Title: Understanding the sleep apnea/insomnia interaction: a CPAP/sham-CPAP trial

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1. RESEARCH STRATEGY

1.1. Significance

1.1.1. How important is insomnia in patients with sleep apnea?

The co-existence of insomnia and sleep apnea has been observed in numerous studies (1,2,4,8,11,12,15-18). One study of 231 patients with sleep apnea noted that 50% (116 subjects) had insomnia complaints by history (19), and many had objective evidence of impaired sleep continuity (19,20). These patients reported more cognitive-emotional complaints (2,21), and were more frequent users of sleeping aids (19,22). Other research has found no evidence of a correlation between the apnea-hypopnea index and insomnia severity, thus suggesting that the two are separate entities that frequently co-exist because of their high individual prevalence (17,23). Yet, the overall prevalence of insomnia in sleep apnea patients is nearly twice that of the prevalence of insomnia alone, thus arguing for a possible association between the two conditions (1,3,18).

1.1.2. What is the potential inter-relationship between sleep apnea and insomnia?

Higher arousal indexes are often noted in sleep apnea patients (24), and percent of time in lighter stages of sleep increases as the respiratory disturbance index increases (24). Sleep apnea may activate the hypothalamic-pituitary-adrenal axis, which may lead to more frequent nocturnal arousals or difficulty falling back asleep (25). The patient's perception of unrestorative sleep could also lead to increased levels of anxiety regarding sleep (3). In addition, sleep apnea patients often have marked daytime sleepiness—since the patient is primarily aware of their insomnia (because many patients are not aware that they have sleep apnea), they may attribute their daytime dysfunction to their insomnia, further increasing their concern about their impaired nocturnal sleep. There may be gender influences, with insomnia possibly more common in women with sleep apnea (26,27), although this has not been universally noted (28). Age is an important consideration since OSA may present with different symptoms in older adults, but remains associated with significant sequelae (29-32).

Taken together, this suggests that there are several possible relationships between OSA and insomnia. OSA may exacerbate insomnia (insomnia due to OSA), or the insomnia may be independent of OSA and associated with an underlying insomnia disorder (insomnia independent of OSA). Since OSA generally occurs throughout the night, it is conceivable that insomnia due to OSA would most likely present as sleep maintenance insomnia. Sleep latency may be decreased because of sleepiness from their OSA. These patients may have improvement of their insomnia with CPAP due to a reduction in nocturnal apneas. Insomnia independent of OSA, alternatively, may be associated with difficulty initiating sleep, a common symptom in primary insomnia, and may have sleep maintenance complaints to a lesser extent. When treated with CPAP alone, these patients may be expected to have no improvement, or even worsening of their sleep latency symptoms due to the discomfort of CPAP. This perspective stands in contrast to the current nosology for sleep medicine, which requires that if OSA is present, the patient cannot, by definition, have an insomnia disorder (6). This nosology specifically identifies insomnia as a symptom of OSA (6).

1.1.3. How stable are the insomnia phenotypes and what is the relationship between sleep maintenance insomnia and early morning awakenings?

Insomnia symptoms can be divided into various phenotypes, such as sleep initiation, sleep maintenance, and early morning awakening, with more recent work emphasizing the former two (2,33). Early morning awakening was initially linked to depression (34) and thus felt to be a unique phenotype; however, several larger studies suggest that there is no association with depression (35-37). Additional evidence that it is not a separate phenotype is that nearly half of all subjects with sleep maintenance symptoms or early morning awakening symptoms will change from one to the other over the course of four months (38). In contrast, sleep initiation symptoms are more stable: out of 61 sleep initiation insomnia subjects, only 4 switched to the pure sleep maintenance or pure early morning awakening phenotype, and out of 59 with sleep maintenance or early morning awakening, only 7 changed to the pure sleep initiation phenotype over four months. The rest either had remission (about 20% in each group), or worsened (developed additional insomnia symptoms)(38). Furthermore, when considering patients with OSA in particular, one retrospective study noted that only the sleep initiation insomnia phenotype (present in 16.6% of OSA patients) had worse adherence to CPAP, while those with sleep maintenance (23.7% of OSA patients) and early morning awakening (20.6% of patients) were similar in their adherence patterns (11). For this reason, our approach will consider sleep initiation problems as one phenotype of insomnia in OSA, and combine sleep maintenance and early morning awakening into another phenotype of OSA, which we will refer to as sleep maintenance.

