrate	☐	☐	☐	☐
Had trouble with poor memory	☐	☐	☐	☐
Felt fatigued	☐	☐	☐	☐
Had difficulty accomplishing daytime tasks	☐	☐	☐	☐
Found it difficult to enjoy social interactions	☐	☐	☐	☐
Felt generally ill	☐	☐	☐	☐
Felt you had a reduced quality of life	☐	☐	☐	☐
Found it difficult to organise your thoughts	☐	☐	☐	☐
Felt depressed	☐	☐	☐	☐

‘

8.4 APPENDIX D – Depression, Anxiety and Stress Scale

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found it hard to wind down	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5	I found it difficult to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (eg, in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life was meaningless	0	1	2	3

8.5 APPENDIX E - The Epworth Sleepiness Scale

How likely are you to fall asleep in the following situation, in contrast to feeling just tired? This scale refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

0 = would **never** doze
1 = **slight** chance of dozing
2 = **moderate** chance of dozing
3 = **high** chance of dozing

Situation:	**Chance of dozing**
Sitting and reading	___
Watching TV	___
Sitting inactive in a public space (eg Theatre or meeting)	___
A passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	___

8.6 APPENDIX F - The Beliefs and Attitudes about Sleep Scale

Several statements reflecting people's beliefs and attitudes about sleep are listed below. Please indicate to what extent you personally agree or disagree with each statement. There is no right or wrong answer. For each statement circle the appropriate number.

1. I need 8 hours of sleep to feel refreshed and function well during the day.

0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE										STRONGLY AGREE

Same rating scale for all subsequent items:

2. When I don't get the proper amount of sleep on a given night, I need to catch up on the next day by napping or on the next night by sleeping longer.

3. I am concerned that chronic insomnia may have serious consequences on my physical health.

4. I am worried that I may lose control over my abilities to sleep.

5. After a poor night's sleep, I know that it will interfere with my daily activities on the next day.

6. In order to be alert and function well during the day, I believe I would be better off taking a sleeping pill rather than having a poor night's sleep.

7. When I feel irritable, depressed, or anxious during the day, it is mostly because I did not sleep well the night before.

8. When I sleep poorly on one night, I know it will disturb my sleep schedule for the whole week.

9. Without an adequate night's sleep, I can hardly function the next day.

10. I can't predict whether I'll have a good or poor night's sleep.

11. I have little ability to manage the negative consequences of disturbed sleep.

12. When I feel tired, have no energy, or just seem not to function well during the day, it is generally because I did not sleep well the night before.

13. I believe insomnia is essentially the result of a chemical imbalance.

14. I feel insomnia is ruining my ability to enjoy life and prevents me from doing what I want.

15. Medication is probably the only solution to sleeplessness.

16. I avoid or cancel obligations (social, family) after a poor night's sleep.

8.7 APPENDIX G - OSA50

OSA50 Screening Questionnaire (SALHN, Version 1.0)

		If yes, SCORE
Obesity	Waist circumference* - Male > 102cm or Female > 88cm	3
Snoring	Has your snoring ever bothered people?	3
Apnoeas	Has anyone noticed that you stop breathing during your sleep?	2
50	Are you aged 50 or over?	2
Total		**……/10**

* Waist measurement to be measured at the level of the umbilicus

Total Scores of 5 or greater indicated possible OSA, and progression to further screening

8.8 APPENDIX H - Overnight sleep diary

The diary starts at **9 a.m.** on the first day

Fill in just before going to bed at night:

Using the letters below, record the following activities at the appropriate times

C – Caffeine (one C for each cup of coffee, tea, chocolate, glass of cola etc.)

A – Alcohol (one A for each standard alcoholic beverage)

F – Food

P – Sleeping pill (Name/s _____)

Rate your level of daytime fatigue in the 'Daytime Fatigue' column by circling the appropriate level (**Hi** = High, **Med** = Medium, **Low** = Low) for your feeling of fatigue generally across that day.

Place a 'down' arrow ( ) at the time you go to bed

Place a ● when you turned out your light

Fill in when you get up in the morning:

Draw a thick line [ ] across the graph over the times you were asleep (including daytime naps)

Leave gaps in the line to show where you believe you were awake during the night.

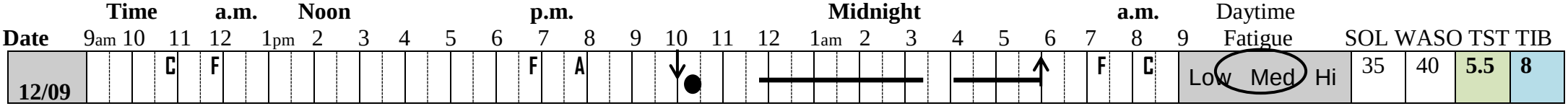
Place an up arrow (↑) at the time you get out of bed

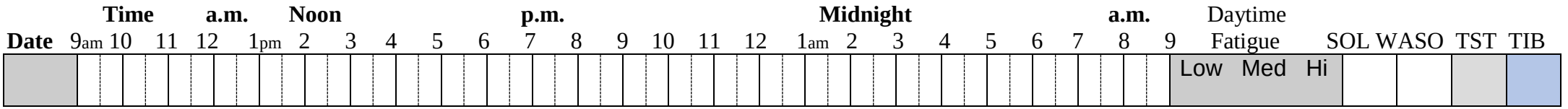
Estimate how long (**minutes**) it took you to fall asleep after turning out the light and enter that estimate in the **SOL (sleep onset latency)** column.

Estimate how long (**minutes**) you felt you were awake during the night after initially falling asleep and before getting out of bed and enter that estimated time in the **WASO (wake after sleep onset)** column.

Estimate how long you slept in total hours and enter that estimate in the **TST (total sleep time)** column.

Determine the amount of time in hours you spent in bed from (↓) to (↑) and enter that figure in the **TIB (time in bed)** column.





Can you please estimate the following:

How did you sleep compare to a normal night? (**Please circle**)

Much worse than usual **A little worse than usual** **About usual** **A little better than usual** **Much better than usual**

If your night was different form a normal night, why was this (i.e., wires uncomfortable, etc.)

_____

_____

How do you feel this morning?

_____

_____

If you had a night using CPAP, how well did you tolerate it?

_____

_____

8.9 APPENDIX I - 7-day sleep diary

The diary starts at **9 a.m.** on the first day

Fill in just before going to bed at night:

Using the letters below, record the following activities at the appropriate times

C – Caffeine (one C for each cup of coffee, tea, chocolate, glass of cola etc.)

A – Alcohol (one A for each standard alcoholic beverage)

F – Food

P – Sleeping pill (Name/s _____)

Rate your level of daytime fatigue in the 'Daytime Fatigue' column by circling the appropriate level (**Hi** = High, **Med** = Medium, **Low** = Low) for your feeling of fatigue generally across that day.

Place a 'down' arrow ( ) at the time you go to bed

Place a ● when you turned out your light

Fill in when you get up in the morning:

Draw a thick line [ ] across the graph over the times you were asleep (including daytime naps)

Leave gaps in the line to show where you believe you were awake during the night.

Place an up arrow ( ) at the time you get out of bed

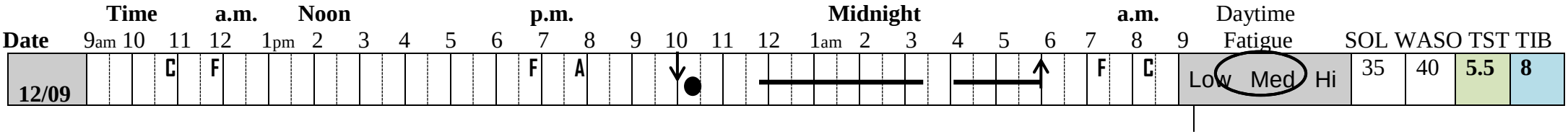
Estimate how long (**minutes**) it took you to fall asleep after turning out the light and enter that estimate in the **SOL (sleep onset latency)** column.

Estimate how long (**minutes**) you felt you were awake during the night after initially falling asleep and before getting out of bed and enter that estimated time in the **WASO (wake after sleep onset)** column.

Estimate how long you slept in total hours and enter that estimate in the **TST (total sleep time)** column.

Determine the amount of time in hours you spent in bed from ( ) to ( ) and enter that figure in the **TIB (time in bed)** column.

