Armodafinil to reduce the sleepiness related side-effects of Sleep Restriction Therapy being used to treat Insomnia Disorder (MODERATE): An open label pilot study compared to historical matched controls

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I would also like to extend my thanks to the staff at the RPAH Hospital Sleep Unit and the Woolcock institute for their support for the trial and to me personally over several years leading up to the completion of this work.

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Finally, I would like to thank my family, particularly my wife Camille, for their patience and support.
Abstract

Introduction

Insomnia is a common disorder with high personal and more broadly societal costs associated with absenteeism and medical comorbidities. An inappropriate reliance on long term pharmacotherapy has proven ineffective and potentially harmful with a range of known side-effects. Cognitive behavioural therapy for insomnia (CBT-I) is commonly regarded as the treatment of choice, however, has significant resource implications for the health system and may contain therapeutically redundant elements. One component of CBT-I, sleep restriction therapy (SRT), as a stand-alone behavioural intervention has been demonstrated to be as effective as multicomponent interventions and may be more readily deployable as a manualised treatment in a primary care setting as part of a ‘stepped care approach’. The MODERATE pilot trial aims to explore the potential benefit of armodafinil, a wakefulness promoter, to offset the side effects of SRT for the treatment of insomnia.

Methods

Participants with insomnia disorder were enrolled in the trial and commenced on sleep restriction therapy (SRT) with adjunctive armodafinil treatment. Both interventions were titrated against sleep diary parameters and side effects, namely excessive daytime sleepiness. The primary outcome measure insomnia severity index score and secondary outcomes; Epworth sleepiness score, self-reported adherence score (SRAS), and safety monitoring were recorded at predefined time points from baseline through to 12 weeks.

Results

Twenty-five participants were enrolled in the trial and began the treatment protocol. Seven participants withdrew prior to the end of the active therapy period. We withdrew two participants from the trial following adverse events and five participants withdrew themselves from therapy with four citing side effects of SRT or pharmacotherapy, a further patient was lost to follow-up. Data for the primary end point (ISI at 12 weeks) was available for 20 of the participants.

Screening mean Insomnia Severity Index (ISI) 20.2 (SD 3.3) was in the moderate severity class (15-21) and fell to a nadir of 9.1 (SE 1.1, p value diff Week 1 <0.0001) at the end of the active treatment phase (end of week 4) numerically rebounding, without statistical significance (both
p>0.05), to 10.2 and 11.2 at weeks 6 and 12 respectively. At the end of the first week of therapy the ESS was 8.3 (SE 1.0) with a subsequent nadir at the end of the active treatment period 4.1 (SE 1.0 p value diff week 1 and week 4 <0.001). Consistently high levels of adherence to SRT were demonstrated over the active treatment period. SRT and Armodafinil were associated with frequent side effects, however, appeared safe and generally acceptable to patients.

**Discussion**

SRT was associated with a robust clinical response in ISI values for insomnia patients. Based upon data from my literature review Armodafinil does not appear to have marked adjunctive effects in addition to SRT alone. We would not recommend the routine use of adjunctive Armodafinil therapy in clinical practice based upon these results.
Statement of Originality

This is to certify that to the best of my knowledge; the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

________________________________________  ____________________________
Signature                                      Date

________________________________________
Name
Funding

University of Sydney Medical School Kickstart Grant (with financial support provided through the Balnaves Foundation) and the National Health and Medical Research Council (NHMRC, Australia) Centre for Research Excellence NeuroSleep, 1060992 provided support for the running of the trial and study personal. The study drug armodafinil was funded from the Kickstart Grant. As the study sponsor, the Woolcock Institute of Medical Research provided non-financial support and did not charge the study for this service. The Woolcock Institute also allowed non-financial support for all patient recruitment, testing and data management. TEVA pharmaceuticals are the manufacturers of armodafinil and gave the armodafinil to the study without cost. TEVA did not have access to identifiable patient information. The investigators made all decisions about how the overall results of the study would be communicated to patients and clinicians: TEVA did not play any role in these decisions.
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Preface

The MODERATE pilot trial was conceived by the trial team prior to my arrival at The Woolcock Institute of Medical Research as a clinician and the University of Sydney as a post graduate student, in 2017. My role as a clinician and researcher from 2017 was to review the eligibility of participants for our trial and to ensure the safety of participants undergoing therapy in conjunction with our trial team.

The trial protocol had been created and ethics approved prior to my involvement in the trial. The Methods section of this thesis is largely paraphrased from the trial protocol (Appendix 1). All additional intellectual and written content contained within this thesis is my own work unless otherwise acknowledged. I hereby declare that I have not submitted this material for another degree at this or any other institution.

The COVID 19 pandemic has reduced our team’s capacity to harmonise the control dataset with the armodafinil dataset prior to submission of this thesis. Formal statistical comparisons will be presented in full in future manuscripts.

_____________________________
Signature

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Name
Chapter 1 Introduction

1.1 Prevalence and Costs of Insomnia Disorder

Insomnia is one of the most prevalent health conditions worldwide\(^1\) and is the most common and socially costly sleep disorder in Australia.\(^2\) Thirty per cent of Australians will be affected by insomnia symptoms, with 10% going on to develop chronic insomnia.\(^2\) The total cost of insomnia to Australia in 2010 was estimated to be $10.9 billion.\(^3,4\) As with estimates of point prevalence, life-time prevalence figures vary widely.\(^4,5\) This may be related to the variability in diagnostic criteria both geographically and temporally. The evolution of diagnostic criteria relating to the concept of primary and secondary insomnia, now defunct, is also likely to contribute to varying prevalence figures (Table 1.1).\(^6\) The relapsing and remitting nature of the disease is also likely to complicate epidemiological investigation. While data estimating prevalence figures for insomnia disorder vary in high income countries like Australia\(^4\), in low and middle-income countries, there is little high-quality data relating to basic sleep health parameters including insomnia symptoms.\(^7\) Deloitte Access Economics calculated the mean point prevalence from a number of recent international studies to be approximately 15%.\(^4\) This result is similar to that identified by the Australian Sleep Health Survey 2016, 11.3%.\(^8\)

Insomnia disorder and general sleep health has come to the fore with a recent Australian parliamentary inquiry demonstrating increasing community awareness that insufficient sleep has multifaceted and far reaching implications.\(^9\) The economic costs that arise from these impacts include:

1. Financial costs associated with health care, informal care provided outside the healthcare sector, productivity losses, non-medical work and vehicle accident costs, deadweight loss through inefficiencies relating to lost taxation revenue and welfare payments; and

2. The non-financial costs of loss of well-being.
1.2 Current and Historical Definitions of Insomnia Disorder

Insomnia can be broadly defined as difficulty initiating or maintaining sleep, or the perception of poor-quality sleep. Current and previous attempts to define insomnia have included; elements of subjective symptom profiles, chronicity of disease, objective quantifiable sleep parameters including sleep latency, time in bed and number of arousals from sleep, frequency of symptoms, and consequent daytime dysfunction. The International classification of sleep disorders (ICSD-3), the International Classification of Diseases, tenth revision (ICD-10), and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) offer authoritative definitions for insomnia disorder. DSM-V criteria were employed in this trial, forming the basis upon which eligibility criteria were created. Specific research criteria have been developed to aid in the categorization of insomnia disorder in research settings. The two main classification systems for insomnia disorder, DSM-IV and ICSD-3, are presented in tabular form in Tables 1.1 and 1.2.
Table 1.1
*Insomnia disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders*

It represents a temporal comparison between fourth and fifth editions adapted from the 2016 report of the Substance Abuse and Mental Health Services Administration (US). \(^{6,11,13}\)

<table>
<thead>
<tr>
<th>DSM-IV</th>
<th>DSM-5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name:</strong> Primary Insomnia</td>
<td><strong>Name:</strong> Insomnia Disorder</td>
</tr>
<tr>
<td><strong>Disorder Class:</strong> Sleep Disorders</td>
<td><strong>Disorder Class:</strong> Sleep-Wake Disorders</td>
</tr>
<tr>
<td>A. The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month.</td>
<td>A. A predominant complaint of dissatisfaction with sleep quantity, associated with one (or more) of the following symptoms:</td>
</tr>
<tr>
<td></td>
<td>1. Difficulty initiating sleep. (In children this may manifest as difficulty initiating sleep without caregiver intervention)</td>
</tr>
<tr>
<td></td>
<td>2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children this may manifest as difficulty returning to sleep without caregiver intervention)</td>
</tr>
<tr>
<td></td>
<td>3. Early morning awakening with inability to return to sleep.</td>
</tr>
<tr>
<td>B. The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important area of functioning.</td>
<td>B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioural, or other important areas of functioning.</td>
</tr>
<tr>
<td></td>
<td>C. The sleep difficulty occurs at least 3 nights per week.</td>
</tr>
<tr>
<td></td>
<td>E. The sleep difficulty occurs despite adequate opportunity to sleep.</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>DSM-5</td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
</tr>
</tbody>
</table>
| **Name:** Primary Insomnia  
**Disorder Class:** Sleep Disorders | **Name:** Insomnia Disorder  
**Disorder Class:** Sleep-Wake Disorders |
| C. The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia. | F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia). |
| D. The disturbance does not occur exclusively during the course of another mental disorder (e.g. major depressive disorder, generalized anxiety disorder, a delirium). | H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia. |
| E. The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition. | H. The insomnia is not attributable to the physiological effects of a substance (e.g. a drug of abuse, a medication). |

**Specify if:**
- With non-sleep disorder mental comorbidities including substance use disorders
- With other medical comorbidity
- With other sleep disorder

**Specify if:**
- Episodic: Symptoms last at least 1 month but less than 3 months.
- Persistent: Symptoms last 3 months or longer.
- Recurrent: Two (or more) episodes within the space of 1 year.

---

*Table 1.1 Legend:* offers a comparison between the DSM-IV and DSM-V categorization of insomnia disorder. The DSM-V makes no distinction between primary and comorbid insomnia. The DSM-IV definition was superseded by a singular diagnosis of insomnia disorder, dependent only upon satisfaction of the diagnostic criteria. This change recognizes the frequently complex, bidirectional relationship between sleep-wake disorders and other mental health and medical problems. In addition, the notion of chronicity is now replaced with the terms episodic, persistent, and recurrent insomnia.
A similar paradigm shift was observed in the evolution of the American Academy of Sleep’s (AASM) International Classification of Sleep Disorders definition (2013). The ICSD-3 (Table 1.2) categorizes insomnia into three subtypes; short-term, chronic and other (not meeting criteria for the other two categories of insomnia). This represents a move away from the ICSD-2 subclassification into primary and comorbid insomnia subtypes.

Table 1.2
Diagnostic criteria for chronic insomnia disorder adapted from ICSD-3.92

A. The patient reports, or the patient’s parent or caregiver observes, one or more of the following:
   1. Difficulty initiating sleep.
   2. Difficulty maintaining sleep.
   3. Waking up earlier than desired.
   4. Resistance to going to bed on appropriate schedule.
   5. Difficulty sleeping without parent or caregiver intervention.

B. The patient reports or the patient’s parent or caregiver observes, one or more of the following related to nighttime sleep difficulty:
   1. Fatigue/malaise
   2. Attention, concentration or memory impairment.
   3. Impaired social, family, occupational or academic performance.
   5. Daytime sleepiness.
   6. Behavioural problems (e.g. hyperactivity, impulsivity, aggression).
   7. Reduced motivation/energy/initiative.
   8. Proneness for errors/accidents.
   9. Concerns about or dissatisfaction with sleep.

C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e. enough time is allotted for sleep) or inadequate circumstances (i.e. the environment is safe, dark quiet and comfortable) for sleep.