What about patients with multiple symptoms, such as both sleep initiation and sleep maintenance symptoms? In our thinking, these patients represent an overlap phenotype category. For any study that seeks to

identify pathophysiology, it is crucial to include only study participants with clearly defined phenotypes because those with overlap or undifferentiated phenotypes may not manifest clear responses to the study interventions. Thus, for the current study, study participants with both symptoms will be excluded. This is similar to the approach we have used in our prior observational trials on insomnia and daytime sleepiness, and it has allowed us to identify clinically meaningful differences in mortality and other key outcomes (39,40). The overlap phenotype represents approximately 10-15% of all sleep apnea patients (2,11).

1.1.4. What are the possible daytime ramifications of OSA with insomnia symptoms?

In addition to the nocturnal affects, insomnia due to OSA and insomnia independent of OSA may have different daytime manifestations. The psychobiological inhibition model of insomnia suggests that normal sleep requires a functioning de-arousal process, and that insomnia is characterized by an inhibition of these de-arousal mechanisms (41,42). For this reason, primary insomnia patients feel fatigued, but do not have objective psychomotor impairments. It is conceivable that patients with insomnia independent of OSA (similar to primary insomnia) may have a similar inhibition of de-arousal processes. However, patients with insomnia due to OSA would not be expected to have inhibition of de-arousal processes, and would manifest increased daytime fatigue and psychomotor impairments from sleep fragmentation from OSA and insomnia (43,44).

1.1.5. How effective is OSA therapy for insomnia symptoms?

The mainstay of treatment for OSA is non-invasive positive airway pressure, frequently administered as continuous positive airway pressure (CPAP). The use of CPAP for OSA, while highly effective, is commonly associated with mask discomfort that limits adherence to treatment (45). Overall, nearly 30-40% of patients stop using CPAP (45). Patients with insomnia may have particular difficulty (3,20,46-48). These patients spend considerable portions of the night awake and can thus have a heightened awareness of the discomfort of the equipment (19). The net result is that it can be very difficult to start positive pressure ventilation on these patients, and insomnia may contribute to non-adherence according to some, but not all, studies (5,12,19).

In the limited treatment data available for patients with OSA and insomnia, treatment of the sleep apnea has resulted in partial improvement in insomnia (13,14). However, for a significant subset of patients, insomnia persists (13,14). Up to 46% of patients on CPAP for OSA (not limited to those with insomnia) report continued nocturnal awakenings, for example (48). This suggests that insomnia in some patients is related to their OSA, while for others, the insomnia is independent of their OSA (3). However, of the two studies that focused on OSA and insomnia, both were unblinded and lacked true control arms (13,14).

1.1.6. What is the reason for including sham-CPAP groups?

Sham-CPAP refers to a CPAP intervention which provides sub-therapeutic pressure and has minimal effect on OSA severity. It is considered the state-of-the-art placebo control for OSA trials and induces minimal changes in AHI based on prior work done by members of our group (49). A double-blind, placebo controlled study is particularly important for insomnia research because the placebo effect can result in improvements of up to 20% in insomnia clinical trials based on our prior work (50,51). (section 6.1.1.8 for additional details)

As noted in an American Thoracic Society symposium on controls for clinical trials, sham devices can control for placebo effects, ensure study blinding and minimize assessment biases (52). In addition, a sham-CPAP intervention will allow us to adjust for any potential worsening of insomnia that may arise related to discomfort from the CPAP mask since both the intervention (CPAP) and control (sham-CPAP) will use a mask. This will help to clearly establish the specific role of CPAP treatment of OSA in altering insomnia symptoms.

1.1.7. What is the reason for including a CPAP+CBT arm?

CBT for insomnia with CPAP (CPAP+CBT) provides two important benefits: 1) Treatment of sleep initiation insomnia, which is not expected to improve with CPAP; and 2) While we anticipate that sleep maintenance insomnia symptoms will improve with CPAP, study participants may have residual sleep maintenance symptoms. Many patients with insomnia in general will not have complete resolution of their symptoms despite optimal therapy. As noted by an NIH consensus panel, insomnia is a chronic condition that can be improved, but rarely cured completely (53). CBT is as effective as pharmacotherapy (and may be more effective for sleep initiation insomnia in particular), carries fewer risks and is more acceptable to patients (54,55). Addition of CPAP+CBT groups will allow us to identify an upper limit of insomnia resolution, and compare this to the changes noted with CPAP+CC and sham-CPAP+CC. If, for example, CPAP+CC improves sleep maintenance insomnia by 50%, while CPAP+CBT improves it by 55%, this suggests that CPAP+CC provides the majority of benefit, but if CPAP+CBT improved symptoms by 80%, then a strong case can be made that there remain significant, potentially treatable residual sleep maintenance symptoms despite CPAP. This would justify including a CPAP+CBT arm in the future multi-site study based on the results of this R34. Previous unblinded pilot