Example



	Time a.m.				Noon				p.m.								Midnight				a.m.									Daytime			
Date	9am	10	11	12	1pm	2	3	4	5	6	7	8	9	10	11	12	1am	2	3	4	5	6	7	8	9	Fatigue			SOL	WASO	TST	TIB
																										Low	Med	Hi				
																										Low	Med	Hi				
																										Low	Med	Hi				
																										Low	Med	Hi				
																										Low	Med	Hi				
																										Low	Med	Hi				
																										Low	Med	Hi				
																															+	+

At the end of the week, add up your daily TST and TIB = **Total for week**

Divide these by 7

÷ ÷

Daily Average

TST TIB

Calculate your Sleep Efficiency at the end of the week by dividing your Daily Average TST by you Daily Average TIB, and Multiplying by 100.

$$\frac{\text{Daily Average TST}}{\text{Daily Average TIB}} = \frac{\square}{\square} \times 100 = \square$$ Your sleep efficiency

8.10 APPENDIX J - Treatment Credibility Questionnaire

We would like you to indicate below how much you believe, *right now*, that the therapy you are receiving will help to reduce your symptoms. Belief usually has two aspects to it: (1) what one *thinks* will happen and (2) what one *feels* will happen. Sometimes these are similar; sometimes they are different. Please answer the questions below. In the first set, answer in terms of what you *think*. In the second set, answer in terms of what you really and truly *feel*.

Set I

1. At this point, how logical does the therapy offered to you seem?

1	2	3	4	5	6	7	8	9
not at all logical				somewhat logical				very logical

2. At this point, how successfully do you think this treatment will be in reducing your symptoms?

1	2	3	4	5	6	7	8	9
not at all useful				somewhat useful				very useful

3. How confident would you be in recommending this treatment to a friend who experiences similar problems?

1	2	3	4	5	6	7	8	9
Not at all confident				somewhat confident				very confident

4. By the end of the therapy period, how much improvement in your symptoms do you think will occur?

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Set II

For this set, close your eyes for a few moments, and try to identify what you really *feel* about the therapy and its likely success. Then answer the following questions.

1. At this point, how much do you really *feel* that the therapy will help you reduce your symptoms?

1	2	3	4	5	6	7	8	9
Not at all				somewhat				very much

2. By the end of the therapy period, how much improvement in your symptoms do you really *feel* will occur?

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

8.11 **APPENDIX K - Treatment Fidelity Checklist**

COMISA RCT – CBT-i Treatment Fidelity Audit Checklist

Purpose: Checklist used to rate audio-recordings of CBT-i sessions for expected content.

Raters: Raters of the audiotapes should be independent of the study and blind to treatment assignment, participant progress and outcomes, and provider identity. Raters should be psychologists skilled in treatment delivery, and be trained to use the treatment manual.

Instructions:
Note session site (AISH or TPCH) and recording number
Note session number/type (session 1-4)
Rate session on scale 1-7 for each element of content. Note as 'not applicable' if an element is not included for a specific reason (e.g. after review, therapist does not proceed with a treatment element)
Rate session (overall) on scale 1-7 for elements of procedure and process (see examples at end)
Rate session on scale 1-7 for the presence of components not specified by the treatment protocol (e.g. other types of therapy)
Provide explanatory comments for variances, low ratings or other concerns.

Site (AISH or TPCH)
Recording number _____
Session 1. Sleep Education & Bed Restriction Therapy (BRT)

Content:	Present			Partial			Absent	na
Nature of Sleep	1	2	3	4	5	6	7	☐
Sleep with Age	1	2	3	4	5	6	7	☐
Sleep Debt	1	2	3	4	5	6	7	☐
Spending too long in bed	1	2	3	4	5	6	7	☐
Explained Bed Restriction Therapy	1	2	3	4	5	6	7	☐
Set new Bedtime Schedules	1	2	3	4	5	6	7	☐
Give sleep diary, sleepiness questionnaire, Participant Manual etc.	1	2	3	4	5	6	7	☐
Confirm attendance at following week's session	1	2	3	4	5	6	7	☐

Procedure	1	2	3	4	5	6	7	☐
Process	1	2	3	4	5	6	7	☐

Components not specified by the protocol	1	2	3	4	5	6	7	☐

Comments:

Session 2. Misperceptions of Sleep & PSG Feedback

Content:	Present			Partial			Absent	na
Review of Session 1	1	2	3	4	5	6	7	☐
Review of Bed Restriction Therapy	1	2	3	4	5	6	7	☐
Explain Sleep Efficiency	1	2	3	4	5	6	7	☐
Discuss Misperceptions of Sleep	1	2	3	4	5	6	7	☐
Feedback about sleep – Explain Hypnogram and Sleep Diaries	1	2	3	4	5	6	7	☐
Give each patient their individual feedback	1	2	3	4	5	6	7	☐
Speak to Each patient	1	2	3	4	5	6	7	☐
Have Patients calculate their own Sleep Efficiency	1	2	3	4	5	6	7	☐
Adjust Bedtime Schedule (extend TIB, reduce TIB, maintain current TIB)	1	2	3	4	5	6	7	☐
Have each patient fill out an Epworth Sleepiness Scale	1	2	3	4	5	6	7	☐
Confirm attendance at following week's session	1	2	3	4	5	6	7	☐

Procedure	1	2	3	4	5	6	7	☐
Process	1	2	3	4	5	6	7	☐

Components not specified by the protocol	1	2	3	4	5	6	7	☐

Comments:

Site (AISH or TPCH) _____
Recording number _____

Session 3. Hyperarousal & Anxiety in Insomnia

Content:	Present			Partial			Absent	na
Review of Session 2	1	2	3	4	5	6	7	☐
Insomnia – What is it?	1	2	3	4	5	6	7	☐
Bonnet and Arand – Insomnia Research	1	2	3	4	5	6	7	☐
Introduce and explain Hyperarousal	1	2	3	4	5	6	7	☐
Reducing Hyperarousal	1	2	3	4	5	6	7	☐
Cognitive Therapy	1	2	3	4	5	6	7	☐
Adjust Bedtime Schedules	1	2	3	4	5	6	7	☐
Confirm attendance at next week's session	1	2	3	4	5	6	7	☐

Procedure	1	2	3	4	5	6	7	☐
Process	1	2	3	4	5	6	7	☐

Components not specified by the protocol	1	2	3	4	5	6	7	☐

Comments:

Site (AISH or TPCH) _____
Recording number _____

Session 4. Review and Relapse Prevention

Content:	Present Partial Absent	na
Review of Session 1	1 2 3 4 5 6 7	☐
Review of Session 2	1 2 3 4 5 6 7	☐
Review of Session 3	1 2 3 4 5 6 7	☐
Relapse Prevention	1 2 3 4 5 6 7	☐
Calculate Sleep Efficiency & Sleepiness scores. Set new Bedtime Schedules	1 2 3 4 5 6 7	☐
Make sure they have Sleep Diaries for following 2 weeks	1 2 3 4 5 6 7	☐
Make sure they have Epworth Sleepiness Scales for following 2 weeks	1 2 3 4 5 6 7	☐

Procedure	1 2 3 4 5 6 7	☐
Process	1 2 3 4 5 6 7	☐

Components not specified by the protocol	1 2 3 4 5 6 7	☐

Comments:

Examples:

Procedure components (procedural and practical aspects of a session) might include:
Opening (including time available and how client has been)
Collaborative outline for session agenda
Eliciting and responding to feedback
Close of session with wrap up summary
Generalisation/continuity strategies (e.g. homework tasks)

Process elements (use of core psychological competencies) are elements that might be expected as part of the session, but are not specific to this intervention:
Open questions
Affirmations
Reflective listening
Use of summaries
Collaboration/seeking permission
Empathy/understanding
Autonomy and support
Pacing/use of time
Guided exploration
Shared understanding/formulation

References & Resources

1. Haddock, G., et al., *Assessing fidelity to integrated motivational interviewing and CBT therapy for psychosis and substance use: the MI-CBT fidelity scale (MI-CTS).* Journal of Mental Health, 2012. 21(1): p. 38-48.
2. Borrelli, B., et al., *A new tool to assess treatment fidelity and evaluation of treatment fidelity across 10 years of health behavior research.* Journal of consulting and clinical psychology, 2005. 73(5): p. 852.
3. Borrelli, B., *The assessment, monitoring, and enhancement of treatment fidelity in public health clinical trials.* Journal of public health dentistry, 2011. 71(s1): p. S52-S63.
4. Bellg, A.J., et al., *Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH Behavior Change Consortium.* Health Psychology, 2004. 23(5): p. 443.
5. Gearing, R.E., et al., *Major ingredients of fidelity: A review and scientific guide to improving quality of intervention research implementation.* Clinical psychology review, 2011. 31(1): p. 79-88.
6. Hoffmann, T.C., et al., *Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide.* BMJ: British Medical Journal, 2014. 348.