D. The sleep disturbance and associated daytime symptoms occur at least three times per week.

E. The sleep disturbance and associated daytime symptoms have been present for at least 3 months.

F. The sleep/wake difficulty is not better explained by another sleep disorder.

Classification systems have traditionally dichotomized insomnia disorder based on duration and presumed pathophysiology. The World Health Organization International classification
of Diseases (ICD-10) maintains the traditional distinction between primary and secondary, or comorbid insomnias (Table 1.3). With the exception of the ICD-10 classification, the concept of primary vs. secondary insomnia disorder has disappeared from authoritative classification guidelines.\textsuperscript{11,12,20} This observed shift in the approach of classification systems to define insomnia disorder is related to a challenge to the traditional conceptualization of pathophysiology and to treatment.\textsuperscript{22} This pivot towards a more holistic diagnostic approach is further illustrated in statements from the 2005 National Institutes of Health Consensus Panel on Manifestations and Management of Chronic Insomnia in Adults\textsuperscript{23} noting:

- Considerable uncertainty exists with respect to the “nature of (the) associations and the direction of causality” in cases of comorbid insomnia.
- The emphasis on the “secondary” nature of many insomnia disorders may promote inadequate treatment.

1.3 Demographic and Social Determinants of Disease

A number of demographic characteristics have been associated with an increased frequency of insomnia symptoms. Insomnia is more prevalent in females\textsuperscript{5} and this finding is consistent across age groups.\textsuperscript{24} This was observed in an Australian study by Henderson et al. demonstrating higher rates of insomnia in elderly women compared to men in 923 individuals aged 70 years or older.\textsuperscript{25} Increasing age regardless of sex is positively associated with insomnia, particularly with symptoms related to difficulties with sleep maintenance.\textsuperscript{5,15} A number of sociodemographic elements are associated with an increased risk of insomnia including marital and socioeconomic status along with the level of previous education attained.\textsuperscript{15} Divorced, separated or widowed individuals, along with those from lower socioeconomic levels and lower levels of previous education, were found by Ohayon, to be at higher risk for insomnia symptoms, a trend demonstrated more profoundly in females.\textsuperscript{15} A New Zealand study found that being unemployed and experiencing socioeconomic deprivation were associated with an increased risk of reporting insomnia symptoms.\textsuperscript{17}

There is a bidirectional relationship between insomnia, depression, and anxiety disorder with high levels of anxiety and depression frequently evident in insomnia patients and conversely, high levels of sleep disturbance in patients with anxiety and depressive disorders.\textsuperscript{6,17-19} This reciprocal relationship has similarly been demonstrated between physical illness and insomnia.\textsuperscript{26} Vgontzas et al. hypothesized that medical morbidity associated with insomnia,
including hypertension, and Type 2 Diabetes would in turn lead to increased mortality. Data from the Penn State Cohort suggested that insomnia with objectively measured short sleep duration in men is associated with increased mortality. Interestingly, a recent meta-analysis describes that a relationship between poorer quality of life values and the broader social, and financial costs of insomnia is evident, however, insomnia doesn’t increase mortality risk.

1.4 Pathophysiology and Therapeutic Targets for Insomnia Disorder

Spielman et al. describe the 3P model of insomnia with the aim of better defining therapeutic targets for investigation. The 3P’s refer to; predisposing, precipitating, and perpetuating factors for insomnia. These include patient related and environmental elements that render patients vulnerable, promote the development of insomnia symptoms acutely, and encourage subsequent chronicity of disease.

Definitive pathophysiological mechanisms cannot be defined, although several neurobiological abnormalities are associated with insomnia. Miller et al. found that brain metabolites; aspartate, glutamine, and creatine in the left occipital cortex, measured by magnetic resonance spectroscopy (MRS) appear to be reduced in insomnia patients with a short sleep time phenotype as compared with insomnia patients with normal sleep times, and healthy controls. Evidence continues to emerge that insomnia is associated with inappropriate physiological arousal; with measurable changes in brain activity consistent with hyperarousal, and activation of the sympathetic nervous system. The later supported by observed sleep-related abnormalities in heart rate, blood pressure and temperature in insomnia patients.

1.5 Treatment for Insomnia Disorder

1.5.1 Benzodiazepine pharmacotherapy for insomnia disorder

The current health system solution to this highly prevalent condition is hypnotic pharmacotherapy. Australian data from the Bettering the Evaluation and Care of Health (BEACH) program demonstrates a higher level of prescribed medications for medical consults related to insomnia in the primary care setting with 81.7 per 100 cases for new consults and 95.2 per 100 cases overall. Furthermore, rates of prescriptions for follow-up reviews suggests long-term treatment with hypnotics is common in primary practice in Australia. This is despite substantial evidence that drugs are only marginally better than placebo and limited evidence for long-term efficacy. Hypnotic therapy also comes with significant risk for a range of
side-effects, some caused by inappropriate use, including falls, car crashes, accidents, and potentially increased overall mortality. 37-39,42,44,45 Examples of benzodiazepines and benzodiazepine receptor agonists recommended for short term therapy of insomnia in Australia include temazepam, zolpidem and zopiclone.46 Hypnotics with short half-lives mainly reduce latency to sleep.30

Melatonin is an endogenous hormone associated with the regulation of circadian rhythm. It has been demonstrated to be a useful first-line intervention to improve sleep continuity variables and QOL for older patients (>55 years).46,47 Melatonin has been shown to reduce sleep latency, but does not increase total sleep time.30 It is licensed in Australia in a prolonged-release formulation for the short-term treatment of insomnia in older adults.30,46

The role of newer pharmacological treatment options like suvorexant (dual orexin receptor agonist) is still to be established, with a dearth of comparative data available and adverse events including, somnolence, fatigue, and abnormal dream content commonly reported.48 Sys and colleagues suggest that preliminary evidence supports the efficacy and safety of agents like suvorexant, and melatonin as pharmacological alternatives to hypnotic drugs.49 In Australia the recommended duration for treatment regimens involving hypnotic therapy or melatonin is for the shortest time possible and not exceeding 2 weeks for hypnotics and three for melatonin.46

1.5.2 Multi-component cognitive behavioural therapy for insomnia disorder

Psychological approaches are likely to produce sustained benefits without the risk of tolerance and adverse effects associated with benzodiazepine therapy.50 Cognitive behavioral therapy for insomnia is widely accepted as the standard non-pharmacological intervention for improving core insomnia symptoms,30,51 and targets maladaptive behaviour and thoughts that may have developed during insomnia or contributed to its development.14 Australian guidelines recommend psychological and behavioural interventions prior to the consideration of pharmacotherapy.46 A typical multi-component CBT-I may include; stimulus control, sleep restriction therapy, and cognitive therapy for insomnia, with lesser contributions from muscle relaxation therapy and biofeedback. Other approaches that may contribute to a multifaceted regimen include sleep hygiene education and paradoxical intention therapy (Table 1.3). These approaches have been used individually and as part of a multicomponent intervention in succession or more commonly concurrently.22 A meta-analysis of cognitive and behavioural therapies including the traditional definitions of primary and secondary insomnia concluded
that CBT-I, either in its components or the full package, was effective in the treatment of insomnia.\textsuperscript{41}

Table 1.3
*Cognitive Behavioural Therapies for Insomnia Disorder, adapted from Morin.*\textsuperscript{52}

<table>
<thead>
<tr>
<th>Activity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulus control</td>
<td>Instructions designed to reassociate the bed/bedroom with sleep and to reestablish a consistent sleep-wake schedule</td>
</tr>
<tr>
<td>Sleep restriction</td>
<td>A method for limiting time in bed to actual sleep time, thereby creating mild sleep deprivation, which results in more consolidated and more efficient sleep</td>
</tr>
<tr>
<td>Relaxation training</td>
<td>Methods aimed at reducing somatic tension or intrusive thoughts interfering with sleep</td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>Psychotherapeutic method aimed at changing faulty beliefs and attitudes about sleep and insomnia</td>
</tr>
<tr>
<td>Sleep hygiene education</td>
<td>General guidelines about health practices and environmental factors that may affect sleep</td>
</tr>
</tbody>
</table>
1.5.3 Drawbacks and adverse effects of CBT-I

There is a large body of evidence demonstrating that CBT-I is an effective treatment for insomnia. However, CBT-I as it stands, suffers from major drawbacks as it requires specifically trained therapists, and is a complex, time consuming composite therapy that may contain therapeutically redundant components. CBT-I has traditionally been delivered face-to-face by a psychological therapist, and so is dependent upon a rare and expensive resource. Espie addresses this by proposing a ‘stepped care’ model, outlined in Figure 1.1. This aims to improve access to specialized CBT-I to patients with the greatest need by creating a hierarchy of 5 levels of stepped care with the intention of referral upstream where there is incomplete therapeutic response, from each step, dependent upon increased resource requirements for time, cost and expertise. Essentially, expert professional consults are reserved for the most complex cases with routine referrals addressed by various lower resource solutions including self-delivered CBT, manualized treatment programs and specialized nursing staff, along with group therapy delivery. Espie et al. describe the successful implementation of a stepped care approach as being dependent upon scalability to a population level. In essence, the treatment focus shifts from the professional to the person, and from the clinic to home implementation. My experience as a sleep Physician practicing in metropolitan, regional, and remote settings is that there is a paucity of therapy options between the upper and lower tiers of the stepped-care pyramid (Figure 1.1). A manualized version of SRT as employed in our trial and delivered in the primary care setting would represent an expansion of therapeutic options to the second tier.
Figure 1.1 A ‘stepped-care’ model for CBT adapted from Espie.\textsuperscript{55}

In the Australian context geography can profoundly affect access to service with 31\% of Australians residing outside of major cities and consequently experiencing potential barriers to accessing standard of care interventions for sleep health.\textsuperscript{56} The recent Inquiry into Sleep Health awareness in Australia identified financial barriers to CBT-I for Australians living outside metropolitan areas and recommended that the Department of Health undertake a review of the Medicare Benefits Schedule, as it relates to sleep health services, and accessing CBT-I via telehealth for patients in regional, rural and remote areas.\textsuperscript{9}

The second drawback, multicomponent CBT-I potentially containing redundant components,\textsuperscript{53} has been specifically addressed in a trial by Epstein and colleagues and found that sleep restriction therapy, delivered in isolation, rather than as a standardized behavioural component of CBT-I, is as effective as multi-component interventions.\textsuperscript{57} The proposition that a manualized version of a single component, behavioural therapy could be delivered in a similar fashion to the ‘stepped care’ model, with a range of health care professionals including and not limited to; nurses, pharmacists, counsellors, and general practitioners, able to deliver therapy, goes
some way to address these drawbacks. Potentially mitigating the complexity, financial and temporal resource burdens, and barriers to treatment access. It also forms the basis of a paradigm shift in the treatment of insomnia and is a central tenant to this trial.

1.5.4 Single component behavioural therapy; a description of sleep restriction therapy

Spielman and colleagues first described sleep restriction therapy in the late 1980s as a treatment for insomnia based upon the recognition that excessive time in bed is one of the important factors that perpetuates insomnia.\(^{58}\)

The original description of the SRT regimen was employed for our trial and is briefly summarized in the following lines and outlined in detail in the methods section.\(^{58}\) SRT is a behavioural therapy that aims to reduce excess time in bed by matching time in bed with total sleep time, therefore improving sleep efficiency. This is achieved by the patient completing a two-week sleep log prior to commencement of therapy to establish the average total sleep time (TST). The therapist then prescribes this TST as the initial time in bed (TIB) with a lower limit of 5 hours. Initial prescriptions dictate a wake time, dependent upon the schedule of the patient, with the sleep window calculated from this point backwards to the time of retiring to bed. Subsequent adjustments to TIB are generally made in 15-minute increments based upon the average sleep efficiency of the preceding 5 days.

1.5.5 SRT: proposed mechanisms for therapeutic response

Spielman et al. describe a landscape in the 1980s where most theories of insomnia focused on factors that precipitate disease and patient characteristics that predispose individuals to insomnia.\(^{59}\) In contrast, sleep restriction for insomnia addresses the factors that perpetuate chronic insomnia.\(^{58}\) The mechanism by which SRT delivers therapeutic benefit is hypothesized by Spielman et al.\(^{60}\) as;
- Strengthening homeostatic sleep pressure;
- Inhibiting perpetuating practices in bed (excessive time in bed);
- Attenuating hyperarousal; and
- Tightening regulatory control of sleep by the endogenous circadian pacemaker.

