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RESEARCH ARTICLE

Armodafinil to reduce the sleepiness related side-effects of sleep restriction therapy being used to treat insomnia disorder: An open label clinical trial pilot study compared with historical controls

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Summary

Sleep restriction therapy (SRT) is an effective stand-alone behavioural intervention for insomnia disorder. However, its daytime side effects, particularly sleepiness, may be troubling for patients and/or may be a necessary part of the patient's treatment journey. This pilot trial aims to explore the potential benefit of armodafinil, a wakefulness promoter. Patients were treated with SRT with open label adjunctive armodafinil (150 mg/day). Thirty-three patients from previous studies that have undergone exactly the same SRT intervention acted as controls. The primary outcome measure was the insomnia severity index (ISI), and secondary outcomes were the Epworth sleepiness scale, sleep restriction adherence scale (SRAS), and safety from baseline through to 12 weeks. We recruited 25 patients into the trial. Data for the primary end point (ISI at 12 weeks) was available for 20 of the participants. The baseline insomnia severity index was 20.2 (SD 3.3) and decreased to 9.1 (SE 1.1), with no change, to 10.2 and 11.2 at weeks 6 and 12 respectively (all $p > 0.05$ compared with baseline). The insomnia severity index values for armodafinil patients were statistically inferior to historical controls at the primary time point of 12 weeks (11.2 vs. 6.7, $p < 0.01$). Sleep restriction therapy plus armodafinil treatment was associated with

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frequent minor side effects but was generally safe and acceptable to patients. Sleep restriction therapy was associated with a robust clinical response in the insomnia severity index values for insomnia patients. Based upon historical control data, armodafinil does not appear to have beneficial adjunctive effects in addition to sleep restriction therapy alone.

KEYWORDS
adverse events, fatigue, iatrogenic, modafinil, sleepy

1 | INTRODUCTION

Insomnia is a common disorder with high personal and more broadly societal costs associated with absenteeism and medical comorbidities (Bartlett et al., 2008; Deloitte Access Economics & Sleep Health Foundation, 2017; Deloitte Access Economics & Sleep Health Foundation, 2011; Ebben & Spielman, 2009; Pallesen et al., 2014). An inappropriate reliance on long-term hypnotics (in some patients this can be years or even a decade or more) has proven ineffective and potentially harmful with a range of known side effects including "hangover" effects, increased risk of falls, increased risk of motor vehicle accidents, and potentially with the Z-class drugs, parasomnias (Buysse, 2013; Glass et al., 2005; Gustavsen et al., 2008; Kripke et al., 2012; Laugsand et al., 2014; Perrier et al., 2014; Vermeeren, 2004; Winkler et al., 2014; Wong et al., 2017). Cognitive behavioural therapy for insomnia (CBT-I) is commonly regarded as the treatment of choice (Cunnington et al., 2013; Morin & Benca, 2012; Morin et al., 2009; "Therapeutic Guidelines. eTG complete", 2020; Trauer et al., 2015; van Straten et al., 2018). However, it has significant resource implications for the health system (Espie et al., 2012) and may contain therapeutically redundant elements (Morgan et al., 2004). One component of CBT-I, sleep restriction therapy (SRT) (Spielman et al., 1987), is a stand-alone behavioural intervention that has been demonstrated to be as effective as the multicomponent CBT-I interventions (Drake et al., 2019; Epstein et al., 2012; Maurer et al., 2021) and may be more readily deployable as a manualised treatment in a primary care setting as part of a "stepped care approach" (Espie, 2009).

Traditionally, CBT-I and specifically sleep restriction therapy have not been subjected to the same rigorous safety investigations that the pharmacotherapies endure (Kyle et al., 2011; Miller et al., 2013). Sleep restriction therapy is often cited by patients as the most challenging component of CBT-I (Chan et al. 2017; Vincent & Lewycky, 2008) and its implementation is associated with side effects during early treatment (Kyle et al., 2014; Maurer, Ftouni et al., 2021). In the original study, the four most frequent side effects were found to be: fatigue/exhaustion, extreme sleepiness, reduced motivation/energy, and headache/migraine (Kyle et al., 2011). Further, the sleepiness-inducing effects of sleep restriction therapy are troubling and unwelcome to patients particularly earlier in the day (Miller et al., 2013) and in our clinical opinion might increase the risk of accidents. On the other hand, we have evidence that this experience may be part of therapeutic chain of effect (Kyle et al., 2011). The equipoise in this situation remains whether this deliberately induced daytime sleepiness is helpful, harmful, or plays no role in the overall success of sleep restriction therapy.