8.12 **APPENDIX L - Treatment Fidelity Report**

Intervention description CBT-i in COMISA (TIDier format) (1)

Items included in the Template for Intervention Description and Replication (TIDieR) checklist: information to include when describing an intervention. Full version of checklist provides space for authors and reviewers to give location of the information (see appendix 3)

Item No	Item
Brief name	
1	Provide the name or a phrase that describes the intervention
	Cognitive Behavioural Therapy for Insomnia (CBT-i) in Comorbid Insomnia and Obstructive Sleep Apnoea
Why	
2	Describe any rationale, theory, or goal of the elements essential to the intervention
	Cognitive Behaviour Therapy for Insomnia (CBT-i) is recommended as first line therapy in the 2008 American Academy of Sleep Medicine (AASM) Clinical Guidelines for the Evaluation and Management of Chronic Insomnia in Adults (2). Three Cochrane Reviews support the clinical use of CBT-i, and a recent major review by the Standards of Practice Committee of the AASM also strongly supports the efficacy of CBT-i (3). The efficacy of CBT-i demonstrated in highly controlled studies also translates to effectiveness in the real world clinical environment (4), including cases where insomnia is associated with certain co-morbid medical conditions. However, the benefit of CBT-i for patients with Insomnia comorbid with Obstructive Sleep Apnoea is uncertain. We have modified and standardized a CBT-i package (5) for use in the OSA population. The core elements have a strong evidence base and are regarded as effective in combination (3). The intervention excluded content focussed on specific aspects of the diagnosis or management of OSA, and any content associated with promoting CPAP adherence directly. Any concerns raised during CBT-i associated with the CPAP therapy were referred back to sleep clinic staff.
What	

Item No	Item
3	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (such as online appendix, URL)
	The CBT-i material for each session was developed into a clinician manual (with scripts), a separate participant manual (with illustrations, guide to the intervention and additional support materials), and a pdf/slide set of illustrative materials used during each session. Content for each session included: Session one - addresses Sleep Education & Bed Restriction Therapy (BRT) Session two - addresses Misperception of sleep and PSG feedback. Session three - addresses Hyperarousal & Anxiety in Insomnia. Session four - addresses intervention Review and Relapse Prevention. In addition to the standard outcome measures, participants in the CBT-i arm completed a treatment credibility questionnaire at the final session. The manuals and associated materials are available from the authors.
4	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities
	#####
Who provided	
5	For each category of intervention provider (such as psychologist, nursing assistant), describe their expertise, background, and any specific training given
	The intervention was provided by psychologists holding postgraduate qualifications and national registration, with hospital service accreditation. The psychologists each had additional background and experience in sleep and insomnia therapy specifically. Training in the trial intervention was provided through an initial group training workshop, with ongoing support via online and phone interactions between the therapists and investigators.
How	
6	Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group

Item No	Item
	The intervention was delivered predominantly in face-to-face individual sessions, although the protocol allowed for small group delivery. Occasional telephone sessions were delivered to maintain the delivery schedule (e.g. if an appointment was missed), with all other aspects of the intervention retained.
Where	
7	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features
	The intervention was delivered at the clinical sites, that is, in a major hospital or medical consulting environment with 'front desk' support and with participant parking provided on site.
When and How Much	
8	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose
	The CBT-i was delivered across four consecutive weekly sessions. Each session designed to take approximately 45-60 minutes.
Tailoring	
9	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how
	All core components of CBT-i were provided to all participants. Specific components were personalized according to algorithms or processes intrinsic to CBT-i. For example, bedtime restriction therapy techniques required specification of bed and wake times, according to psychologists' clinical judgements of participants' baseline self-reported sleepiness, sleep dairy reports, and changes in sleepiness and sleep parameters. Other aspects, such as psychoeducation on sleep, were oriented to each participant's individual overnight sleep study.
Modifications	
10*	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how)
	No modifications to the intervention were made during the course of the study.
How well	

Item No	Item
11	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them
	Intervention fidelity was assessed in two ways. First, the psychologist delivering the intervention completed a checklist at the end of each session. This checklist included all core intervention components intended for that session, with comment on any other issues that may have impacted on delivery. All psychologist checklist responses were entered into the clinical record forms and trial database. Second, all intervention sessions were recorded with unobtrusive digital recorders with the permission of the participants. A fidelity criteria checklist was developed for each session (based on recommendations; 6-9). The checklist included identification of the presence core intervention components specified for that session (6-10 items), identification of any content that wasn't specified by the protocol (1 item), and rating of procedure and process (2 items; generic psychologist skills implicit in delivery but not specific to this intervention). A random selection of CBT-i sessions (10%) were assessed against this checklist by a single independent expert. This rater was a psychologist with equivalent qualifications and experience to those of the intervention clinicians, blind to the study but with reference to the intervention manual). The recorded session content was rated on a Likert-like scale from 1 (present) to 7 (absent). These session checklists are available from the authors.
12*	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned
	Independent ratings; Mean ratings for both content and procedure/process across 31 session recordings was 1.1, and in no case was specified content noted as partial or absent. Mean rating for components not specified was 6.3, and in no case was unspecified component rated as present or partial.

*If checklist is completed for a protocol, these items are not relevant to protocol and cannot be described until study is complete.

References

1. Hoffman TC, Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., Altman, D. G., Barbour, V., Macdonald, h., Johnston, M., Lamb, S. E., Dixon-Woods, M., McCulloch, P., Wyatt, J. C., Chan Phelan, AW., & Michie, S. Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *British Journal of Medicine*. 2014;348:p1687.
2. Schutte-Rodin S, Broch, L., Buysse, D., Dorsey, C. & Sateia, M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *Journal of Clinical Sleep Medicine*. 2008;4(5).
3. Morgenthaler T, Kramer, M., Alessi, C., Friedman, L., Boehlecke, B., Brown, T., Coleman, J., Kapur, V., Lee-Chiong, T., Owens, J., Pancer, J., & Swick, T. Practice parameters for the psychological and behavioral treatment of insomnia: An update. An American Academy of Sleep Medicine report. *Sleep*. 2006;29(11):1415-9.
4. Espie C, Inglis, S. J., Tessier, S., & Harvey, L. The clinical effectiveness of cognitive behaviour therapy for chronic insomnia: Implementation and evaluation of a sleep clinic in general medical practice. *Behaviour Research and Therapy*. 2001;39:45-60.
5. Morin CM, & Espie, C. A. *Insomnia: A clinical guide to assessment and treatment*. NY: Kluwer Academic Publishers; 2003.
6. Borrelli, B., et al., A new tool to assess treatment fidelity and evaluation of treatment fidelity across 10 years of health behavior research. *Journal of consulting and clinical psychology*, 2005. 73(5): p. 852.
7. Borrelli, B., The assessment, monitoring, and enhancement of treatment fidelity in public health clinical trials. *Journal of public health dentistry*, 2011. 71(s1): p. S52-S63.

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9. Gearing, R.E., et al., Major ingredients of fidelity: A review and scientific guide to improving quality of intervention research implementation. *Clinical psychology review*, 2011. 31(1): p. 79-88.

8.13 APPENDIX M - Statistical Analysis Plan (For Chapter 5)

Title: Treating insomnia co-morbid with obstructive sleep apnoea: a randomized controlled clinical effectiveness trial.
Site: Flinders University of South Australia, Repatriation General Hospital, South Australia; The Prince Charles Hospital, Queensland.
Queensland University of Technology
The University of Queensland
Funding: National Health and Medical Research Council; 2013. NHMRC Identifier: 1049591.