The evidence that mechanisms originally proposed by Arthur Spielman were the mediators of beneficial treatment outcomes for SRT, was examined in a systematic review by Maurer et al.\(^{28}\) The study suggested that SRT targets some of the hypothesized processes but specifically designed mechanistic evaluations are needed. Further to this finding a new hypothesis for a mechanistic model of SRT is proposed. SRT effectively treats insomnia because it influences cognitive-behavioural and physiological pathways simultaneously and reciprocally, primarily in three ways. Dubbed the Triple-R model,\(^{28}\) the proposed mechanisms are:

1. Restricting time in bed awake;
2. Regularizing timing of sleep and wake, and consequently; and
3. Re-conditioning the association between bedroom factors and sleep.\(^{28}\)

1.5.6 SRT: adverse effects, unwanted or necessary for therapeutic response?

Traditionally CBT-I has not been subjected to the same rigorous investigation that the pharmacotherapies endure, regarding monitoring for side-effects and adverse outcomes. Kyle et al. note that the presumption that psychological therapies are devoid of side-effects is naïve, particularly the behavioural treatments for insomnia.\(^{61}\) Historically there has been a lack of information regarding the possible negative outcomes of SRT. In fact, it wasn’t until 2013 that it was shown that SRT was associated with reduced TST and as a consequence, increased daytime sleepiness and objective performance impairment.\(^{62}\) SRT comes with its own significant side-effect profile with one study reporting side effects as common, the four most frequent side effects were found to be; fatigue/exhaustion, extreme sleepiness, reduced motivation/energy and headache/ migraine.\(^{61}\) Interestingly the frequency and pervasiveness of symptoms was associated positively with post-treatment improvements in sleep quality, raising the question of whether the side effects of SRT are necessary for successful outcomes of therapy.\(^{61}\)

Miller and colleagues found a transitory increase in sleepiness and fatigue and a decrease in alert cognition associated with initiation of SRT.\(^{62}\) The identification of side-effects, both
common and serious has profound implications for the clinician delivering SRT with regard to patient safety, particularly in the initial intervention stage of therapy when daytime sleepiness and vigilance levels are likely to be more significantly affected (See Figure 1.2.). The physiological impact of worsening daytime sleepiness on improved sleep quality, “the no pain no gain assumption”, and the role that offsetting this symptom might have on adherence to SRT and subsequent improvement in insomnia symptoms are the subject of the trial this thesis reports. It is also necessary to consider the possibility that without the acute side effects associated with institution of SRT, therapeutic gains in sleep quality improvement may not be achieved. 61
The role of wake promoting agents in insomnia, a review of the literature

There appear to be only 2 trials investigating the role of wake promoting agents (armodafinil/modafinil) for the treatment of insomnia or for the mitigation of side effects of psychological therapies employed to treat insomnia. Two randomized, double-blind placebo-controlled trials...
have evaluated the role of either armodafinil or modafinil in the treatment of insomnia. Both trials employed a multicomponent CBT-I intervention rather than stand-alone SRT with a wake promoting agent. In addition to this the trial undertaken by Roscoe and colleagues focused on cancer survivors, a special population producing results that may not be generalizable to the full spectrum of general insomnia patients imagined by Espie and colleagues for the stepped care model.

Perlis and colleagues were the first to investigate the potential role of wake promoting agents as primary or adjunctive therapies in the treatment of insomnia. Twenty-seven insomnia patients were randomized to one of three groups:

- CBT-I + modafinil (100mg);
- Contact control + modafinil (100mg); and
- CBT-I + placebo

The primary outcomes measured were sleep-continuity variables collected through sleep diaries (sleep latency SOL, wake-time after sleep onset WASO, and total sleep time TST). Modafinil did not demonstrate added benefit to CBT-I for measured sleep continuity variables, however, it did demonstrate a statistically non-significant reduction in daytime sleepiness (ESS), and subsequent improved adherence with prescribed time in bed procedures as part of SRT, a component of the multifaceted CBT-I therapy. The suggestion that wake promoting agents may offset the side-effects of sleep restriction therapy and improve adherence to treatment provides the rationale for further studies including our trial.

Roscoe and colleagues investigated the efficacy and safety of armodafinil to augment CBT-I in cancer survivors with insomnia in a phase-2 study. Initially the trial focused on those with insomnia and a breast cancer diagnosis with subsequent broadening of scope to include all cancers, as recruitment was difficult. Ninety-six patients were randomized to one of four groups:

- CBT-I + placebo;
- CBT-I + armodafinil (3 days at 50mg, 40 days at 100mg, 4 days at 50mg);
- Placebo only; and
- Armodafinil only (3 days at 50mg, 40 days at 100mg, 4 days at 50mg).

The primary outcome was defined as response of chronic insomnia symptoms to therapy measured by the insomnia severity index (ISI). The Pittsburgh Sleep Quality Index (PSQI)
was employed to measure overall sleep quality, a secondary outcome. CBT-I was found to produce reductions in ISI and overall sleep quality (PSQI) post treatment, with sustained results at 3 months. Armodafinil did not improve the efficacy of CBT-I when given concurrently nor as a single therapy intervention affect insomnia severity or sleep quality compared to placebo.\textsuperscript{64}

Several articles have been published subsequently based upon the data from Roscoe and colleagues examining secondary outcome data. Garland and colleagues\textsuperscript{66} examined whether CBT-I, armodafinil, or both interventions result in; greater improvement in sleep continuity and daytime sleepiness, and whether armodafinil alone, and/or when combined with CBT-I affected adherence with CBT-I. The addition of a wake promoting agent did not differentially improve sleep continuity variables, daytime sleepiness (ESS) or adherence with CBT-I.\textsuperscript{66} Potential mechanisms for this observation were postulated to be; a ceiling effect on therapy relating to previously observed robust clinical improvements with CBT-I alone, inadequate dosing, and adherence concerns.

Heckler and associates,\textsuperscript{67} in a secondary analysis of Roscoe et al.,\textsuperscript{64} examined self-reported fatigue and found that improvements in nighttime sleep was directly responsible for the observed improvements in cancer related fatigue. Armodafinil did not independently improve daytime fatigue in cancer patients and once again was found to have no additional effect upon efficacy of CBT-I. The authors raised the possibility that these findings may not be generalizable to the greater insomnia population.

A third report based on the original trial by Roscoe and colleagues,\textsuperscript{64} investigates the potential benefits of CBT-I and armodafinil on Quality of life (QOL), assessed by the Functional Assessment of Cancer Therapy- General.\textsuperscript{68} An enduring improvement in QOL was found to be associated with CBT-I, endpoint data was collected at an average of 23 weeks. On the other hand, armodafinil did not have a demonstrable effect on QOL or on the efficacy of CBT-I.
1.6 Safety and Acceptability of Wake Promoting Agents; a Review of the Literature

Modafinil / armodafinil (unlike modafinil, armodafinil contains only one enantiomer-R-Modafinil) is a wake-promoting drug licensed in Australia for Narcolepsy, Shift-work sleep disorder and as an adjunct to CPAP therapy in obstructive sleep apnoea syndrome in order to improve wakefulness. It is also a modestly effective treatment for daytime sleepiness in sleep apnoea patients not on mechanical therapy. The study drug is not approved as an adjunct to SRT for the treatment of insomnia in Australia or elsewhere.

The rationale for armodafinil as a short-term adjunct to increase effectiveness of SRT is as follows –

- The main adverse effect of SRT is daytime sleepiness. armodafinil counters this.
- By keeping patients awake during the day, armodafinil would enhance the normal homeostatic pressure to sleep in late evening and avoid napping during the day that would reduce this drive and impede the effectiveness of SRT.
- By reducing daytime sleepiness and fatigue, armodafinil may diminish the cognitive arousal associated with insomnia and improve SRT effectiveness.

We have selected armodafinil as a wakefulness promoter with the best safety and lowest side effect profile with low abuse potential.  

Armodafinil / modafinil is currently generally regarded as a very safe pharmacological agent when used in therapeutic doses. Despite one study that has raised concern about a pressor effect with 3 days therapy, there have been no systematic reports of blood pressure elevation in the many diverse clinical populations studied with the armodafinil / modafinil over longer time periods. Furthermore, a trial by our group measured blood pressure as a proxy for sympathomedullary activation as part of safety and tolerability of modafinil to address OSA patients with mild to moderate sleep apnoea in the absence of CPAP therapy. In this trial no significant changes in blood pressure indices were observed with armodafinil therapy, however, this was not regularly measured across all timepoints. No serious side effects were observed and the drug was well tolerated, a result further supported by another of our previous trials employing modafinil to offset daytime sleepiness for OSA patients during a brief (one weekend) withdrawal of CPAP therapy.
No serious adverse events were reported in either of the original trials investigating adjunct wake promoting drugs for the treatment of insomnia with CBT-I. Roscoe et al.\textsuperscript{64} report that of 88 patients commencing the trial 73 completed the intervention with three adverse events noted; one episode of lower limb paresthesia, and two episodes of headache. Four of the initial 30 participants withdrew from Perlis et al. trial with headache and stomach upset reported by two participants from the modafinil + contact control group and life-event reasons cited for the remaining two individuals from the placebo +CBT-I group.\textsuperscript{63} Overall wakefulness promoters appeared safe and well tolerated by participants in these trials.

Following the completion of our trial changes to wakefulness promoter prescribing guidelines have come into effect. The category in Australia for prescribing medicines in pregnancy has been updated from Category B3 to Category D and product information stipulates a contraindication to therapy in pregnancy and in patients who may become pregnant.\textsuperscript{75}

1.7 Study Objectives and Research Hypotheses

1.7.1 Objectives

1. Primary objective: To determine if armodafinil can be used to moderate the effects of SRT for Insomnia Disorder in a preliminary proof-of-concept trial. Data will enable the evaluation of acceptability, tolerability, safety, and efficacy (ISI) and of armodafinil, specifically in the context of SRT alone for insomnia disorder.

2. Secondary objectives: Determine if armodafinil during SRT for insomnia disorder improves the initial transient adverse effects of increased sleepiness (ESS 1-week version) during weeks 1-4 of SRT.

3. Other secondary objectives: To evaluate the effect of armodafinil during SRT for Insomnia Disorder on adherence to SRT, health-related quality of life (SF-12), actigraphic and sleep diary defined sleep-wake parameters: TST, SOL, WASO, percentage sleep efficiency (%SE), ratings of sleep quality, and total time in bed (TIB).
1.7.2 Research hypotheses

1. Overall insomnia severity measured at 12 weeks will reduce significantly more in patients receiving adjunctive Armodafinil and SRT compared to SRT only (non-drug historical controls). This data was unavailable for formal statistical comparison at the time of writing this thesis, however, it is anticipated that once harmonised it will form the basis of a future report in a peer reviewed journal.

2. We hypothesised that adjunctive Armodafinil would enhance SRT by reducing side-effects and improving adherence resulting in an overall reduction in Insomnia Severity during weeks 2-4 of therapy measured by a repeated 1-week version of the Epworth Sleepiness Scale.

3. We hypothesised that the baseline self-efficacy score or a change in this value may be predictive of response to therapy (see Figure 3.5).

Sleep diary defined sleep-wake parameters were employed throughout the trial for the clinical purpose of guiding titration of SRT and pharmacotherapy. As a result of the exhaustion of available resources for the trial actigraphy data was not collected in enough patients to facilitate statistical analysis. We abandoned our initial intention to investigate the presence of genetic polymorphisms COMT and PER3 upon response to armodafinil as a result of resource limitations and negative findings from our group in other trials. 43,76
Chapter 2 Methods

2.1 Trial Design and Duration

The MODERATE pilot trial was designed as a nonrandomised open label trial with armodafinil for 4 weeks, in patients with insomnia implementing SRT. Thirty historical controls from studies that have undergone the exact same SRT intervention previously without armodafinil were anticipated to act as controls for this study (from the UK: \(^7\) n=16 + n=6 (unpublished); and Australia: n=8: ACTRN# 12612000057886). Those data were collected between November, 2011 – November, 2013. It was anticipated that 30 patients with Insomnia Disorder would be recruited on a 1:1 ratio to the historical controls to undergo SRT and armodafinil. The primary outcome measure was insomnia severity measured by the Insomnia Severity Scale. The protocol duration was 14 weeks in total consisting of a 2-week lead in period + 4 weeks of intervention and a final primary end point follow-up at 12 weeks from treatment start. Additional follow-up assessments took place during weeks 1, 2, 3, 4 and 6 from treatment start. The trial was registered with the Australian and New Zealand Clinical Trial Registration number 12614001293651.