A potential pharmacological solution to this sleepiness is the wakefulness promotor ar/modafinil, licensed in Australia for narcolepsy, shift-work sleep disorder, and as an adjunct to CPAP therapy in obstructive sleep apnea syndrome (Chapman et al., 2014; Williams et al., 2010). Perlis and colleagues were the first to describe the potential role of modafinil (100 mg) as an adjunct to CBT-I, where it did not improve sleep diary metrics but did improve adherence and sleepiness compared with CBT-I alone (Perlis et al., 2004). Our goal differed in that we wanted to test the acceptability, tolerability, and safety of 50–150 mg armodafinil adjuvant to stand-alone sleep restriction therapy in a larger series of patients. This pilot trial also aims to explore the potential benefit of armodafinil to offset the side effects and to increase the efficacy of sleep restriction therapy for the treatment of insomnia compared with historical controls treated with sleep restriction therapy alone (Kyle et al., 2014). We hypothesised that armodafinil treated patients would have less sleepiness during the 4 weeks of armodafinil therapy than controls and would also have better insomnia severity at 12 weeks.

2 | METHODS

2.1 | Design

This pilot trial was designed as a non-randomised open label trial with armodafinil for 4 weeks, in patients with insomnia implementing sleep restriction therapy. Thirty historical controls from studies that have undergone exactly the same sleep restriction therapy intervention using an identical treatment protocol, but previously without armodafinil, were chosen a priori to act as controls for this study (from the UK (Kyle et al., 2014): $n = 16 + n = 6$ (unpublished); and Australia: $n = 11$: ACTRN# 12612000057886). The control data were collected between November 2011–November 2013 (Sydney) and in 2010–2012 (Glasgow). The actual number of control patients included when we combined these datasets after the current data collection turned out to be 33 patients (22 from Glasgow, 11 from Sydney), and all these patients were then included as historical controls. We had anticipated that 30 patients with insomnia disorder would be recruited in

the current study of SRT + armodafinil based on a 1:1 ratio to the expected number of historical controls. We selected a single arm design as our pilot design to maximise our ability to collect safety and tolerability data on this approach which we had not tested previously.

Because of these design choices there is no randomisation, allocation concealment, or blinding. The protocol was approved by the Bellberry Ethics Committee (2016–02-104-PRE-2) and registered prospectively with the Australian and New Zealand Clinical Trial Registry (ACTRN# 12614001293651) and can be provided on request from the authors. There were four changes to the protocol following approval and registration. The first was to abandon the collection of actigraphy data as our trial budget was insufficient to fund the purchase of dedicated actigraphs. The second was to abandon the analysis of sleep diary data due to insufficient quality as the patients were unable to reliably complete them. The third was to analyse the changes in the insomnia severity index (ISI) as well as the pre-specified analysis of the raw values. The fourth change was that we originally intended to collect blood specimens for PER3 and COMT polymorphisms to phenotype treatment response, but we were unable to do this due to insufficient financial resources.

The protocol duration was 14 weeks in total, consisting of a 2 week lead-in period, 4 weeks of intervention (SRT + armodafinil), 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.

2.2 | Patients

All study procedures were conducted at the Woolcock Institute of Medical Research, Sydney, NSW, 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. Patients were initially screened online using a questionnaire and those that met initial inclusion criteria were invited to the Woolcock Institute for clinical screening conducted by a sleep medicine physician.

2.3 | Eligibility criteria

Male and female patients between the ages of 18 and 70 years were eligible for inclusion. Patients needed to be literate in English and to be able to provide informed consent. A diagnosis of insomnia was based upon criteria from the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (American Psychiatric Association, 2013) and patients had to report an ISI of 15 or more. A previous history of CBT or armodafinil therapy, or the inability to remain hypnotic-free for a period of 4 weeks prior, and throughout the investigation, were exclusion criteria. A negative pregnancy test and accepted method of barrier contraception was required for female trial patients. Patients with a significant history of a medication-related hypersensitivity reactions and/or serious medical or psychiatric comorbidities were excluded. Our trial pharmacists excluded individuals taking regular medications with potential drug interactions with ar/modafinil.

2.4 | Interventions

2.4.1 | Pharmacotherapy with armodafinil

Each patient was given the study drug, armodafinil (1 × 50 mg tablet: initially 50 mg, rising in 50 mg amounts to a maximum of 150 mg oral dose, under guidance from a study medical practitioner) once daily (taken before 09:00 am) for 4 weeks. The full quantity of medications required for the 4 week period was supplied at this visit (i.e. 90 tablets which allowed an extra 3 days medication at full dose). Up-titration of armodafinil was based on the discretion of an assigned medical practitioner in consultation with the patient during the study. Patients were started on a dose of 50 mg per day and were required to use this dose for at least 3 days before being given permission to up-titrate the dose to a maximum of 150 mg per day by the end of the first week of sleep restriction therapy. Adherence to medication was ascertained by a pill count undertaken by a study pharmacist (IJ or BS) from returned pill containers during the follow-up.