Acronyms:
Cognitive Behavioral Therapy for Insomnia – CBT-i
Continuous Positive Airway Pressure - CPAP
Polysomnography - PSG

Design statement: This study is a prospective, parallel-arm randomized control trial (see example Figure 1). A two (initial treatment condition: CBT-i, vs. treatment as usual-control) by four (time: Baseline, 6-weeks, 3-months, 6-months) mixed design will be used to investigate the effectiveness of initial CBT-i, versus no treatment for insomnia, on subsequent objective CPAP adherence, and long-term improvements in insomnia and obstructive sleep apnoea.
Participants will include 140 patients with co-morbid insomnia and sleep apnea, who will be recruited through two sleep disorder units in Australia; The Repatriation General Hospital in Adelaide, South Australia, and The Prince Charles Hospital in Brisbane, Queensland.

1.1 Hypotheses to be tested:

The primary null hypotheses are that for CBT-i prior to CPAP treatment vs. CPAP treatment alone, there will be no difference in;
Objectively measured average nightly CPAP adherence (Data collected from CPAP-initiation to 6-month follow-up).
Change in PSG-derived sleep efficiency from baseline to 6-months (i.e. percentage of time in bed spent asleep).

It is hypothesized that, relative to the control condition, CBT-i will result in:
Greater average nightly minutes of CPAP use
Greater improvements in PSG-derived sleep efficiency from baseline to 6-month follow-up (i.e. percentage of time in bed spent asleep).

1.2. Statistical analysis of primary analyses:

Primary Analysis 1: CPAP adherence.

Adherence to CPAP is defined as the average number of minutes per night of use, measured over three time points (CPAP setup to 1-week, 1-week to 3-month follow-up, and 3-month to 6-month follow-up), and will be treated as a continuous variable. Objective adherence data will be manually downloaded after 1-week of use, and at 3- and 6-month follow-ups. The

primary analysis is average nightly adherence from CPAP-setup to 6-month follow-up. The difference in average objective nightly CPAP adherence from CPAP setup to 6-months will be assessed between groups using **Linear Mixed Model** analyses on an intention to treat basis. This analysis will also be used to examine the interaction between group and time (CPAP setup to 1-week, 1-week to 3-month follow-up, and 3-month to 6-month follow-up) on average nightly CPAP adherence (further described in secondary hypothesis 5b).

These results will be presented in a tabular format (See Example Table 1, Figure 1)

Missing Data: This analysis will be conducted on an intention to treat basis. Randomized controlled trial participant withdrawal or rejection of CPAP treatment commonly results in missing data, however in this case, rejection of CPAP or withdrawal from the trial due to CPAP rejection will reflect '0' minutes of CPAP use for each night from the point of CPAP rejection, to the calculated 6-month review date. For any participants who begin using CPAP but rejected/withdrew before 6-month follow-up, average adherence will be calculated over all nights of CPAP use, and non-use for each follow-up period. Any participants who immediately reject CPAP therapy (i.e. never use throughout the trial), will be given a score of '0' minutes average nightly adherence.

Sensitivity Analysis:

Data will be inspected for proportion and patterns of missing data. Data will be defined as missing completely at random, missing at random, and missing not at random according to pre-defined criteria (1). If data are missing not at random, a sensitivity analysis will be conducted to determine the effect of missing data on primary analysis 1.

Primary Analysis 2: Sleep Efficiency.

Sleep efficiency will be measured via overnight home-based objective sleep studies (i.e. at home PSG) at baseline, 6-weeks, and 6-month follow-up. Sleep efficiency represents the percentage of time in bed that is spent objectively asleep. Total sleep time will be scored per *American Academy of Sleep Medicine* criteria (2). Time in bed parameters will be calculated according to physiological traces indicating in bed and final rise times, and participant self-report on the night of the PSG. Specifically, participants will indicate bed times, and rise times on an overnight sleep diary, during the evening and following morning of their PSG study. Sleep study scorers will then examine changes in physiologic data occurring at each of these indicated times (including position sensor changes from up-right to non-upright position, oximeter and nasal cannula attachment, and clear movement artefact) to estimate the specific times (to the nearest 30-second epoch) that participants went to bed and finally rose. The change in sleep efficiency between groups from Baseline to 6-month follow-up will be analyzed with **Linear Mixed Model** analyses. Individual sleep efficiency changes will also be modelled on sleep efficiency at 6-week follow-up. The dependent variable will be objective sleep efficiency, and the independent variable will be group assignment. The hierarchical nature of the design will represent repeated measures nested within individual participants, nested within higher-order groups (conditions).

These results will be presented in a tabular format (See Example Table 1).

Missing Data: This analysis will be conducted on an intention to treat basis. All baseline sleep efficiency data are expected to be collected, as a baseline sleep study is a prerequisite

for randomization into the trial. Mixed model analyses will be used and will account for any missing data, provided that it is either 'missing at random' or 'missing completely at random' (1, 3). Chi-square tests will be conducted to examine differences in proportions of missing data between conditions, to confirm that data adhere to 'missing at random' assumptions, and confirm the appropriate use of mixed models analyses.

Sensitivity Analysis:

Data will be inspected for proportion and patterns of missing data. Data will be defined as missing completely at random, missing at random, and missing not at random according to pre-defined criteria (1). If data are missing not at random, a sensitivity analysis will be conducted to determine the effect of missing data on primary analysis 1.

1.2 Statistical Analysis of Other/Secondary Outcomes:

The following pre-planned secondary outcomes analyses will also be undertaken:

Secondary Hypothesis 1.
An analysis to assess the effectiveness of the CBT-i intervention.
The hypothesis that will be tested is that participants treated with CBT-i will experience significantly greater improvements in global insomnia severity (Insomnia Severity Index), and night time insomnia symptoms (sleep diary average for: total sleep time, sleep onset latency, wake after sleep onset, and sleep efficiency) from baseline to 6-week follow-up, compared to participants in the treatment-as-usual condition.

This 'CBT-i effectiveness check' will be analyzed on an intention to treat basis using mixed models analyses. The results will be presented in a tabular format (See Example Table 1).

Secondary Hypothesis 2.
An examination of changes in insomnia severity (Insomnia Severity Index and sleep diary average: total sleep time, sleep onset latency, wake after sleep onset, and sleep efficiency), between groups, during treatment.

The hypothesis that will be tested it that participants treated with CBT-i will experience significantly greater improvements in global insomnia severity (Insomnia Severity Index), and night time insomnia symptoms (sleep diary average: total sleep time, sleep onset latency, wake after sleep onset, and sleep efficiency) from baseline to 6-month follow-up, compared to participants in the treatment-as-usual condition.

The above intention to treat, mixed model analysis will be extended to examine between-group differences in changes in sleep diary parameters from baseline to 6-month follow-up. Sleep diary responses from baseline, 6-week, 3-month, and 6-month follow-up will be used to model any missing data. These results will be presented in a tabular format (See Example Table 1).

Secondary Hypothesis 3.
An examination of changes in daytime impairment, and quality of life symptoms between groups, during treatment.

The hypothesis that will be tested is that participants treated with CBT-i will experience significantly greater improvements in subjective daytime sleep propensity (Epworth Sleepiness Scale), fatigue (Flinders Fatigue Scale), and depression, anxiety and stress (DASS: Depression, Anxiety and Stress Scale, Sub-scales) from baseline to 6-month follow-up, compared to participants in the treatment-as-usual condition.

These outcomes will be analyzed on an intention to treat basis, with mixed models analyses. Questionnaire responses from baseline, 6-week, 3-month, and 6-month follow-up will be used to model missing data. These results will be presented in a tabular format (See Example Table 1).

Secondary Hypothesis 4.
An examination of changes in objective total sleep time, and wake after sleep onset (via-PSG), between groups, during treatment.

The hypothesis that will be tested is that participants treated with CBT-i will experience a significantly greater increase in objective total sleep time, and decreased wake after sleep onset, from baseline to 6-month follow-up, compared to participants in the treatment-as-usual condition.

These sleep parameters will be analyzed on an intention to treat basis, with mixed models analyses. These results will be presented in a tabular format (See Example Table 1).

Secondary Hypotheses 5a- 5c.
The following pre-planned CPAP adherence outcomes, between groups, will be undertaken;

Proportion of participants immediately rejecting CPAP.

It is hypothesized that a significantly greater number of participants in the control condition will immediately reject CPAP therapy, following the CPAP titration, or CPAP setup, compared to the CBT-i condition. Immediate CPAP rejection will be defined as participants rejecting CPAP therapy on the CPAP titration night, participants refusing to collect CPAP equipment or attend CPAP set-up, or discontinuation and return of CPAP equipment without ever using equipment.

Fischers exact tests will be used to examine differences in rates of CPAP rejection (Rejected, vs. Accepted), between groups.