studies suggest an added benefit of CBT+sleep apnea treatment, but results were inconsistent (13,14). Furthermore, because insomnia symptoms are influenced by placebo effects, these open-label study findings are of limited utility. Of note, while CPAP+CBT offers several potential study benefits, untreated sleep apnea (as would be the case with sham-CPAP) is a relative contra-indication for the administration of CBT (56,57). This is in part because the sleep restriction component of CBT may further increase the risk of sleepiness-related accidents in the setting of untreated sleep apnea (which by itself often leads to underlying daytime sleepiness). Thus a sham-CPAP+CBT arm is not ethically appropriate (section 6.1.4.2). In patients with insomnia (without sleep apnea), CBT's sleep restriction has few daytime effects because these patients may have hyperarousal and thus minimal underlying daytime sleepiness (42,58) that can be exacerbated by sleep restriction.

In summary, the benefit of including a CPAP+CBT arm is that it tests the effects of more than one treatment (CPAP and CBT), which will permit analysis of potential additive effects of those treatments, as noted by Piantadosi (59). The main limitation is the exclusion of a sham-CPAP+CBT arm for safety concerns.

1.1.8. How will the full-scale trial resulting from this pilot improve scientific knowledge and clinical practice?

The presence of insomnia in OSA may occur in up to 29-50% of patients; this comorbid condition may thus affect several million patients. While data from existing cross-sectional studies are concerning, they cannot answer the fundamental question of whether insomnia in OSA is usually due to the OSA, or whether there exist a separate subset of patients who have insomnia independent of their OSA. This central question can best be assessed within the framework of a randomized controlled trial in which patients with OSA and insomnia are treated with CPAP+CC, sham-CPAP+CC and CPAP+CBT. Cases where the OSA is the primary factor contributing to the insomnia will improve with CPAP, while those who have insomnia independent of their OSA will continue to have symptoms. The CPAP+CBT groups will assess for any additive benefit of dedicated insomnia therapy. The ramifications of this are significant. From a mechanistic perspective, it will provide insights into the etiology of specific insomnia phenotypes in OSA. From a clinical perspective, it will improve the clinical care of the large number of patients with OSA and insomnia. There is a growing appreciation that insomnia may interfere with CPAP therapy. By determining if insomnia in patients with OSA is a heterogeneous disorder in which some may have insomnia independent of OSA and if additional, concurrent insomnia therapy (with CBT) is necessary, we can determine the identifying characteristics of these patients and develop treatments for this group that address both their insomnia and OSA. This insight would lead to fundamental shifts in the clinical approach towards OSA. The presence of insomnia may also influence CPAP adherence, a major concern in delivering effective OSA care (3,5). Consistent with the goals of this Program Announcement, the major objectives of this preliminary clinical trial will be to identify the appropriate study sample size, assess study feasibility and determine insomnia phenotype effects on adherence which will be crucial for the development of a larger, multisite study to definitively address this issue.

1.2. Research Strategy: Innovation

1.2.1. Conceptual innovation:

The proposed project is conceptually innovative in that it approaches insomnia in OSA patients as a heterogeneous disorder that can be either due to OSA or independent of OSA. This stands in contrast to the operant clinical paradigms that view insomnia as being due to OSA. A further conceptual innovation is the hypothesis that these different insomnia and OSA phenotypes will have unique daytime manifestations due to the different etiology that underlies insomnia in these two conditions. Based on the psychobiological inhibition model of insomnia, we anticipate that subjects with insomnia independent of OSA will have minimal objective daytime manifestations of sleepiness, while those with insomnia due to OSA will have more prominent impairments and considerable improvement in objective daytime deficits with CPAP relative to sham-CPAP.