2.4.2 | Protocol-based **SRT** intervention

All patients received sleep restriction therapy in person by members of our trial team (including an experimental psychologist [CBM], a pharmacist [IJ], and a physician [DJJ]). Patients received a standardised sleep restriction therapy programme designed by the authors (psychologists CBM, SDK, CAE) used across trials (Kyle et al., 2014; Miller et al., 2013), which was based on the original work by Spielman et al. (1987). Sleep restriction therapy aims to reduce excessive time spent in bed and to reset sleep by matching time in bed (minimum of no less than 5 hours) to the perceived total sleep time (captured by baseline sleep diaries). The sleep restriction therapy intervention involved one main session to deliver the treatment rationale and instructions and covered rationale, sleep window calculation, and troubleshooting around potential implementation difficulties. This was followed by four weekly additional brief, in person or telephone interactions to help review progress and to titrate sleep efficiency. The initial sleep window was based on 2 weeks of baseline sleep diaries, reflecting average subjective self-reported diary capture of TST (Total Sleep Time; not calculated from standard sleep diary parameters). For weekly sleep window titration: once a high rate of sleep efficiency (90%) was achieved, (total time asleep divided by time in bed, multiplied by 100) time in bed was extended by 15 min (normally by retiring to bed earlier). If sleep efficiency was 85%–89%, the time in bed was maintained. If sleep efficiency was less than 85%, the time in bed

was reduced by 15 min (Kyle et al., 2014). The minimum sleep window was set to no less than 5 h. Our clinical team estimates that the typical depth of sleep restriction therapy prescribed using this algorithm was about 5.5–6 h per night for the first week in most patients.

2.5 | Outcome measures

Acceptability was quantified using the proportion of eligible patients who agreed to be enrolled. Tolerability was quantified by the proportion of enrolled patients who completed the 4 week combination therapy protocol.

2.5.1 | Primary efficacy outcome

The insomnia severity index (Morin et al., 2011) at specifically 12 weeks from the start of sleep restriction therapy, by either paper copy or online via emailed link to our secure online trial database was the primary efficacy outcome. We chose to define the primary endpoint at 12 weeks (i.e. 8 weeks after pharmacotherapy had ceased) because this was considerably after any effect could be caused by a direct pharmacological effect. Therefore any effect observed by then must have been due to the effect of armodafinil in augmenting the effects of sleep restriction therapy. We also measured the insomnia severity index at screening (baseline), weeks 1, 2, 3, 4, and 6 from treatment start. The insomnia severity index data in the control group from Sydney was not collected as part of the protocol in week 12 or in the Glaswegian patients in weeks: 1, 2, 3, and 6. A responder was a patient whose ISI score improved by six or more points between screening and 12 weeks. A "remitter" was a patient whose ISI score was lower than eight at 12 weeks.

2.5.2 | Secondary efficacy outcomes

A weekly version of the Epworth sleepiness scale (ESS) (Kyle et al., 2014) was used to monitor daytime sleepiness. For the current pilot trial patients, we measured this at screening (baseline), weeks 1, 2, 3, 4, 6, and 12 from treatment start. The ESS data were not collected in the protocol for the Sydney control patients in week 12 and were not collected for the Glaswegian patients in week 6. Active safety mood screening before and during sleep restriction therapy for insomnia disorder was measured through the depression anxiety stress scales (DASS-21) (Lovibond & Lovibond, 1996). Scores were largely employed to monitor the tolerability and safety of treatment, and to inform the need for clinician review as appropriate. In addition, potential adverse effects were detected by means of a weekly sleep restriction therapy side effect inventory (Kyle et al., 2011), a questionnaire to examine specific difficulties anticipated with sleep restriction therapy which may also reflect their experience of combined SRT + armodafinil. Subjective daily diary patient estimations of sleep–wake parameters were recorded for: total sleep time, sleep onset latency, wake-time after sleep onset, and sleep quality), and adherence to sleep restriction therapy (total amount of time spent in bed). We used a diary based on the American Academy of Sleep Medicine (AASM) consensus sleep diary (Carney et al., 2012). We measured parameters at screening for 2 weeks (weeks −2 to 0 from the treatment start) and weeks 0–1, 1–2, 2–3, and 3–4, from treatment start. We listed sleep diary-derived outcome measures in our clinical trial registration but found that whilst these measures were useful in clinically guiding sleep restriction therapy, it became evident early in the trial that the patients were not able to complete diaries anywhere near fully enough to allow meaningful statistical analyses. A sleep restriction adherence scale (SRAS) was completed on a weekly basis throughout the first 4 weeks of sleep restriction therapy and serves as a subjective measure of adherence to sleep restriction therapy (Kyle et al., 2012). Patients can rate themselves between a score of 5 and 30 indicating perfect adherence (Miller et al., 2013). This scale is based on the Medical Outcomes Study General Adherence Scale (MOS-A47), and modified to probe adherence to different aspects of the sleep restriction therapy. Preliminary psychometric evaluation of an SRAS, with 42 insomnia patients undergoing sleep restriction therapy, revealed high internal consistency (Cronbach's $\alpha = 0.92$; range of item-deletion $\alpha = 0.89$–0.93, mean $\alpha = 0.91$). We measured this at weeks 0–1, 1–2, 2–3, and 3–4, from the treatment start. The 12-Item Short-Form Health Survey (SF-12) (Ware et al., 1995; Ware et al., 2002) measured the health-related quality of life at baseline and at the trial end point. The sense of perceived self-efficacy was measured through the 10-item General Self-Efficacy Scale measured at screening (baseline) and at the follow-up 12 weeks from the treatment start (Schwarzer & Jerusalem, 1995). A reviewer of this manuscript also suggested that we include medication adherence as a post-hoc outcome. This was measured using pill counts from returned medication bottles undertaken by our trial pharmacists (I and BS).