Differences in point-to-point CPAP adherence throughout the trial.

It is hypothesized that the control condition will experience a significantly greater decrease in average CPAP adherence from 1-week, to 3-month, to 6-month follow-up, compared to the CBT-i condition.

Objective CPAP adherence data will be collected over three interim time points. These include; CPAP setup to 1-week, 1-week to 3-months, and 3-months to 6-months. It is expected that average CPAP adherence will decrease over time in both conditions but the rate of decline will be less in participants allocated to CBT-i. This hypothesis will be analysed on an intention to treat basis with mixed model analyses. These results will be presented in a tabular and Graphical format (See example Table 1 and example Figure 2).

Investigation of per-protocol CPAP adherence (i.e. average nightly adherence, from setup to 6-months, between groups, including only participants who initially accepted CPAP/used CPAP at home).

As Primary Hypothesis 1, however conducted as per-protocol analysis. Therefore, only participants who accepted a home trial of CPAP, following CPAP titration studies will be included.

It is hypothesized that among individuals who engage in a home trial of CPAP, the CBT-i condition will display significantly greater average nightly CPAP adherence from baseline to 6-month follow-up, compared to the control condition.

This per-protocol analysis will be examined with an independent samples t-test, including only participants who initially accepted and used CPAP.

1.4 Model Validation:

Diagnostic tests to examine homescedasticity and normality of residuals will be carried out to ensure model validity, and transformations employed where necessary. Goodness of fit with various covariance structures will be used to select final models.
Missing data assumptions will be examined in more detail in sensitivity analyses.

1.5 Statistical Analysis of Adverse Events:

All adverse events will be reported and differences in adverse events between groups will be assessed using Pearson's chi square test without continuity correction or Fisher's exact test if the expected number in any cell in the contingency table is less than 5.

1.6 Power and Sample Size:

All calculations assume an overall Type 1 error rate of 0.05% and a Type 2 error rate of 20%. A total sample of 126 participants (63 per group) provides 80% power to detect an improvement of 1.25 hours per night in CPAP adherence, based on standard deviations for CPAP use in treatment as usual groups of approximately 2.5 hours /night (4). However, we will enroll a total of 140 participants to allow for 10% attrition. A >1.25 hours /night in CPAP adherence is expected after CBT-i because of increases in sleep efficiency and greater overall CPAP treatment acceptance and tolerance; the consensus amongst the participating sleep physicians is that a change of <1.25 hours /night is unlikely to be clinically significant. A 5% change in PSG-derived sleep efficiency is considered clinically significant and the minimum expected from other CBT-i trials (5). Our sample of 140 provides 80% power to detect this difference assuming a standard deviation in the order of 7.5 (6). For the Insomnia Severity Index, we have 80% power to detect difference of 3.4 ISI units (moderate clinical change in ISI is approximately 8.5), assuming a standard deviation in the order of 5 (6). These are conservative as we have assumed no correlation between baseline and follow-up readings for sleep efficiency and Insomnia Severity Index.

1.7 Additional Pre-Planned Publications:

In addition to the primary publication of results, there are several additional pre-planned publications;

Effectiveness of Cognitive and Behavior Therapy for Insomnia in patients with co-morbid Obstructive Sleep Apnea: A Randomized Controlled Trial

An economic analysis will be conducted alongside the trial to determine whether the costs of the CBT-i strategy are outweighed by cost savings (due to productivity gains and/or reduced health care utilization during the trial-period). This analysis will include patient and productivity costs, quality of life outcomes, and Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Schedule (MBS) utilization for all trial participants.

An exploratory analysis of between-group changes in objective sleep parameters (and physiologic night time manifestations of insomnia and OSA) from baseline to 6-week follow-up. This will also include an examination of how changes in these objective data during CBT-i (or control) are associated with future acceptance and use of CPAP therapy.

Statement and Signatures etc.

R Doug McEvoy
Study Principal Investigator [signature removed in uploaded version]

Paul Willliamson
Statistician [signature removed in uploaded version]

On behalf of the other investigators
Simon Smith, Leon Lack, James Douglas, Ching Li Chai-Coetzer, Peter Catcheside, Alexander Sweetman

Example Tables:

Table 1. Baseline Sociodemographic and Clinical Characteristics of Participants

Characteristic, baseline data	**CBT-i (n= 70)**	**Control (n = 70)**	**All Participants (n=140)**
Age, mean (SD), y	X.X (X)	X.X (X)	X.X (X)
Site, No. (%)			
Adelaide	X (X)	X (X)	X (X)
Brisbane	X (X)	X (X)	X (X)
Education duration, mean (SD), y	X.X (X)	X.X (X)	X.X (X)
Sex, No. (%)			
Female	X.X (X)	X.X (X)	X.X (X)
Male	X.X (X)	X.X (X)	X.X (X)
Site, No. (%) Adelaide	X.X (X)	X.X (X)	X.X (X)
Body Mass Index, mean, (SD)	X.X (X)	X.X (X)	X.X (X)
Occupation, No. (%)			
Employed	X.X (X)	X.X (X)	X.X (X)
Retired	X.X (X)	X.X (X)	X.X (X)
Homemaker	X.X (X)	X.X (X)	X.X (X)
Unemployed	X.X (X)	X.X (X)	X.X (X)
Questionnaire Outcomes			
Insomnia Severity Index, mean (SD)	X.X (X)	X.X (X)	X.X (X)
Epworth Sleepiness Scale, mean (SD)	X.X (X)	X.X (X)	X.X (X)
Flinders Fatigue Scale, mean (SD)	X.X (X)	X.X (X)	X.X (X)
Depression (DASS), mean (SD)	X.X (X)	X.X (X)	X.X (X)
Anxiety (DASS), mean (SD)	X.X (X)	X.X (X)	X.X (X)
Stress (DASS), mean (SD)	X.X (X)	X.X (X)	X.X (X)
Overnight Sleep Study			
Total Sleep Time, mean (SD), min	X.X (X)	X.X (X)	X.X (X)
Wake after sleep onset, mean (SD), min	X.X (X)	X.X (X)	X.X (X)
Sleep Efficiency, mean (SD), %	X.X (X)	X.X (X)	X.X (X)
Apnea/Hypopnea Index, mean (SD)	X.X (X)	X.X (X)	X.X (X)
Arousal Index, mean (SD)	X.X (X)	X.X (X)	X.X (X)
Sleep Diary			
Total sleep time, mean (SD), min	X.X (X)	X.X (X)	X.X (X)
Sleep onset latency, mean (SD), min	X.X (X)	X.X (X)	X.X (X)
Wake after sleep onset, mean (SD), min	X.X (X)	X.X (X)	X.X (X)
Sleep efficiency, mean (SD), %	X.X (X)	X.X (X)	X.X (X)

Abbreviations: CBT-i, cognitive behavioral therapy.

Table 2. Changes in CPAP adherence, and sleep variables and psychological variables between groups, during treatment.

	Cognitive and Behavioral Therapy for Insomnia							**Control**							**Interaction**		
	Baseline (SD)	**6-weeks (SD)**	**3 month (SD)**	**6-month (SD)**	**Main Effect**			**Baseline (SD)**	**6-week (SD)**	**3 month (SD)**	**6-month (SD)**	**Main Effect**			**F**	η^2	***p***
					F	η^2	***p***					**F**	η^2	***p***			
CPAP Adherence (min)				XX (XX)							XX (XX)				X	X	X
CPAP Adherence (min)				XX (XX)							XX (XX)				X	X	X
Adherence over time (min)		XX (XX)	XX (XX)	XX (XX)	X	X	X		X (XX)	XX (XX)	XX (XX)	X	X	X	X	X	X
Residual AHI from machines		XX (XX)	XX (XX)	XX (XX)	X	X	X		X (XX)	XX (XX)	XX (XX)	X	X	X	X	X	X
Objective Sleep Outcomes																	
Sleep Efficiency	XX (XX)	XX (XX)		XX (XX)	X	X	X	XX (XX)	XX (XX)		XX (XX)	X	X	X	X	X	X
Total Sleep Time	XX (XX)	XX (XX)		XX (XX)	X	X	X	XX (XX)	XX (XX)		XX (XX)	X	X	X	X	X	X
Wake After Sleep Onset	XX (XX)	XX (XX)		XX (XX)	X	X	X	XX (XX)	XX (XX)		XX (XX)	X	X	X	X	X	X

CPAP, Continuous Positive Airway Pressure; AHI, Apnea/Hypopnea Index.