2.2 Study Setting

All study procedures were conducted at the Woolcock Institute of Medical Research, Sydney, Glebe, NSW, 2037, Australia. The Woolcock Institute has a sleep research centre and a medical clinic from which we primarily recruited patients. We also aimed to recruit volunteers; with local community advertising, online advertising at the Woolcock Institute of Medical Research website, from Royal Prince Alfred Hospital Sleep Disorders clinic and the Woolcock Institute of Medical Research Sleep Disorders Clinic.

2.3 Eligibility Criteria

2.3.1 Inclusion criteria

1. Males & Females aged 18-70 years.
2. Able to give informed written consent.
3. Literacy in English.
4. Symptoms of Insomnia Disorder as diagnosed by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for Insomnia Disorder specifically: Difficulty initiating or maintaining sleep or waking up too early for at least 3 nights per week, for at least 3 months, with adequate opportunity and circumstances for sleep and at least one daytime impairment related to the sleep difficulty,\textsuperscript{11} assessed by telephone screening interview.\textsuperscript{78}

5. Insomnia Severity Index scale scores of 15 or more.

6. Never previously treated with CBT-I or armodafinil.

7. At least one month hypnotic free and willing to not take hypnotics for the duration of the trial.

8. Female patients with the ability to fall pregnant must use a medically accepted method of barrier contraception throughout the 14 weeks of the study.

2.3.2 \textit{Exclusion criteria}

1. Pregnancy or lactation - during the face-to-face screening visit the patients were asked by a medical practitioner whether they were breastfeeding or whether there was any chance they could be pregnant (see also inclusion criteria #8). If patients were not well established in their use of medically acceptable contraception in the opinion of the medical practitioner then the participant was asked to undertake a urine-based pregnancy test to rule out pregnancy. The investigators provided the urine-based test kit to the potential participant free of charge.

2. Patients with moderate-severe skin allergies and/or eczema. Any history of clinically significant cutaneous drug reaction or a history of clinically significant hypersensitivity reaction, including multiple allergies or drug reactions.

3. Past or present seizure disorder; a history of psychosis, depression or mania; current mood disorder; or a clinically significant head trauma (eg, brain damage).

4. History of a suicidal ideation, or a history of a suicide attempt, or was currently a suicidal risk.

5. History of significant aggression or violence or exhibits homicidal ideation or violent intentions.
6. Active, clinically significant gastrointestinal, cardiovascular, hepatic, renal, hematologic, neoplastic, endocrine, neurologic, immunodeficiency, pulmonary, dermatologic, or other major clinically significant disorder/disease.

7. Any history of left ventricular hypertrophy or mitral valve prolapse.

8. A clinically significant deviation from normal in ECG, physical examination, or vital sign.

9. Use of any medication known to induce metabolism via cytochrome P450 system (CYP450) 3A4/5 within 14 days prior to the baseline visit.

2.4 Study Interventions

2.4.1 Pharmacotherapy with armodafinil

Each patient was given the study drug, armodafinil (1x50mg tablets: initially 50mg, rising in 50mg amounts to a maximum of 150mg oral dose, under guidance from the study medical practitioner) once daily (taken before 09:00am) for 4 weeks. The full 4-week dose was provided to the patient prior to therapy. Up-titration of armodafinil was based on the discretion of the assigned medical practitioner, usually myself, in consultation with the patient during the study. Patients were started on a dose of 50mg per day and were required to use this dose for at least three days before being given permission up-titrate the dose to a maximum of 150mg per day. This is an open label trial that is not blinded and therefore all participants received an active drug. There was no placebo.

2.4.2 SRT intervention

All patients were coached on SRT implementation and titration by members of our trial team including a psychologist (C.M.), a pharmacist (I.J.), and a physician (D.J.). SRT aims to reduce excessive time spent in bed and reset sleep by matching time in bed (minimum of no less than five hours) to perceived TST (from weekly sleep diaries). For titration: once a high rate of sleep efficiency (90%) was achieved (time asleep divided by time in bed multiplied by one hundred) time in bed was extended by fifteen minutes each week (normally by retiring to bed earlier). If sleep efficiency was less than 90% time in bed was maintained. Or it was reduced by 15 minutes if sleep efficiency was less than 85%.
2.5 Trial Outcome Measures

2.5.1 Primary outcomes

Insomnia severity measured self-report capture of the Insomnia Severity Index at 12 weeks from the start of SRT, by either online or paper version via emailed link to our secure online trial database.

Timepoint: We measured this at screening (baseline), weeks 1, 2, 3, 4, 6 & 12 from treatment start. Week 12 of treatment was the primary endpoint.

2.5.2 Secondary outcomes

1. Daytime sleepiness before and during SRT for Insomnia Disorder was measured by a weekly version of the Epworth Sleepiness Scale (ESS). 77
   Timepoint: We measured this at screening (baseline) and treatment baseline along with weeks 1, 2, 3, 4, 6 & 12 from treatment start. Weeks 1, 2, 3 & 4 from treatment start are combined secondary endpoints.

2. Active Safety Mood Screening before and during SRT for Insomnia Disorder measured through the Depression Anxiety Stress Scales (DASS-21). 79
   Timepoint: We measured this at baseline and screening (baseline), weeks 1, 2, 3, 4, 6 & 12 from treatment start.

3. Objective actigraphic sleep-wake parameters (total sleep time, sleep onset latency and wake-time after sleep onset) and adherence to SRT (total amount of time spent in bed). Actigraphic data was captured on the minority of patients due to a lack of equipment and was not formally analysed due to resource limitations. SRAS values are presented in Table 3.3.
   Timepoint: We measured this at screening (baseline) for two weeks (weeks -2-0 from treatment start) and weeks 0-1, 1-2, 2-3, and 3-4, from treatment start.

4. Subjective daily-diary sleep-wake parameters (total sleep time, sleep onset latency, sleep efficiency, ratings of sleep quality and wake-time after sleep onset) and adherence to SRT (total amount of time spent in bed). Sleep diary data was clinically interpreted and employed to guide therapy.
Timepoint: We measured this at screening (baseline) for two weeks (weeks -2-0 from treatment start) and weeks 0-1, 1-2, 2-3, and 3-4, from treatment start.

5. Adherence to the SRT intervention measured through the SRT adherence scale.
   Timepoint: We measured this at weeks 0-1, 1-2, 2-3, and 3-4, from treatment start.

6. Health-related quality of life measured through the Short-form 12-question health survey.
   Timepoint: We measured this at screening (baseline) and at the follow-up 12-weeks from treatment start.

7. Self-efficacy measured through the Self-efficacy questionnaire.
   Timepoint: We are measured this at screening (baseline) and at the follow-up 12-weeks from treatment start.

8. Active safety: treatment related side effects measured through the Side Effects Inventory.
   Timepoint: We are measured this at the final follow-up timepoint only, 12-weeks from treatment start.

2.6 Sample Size

The sample size was not statistically calculated for this pilot study, however, was designed to match on a 1:1 ratio to the 30 non-drug historical patient controls.

2.7 Recruitment

The primary recruitment site for the 30 participants was the Woolcock Institute of Medical Research, Sydney, Glebe, NSW, 2037, Australia. All study procedures were conducted in the sleep research centre and clinic at the Woolcock Institute (see section 2.3). The following recruitment sources were utilised in order to recruit the study sample:
1. The Woolcock Volunteer database hosts patients’ details who have provided consent to be contacted about clinical trials. Any appropriate candidates were contacted from this list.

2. Participants were recruited through RPAH-Woolcock Institute affiliated Sleep Physicians.

3. Advertisements were displayed in and around waiting rooms at the institutions listed above.

2.8 Data Collection, Methods, and Analysis

2.8.1 Data collection methods

1. Primary outcome: insomnia severity

   The Insomnia Severity Index (ISI) was captured either electronically or through a paper-based questionnaire, posted to the patients’ address. The ISI is a seven-item questionnaire used to examine overall insomnia severity (past two weeks). It consists of a five-point Likert type scale for each item (ranging from “no problem” = 0 – “severe problem” = 4). All items are summed and total scores range from 0-28. The ISI was chosen as it has been validated with cut-off scores for clinical insomnia and can define moderate-severe insomnia (more than or equal to a score of 15 with 99.4% sensitivity and 91.8% specificity in clinical samples of insomnia.\footnote{80} It can also be used to define responders (a reduction of 6 or more points on the ISI)\footnote{81} and treatment remitters (score of less than 8).\footnote{73} Only patients with ISI scores of 15 or more were included in this trial.

2. Secondary outcome: daytime sleepiness

   A weekly version of the Epworth Sleepiness Scale (ESS) were used to monitor daytime sleepiness before and during SRT for Insomnia Disorder. The ESS is an eight-item questionnaire used to probe subjective levels of sleepiness under different daytime conditions (watching TV, reading, driving etc.). It consists of a four-point Likert type scale for each item (ranging from: “would never doze” = 0 - “high chance of dozing” = 3). All items are summed and total scores range from 0-24. As a guide, a score of 11 or more may indicate daytime sleepiness due to a sleep disorder like obstructive sleep apnoea and a high score of 17 or more may indicate narcolepsy.\footnote{77}
3. Secondary outcome: Active Safety Mood Screening

Patients were asked to complete the 21-item version of the Depression Anxiety Stress Scales (DASS-21) before and during SRT for Insomnia Disorder. The DASS-21 has a four-point Likert type scale for each item (ranging from “Did not apply to me at all” = 0 - “Applied to me very much, or most of the time” = 3). To score, items are summed for and scores range from 0-42 for each specific domain (Depression, Anxiety and Stress). This was implemented to monitor the effects of treatment on Depression Anxiety Stress Scales each week for four weeks of SRT and armodafinil. The DASS-21 has previously been used in insomnia and sleep research to profile mood states. Unlike other mood questionaries, the scale does not enquire about sleep and makes this scale more suitable for this type of study. Severe scores (Depression >20; Anxiety > 14; Stress > 26) were followed-up after consultation with myself over the telephone each week.

4. Secondary outcome: objective sleep-wake parameters

Actigraphy was abandoned due to resource limitations.

5. Secondary outcome: subjective sleep-wake parameters

Subjective daily diary patient estimations of sleep-wake parameters were used in this study for the parameters: total sleep time, sleep onset latency wake-time after sleep onset, and sleep quality) and adherence to SRT (total amount of time spent in bed). Sleep diaries are widely used in sleep science, and they are fundamental to understanding the subjective complaints of patients with insomnia disorder. Patients were asked to complete the diary before they commenced their day and refer back to the previous night’s sleep with approximations to the nearest 5 minutes. When compared to gold standard PSG and actigraphy, sleep diaries tend to be less accurate because healthy participants tend to overestimate their TST, whereas patients with insomnia underestimate their sleep time. The sleep diary is the gold standard subjective assessment of sleep and an extremely important assessment of insomnia. The subjective complaint is considered primary, and was used to quantify the progress of SRT for Insomnia in this trial using %SE. In this trial we used a diary based on the American Academy of Sleep Medicine (AASM) consensus sleep diary. The proposed consensus sleep diary is currently a live document available for use, but it still requires
validation, testing, and refinement. We employed the sleep diary to guide clinical titration of SRT rather than an efficacy outcome measure.