2.5.3 | Adverse events

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 the study drug or sleep restriction therapy 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 prior to the patient starting or receiving the study intervention, the event would be reported as not related to study drug or sleep restriction therapy. All adverse events occurring after entry into the study and until hospital discharge were recorded.

2.6 | Statistical analyses and sample size

The sample size was pragmatically selected for this pilot study to construct approximately a 1:1 ratio to the anticipated 30 non-drug historical patient controls we thought we had access to (actually 33). All patients were analysed in the groups they were assigned to regardless of their adherence to ar/modafinil or SRT. For continuous repeated measures data, we employed linear mixed effects models on all 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. This method is also useful for dealing with missing data and we entered all 25 patients into the analyses. Patients were classified as random effects, and time and treatment were classified as fixed effects. The value of the outcome measure at screening was entered as a covariate. The potential treatment effects of armodafinil were compared with historical control data only for the primary outcome (ISI) the first named secondary outcome (ESS) and a Sleep Restriction Adherence Scale (SRAS, Supplemental Table S1). We examined the residuals to assess model assumptions and goodness-of-fit. Change scores of continuous data collected at baseline and post-treatment only were examined by *t*-tests. Version 9.4 of SAS (Cary, NC) was used to conduct analyses. For all tests, 2-sided *p*-values were used with alpha =<0.05 level of significance. There were no interim analyses for efficacy (just data completeness).

3 | RESULTS

3.1 | Patient enrolment and trial timeline

The first SRT + armodafinil treated patient started the trial in March 2017 and the last participant completed the trial in May 2019. We ceased recruitment at five patients short of the intended 30 as we had exhausted the trial budget. The basic demographics and clinical characteristics of each group are shown in Table 1. 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. All participants had long-standing insomnia symptoms, all exceeding 2 years, with 20 participants experiencing symptoms for 10 years or longer and 13 participants beyond 20 years.

3.2 | Efficacy and active safety outcomes

Figure 1 is a patient flow chart which also presents the data relevant to acceptability and tolerability of the combination therapy as well as the reasons for withdrawals or attrition from all parts of the study. Acceptability was quantified using the proportion of eligible patients who agreed to be enrolled which was 25 of an eligible 36 (69%). Tolerability was quantified via the proportion of enrolled patients who completed the 4 week combination therapy protocol (i.e. 18 of 25 or 72%). Of the 25 patients who began the trial, the clinical notes based on sleep diaries indicate that 11 patients exceeded 90% sleep efficiency by the end of the sleep restriction therapy (44%), 11 did not exceed 90% SE (44%), and sleep diaries were not complete enough to be clinically interpretable in three patients (12%). The changes in efficacy and active safety measures in the armodafinil+SRT treated patients and the historical controls is listed in Table 2. The comparison of the efficacy of the armodafinil approach to the historical controls is presented in Figure 2 for the insomnia severity index and Figure 3 for the ESS. Figure 2 shows the clinically significant reduction in ISI scores associated with sleep restriction therapy sustained up to 12 weeks in both the armodafinil+-SRT group and the historical SRT alone controls (Panel A is the raw values and Panel B is the reduction in ISI score from screening). The insomnia severity index scores in the armodafinil treated group are however statistically inferior to that achieved by the historical controls

TABLE 1 Demographic information along with baseline values for primary and secondary outcome measurements

	Armodafinil pilot patients ($n = 25$)		Glasgow controls ($n = 22$)		Sydney controls ($n = 11$)	
Variable	**Mean (SD)**	**Min-Max**	**Mean (SD)**	**Min-Max**	**Mean (SD)**	**Min-Max**
Age	44.5 (15.7)	18–70 years	44.2 (11.6)	25–65	45.5 (11.3)	25–60
Gender males/ females	10/ 15	60% Female	8/14	64% Female	2/9	81% Female
Years with insomnia	Coded in categories see Results	All more than 2 years	NC	NC	11.3 (10.9)	1–40
Epworth sleepiness scale (ESS)	6.9 (4.3) 6 above 10	0–14	5.4 (4.3) 2 above 10	0–18	4.7 (2.6) 1 above 10	1–11
Insomnia severity index (ISI)	20.2 (3.3)	15–26	17.5 (3.6)	8–23	19 (3.1)	15–25
DASS Depression	11.6 (10.3)	0–34	NC	NC	8.5 (8.0)	0–22
DASS anxiety	8.7 (8.3)	0–26	NC	NC	5.6 (5.0)	0–14
DASS stress	19.1 (8.1)	0–30	NC	NC	14.5 (7.2)	0–28
Self-efficacy scale	29.9 (3.5)	24–35	NC	NC	32.2 (4.0)	26–38

Abbreviations: ESS, Epworth sleepiness scale (score range 0–24); ISI, insomnia severity index (score range 0–28); DASS, depression, anxiety, and stress scale (score range 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); NC, not collected.