Table 3. Changes in subjective sleep parameters and questionnaire outcomes between groups, during treatment.

	Cognitive and Behavioral Therapy for Insomnia							**Control**							**Interaction**		
	Baseline (SD)	**6-weeks (SD)**	**3 month (SD)**	**6-month (SD)**	**Main Effect**			**Baseline (SD)**	**6-week (SD)**	**3 month (SD)**	**6-month (SD)**	**Main Effect**			**F**	η^2	***p***
					F	η^2	***p***					**F**	η^2	***p***			
Questionnaire Outcomes																	
Insomnia Severity Index	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	X	X	X
Flinders Fatigue Scale	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	X	X	X
Epworth Sleepiness Scale	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	X	X	X
Depression	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	X	X	X
Anxiety	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	X	X	X
Stress	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	X	X	X
Sleep Diary Outcomes																	
Total Sleep Time	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	X	X	X
Sleep Onset Latency	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	X	X	X
Wake After Sleep Onset	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	X	X	X
Sleep Efficiency	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	XX (XX)	XX (XX)	XX (XX)	XX (XX)	X	X	X	X	X	X

Example Figures:

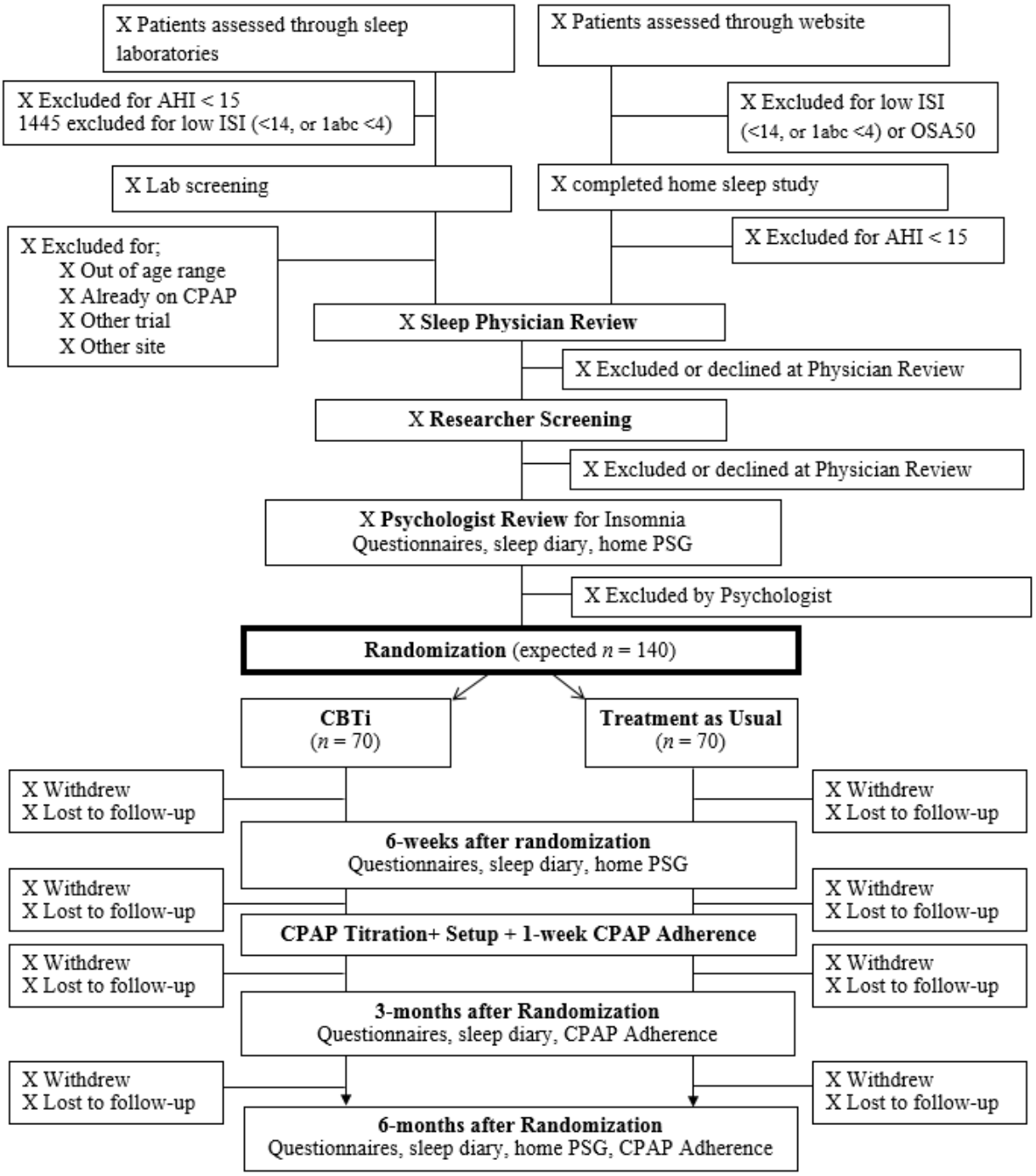

Figure 1. Participant Screening and Flow Diagram.

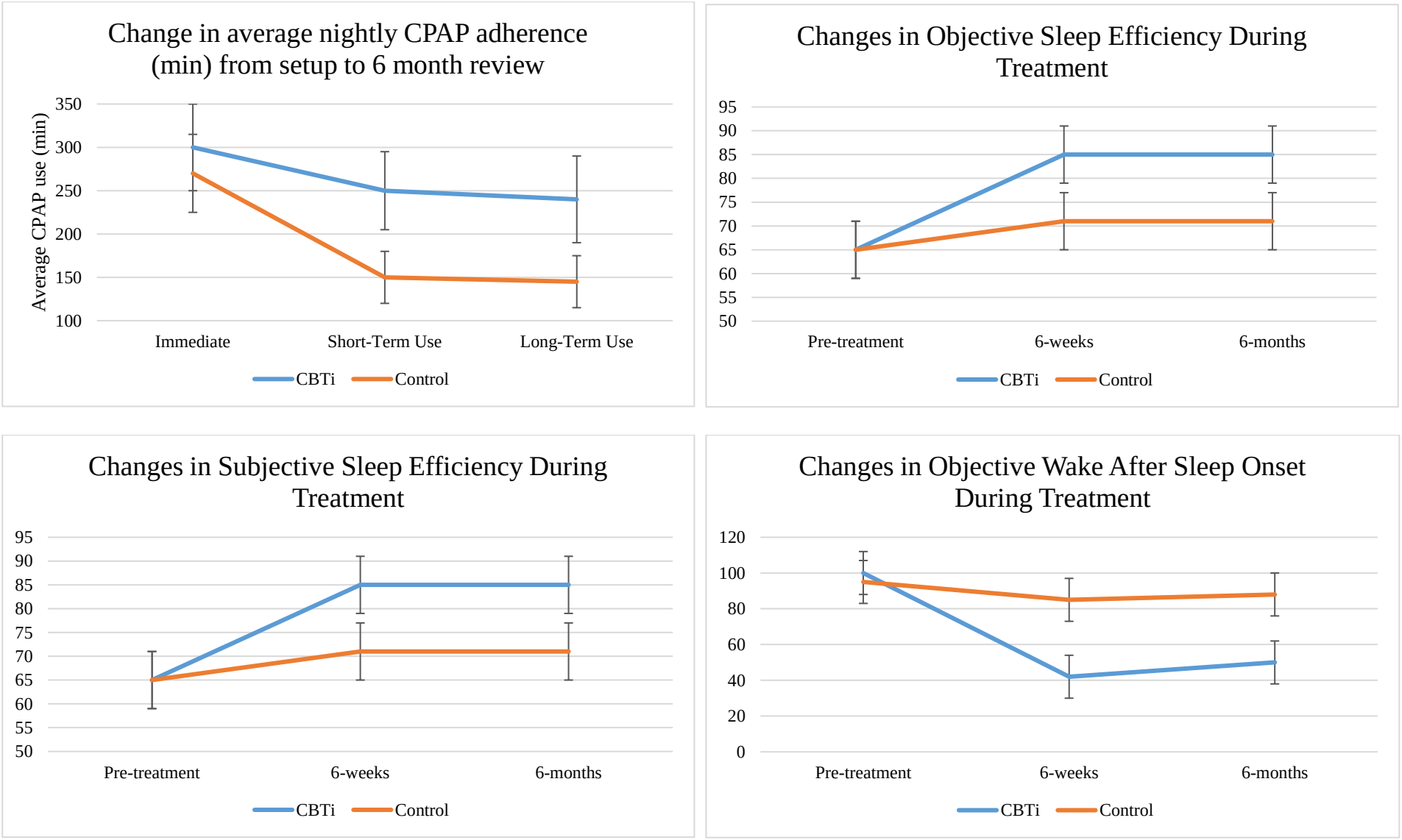

Figure 2. Changes in CPAP adherence (a) and objective (b, c) and subjective (d) sleep parameters during treatment (±95% CI). Data are illustrative only, to provide example.