6. Secondary outcome: adherence to SRT

Subjective Adherence to the SRT intervention measured through the SRT adherence scale scores. The sleep restriction adherence scale (SRAS) was completed on a weekly basis throughout the first four weeks of SRT and serves as a subjective measure of adherence to SRT. The scale is based on the Medical Outcomes Study General Adherence scale (MOS-A47), and modified to probe adherence to different aspects of SRT. The SRAS has five items each with a six-point Likert type scale (ranging from “None of the time” = 1 - “All of the time” = 5). To score, all items are summed and total scores range from 5-30, with higher scores indicative of greater levels of adherence. Preliminary psychometric evaluation of the SRAS, with 42 insomnia patients undergoing SRT, revealed high internal consistency (Cronbach’s $\alpha$=0.92; range of item-deletion $\alpha$=0.89–0.93, mean $\alpha$=0.91). SRT specific research remains a nascent field and measures of tolerance, adherence and treatment effect remain understudied.

7. Secondary outcome: health-related quality of life

Health-related quality of life measured through the Short-form 12-question health survey (SF-12). The SF-12 is a short form of the SF-36, a widely used health survey. The 12 items are rated on Likert type scales and scoring algorithms derive the following 8 subscales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Reliability coefficients for the 8 subscales range from 0.73 to 0.87 in the general population and it has been suggested that this questionnaire appears sensitive to insomnia impairment and treatment and has normative data available.

8. Secondary outcome: self-efficacy as a predictor for combined SRT and armodafinil treatment effect

Sense of perceived self-efficacy was measured through the 10-item General self-efficacy scale. For each item, scores are based on a Likert scale and range from “Not at all true” = 1 - “Exactly true” = 4. All items are summed to produce a total score with a range of 10-40. Overall, higher self-efficacy scores reflect a more optimistic self-belief and ability to perform in novel or difficult tasks and cope with adversity, implying
internal attributions of success. Cronbach’s alpha is ranges from .76 to .90 and the scale is known to be valid in numerous observational studies and can be used before and after treatment in a wide range of conditions to monitor changes in quality of life.

9. Safety outcome: Sleep Restriction Therapy Side Effect Inventory

Side effects of SRT were quantified by a newly developed questionnaire – the SRT side Effect Inventory which is tailored to examine specific difficulties with SRT. The questionnaire asks patients to think in what way SRT may have interfered with normal functioning (by thinking back to before treatment). It asks patients whether or not they have experienced any of the 14 symptoms (yes or no) that have been shown to be adversely associated with implementing SRT. If patients answer yes, they are then asked to rate on a 5-point scale the severity of this symptom (ranging from “Not at all true” = 1 - “Very much” = 5). All items are summed and higher scores indicate greater interference to daytime functioning attributed to SRT implementation. Patients are also asked to enter in and rate any 3 other unwanted symptoms that may have impacted on their daily functioning due to SRT if applicable.

10. Safety outcome: Patient reported Adverse Event and Serious Adverse Events

Adverse events and serious adverse events (defined in section: 22 Harms, Appendix 1) were documented using a standard Adverse Event and Serious Adverse Event form. The study monitored for potential adverse effects through both a weekly Sleep Restriction Therapy Side Effect Inventory and an Active Safety Mood Screening questionnaire (DASS-21).

2.8.2 Retention

Once a patient was enrolled every reasonable effort was made to follow the patient for the entire study period and to obtain the primary outcome variable, the ISI. The study staff developed and implemented standard operating procedures aiming to achieve a high level of follow-up. Periodic communication reminders by telephone and email were used to ensure follow-up of the outcomes of the study at data collection time points. Discrepancies in data collection were communicated to the study co-ordinator in order to gather any outstanding data or to record difficulties with collecting study outcomes.
Early discontinuation of either therapy for any reason was not a reason for withdrawal from the study. If a participant failed to return for follow up or discontinued for personal reasons, attempts were made to determine whether the reason for not returning is not an adverse event (bearing in mind that the participant is not obliged to state reasons). We decided that participants with clinically significant abnormalities requiring discontinuation would be followed until recovery from the abnormality, if possible. Participants were able to withdraw from the study for any reason at any time. The investigators retained the right to withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the principal investigators (D.J.B., B.Y.).

2.9 Data Management

All data was captured or entered electronically on a web-based platform. This was undertaken at the Woolcock Institute of Medical Research or securely through a cloud-based platform developed and maintained by the Woolcock Institute of Medical Research (Research Tools). Any original study forms were entered and kept on file at the Woolcock Institute of Medical Research. Patient files were stored in numerical order and in a secure place and manner. All patient files will be maintained for 15 years after the completion of the trial.

2.10 Statistical Methods

For continuous repeated measures data, we employed linear mixed effects models on all of the data collected at all time-points but with specific hypotheses testing at the pre-determined time-points depending on the outcome being tested using least square means differences. We examined the residuals to assess model assumptions and goodness-of-fit. Change scores of continuous data collected at baseline and posttreatment only were examined by T-tests. P-values are reported to three decimal places with p-values less than 0.001 reported as p <0.001. Version 9.4 of SAS (Cary, NC) was used to conduct analyses. For all tests, we will use 2-sided p-values with alpha = <0.05 level of significance. All statistical analysis was undertaken by the trial statistician Nathaniel S. Marshall.
2.11 Harms

An adverse event in this trial was defined as any untoward medical occurrence in a patient without regard to the possibility of a causal relationship. A serious adverse event for this study was defined as any untoward medical occurrence that was believed by the investigators to be causally related to study-drug or SRT and resulted in any of the following: Life-threatening condition (that is, immediate risk of death); severe or permanent disability, prolonged hospitalisation, or a significant hazard as determined by the trial management committee. All adverse events were collected after the patient provided consent and enrolled into the study. It was intended that if a participant experienced an adverse event after the informed consent document was signed but the patient had not started to receive study intervention, the event would be reported as not related to study drug or SRT. All adverse events occurring after entry into the study and until hospital discharge were recorded.

2.12 Research Ethics Approval

This protocol, informed consent form, participant information sheet, study advisement, SRT intervention, and other requested documents were reviewed and approved by the study sponsor (The Woolcock Institute) and the ethical review committee. The trial management committee made safety and progress reports to the ethical review committee (Bellberry Ltd.) annually and within three months of study completion. These reports included the total number of participants enrolled and completed plus accumulated safety data.
Chapter 3 Results

Figure 3.1 demonstrates participant flow through the study from electronic registration for the trial to the 12-week follow-up timepoint. The first patient started the trial in March 2017 and the last participant completed the trial in May 2019. Six hundred and three participants initially expressed interest in the trial electronically or were referred from local physicians or the Woolcock clinic as potential candidates. Forty-five eligible and consenting individuals attended a screening visit with a medical officer. Clinical screening failures can be broadly grouped into three categories: failure to satisfy trial eligibility criteria (n=5), individual participant’s choice to decline the trial protocol (n=7), and there were eight participants who initially consented, were deemed eligible, and subsequently declined further contact. Twenty-five participants were enrolled in the trial and began the treatment protocol (see Figure 3.1).
3.1 Recruitment

Seven participants withdrew prior to the end of the active therapy period (4-week time point). We withdrew two participants from the trial following one serious adverse event and one adverse event that we deemed unrelated to therapy (see section 3.8). Five participants withdrew themselves from therapy with three citing side effects of SRT, a further patient describing
intolerance of both SRT and armodafinil, and one participant who we assume withdrew from therapy due to the patient declining further contact with the research team. Regardless of whether participants were adherent with therapy we attempted to ascertain outcome data for all 25. Under the intention to treat principle, all 25 patients enrolled were included in all analyses with missing data managed with least squared means procedures. Data for the primary end point (ISI at 12 weeks) was available for 20 of the participants after the attempted census of all enrolled patients regardless of adherence with treatment.

The trial was terminated prior to recruitment of the intended sample size of 30 participants due to expenditure of the pilot budget (See funding statement page vii). Our recruitment rate was slower than anticipated due to a higher than expected screen fail rate (Figure 3.1).

### 3.2 Patient Characteristics

The mean age of participants was 44.5 years with a range from 18-70 years (Table 3.1). Fifteen females and 10 males commenced active therapy. Mixed insomnia patients were the predominant subtype (n=18) with five patients reporting sleep maintenance symptoms and a further two reporting difficulties with initiating sleep (Table 3.2). All participants had long standing insomnia symptoms, all exceeding two years, with 20 participants experiencing symptoms for 10 years or longer and 13 participants beyond 20 years (see Inclusion criteria section 2.4.1).
Table 3.1
Demographic information along with baseline values for primary and secondary outcome measurements.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Minimum and maximum values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.5 (15.7)</td>
<td>18-70 years</td>
</tr>
<tr>
<td>Gender males/ females</td>
<td>10/ 15</td>
<td></td>
</tr>
<tr>
<td>Epworth Sleepiness Scale (ESS)</td>
<td>6.9 (4.3)</td>
<td>0-14</td>
</tr>
<tr>
<td>Insomnia Severity Index (ISI)</td>
<td>20.2 (3.3)</td>
<td>15-26</td>
</tr>
<tr>
<td>DASS Depression</td>
<td>11.6 (10.3)</td>
<td>0-34</td>
</tr>
<tr>
<td>DASS Anxiety</td>
<td>8.7 (8.3)</td>
<td>0-26</td>
</tr>
<tr>
<td>DASS Stress</td>
<td>19.1 (8.1)</td>
<td>0-30</td>
</tr>
<tr>
<td>Self-efficacy Scale</td>
<td>29.9 (3.5)</td>
<td>24-35</td>
</tr>
</tbody>
</table>

Table 3.1 Legend: ESS: Epworth Sleepiness Scale (score range 0-24), ISI: Insomnia Severity Index (score range 0-28), DASS: Depression, Anxiety, and Stress Scale (score range from 0-42 for each specific depression, anxiety, and stress domain), and severe scores are indicated by depression >20, anxiety >14, and stress >26), Self-Efficacy Scale (score range 10-40).

Table 3.2
Insomnia subtype classification diagnosed at initial medical review for MODERATE trial participants.

<table>
<thead>
<tr>
<th>Insomnia subtype</th>
<th>Frequency of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>2</td>
</tr>
<tr>
<td>Maintenance</td>
<td>5</td>
</tr>
<tr>
<td>Mixed</td>
<td>18</td>
</tr>
</tbody>
</table>
Table 3.3
Primary and secondary outcome measures at prespecified timepoints expressed as mean and standard deviation.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timepoints (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening</td>
</tr>
<tr>
<td>Insomnia Severity Index</td>
<td>20.2 (3.3)</td>
</tr>
<tr>
<td>ESS</td>
<td>6.9 (4.3)</td>
</tr>
<tr>
<td>DASS-21</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.4 (1.5)</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.3 (1.1)</td>
</tr>
<tr>
<td>Stress</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.4 (1.6)</td>
</tr>
<tr>
<td>SRAS</td>
<td>NA</td>
</tr>
<tr>
<td>SF-12</td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>47.4 (10.4)</td>
</tr>
<tr>
<td>Mental</td>
<td>40.3 (12.1)</td>
</tr>
</tbody>
</table>

Table 3.3 Legend: ISI: Insomnia Severity Index (score range 0-28) Screening values +/- SD and subsequent timepoints +/- SE, ESS: Epworth Sleepiness Scale (score range 0-24) Screening values +/- SD and subsequent timepoints +/- SE, DASS: Depression, Anxiety, and Stress Scale (score range from 0-42 for each specific depression, anxiety, and stress domain), SRAS: Sleep restriction adherence scale (score 5-30) SF-12: Short-form 12-question health survey (expressed as mean and SD). Values that have a statistically significant difference relative to Week 1 of therapy are represented in bold font.
Figure 3.2 Legend: Mean ISI values (+/- SD for screening values and SE for all other timepoints) with SRT and Armodafinil therapy are plotted in black. Results from Kyle et al. are presented in grey for visual comparison as a mean value and SD. ISI values of 15 and 8 are highlighted with a dotted line representing; at least moderate severity disease as a prerequisite for inclusion in the trial, and remission of insomnia symptoms respectively. *Indicates that the value is statistically significant compared to week 1 (p<0.05).