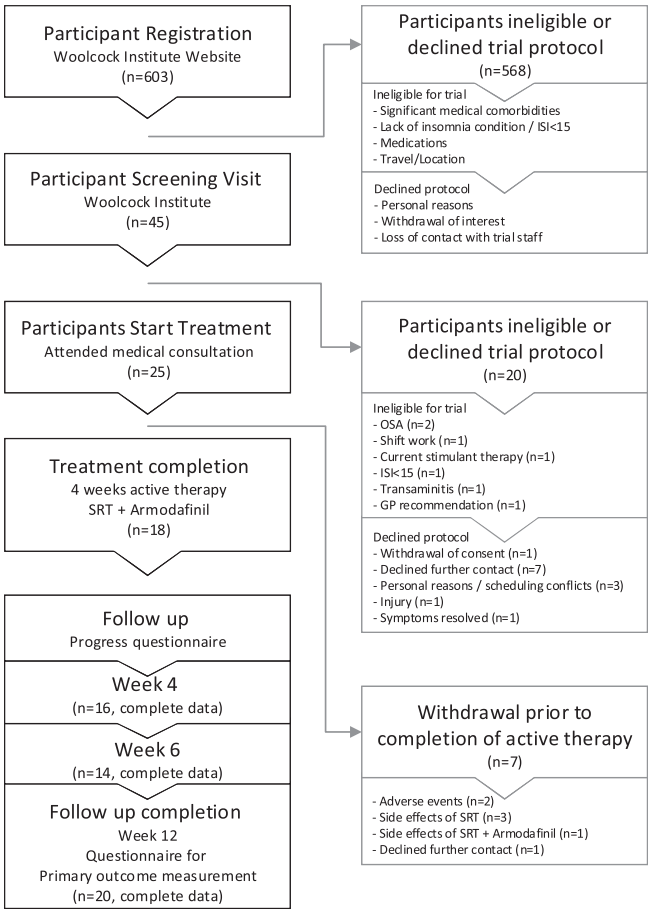

FIGURE 1 Participant flow diagram from registration to the final time point and primary outcome measure insomnia severity index value at 12 weeks for the patients undergoing therapy with sleep restriction therapy and armodafinil

at the primary time point of 12 weeks ($p < 0.007$ in both panels). Figure 3 shows the slight increase in the Epworth sleepiness scale scores in association with the initial weeks of sleep restriction therapy in both groups and the improvement in that metric up to 12 weeks. At no point were the two treatment groups significantly different in their ESS scores. Fourteen patients were responders (56% with ISI reduction of at least 6 points), six were non-responders and for five patients we did not have an ISI score at 12 weeks. Six patients reported remission of their insomnia at 12 weeks (24% with ISI score below 8 points). The within patient analysis of the secondary outcomes in just the armodafinil treated patients is shown in Supplemental Table S1 (i.e. outcomes not being compared with historical controls by design). Medication adherence was measured by pill counts where a patient who used 84 of the 50 mg tablets would have been using the full 150 mg dose for the whole 28 days. In the 24 patients who returned their pill bottles the average patient used 33.1 doses (range 0–60, SD = 17.6). There were no subgroup, ancillary, or adjusted analyses.

3.3 | Side effects and adverse events

Treatment side effects in the SRT + armodafinil treated patients were commonly reported (Table 3). The most commonly reported symptoms related to effects upon: mood, excessive daytime sleepiness, fatigue, and motivation/energy. Side effects were most frequently reported during the second therapy week and were least problematic at the end of week 4. One adverse event and one serious adverse event led to us withdrawing two 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 an episode of reduced cognition not otherwise specified, subsequently deemed unrelated to the trial by the trial medical practitioners.

4 | DISCUSSION

The objectives of this pilot trial were to determine if armodafinil was acceptable, tolerable, safe, and efficacious when used as an adjunctive therapy for sleep restriction therapy. We found that the combination of SRT and armodafinil was acceptable to approximately two thirds of the eligible patient population (see Figure 1). Approximately one third of the patients were unable to tolerate the combination therapy and discontinued either SRT, armodafinil, or both. Side effects were common but minor and transitory, and only one of the withdrawals from the trial seemed related to the addition of armodafinil. At no point during the trial was the response of the armodafinil-treated patients, as measured

TABLE 2 Changes in efficacy measures through 12 weeks of follow-up in Armodafinil treated and control patients