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8.14 APPENDIX N - Participant information form

Repatriation General Hospital, Daws Road, Daw Park, SA 5041. Ph (08) 8276 9666; Fax (08) 8277 9401

PARTICIPANT INFORMATION SHEET

Project title
The COMISA study: A new treatment strategy for patients with combined insomnia and sleep apnoea

Full scientific project title:
Treating Comorbid Insomnia with Obstructive Sleep Apnoea (COMISA): A randomized controlled clinical effectiveness trial

Researchers:
Prof. R. Doug McEvoy MBBS, MD, FRACP
Dr. Simon Smith, PhD
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A/Prof. Nick Antic MBBS, PhD, FRACP
A/Prof Peter Catcheside, BSc(Hons), PhD
Dr. Ching Li Chai-Coetzer, MBBS, PhD, GCPH, FRACP

You are invited to participate in a research study of a non-drug (behavioural) treatment designed to help people who have two overlapping sleep disorders of insomnia plus obstructive sleep apnea (OSA). This will test if patients with both conditions cope better with Continuous Positive Airway Pressure (CPAP) treatment of their OSA and improve their sleep and general well-being.

Before you decide if you wish to participate or not, it is important for you to understand why the study is being done and what is involved. Please take the time to read the following information carefully and to ask further questions and discuss it with your partner or others if you wish. Your decision to participate or not is entirely up to you and will not in any way affect the treatment you receive or your relationship with the staff caring for you now or in the future.

WHY HAVE I BEEN INVITED TO PARTICIPATE?

We are seeking patients who have been identified to have obstructive sleep apnoea and co-existing symptoms of chronic insomnia AND who have been recommended by their doctor to have CPAP treatment.

WHAT IF I DON'T WANT TO TAKE PART IN THIS STUDY, OR IF I WANT TO WITHDRAW LATER?

Your participation in this study is entirely voluntary and you have the right to participate or not, or to withdraw from the study at any time without giving a reason if you choose. If you decide not to participate in this study, or if you withdraw from the study later on, you may do so freely, without affecting the treatment or standard of care you will receive now or in the future.

WHAT IS THE AIM OF THE PROJECT?

Previous studies suggest that overlapping (or co-existing) insomnia and OSA occurs much more commonly than was previously thought, and that insomnia in patients with OSA may make it more difficult for them to be treated successfully with CPAP.

The aim of this project is to test whether treatment of insomnia before commencing CPAP treatment for OSA will allow patients with co-existing OSA and insomnia to cope better with CPAP and improve their sleep and general well-being.

WHAT DOES PARTICIPATION IN THIS PROJECT INVOLVE?

If you agree to participate you will be asked to attend the Adelaide Institute for Sleep Health at the Repatriation General Hospital. You will be asked to tell the researchers conducting this investigation if you are participating in any other research studies. You may be asked what your role in that study is, to ensure that it will not influence the current study, or that this study will not influence the other study you are involved in. In addition, should you require elective or emergency surgery or other medical care, you should inform the doctor looking after you about your involvement in this study. You may also be asked some simple questions relating to your current medication use and health status to ensure you meet the study requirements. Access to your personal medical records may also be required for this study.

You will be asked to visit the clinic a number of times over 6 months.

Screening Visit

The screening visit will only be required for those people who have completed the online screening questionnaires. At this visit you will be asked to:
Sign a consent form to indicate that you understand the study and what is involved and that you agree to participate.
Be instructed on the use of, and take home an Apnea Link recording device which is used to determine the need for further clinical diagnosis of obstructive sleep apnoea.
If the ApneaLink report indicates the need for a clinical diagnosis of Obstructive Sleep Apnoea, and a GP referral has been received, an appointment will be made for a home diagnostic sleep study. One of our sleep technicians will stick on electrodes to monitor brain, eye movement, muscle, respiratory and heart activity using a home sleep study recording device. You will be instructed how and when to turn on and off the recording device and you will then be asked to take it home to undergo a 1-night further sleep assessment and return the device the following day.

First Visit

The first visit will last around 1 hour, during which you would be asked to:
Sign a consent form to indicate that you understand the study and what is involved and that you agree to participate (unless previously signed at the Screening Visit).
Sign a consent form for the transfer of data from the CPAP machine to Respironics along with your Personal Information for the provision of healthcare services and monitoring of CPAP therapy.

You will be asked to fill out a consent form authorising the study access to your complete Medicare and Pharmaceutical Benefits Scheme (PBS) data as outlined on the back of the consent form. Medicare collects information on your medical visits and procedures, and the associated costs, while the PBS collects information on the prescription medications you have filled at pharmacies. The consent form is sent securely to the Department of Human Services who holds this information confidentially. The data collected will be used to conduct an economic analysis of the benefits of the trial intervention.

Fill out several questionnaires which will take approximately 40 minutes in total to complete. The questionnaires include:
Insomnia Severity Index (ISI)
Epworth Sleepiness Scale (ESS)
Depression, Anxiety, Stress Scales (DASS)
A questionnaire screening for sleep disorders other than OSA and insomnia
Assessment of Quality of Life (AQoL-8D)
Functional Outcomes of Sleep Questionnaire (FOSQ)
Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16)
Daytime Feelings and Functioning Scale (DFFS)
Flinders Fatigue Scale (FSS)
European Quality of Life – 5 dimensions questionnaire (EQ-5D-5L)
iMTA Productivity Cost Questionnaire (iPCQ)
Sleep and General Health Questionnaire

Take home and complete a diary of your sleep every day for 7 days.

Second Visit
After 2 weeks, you would be asked to visit the clinic during which you would be asked to:
Undergo a brief interview by a trained sleep psychologist to establish if you have insomnia.
Your sleep diary will be reviewed to ensure that you meet all the study criteria for the full study.
At the end of your second visit and if your diagnostic sleep study was completed in the sleep laboratory, an appointment will be made for a home sleep study within approximately 1 week. One of our sleep technicians will stick on electrodes to monitor brain, eye movement, muscle, respiratory and heart activity using a home sleep study recording device. You will be instructed how and when to turn on and off the recording device and you will then be asked to take it home to undergo a 1-night further sleep assessment and return the device the following day.

At that point, and having established that you meet all the study criteria, you will be randomly assigned (as with the toss of a coin) to be in either the "cognitive behaviour therapy insomnia treatment (CBT-i)" group OR the "treatment as usual (TAU)" group.

You will have your weight and height measured to determine your Body Mass Index, and your waist, hip and neck circumferences will also be measured.

<u>If you are allocated to the CBT-i group</u> you will begin the first of 4 treatment sessions with a trained clinical psychologist experienced in the treatment of insomnia. The other 3 treatment sessions will be scheduled at approximately one-weekly intervals thereafter. Each of these insomnia sessions will be take approximately 1 hour and will include:
Education on Sleep & Healthy Sleep Habits and Stimulus Control & Bed Restriction to help improve sleep and reduce 'cues' that may be contributing to insomnia
Cognitive Therapy to help control pre-sleep thoughts, and provide strategies for dealing with intrusive worries

If you are allocated to the TAU group you will be simply asked to wait six weeks before further assessment. This is the normal waiting time for this type of treatment, so you will not be disadvantaged by being in this group. You will also have the opportunity to access CBT-i treatment after the trial if you wish.

6-week follow-up assessment
All participants will be asked to start keeping a sleep diary for one week before they attend this next follow-up visit at the sleep clinic.

At this visit, which will take about 1 hour, you will be asked to again fill out all the questionnaires that you previously completed and to take home a sleep study recording device to measure your sleep at night as before and to return the sleep study recording device the following day. You will be asked to complete an overnight sleep diary for this night.