**Figure 3.2 Insomnia severity index changes through treatment with Sleep Restriction Therapy and armodafinil.**

### 3.3 Primary Outcome ISI Score

ISI values were available for 20 of the 25 participants at week 12. We had data for 106 of the 150 potential data points across all patients and all time points including 20 at the crucial 12-week end point. Compared to screening the ISI was improved at all time points (all p<0.0001) (Figure 3.2). Screening mean ISI 20.2 (SE 3.3) was of moderate severity (15-21) and fell to a nadir of 9.1 (SE 1.1) at the end of the active treatment phase numerically rebounding, without statistical significance (both p>0.05), to 10.2 and 11.2 at weeks 6 and 12 respectively. The mean baseline value fell in the moderate severity range (15-21), several points higher than the prerequisite 15 required for admission to the trial. Insomnia remission, defined as an ISI <8, is demonstrated as a dotted line in Figure 1.2. six (24%) of participants were classified as remitters following treatment, 14 patients were non-remitters and data for five patients was unknown. Insomnia response, defined as a reduction in the ISI of 6 points or more, is
represented as a dotted line in Figure 3.3. A total of 14 (56%) participants were classified as responders with six non-responders and five participants unknown (Figure 3.3).

Figure 3.3 Legend. A response to therapy demonstrated by a reduction in ISI ≥ 6 points is represented by the dotted line. All values are statistically improved from screening (p<0.05).

**Figure 3.3** Mean change in ISI values (+/- SE) for timepoints following the commencement of treatment (all values p<0.05).

### 3.4 Secondary Outcome Daytime Sleepiness (ESS)

There was a significant increase in ESS scores from screening to week 1 of therapy (Figure 3.4). ESS plateaued in the second treatment week and then continued to fall over the period of active therapy. A subsequent rise in ESS was noted at the final timepoint. Values for the mean ESS remained below the accepted excessively sleepy threshold (11) at baseline and over the trial period. Individual participant data at baseline demonstrated that 6 of the participants had an ESS equal to or greater than 11. This number remained stable at the end of the first week of therapy despite an increase in the mean value to the highest observed in the trial. Two individuals remained in the excessively sleepy category at the final timepoint with a single
standout value of 21 recorded by the participant electronically. The datapoint was analysed as it was recorded and subsequently the trial team was unable to contact the participant to confirm the accuracy of this value.

Figure 3.4 Legend. Mean (+/- SD for screening values and SE for all other timepoints) Epworth Sleepiness Scale (ESS) throughout treatment weeks for our trial are presented in black. Mean (+/- standard error) scores for Kyle et al. 77 are presented in grey. Values associated with a significant p value (p<0.05) are marked with *.

**Figure 3.4** Mean (+/- SE) Epworth Sleepiness Scale (ESS) scores across timepoints.

### 3.5 Secondary Outcome Adherence (SRAS)

SRAS values were collected for 68 out of a potential 100 data points (Table 3.3). Scores were high in the initial treatment week 25.8/30 (SE=1.4). Compared to week 1 the values for week 2 (p=0.03), week 3 (p=0.055), and week 4 (p=0.04) were lower.
3.6 Secondary Outcome Self-Efficacy

The mean scores at baseline for those demonstrating a response to therapy (n=12) was 30.6 (3.3) and for non-responders 28 (3.4). No statistically significant difference was observed between the two groups (p=0.15). The mean perceived self-efficacy scores for all participants, measured at screening 29.9 (SE 3.5) and the 12-week time point 27.9 (SE 7.6), did not significantly change (1.9; 95%CL -1.1-5.0, T=1.35, p=0.20).

Figure 3.5 legend. Individual self-efficacy scores for participants responding (remitters and responders) to SRT and Armodafinil therapy are plotted in red with those not responding plotted in black. In addition to the unavailable data points for ISI values at the final timepoint 2 further SES values were unavailable (n=18), both of those patients demonstrating a response to therapy as assessed by a reduction ≥6 or more in ISI. There was no apparent correlation between self-efficacy at any timepoint and the likelihood of responding or remitting, as defined by ISI, to combined SRT and Armodafinil therapy for insomnia.

Figure 3.5 Individual self-efficacy scores for participants at screening and the 12-week timepoint.

Whilst the mean self-efficacy score did not statistically change, we did notice that the standard error was notably larger at follow-up compared to baseline. Figure 3.5 was created to test the hypothesis (hypothesis 3 section 2.1.2) that the baseline self-efficacy score or a change in this value may be predictive of response to therapy. There was no apparent correlation between
self-efficacy at any timepoint and the likelihood of responding or remitting, as defined by ISI, to combined SRT and armodafinil therapy for insomnia in this relatively small sample.

3.7 Secondary Outcome Health Related Quality of Life Scores (SF-12)

The SF-12 was assessed at baseline and the final 12-week timepoint and is presented in Table 1.3 as mean scores in their physical and mental component parts. A mean improvement of over 2 points was observed across both domains, and over 4 points in the mental component. This satisfies the criteria for the minimally important difference (MID) in scores thought to be clinically significant (2 points), and suggests a minimally clinically meaningful change over time (2-4 points).90

Table 3.4
Result from the Sleep Restriction Therapy (SRT) Side-Effect Inventory and specific side-effects identified by participants throughout the trial.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of Participants Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WEEK 1</td>
</tr>
<tr>
<td>1. Low mood</td>
<td>5</td>
</tr>
<tr>
<td>2. Fatigue/exhaustion</td>
<td>10</td>
</tr>
<tr>
<td>3. Extreme sleepiness</td>
<td>10</td>
</tr>
<tr>
<td>4. Feeling agitated</td>
<td>4</td>
</tr>
<tr>
<td>5. Difficulty remembering things</td>
<td>7</td>
</tr>
<tr>
<td>6. Bodily pain</td>
<td>2</td>
</tr>
<tr>
<td>7. Headache/migraine</td>
<td>7</td>
</tr>
<tr>
<td>8. Euphoria/intense increase in mood</td>
<td>1</td>
</tr>
<tr>
<td>9. Difficulty concentrating and focusing on things</td>
<td>8</td>
</tr>
<tr>
<td>10. Reduced motivation/energy</td>
<td>7</td>
</tr>
<tr>
<td>11. Changes in hunger/appetite</td>
<td>4</td>
</tr>
<tr>
<td>12. Blurred vision</td>
<td>0</td>
</tr>
<tr>
<td>13. Dizziness</td>
<td>2</td>
</tr>
<tr>
<td>14. Feeling irritable</td>
<td>8</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>Number of Participants Reporting</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
<td>WEEK 1</td>
</tr>
<tr>
<td>Other/adverse events reported by participants:</td>
<td></td>
</tr>
<tr>
<td>1. Vomit</td>
<td>1</td>
</tr>
<tr>
<td>2. Very alert at bed time</td>
<td>1</td>
</tr>
<tr>
<td>3. Restless legs</td>
<td>1</td>
</tr>
<tr>
<td>4. Acne on face</td>
<td>1</td>
</tr>
<tr>
<td>5. Not having a clear head - heaviness, perhaps this is because of the</td>
<td></td>
</tr>
<tr>
<td>medication/sleepiness</td>
<td></td>
</tr>
<tr>
<td>6. Mild shaking</td>
<td>1</td>
</tr>
<tr>
<td>7. Feeling anxious</td>
<td>1</td>
</tr>
<tr>
<td>8. Dry eyes, dry skin</td>
<td>1</td>
</tr>
<tr>
<td>9. Thirsty (toilet runs high) and groggy</td>
<td>1</td>
</tr>
<tr>
<td>10. Overwhelmed, a great deal of feelings contained inside sometimes coming</td>
<td></td>
</tr>
<tr>
<td>out as frustration, anxiety, or sadness</td>
<td></td>
</tr>
<tr>
<td>11. Increased tinnitus with armodafinil</td>
<td>1</td>
</tr>
<tr>
<td>12. Feeling unbalanced as in a Meniere's attack</td>
<td>1</td>
</tr>
<tr>
<td>13. Low mood, migraine and bodily pain symptoms were experienced before the</td>
<td>1</td>
</tr>
<tr>
<td>medicine and while taking part in this trial</td>
<td></td>
</tr>
<tr>
<td>Severe restless legs</td>
<td></td>
</tr>
</tbody>
</table>

### 3.8 Secondary Outcome Safety

Treatment side-effects were commonly reported by participants (Table 3.4). The most commonly reported symptoms related to effects upon; mood, motivation, EDS, fatigue, and motivation. Side effects were most frequently reported during the second therapy week and were least problematic at the end of week 4. Individuals were encouraged to report side-effects and experiences outside of those listed in the inventory in free text. One adverse event and one
serious adverse event lead to us withdrawing the participants from the study prior to completion of active therapy. One patient had an exacerbation of Meniere’s disease and the other required hospitalisation for a condition deemed unrelated to the trial by the safety committee (see section 3.9). Active safety mood screening (DASS-21) scores were statistically and clinically unchanged over the active therapy phase (Table 3.3). These scores were used primarily to monitor patient wellbeing and prompt clinical review as indicated. These data are presented in Table 1.2 and broken down into the depression, anxiety, and stress components of the questionnaire.

3.9 Case Report of a Serious Adverse Event

I admitted a 48-year-old office worker to the trial with long standing, isolated, sleep onset insomnia. This patient satisfied inclusion criteria for the trial and at the time of medical review I could not detect any exclusion criteria that might deem the patient inappropriate for investigation. The patient received the initial 45-minute face-to-face sleep restriction therapy session and subsequently implemented the treatment with commencement of armodafinil pharmacotherapy as per protocol. The patient’s treatment was complicated by an acute inpatient admission secondary to reduced cognition not otherwise specified. The patient was reviewed by a multidisciplinary specialist team including; emergency medicine, toxicology, psychiatry, and neurology. Extensive investigation identified no clear cause for the acute presentation. A number of central nervous system depressant compounds were found at the patient’s residence, by the patient’s family, and brought to the treating Physician’s attention. The armodafinil was recovered from the patient’s home and a pill count excluded excessive consumption of the drug. The patient recovered without significant intervention and was discharged following a prolonged admission. This complication was recorded as a severe adverse event and we deemed the patient’s symptoms unlikely to be associated with either the sleep restriction therapy or armodafinil treatment interventions in the trial.
Chapter 4 Discussion

4.1 Outcomes

The primary objective of this proof of concept trial was to determine if armodafinil can be used to moderate the effects of SRT as a stand-alone behavioural modality for the treatment of insomnia disorder. Our study observed an improvement in the primary outcome of ISI at the 12-week endpoint with the combination of SRT and armodafinil therapy. Individual-level historical control data was not available in a harmonised format at the time of writing of this manuscript preventing formal statistical analysis of the predicted therapeutic gains associated with armodafinil in addition to stand-alone SRT. Visual clinical comparison of our data with reported data examining the therapeutic effect of SRT in the absence of wakefulness promoters, suggests that armodafinil in addition to SRT does not confer additional therapeutic effect on insomnia severity (see Figure 3.1). Data from Kyle et al was employed for comparison as it will form part of the historical control dataset still under construction and because the SRT intervention was the same as the protocol used in our study.

Participants in our trial demonstrated low ESS values at baseline and throughout the trial period. An initial increase in ESS with commencement of SRT was observed with subsequent declines as expected. When compared to findings from previous trials, armodafinil did not appear to notably mitigate the expected trajectory of ESS values by enough to justify routine adjunctive treatment.

Adherence, as measured by the SRAS, remained consistently high throughout. Comparative data are lacking, however, the absence of the wakefulness promoter effect on ESS would suggest that one of the key mechanisms proposed in the rationale, by which adjunctive armodafinil therapy would be expected to improve clinical outcomes, was not evident.

Side-effects were frequent and minor and one serious adverse event was reported supporting the weight of evidence previously demonstrating safety and acceptability of wakefulness promoters in appropriately selected patients. Recent data and changes to prescribing guidelines in Australia suggest that patient selection should not include those who are pregnant or who are likely to become so.

4.2 Recruitment
Recruitment to the trial proved more difficult than anticipated, leading to a smaller number of patients enrolled than originally planned and a prolonged recruitment period, causing exhaustion of the trial budget. Trial registration numbers were encouraging, however, the progression of candidates to initial review and subsequent inclusion in the trial was diminished by stringent exclusion criteria, necessary for patient safety. The use of an off-label medication as part of the trial protocol necessitated a focus on exclusion of patients with significant medical or psychiatric conditions to avoid potential side effects of therapy. The vetting of patients on these grounds resulted in successful participants resembling those diagnosed as primary insomniacs based upon historical diagnostic criteria. As outlined above, previously a distinct dichotomy existed between primary and secondary causes of insomnia ignoring the bidirectional relationship between particularly mood disorder and sleep disturbance. This may have led to a more homogenous group of participants and may affect the generalizability of the results.