	Armodafinil and SRT treated patients ($n = 25$)							Combined Glasgow and Sydney historical control data ($n = 33$)						
	Time point (weeks)							Time point (weeks)						
Outcome	Screen	1	2	3	4	6	12	Screen	1	2	3	4	6	12
Insomnia severity index (ISI)	20.2 (3.3)	15.4 (1.0)	13.3 (1.1)	11.9 (1.1)	9.1 (1.1)	10.2 (1.1)	**11.2 (1.0)***	18.0 (3.5)	12.8 (1.4)	12.1 (1.3)	10.8 (1.3)	9.9 (0.8)	8.6 (1.4)	**6.7 (1.0)***
Change in ISI	NC	4.3 (1.0)	6.5 (1.0)	7.9 (1.0)	10.7 (1.0)	9.5 (1.0)	**8.5 (0.9)***	NC	6.2 (1.4)	6.9 (1.3)	8.3 (1.3)	9.2 (0.8)	10.5 (1.4)	**12.3 (1.0)***
ESS	6.9 (4.3)	8.3 (1.0)	8.1 (1.0)	5.9 (1.0)	4.1 (1.0)	4.8 (1.0)	6.1 (1.0)	5.2 (3.8)	7.4 (0.8)	7.9 (0.8)	6.9 (0.8)	6.2 (0.8)	6.1 (1.2)	3.5 (0.9)
SRAS	NC	25.8 (1.3)	23.0 (1.3)	23.3 (1.2)	23.0 (1.3)	NC	NC	NC	25.8 (1.0)	24.7 (1.0)	24.6 (1.0)	24.0 (1.0)	NC	NC

Note: The screening values are the arithmetic mean and standard deviation. The values given for weeks are the means calculated by the mixed models using the least squared means procedure and their standard errors. Change in ISI scores are given in points of improvement where a positive integer indicates the ISI score moved in the intended direction (i.e. an improvement is a positive integer).

p-values for comparison of treatments in SRAS week 1 = 0.9813, week 2 = 0.3408, week 3 = 0.3957, week 4 = 0.5317, Overall all weeks $p = 0.4556$. NC, not collected. ESS, Epworth sleepiness scale; SRAS, sleep restriction adherence scale.

*Indicates that there is a statistically significant difference ($p < 0.01$) between the armodafinil patients and the control patients for that week.

by the insomnia severity index, superior to that achieved by historical controls. Whilst we observed an improvement in the primary outcome of insomnia severity index at the 12 week end point for the combined SRT + armodafinil group, this effect was statistically inferior to that achieved with historical SRT control patients. Furthermore, our hypothesised improved control of unwanted daytime sleepiness via armodafinil was not observed at any time point. This null finding may have been caused by a somewhat smaller rise in daytime sleepiness during sleep restriction therapy than had been anticipated and it could be in another external group that armodafinil might work better if the rise is larger. Self-reported adherence, as measured by an SRAS, remained consistently high throughout in both groups (see Table 2). The absence of the wakefulness promoter effect on the Epworth sleepiness score 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. However, it could be that the ESS is not sensitive to the particular experience of insomnia patients having both SRT and armodafinil at the same time. The addition of a prescription of 150 mg armodafinil does not appear to improve the treatment effects of sleep restriction therapy and comes with additional clinical complexity, cost, and side effect profile. However, our use of an historical control group might have caused a bias making armodafinil look much worse than it might in a properly randomised study.

Two previous randomised, double-blind placebo-controlled trials have evaluated the role of either armodafinil or modafinil in the treatment of insomnia (Perlis et al., 2004; Roscoe et al., 2015). Both trials employed a multicomponent CBT-I intervention rather than stand-alone SRT with their wake promoting agent. 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 (Perlis et al., 2004). Twenty seven insomnia patients were randomised to one of three groups; CBT-I + modafinil, contact control+modafinil, and CBT-I + placebo. Modafinil did not demonstrate added benefit to CBT-I for the measured sleep continuity variables, however, it did demonstrate a statistically non-significant reduction in daytime sleepiness (ESS), and a subsequent improved adherence with the prescribed time in bed procedures as part of sleep restriction therapy, a component of the multifaceted CBT-I therapy. Roscoe and colleagues investigated the efficacy and safety of armodafinil to augment CBT-I in cancer survivors with insomnia in a phase 2 study. Armodafinil was not found to have added benefits in insomnia severity, nor improvements in addition to CBT-I alone, nor as a single therapy intervention compared with placebo.

Our sleep restriction therapy programme seems to have had a similar clinical effect to other groups' independent programmes. Epstein and colleagues undertook a randomised controlled trial examining the effect of single and multicomponent behavioural treatments in older adults (>55 years) (Epstein et al., 2012). 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%, which is slightly lower than the proportion in our trial 56% ($n = 14$),