CPAP: commencement and follow up
An overnight appointment will be made for you at the sleep centre within a week of your 6 week follow up assessment to establish your CPAP treatment. You will be asked to complete an overnight sleep diary for this night. This will be followed by an appointment with a trained CPAP consultant who will start you on home CPAP treatment for your OSA.

This will involve:
explaining to you how CPAP works
fitting you with a comfortable nose or face mask
showing you how to operate, clean and maintain the CPAP machine and mask

This visit should take about an hour. You will then be phoned by the CPAP therapy consultant to check on your progress with CPAP at three days and twenty one days following the start of treatment and reviewed in person at the clinic one week and one month after starting treatment. All participants will be asked complete an Insomnia Severity Index questionnaire and to start keeping a sleep diary for one week before the one month review.

3-month follow-up assessment
At this clinic visit, which will take up to 1 hour you will complete all the questionnaires you filled out previously, the CPAP nurse will review your progress with the CPAP treatment, including taking a reading from the machine as to how many hours you have used the machine over the previous months. You are asked to attend whether or not you have continued to use CPAP.

All participants will be asked to start keeping a sleep diary for one week before they attend this next follow-up visit at the sleep clinic.

6-month follow-up assessment
At this clinic visit, which will take about 1 and one-quarter hours you will complete all the questionnaires you filled out previously, the CPAP nurse will review your progress with the CPAP treatment, including taking a reading from the machine as to how many hours you have used the machine over the previous months.

All participants will be asked to start keeping a sleep diary for one week before they attend this next follow-up visit at the sleep clinic.

You will be then be asked to take home a sleep study recording device to measure your sleep at night as before and to return the sleep study recording device the following day. You will be asked to complete an overnight sleep diary for this night. Your commitment to the research study will then be finished.

Benefits:
By participating in the trial you will be be helping to answer an important question about how best to treat patients who have both insomnia and OSA, where best treatment options are currently unknown. You may benefit from improved treatment, although we cannot guarantee you will benefit more than with the current standard treatment.

What will happen to me at the end of the study?
At the end of the study you would continue on CPAP as is standard for this treatment. If you have not yet received the CBT-i treatment and would like to you will be able to access this treatment at the end of the trial.

Risks:
There are no reasonably foreseeable risks of injury or significant discomfort from participation in this study. CPAP is a very well established standard treatment for OSA. The risks of significant problems from the treatment are very low and far out-weigh the health and sleepiness related accident risks associated with untreated OSA. A properly fitted and worn mask should not be uncomfortable, but can occasionally cause some problems such as discomfort, skin irritation, dry eyes or dry mouth. If you experience any problems with the mask or CPAP you should discuss this with the study personnel who will likely be able to help.

OSA often causes excessive daytime sleepiness, which has the potential to impair daytime functioning, contribute to increased risk of driving and other accidents, and to affect health and social functioning. If you are *not* already excessively sleepy in the daytime and you receive CBT-i you may be advised to restrict your sleep to help increase sleepiness at bedtime to help break the insomnia cycle, and this will make you sleepier than normal. If you are excessively sleepy during the day you need to be aware of sleepiness related risks and plan your days activities accordingly to avoid placing yourself and others at risk of accidents.

The normal waiting time to start CPAP after a sleep study is around 6 weeks so you will not be disadvantaged by participating in the study. CBT-i and education about sleep habits are part of normal treatment for insomnia and have no foreseeable risks.

Compensation:
It is very unlikely, but you could feel some distress from participation in this study. If this occurs and you wish, you may withdraw from this study and your care will not be affected in any way. By participating in this study you do not give up any of your legal rights.

The study will not cost you anything to participate and you will not receive any payment for participation. Reasonable trial related travel expenses can be reimbursed.

Confidentiality:
All records containing personal information will be stored securely and will remain confidential. No information which could lead to your identification will be released, except as required by law.

If you consent to take part in this study, your medical records and the data collected for the study will be looked at by the research team. They may also be looked at by representatives of regulatory authorities and by authorised people from the hospital to check that the study is being carried out correctly. All these people will have a duty of confidentially to you as a research participant and no information that could identify you will be given to anyone else. We plan to publish the overall results of the study in medical/scientific journals, but all results will be de-identified and will not traceable to you as an individual.

With your consent, your general practitioner will be informed of your participation in this study so that, if you need to see him/her for any reason, he/she will be aware that you are taking part in the study.

We will be asking for your consent to access select personal Medicare and/or Pharmaceutical Benefits Scheme claims information relevant to the research objectives of this study. This includes date of service, item number and description, provider charge, date of referral,schedule fee, benefit paid, date of prescription, date of supply, patient contribution & net benefit. Your MBS and PBS information is a record of every medical service you have received, every time you have visited the doctor, and all the prescription medicines you have received. This information will be used to analyse the costs of health resources for the study.

All data will be kept for a period of 15 years followed by destruction following standard confidential waste procedures. This period was chosen as it is in line with requirements at the Adelaide Institute for Sleep Health. Electronic data will be kept in password-protected files on a hospital file server, where network access is restricted.

Publication:
We aim to publish the results of this study in medical/scientific journals and to present the study findings at conferences and other professional forums. Confidentiality will be respected at all times and your identity will not be revealed.

Withdrawal:
Your participation in this study is entirely voluntary and you have the right to participate or not, or to withdraw from the study at any time without giving a reason if you choose. If you decide not to participate in this study, or if you withdraw from the study later on, you may do so freely, without affecting the treatment or standard of care you will receive now or in the future.

Outcomes:
At the end of your involvment in the trial we can provide you with a summary of your results and discuss these with you if you would like. We can also provide your normal doctor with a copy, or arrange for one of our clinic doctors to discuss your results and possible further treatment options with you.

How is this study being paid for?
This is a researcher led study that has received National Health and Medical Research Council (NHMRC) project funding to cover salary and other costs associated with running the trial. None of the investigators will receive any personal financial benefit for their involvement in the study.

Contact:
Should you require further information about the study, please contact the Adelaide Institute for Sleep Health (phone: 8275 1187, fax 8277 6890) and ask for a member of staff inolved in the COMISA study or email the study coordinator at Amanda.O'Grady@health.sa.gov.au.

If you are already enrolled in the study and need to contact a staff member out of hours please call the sleep laboratory on 8275 1149 and mention that you are in the COMISA study.

Complaints:
This study has been reviewed by the Southern Adelaide Clinical Human Research Ethics Committee. If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Executive Officer, SAC HREC at the Flinders Medical Centre (8204 6453) or email research.ethics@health.sa.gov.au.

8.15 **APPENDIX O - Participant Consent Form**

Repatriation General Hospital, Daws Road, Daw Park, SA 5041. Ph (08) 8276 9666; Fax (08) 8277 9401

CONSENT TO PARTICIPATION IN RESEARCH

I, ...
(first or given names)(last name)

give consent to my involvement in the research project

.....
(short title)

I acknowledge the nature, purpose and contemplated effects of the research project, especially as far as they affect me, have been fully explained to my satisfaction by

.....
(first or given name) (last name)

and my consent is given voluntarily.
I acknowledge that the detail(s) of the following has/have been explained to me, including indications of risks; any discomfort involved; anticipation of length of time; and the frequency with which they will be performed:

Completing up to 4 home sleep studies to assess sleep quality; 2 before and 6 weeks and 6 months after starting treatment.
Having my weight and height measured and my waist, hip and neck circumferences measured following randomisation into the Trial.
Commencing Constant Positive Airway Pressure (CPAP) treatment for obstructive sleep apnoea (OSA). This is the standard treatment for OSA.
Being randomised (by chance like tossing a coin) to receive either treatment as usual (CPAP alone) or Cognitive Behaviour Therapy for insomnia before starting CPAP.
Returning to the sleep clinic for study followup measurements, including questionnaires about sleep and daytime function and quality of life (before and then at 6 weeks, 3 months and 6 months after starting treatment), and CPAP device downloads.

I have understood and am satisfied with the explanations that I have been given.
I have been provided with a written information sheet.
I understand that my involvement in this research project may not be of any direct benefit to me and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the researchers in any respect.
I declare that I am over the age of 18 years.
I acknowledge that I have been informed that should I receive an injury as a result of taking part in this study, I may need to start legal action to determine whether I should be paid.

Signature of Research Participant : Date: ..

I, ... have described to .....
the research project and nature and effects of procedure(s) involved. In my opinion he/she understands the explanation and has freely given his/her consent.

Signature: ..... Date: ..
Status in Project:.....