A significant loss of participants was observed following the initial screening visit with a medical officer, only five of whom did not satisfy trial eligibility criteria. Various reasons were provided by those participants declining the trial protocol (n=7), and are outlined in the consort flow diagram (Figure 1.1). The reasons for declining further contact with the trial team remain speculative. However, it is my opinion that the initial medical consultation and SRT education session are of significant therapeutic significance in themselves, potentially leading to improvement in insomnia symptoms and potentially attrition from the trial. The burden of regular contact with the trial team and inherent side effects of SRT are likely to have contributed, along with the uncertainty of an off-label drug that would seem at first glance to have a mechanism of action counterproductive to the treatment of insomnia disorder. The natural history of insomnia as a waxing and waning condition may also have contributed to the observed attrition, with possible improvement in clinical symptoms spontaneously or as a result of early treatment interventions causing patients to withdraw from the trial procedures.

4.3 Primary Endpoint ISI

We demonstrated that the combination of SRT and armodafinil was effective in improving the primary outcome measure of ISI at the 12-week timepoint from initiation of active therapy. No previous trials have investigated the role of combination therapy with a wakefulness promoter and stand-alone SRT therapy rather than a multicomponent intervention. There was the intention to explore the added therapeutic benefit of armodafinil in addition to SRT alone, by
employing historical control patients who had undertaken identical SRT regimens in the absence of adjunct wake promoting agents. At the time of preparation of this thesis these data were unavailable for firm statistical analysis. However, I can qualitatively compare these findings to historical reports (see Figure 3.2). 77

Armodafinil did not confer added therapeutic effect to SRT alone when compared to data from Kyle and colleagues’ 77 trial examining SRT therapy in the absence of a wake promoting agent. The magnitude of the reduction in ISI in our study mirrored the results of this trial as represented in Figure 3.2. The ISI values observed in our study indicated more severe symptoms at baseline (Table 3.3 and Figure 3.3) when compared to historical data.77 However, scores were comparable in terms of falling into the moderate severity scale. 80 Within the limitations of this trial including; size, and the potential consequence of differing approaches to statistical analysis between our data and reported data, the trend in ISI values over time points was similar in my opinion. Baseline ISI values in our participants was 20.2 compared to reported data 17.4. Subsequent reduction in insomnia severity was observed across both data sets at week 4; 9.1 and 7.7, and week 12; 11.2 and 5.1 for ours and reported data respectively. The closeness of this trend does not support the hypothesis that the addition of a wakefulness promoting agent improves ISI values, as a measure of treatment efficacy for insomnia disorder in addition to SRT alone.

Epstein and colleagues undertook a randomized controlled trial examining the effect of single and multicomponent behavioural treatments in older adults (>55 years). 57 The proportion of patients that demonstrated improvements in insomnia symptoms sufficient to satisfy the definition of remitters (ISI <8) (Figure 3.2) in our trial of 24% (n=6) is similar to that observed by Epstein and colleagues in the isolated SRT treatment arm of their trial (23%). The proportion of responders (reduction in ISI ≥6) was reported to be 50%, lower than the proportion in our trial 56% (n=14), potentially related to differences in baseline characteristics, particularly age. The benefit of armodafinil to offset the side effects of SRT and improve clinical outcomes in older adults may be the subject of future research trials. However, the use of off-label wakefulness promoters in this age group is likely to be a barrier to recruitment, with an inherently increased burden of medical comorbidities likely precluding pharmacotherapy.

The potential for additional benefits of wake promoting agents beyond the therapeutic effects of multicomponent CBT-I, was not demonstrated in either of the two randomized control trials previously undertaken to explore this. 63,64 In an analysis of a secondary endpoint health related
quality of life from the original randomized control trial by Roscoe and colleagues,\textsuperscript{64} Peoples and colleagues\textsuperscript{68} postulated that the absence of additional benefit from armodafinil, on CBT-I for insomnia in cancer survivors may represent a ceiling effect of a robust psychological and behavioural intervention. The observed lack of additional benefit with armodafinil in our trial could be attributed to a similar mechanism. The magnitude of therapeutic response to SRT may render further incremental improvements in response difficult to measure and therefore clinically insignificant.

Importantly, the potential for a negative influence of adjunct wake promoting agents on SRT processes leading to poorer patient outcomes needs to be considered. The “no pain, no gain” hypothesis put forward by Kyle and colleagues suggests that the frequency of acute adverse effects of SRT experienced was positively correlated with improvement in ISI at their final 12-week time point, when compared to baseline results.\textsuperscript{61} Maurer and colleagues propose the possible therapeutic mechanisms for SRT in terms of the Triple R model:

1. Restricting time in bed,

2. Regularising timing of sleep and wake, and consequently; and

3. Reconditioning the association between bedroom factors and sleep.\textsuperscript{28}
The rationale for employing a wake promoting agent in our trial was to attenuate the resultant worsening in daytime sleepiness, to improve adherence SRT, and to promote a subsequent therapeutic effect on insomnia severity (ISI). The suggestion that the adverse events associated with SRT are necessary to provoke a therapeutic response challenges the hypothetical model proposed by our trial and would suggest that the addition of armodafinil to diminish side effects of SRT may be detrimental to treatment outcomes. If this were the case it would be expected that adherence with SRT would be similarly diminished. Any detrimental effect that armodafinil may have had on the proposed mechanisms by which SRT exerts its therapeutic effect would once again require control data. However, the striking similarity between data from our trial and data from Kyle and colleagues would suggest that armodafinil did not notably adversely affect response to SRT. Data from this trial lends itself to comparison with our findings as the trial team includes common researchers and the trial design was similar.
4.4 Secondary Outcome: ESS

The ESS was employed to monitor the participants’ propensity to fall asleep during the day before, during, and following the intervention period. Mean scores were low at baseline and remained below the accepted values for excessive daytime sleepiness at all time points. The normal range of ESS is traditionally suggested to be zero to 10. The observation that mean ESS scores were consistently below the excessively sleepy threshold at all timepoints is in keeping with previous findings that patients with insomnia often have low ESS, indicative of a low sleep propensity. Kyle and colleagues propose that the evidence for subjective (and objective) sleepiness in primary insomnia remains equivocal. This finding was mirrored by Souza and colleagues, demonstrating no significant association between EDS and insomnia in the Brazilian general population. Rosenthal and Meixner describe a wide range of ESS scores for patients presenting with a complaint of insomnia. However, their retrospective data demonstrated frequent comorbid sleep conditions that would have excluded individuals from our current trial.

Our findings mirror that of Kyle and colleagues, demonstrating an initial increase in ESS values in the active treatment phase of SRT with a subsequent fall to below baseline values. The striking similarity mean ESS values in our investigation when compared to Kyle et al. would suggest no additional benefit with armodafinil therapy as an adjunct to offset the side effects, namely EDS, of SRT for the treatment of insomnia. The same SRT protocol was employed in both trials further strengthening the significance of comparative observations. Our data were also consistent with findings from Miller et al. demonstrating a reduction in sleepiness at the three-week timepoint following SRT delivery, a trial not employing adjunct therapy. This could suggest that improvements in ESS observed in our trial were related to the therapeutic benefits of SRT alone.

The rationale for armodafinil as a short-term adjunctive treatment to increase effectiveness of SRT was as follows:

- The main adverse effect of SRT is daytime sleepiness. Armodafinil counters this.
- By keeping patients awake during the day, armodafinil would enhance the normal homeostatic pressure to sleep in late evening and avoid napping during the day that would reduce this drive and impede the effectiveness of SRT.
By reducing daytime sleepiness and fatigue, armodafinil may diminish the cognitive arousal associated with insomnia and improve SRT effectiveness. 63

Hyperarousal and the increased activation of the nervous system observed in insomnia patients30,63 was identified as a potential target for therapy. Objective measurement of markers for autonomic nervous system activation was not undertaken in our trial. Persistent hyperarousal in our participants could explain the lack of additional benefit observed with Armodafinil therapy mediated directly or via the lack of observable difference in ESS values between our trial and published data77.

A key component of our trial rationale was that the addition of a wakefulness promoter may decrease EDS, known to be a common and potentially serious complication of SRT, 62 thereby improving adherence. The absence of additional benefit with adjunct armodafinil therapy beyond that observed for SRT alone, may be explained by low and persistent ESS scores observed throughout the trial. The low ESS values might suggest the absence of at least one of the proposed mechanisms by which armodafinil would exert its therapeutic effect. The current trial is not sufficiently powered to investigate the benefit of armodafinil for those individuals with higher ESS values at baseline and following therapy. I suggest that future research may be directed at the role of wakefulness promotion in insomnia patients with abnormal high ESS values, given the plausible biological mechanism described above. Clinically it would seem more appropriate to provide adjunct therapy to those experiencing more severe symptoms and side-effects of SRT. Further to this, the potential role for wake promoting agents in the treatment of comorbid insomnia and sleep apnoea patients to the author’s knowledge has not been investigated.

When assessing what if any effect the addition of a wakefulness promoter has upon ESS it is necessary to establish a minimum clinically important difference across time and with treatment. A previous trial by Patel and colleagues 94 suggested a change in ESS between -2 and -3 demonstrates clinical significance in patients with obstructive sleep apnoea. Scrima and colleagues 95 concluded that a reduction in the ESS value of ≥25% was a useful threshold to identify narcolepsy patients responding to therapy. Furthermore, a relationship between the severity of OSA, measured by the Respiratory Disturbance Index (RDI) and the ESS has been demonstrated. 96,97 ESS is not a validated measure of treatment effect for insomnia. However, it has been employed in our trial and some previous reported trials as a proposed measure of effect and potential mediator of response to SRT. 57,77
Employing the definition of clinically significant change suggested by Scrima et al., we observed a clinically significant fall in the ESS from baseline to the end of therapy time point (4 weeks), and a subsequent rise in the ESS value at the final time point. The rise from the 4-week time point (completion of active therapy) was both statistically and clinically significant (See Figure 3.2). The cause for the subsequent rise in ESS observed at week 6 and 12 is likely the result of small participant numbers (n=25) and the effect that outlier values can exert upon mean values. One participant had an ESS 13 at week 6 and 21 at week 12. This may represent a drug withdrawal effect. In this case it would be expected that the ESS would be higher at the unmeasured time point at 5 weeks with respect to the measured values at week 4 and 6, with continued decline following this. The trend upwards at the 12-week timepoint is not in keeping with this hypothesis.

The R-enantiomer of modafinil, armodafinil is eliminated at a threefold slower rate than modafinil. The potential for the pharmacokinetics of armodafinil to pose a problem in some insomnia-prone patients was identified by the research team prior to the commencement of the trial. There is insufficient data in the literature to offer insight into this possibility. However, the apparent absence of observed drug effect therapeutically or otherwise, does not support this potential complication.

We hypothesised that the combination of SRT and armodafinil therapy would be associated with an initial rise in daytime sleepiness with a subsequent reduction to below baseline at the end of active therapy. The similarity between ESS values in our data and reported data, as outlined above suggests that our attempt to treat the EDS associated with SRT was unsuccessful. Armodafinil appears not to either aid or interfere meaningfully with SRT effectiveness as mediated by its’ effect on daytime sleepiness.

4.5 Adherence

Our rationale dictates that improvements in insomnia symptoms, related to adjunctive armodafinil therapy, would be related to improved adherence with SRT as a result of relief of side-effects including excessive daytime sleepiness. This proposed mechanism of action is not supported by our findings.