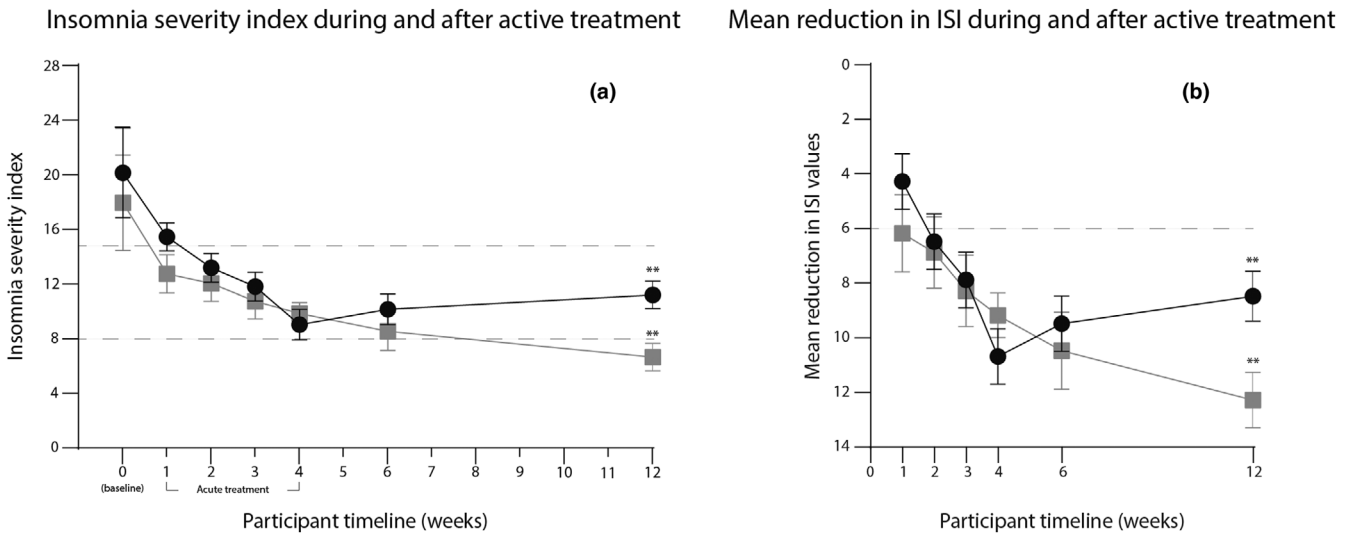

FIGURE 2 Comparison of armodafinil ($n = 25$, black line) treated sleep restriction patients to historical controls ($n = 33$, grey line). Mean (±SD for screening values and SE for all other time points) insomnia severity index (ISI) throughout treatment weeks. (a) Raw Insomnia Severity Index (ISI values 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). (b) Changes in the insomnia severity index from screening (a response to therapy demonstrated by a reduction in ISI ≥6 points is represented by the dotted line). The apparent differences between the treatment groups are not statistically significant at any time point except for at the primary time point of 12 weeks $p < 0.007$ for both panels

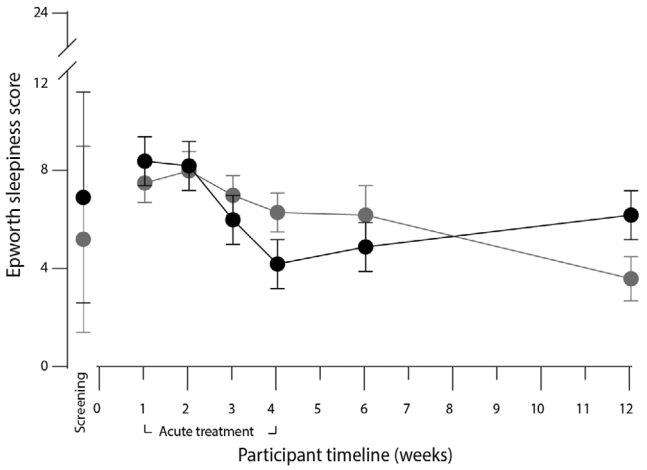

FIGURE 3 Comparison of armodafinil ($n = 25$, black line) treated sleep restriction patients to historical controls ($n = 33$, grey line). Mean score (±SD for screening values and SE for all other time points) of the Epworth sleepiness scale (ESS) throughout treatment weeks. ESS scores did not statistically differ between groups at any time point or overall ($p = 0.6887$)

potentially related to differences in baseline characteristics, particularly age. The benefit of armodafinil to offset the side effects of sleep restriction therapy and to improve clinical outcomes specifically in older adults may be the subject of future research trials.

Our study has several notable limitations in addition to the modest sample size and the reliance on self-reported outcome measures (including adherence to SRT). We did not employ standard robust clinical trial methodology including randomisation, allocation concealment, or blinding. Our control group was a blended data set of previously SRT-treated patients from two geographically separated cities (Sydney and Glasgow). We make no claim that these are patient groups can be regarded as "matched". This means that there could be very important differences in time, place, and patient characteristics that could cause bias and that might obscure the true effect of adjunctive armodafinil. We selected an historical control group because they had undergone an almost identical sleep restriction therapy protocol. However, there were some differences in the data collection frequency in the two key outcome metrics (ISI, ESS). For instance the 12 week insomnia severity index and ESS data were not collected in the 11 Sydney control patients, and ESS data were not collected at week 6 in the Weegies. The statistical model that we used has a limited ability to control for data like these that are missing by design. The combined effect of these notable biases is probably towards finding a favourable effect for armodafinil. However, what we observed was a series of null findings and for the primary end point (ISI at 12 weeks), the SRT + armodfanil group was associated with attenuated benefit relative to the historical controls. It is possible that starting patients on a higher dose immediately or recommending that patients take the drug slightly later in the day may have improved the patient's ability to adhere to their prescribed bedtime better. However, the previous study (Perlis et al., 2004), which had reported promising results, used 100 mg of modafinil. Our starting dose was 50 mg which was up-titrated after 3 days to 150 mg. There is conflicting evidence as to whether that difference in dose could cause meaningful clinical differences in sleepiness (Chapman et al., 2016; FDA, 2017; Tembe et al., 2011). Our medication return data (pill counts) does indicate that our patients only ingested a mean of 33 (range 0–60) of the potential 84 tablets they could have taken, generally indicating that a typical patient elected to only take around