Adherence was measured with the SRAS, originally introduced by Miller and colleagues in a trial examining the daytime symptoms associated with SRT, and originally based upon
unpublished data in 42 insomnia patients, reported to demonstrate high levels of internal consistency. Higher values for the SRAS are thought to be indicative of more efficacious levels of adherence with SRT. 62 We propose that our data demonstrates high and consistent adherence with SRT over the active treatment time points (Table 1.1). The possibility of a ceiling effect related to adherence scores may be present, offsetting the potential for gains to be made via reductions in daytime sleepiness with armodafinil, and potentially explaining the observed absence of improved efficacy beyond that expected with SRT.

Perlis and colleagues 63 suggest that the addition of modafinil to CBT-I improves adherence. However, they also concede that the study design was not designed to look at this.

Our data do not suggest any helpful or harmful effect of armodafinil on SRT adherence.

4.6 Safety

Recognized complications of SRT were observed frequently and peaked in the second treatment week. Fatigue or exhaustion were the most frequently reported side effects with low mood, extreme sleepiness, difficulty concentrating, and reduced motivation also frequently reported. Similar types of side-effects are described in previous trials, in the absence of a wakefulness promoter with regard to reported side effects. 62,77 Miller and colleagues 62 observed significant elevations in sleepiness/ fatigue and significant reductions in alert cognition and positive mood with initial implementation of SRT. Furthermore, Kyle et al. 77 demonstrated objective deterioration in psychometric vigilance tasks in the initial period of SRT. We observed a broad range of side effects associated with combination SRT and armodafinil therapy (Table 3.4). Side effects were reported frequently, however, were deemed minor by the trial team. The MODERATE pilot trial aimed to investigate the potential for a wake promoting agent to offset the side effects of sleep restriction therapy and proposed this as a possible mechanism to improve adherence, and in turn the primary outcome, insomnia severity. Our observation that fatigue and sleepiness were both frequently reported and rated as severe by participants may indicate that the symptoms experienced by participants undergoing SRT are less responsive to armodafinil therapy than EDS related to other indications. Furthermore, common side-effects experienced by participants (Table 3.4) were more likely to be related to SRT than Armmodafinil. A prior trial involving 18 patients 61 undertaking the same SRT protocol reported the most frequent side-effects of; ‘reduced energy and motivation’ (100% of sample), ‘extreme sleepiness’ (94%), ‘reduced energy/motivation’ (89%) and ‘headache/ migraine’
(72%). The most frequently reported side-effects in our trial were the same with the exception of; ‘difficulty concentrating and focusing on things’ being reported more frequently than ‘headache/migraine’. Other side-effects of wake promoting agents commonly observed in clinical practice like dry mouth, anorexia, diarrhoea, and agitation were not commonly reported.

Recent changes to wakefulness promoter prescribing guidelines came into effect following the closure of our trial. Based upon recent post marketing data from the US modafinil and armodafinil pregnancy registry, armodafinil/modafinil is now contraindicated in pregnancy and in patients who may become pregnant. This update is based upon findings of major congenital anomalies associated with use in pregnancy of approximately 17.3% compared to 3% in the general population. In our trial female patients of reproductive potential were required to have a negative pregnancy test and were educated about the need to employ appropriate contraception during the trial and for a period of one month following ceasing the medication. While current standard of care treatment with modafinil/armodafinil dictates appropriate contraception, the recently confirmed teratogenic properties of these drugs represents a further barrier to their use.

In my experience the question of potential cardiovascular complications is frequently encountered in clinical practice when employing wakefulness promoters. The potential for adverse cardiovascular effects from modafinil was attributed, by Taneja and colleagues, to sympathomedullary activation. This was the proposed mechanism for the small but significant increases in heart rate and both systolic and diastolic blood pressure observed in their double-blind crossover trial (n=12). This is in contrast to data previously published from our institution in two trials demonstrating no significant change in blood pressure values, from baseline to the end of treatment during a 2 week trial investigating the role of modafinil in OSA patients not using standard therapies, and similarly no significant blood pressure changes in a group of OSA patients taking modafinil under investigation for therapy related changes in psychomotor vigilance. A meta-analysis of clinical trials of either modafinil or armodafinil for the treatment of residual sleepiness in CPAP-treated OSA patients demonstrated that therapy tripled the number of adverse events, doubled the adverse events leading to withdrawal but importantly did not increase serious adverse events and did not lead to clinically significant elevations in blood pressure.
Armodafinil was demonstrated to be safe and acceptable to participants in our trial. Active side effect monitoring was undertaken with a side effect inventory (Table 3.1). Two participants were removed from the trial. Only one of these was related to symptoms potentially attributed to armodafinil therapy (exacerbation of Meniere’s disease). No major adverse events were attributed to the study drug. Side-effects were common and minor (Table 3.4). This data supports the considerable body of previous work supporting wakefulness promoting agents as generally safe and acceptable to patients for the treatment of excessive daytime sleepiness related to various sleep disorders. Clinically it is important to keep in mind that non-amphetamine psychostimulants are not without frequent side-effects that would appear to be minor, but can be distressing for patients. 102

4.7 Quality of Life Measures

Despite limited data and differing definitions of insomnia severity across studies an association between health-related quality of life and insomnia severity consistently emerges. 87 From the limited treatment studies it is clear that improving sleep, in some cases, can lead to statistical improvements in aspects of health related quality of life. 87 A clinically meaningful change in health-related quality of life values in response to therapy has not yet been established for insomnia disorder specifically. 87 Darchia and colleagues 90 suggested that previous research has focused on a minimally important difference (MID). While an agreed value for the MID has not been defined for insomnia disorder, specifically MIDs between 2 and 4 points on health-related quality of life (HRQoL) measures are thought to be clinically important. In the context of our trial there was a 4-point improvement in the mental component of the SF-12 score between screening (baseline) and 12-week values demonstrating a MID and potentially a clinically meaningful change for participants. The contribution made by the addition of armodafinil to this finding would require comparative data from historical controls. The lack of SF-12 data in comparable SRT trials means I cannot comment on additional benefit afforded by armodafinil therapy.

4.8 Self-Efficacy

There was no significant difference in baseline self-efficacy scores between those participants that demonstrated a response to therapy and those that did not (see Figure 3.4). Similarly, there was no significant change in the mean scores for all participants at the endpoint compared with baseline values. Although not a prespecified condition in the study protocol we hypothesised
that higher self-efficacy scores (SES) would predict response to therapy. This was not supported by our observations. Furthermore, we observed that the application of an arbitrary cut-point in absolute SES scores, for the purpose of this argument, was not predictive of therapeutic gain. Our trial is not sufficiently powered to definitively rule out the potential for SES to predict response to SRT, however, this insight would be clinically useful and could form the subject of future research.

4.9 Limitations

This pilot study was limited by the small and select sample size. The use of armodafinil in an off-label setting demanded a robust approach to participant selection and resultant challenges to recruitment. Exclusion criteria were largely safety driven. The exclusion of participants with comorbid conditions deemed to be ‘higher risk’ may render the studied cohort more homogenous than the diverse presentation encountered in clinical practice, limiting generalizability of the findings. The inherent confounding influence of non-randomized, open label trials needs to be considered when evaluating the strength of conclusions drawn from our observations. The initial intention was to employ historical controls who had undergone SRT under the same conditions, however, at the time of completion of this manuscript control data remained unharmonised. The intention is to submit an article to a peer reviewed journal following the reanalysis of observations from this trial once control data is fully statistically analysed. Individual patient data is being coordinated between international investigators in Glasgow, Oxford and Sydney for analysis. Current efforts are hampered by the COVID-19 pandemic (see Acknowledgements).

Attempts to quantify armodafinil’s treatment effect size were limited to comparisons with trials investigating the role of similar medications and or psychological and behavioural-based therapies in the treatment of insomnia disorder. Such trials were heterogenous in terms of the inclusion of wakefulness promoters and the nature of these drugs, along with the approach to single or combined psychological interventions. Despite these limitations this trial adds much needed detail to the utility of psychological and behavioural therapies, and adjunct wakefulness promoting treatments along with safety and acceptability data, for the treatment of insomnia disorder.

4.10 Conclusions
Insomnia is a major public health problem with high prevalence, impacts on daily life and comorbidity with other disorders and societal costs. Further to this it is widely accepted that CBT-I, either its components or the full package, is effective in the treatment of insomnia disorder. CBT-I is commonly regarded as the treatment of choice for persistent insomnia and has been shown to produce sustained benefits in the absence of the risk of tolerance and adverse effects commonly associated with pharmacological approaches. It has been demonstrated that multicomponent CBT-I may comprise some therapeutically redundant components. Stand-alone SRT is efficacious for the treatment of insomnia disorder and has been tested in isolation and found to be as effective as multi-component interventions.

The current health system approach to insomnia disorder relies heavily on hypnotic therapy, despite marginal gains on placebo, and evidence of a range of significant side-effects. While the adverse effects associated with sedative hypnotic therapy is routinely studied in a randomized, placebo controlled trials to guide regulatory approval, there is a dearth of side effect data for psychological and behavioural interventions. Kyle and colleagues propose an association between acute sleep restriction and reduced objective total sleep time, increased daytime sleepiness, and objective performance impairment. Miller and colleagues similarly describe an increase in sleepiness / fatigue, and a decrease in alert cognition associated with initial SRT therapy. A mechanistic role for these side-effects in the therapeutic effect of sleep restriction therapy has been postulated. Whether the adverse effects in question are harmful or necessary for therapeutic effect remains a question with clinical equipoise. The potential benefit of armodafinil, a wakefulness promoter, to offset the side effects of SRT to treat insomnia disorder was the central justification of this trial. Our null results unfortunately do not advance this interesting potential clinical mechanism debate.

In addition to potential transient side effects related to psychological and behavioural interventions for insomnia, these therapies have traditionally represented a significant resource burden when delivered in a clinic by a psychological therapist. A ‘stepped care’ approach was proposed by Espie to address this with the goal of reserving more specialized and expensive care for those that remained unresponsive to less resource heavy interventions. Our pilot study, reported here, aimed to take this principle one step further investigating the utility of a short 4-week course of armodafinil combined with a simple manualised SRT that can be used by a range of clinicians and would be easily deployable in primary care settings. The implications for reduction in resource burden are twofold; with a reduced need to access to
specialized health care, and by offering a stand-alone behavioural therapy rather than CBT-I, a multicomponent intervention containing potentially redundant components. Sleep restriction therapy has greater promise of potential dissemination into primary care and sleep medicine clinics than multimodal treatments, because it is relatively easy to explain to patients, takes little time to learn as a clinician, and is simpler to implement. SRT was delivered in our trial by a number of health care specialists with demonstrable therapeutic effect, supporting the assertion that a manualised version of SRT would be practical and useful when delivered in a primary care context. This is particularly true in general practitioner or nurse practitioner led care, where SRT could have been implemented with a short course of armodafinil, rather than the standard practice of hypnotic prescription. A potential limitation of this model would be the need for a practitioner with prescribing authority and the financial cost of the drug.

The MODERATE pilot trial is the only study exploring the benefit of adjunctive armodafinil therapy to offset the side effects of stand-alone sleep restriction therapy for the treatment of insomnia. SRT and armodafinil treatment improved insomnia symptoms, as assessed by the primary outcome measure of ISI at 12 weeks following initiation of therapy. Adjunctive armodafinil therapy did not confer additional therapeutic gains beyond that expected from SRT alone, based on data from similar clinical trials in the literature. Reported findings of stand-alone SRT and potential side-effects thereof are limited to a small number of investigators, the most prominent authors of those trials are current investigators in this trial. It is my belief that these data are as comparable as can be possible outside of a properly randomized trial. Our observations add weight to the body of clinical evidence that supports the safety and acceptability of armodafinil treatment in various clinical contexts, except where there is a risk of pregnancy. The routine use of armodafinil therapy in addition to SRT for the treatment of insomnia is not supported by our findings, and we see no justification based on this proof of concept trial for a properly powered phase 2b trial.
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Appendices

Appendix 1: MODERATE Pilot Trial

Armodafinil to reduce the sleepiness related side-effects of Sleep Restriction Therapy being used to treat Insomnia Disorder: An open label pilot study compared to historical matched controls: MODERATE Pilot Trial. Australian and New Zealand Clinical Trial Registration (ANZCTR) Number: 12614001293651.