TABLE 3 Result from the sleep restriction therapy (SRT) side-effect inventory and specific side-effects identified by armodafinil+SRT treated participants throughout the trial (no control participant data)

	Number of patients reporting			
Adverse events	**Week 1**	**Week 2**	**Week 3**	**Week 4**
1. Low mood	5	10	11	6
2. Fatigue/exhaustion	10	15	14	10
3. Extreme sleepiness	10	13	10	8
4. Feeling agitated	4	9	6	5
5. Difficulty remembering things	7	8	7	4
6. Bodily pain	2	3	4	3
7. Headache/migraine	7	6	6	4
8. Euphoria/intense increase in mood	1	3	2	2
9. Difficulty concentrating and focussing on things	8	13	13	6
10. Reduced motivation/energy	7	10	13	8
11. Changes in hunger/appetite	4	6	6	5
12. Blurred vision	0	4	2	1
13. Dizziness	2	4	3	4
14. Feeling irritable	8	9	8	7

	Number of patients reporting			
Other adverse events	**Week 1**	**Week 2**	**Week 3**	**Week 4**
1. Vomit	1			
2. Very alert at bed time	1			
3. Restless legs	1	1	1	
4. Acne on face	1			
5. Not having a clear head – Heaviness, perhaps this is because of the medication/sleepiness		1		
6. Mild shaking		1		
7. Feeling anxious			1	
8. Dry eyes, dry skin			1	
9. Thirsty (toilet runs high) and groggy			1	
10. Overwhelmed, a great deal of feelings contained inside sometimes coming out as frustration, anxiety, or sadness			1	
11. Increased tinnitus with armodafinil			1	
12. Feeling unbalanced as in a Meniere's attack			1	
13. Low mood, migraine and bodily pain symptoms were experienced before the medicine and whilst taking part in this trial				1
14. Severe restless legs				1

50 mg per day, four patients taking around two tablets per day (100 mg) and no patients taking close to upper prescribed amount.

The routine use of armodafinil therapy in addition to sleep restriction therapy for the treatment of insomnia is not supported by our findings. However, our use of an historical control group could possibly have caused various biases that might have made adjunctive armodafinil appear worse than it really is. Despite access to pharmacotherapy, the patients did not elect to take the full prescribed dose through the treatment period. Our pilot trial has not convinced us to seek funding for a properly powered phase 2b trial based upon the lack of a clear efficacy signal, in addition to emergent concerns about the potential teratogenic effects of ar/modafinil in a patient population enriched with women in their child-bearing years (Damkier & Broe, 2020).

DISCLOSURE OF ANY OFF-LABEL OR INVESTIGATIONAL USE

The use of armodafinil to treat the side effects of sleep restriction therapy is investigational use.

AUTHOR CONTRIBUTIONS

Conceptualisation: Christopher B. Miller, Delwyn J. Bartlett, Ron R. Grunstein, Brendon J. Yee, and Nathaniel S. Marshall; Methodology: Christopher B. Miller, Delwyn J. Bartlett, Simon D. Kyle, and Nathaniel S. Marshall; Formal analysis: Daniel J. Judge and Nathaniel S. Marshall; Investigation: Daniel J. Judge, Christopher B. Miller, Delwyn J. Bartlett and Ibrahim Jomaa; Resources: Christopher B. Miller and Simon D. Kyle; Data Curation Management: Daniel J. Judge, Christopher B. Miller, Caitlin R. Semsarian, Simon D. Kyle, and Nathaniel S. Marshall; Writing – Original Draft: Daniel J. Judge and Nathaniel S. Marshall; Writing – Review & Editing: Daniel J. Judge, Christopher B. Miller, Caitlin R. Semsarian, Colin A. Espie, Simon D. Kyle, Brendon J. Yee, and Nathaniel S. Marshall; Supervision: Delwyn J. Bartlett, Brendon J. Yee, Ron R. Grunstein, and Nathaniel S. Marshall; Project administration: Daniel J. Judge, Christopher B. Miller, Ibrahim Jomaa, and Nathaniel S. Marshall; Funding acquisition: Christopher B. Miller.

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CONFLICT OF INTEREST

No authors listed had a conflict of interest associated with this trial.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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