1.2.2. Methodological innovation:

There are several innovative methodological aspects of the study. First, the study will use a CPAP intervention to differentiate insomnia phenotypes in OSA, thus utilizing a rigorous study design to establish causality. Previous work included cross-sectional comparisons that considered insomnia phenotype associations with OSA, but could not assess causality. Second, this is the first study of OSA and insomnia to incorporate sham-CPAP. This will control for placebo effects, an important consideration in insomnia trials. Furthermore, sham-CPAP and contact-controls (CC) will ensure study blinding, an element not present in previous open-label studies, including previous unblinded CBT studies in OSA (13,14). Third, the study examines CPAP adherence as a key study outcome. This enhances the study's clinical ramifications. Fourth, we will measure both subjective and objective daytime sleepiness as we hypothesize that patients with insomnia independent of OSA will have persistent subjective perceptions of fatigue, despite manifesting minimal objective deficits consistent with a hyperarousal component to their insomnia. These innovative methodological

approaches will be assessed for feasibility in this preliminary study, thereby helping to design a future, definitive multi-site study incorporating these techniques as per the intent of the Program Announcement (PA).

1.3. Research Strategy: Preliminary Data

1.3.1. Sleep Initiation and Sleep Maintenance Insomnia phenotypes

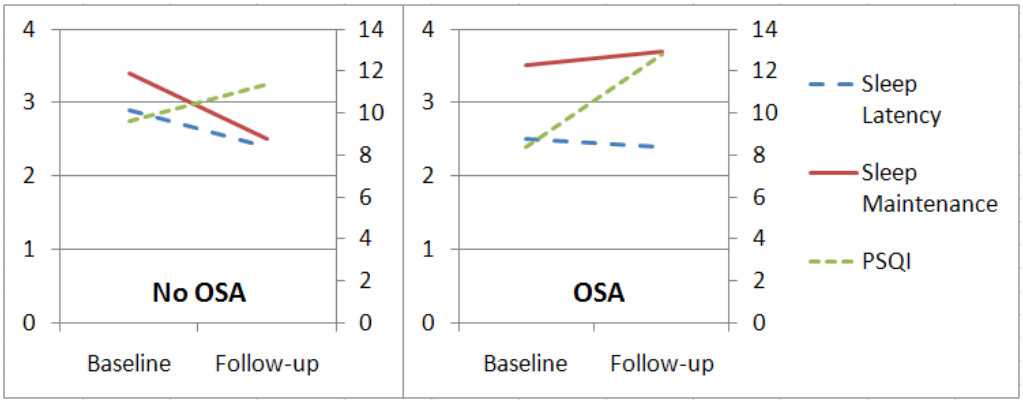
Evidence in support of our ability to define insomnia phenotypes can be derived by assessing stability over time in our own studies.The table below shows pooled data (n=26) from the placebo arms of two clinical trials of insomnia (of 4 and 6 weeks duration), divided into sleep initiation (*) and sleep maintenance phenotypes (**), and 106 study participants who volunteered for multiple studies and had been screened at separate times, also divided into sleep initiation (^) and sleep maintenance groups (^^). In general, a stable phenotype was observed in 68.9-86.9% of study participants using our assessment approach.

Phenotype	N	Interval (months)	Stable Phenotype	Changed Phenotype	Dual symptoms	Resolved
Sleep Initiation*	11	1 - 1.5	72.7%	9.1%	0.0%	18.2%
Sleep Initiation^	45	9.7	68.9%	13.3%	15.6%	2.2%
Sleep Maintenance**	15	1 - 1.5	80.0%	0.0%	6.7%	13.3%
Sleep Maintenance^^	61	8.3	86.9%	1.6%	11.5%	0.0%

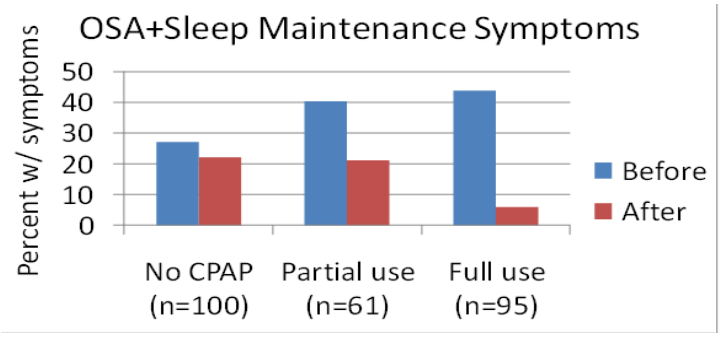
Changed phenotype: refers to conversion from one phenotype to another at the second assessment; Dual symptoms: These subjects have developed symptoms of both sleep initiation and sleep maintenance at the second assessment. There is a higher percentage of "resolved" symptoms in study participants from placebo arms of clinical trials possibly due to placebo effect, while those who presented for screening for different insomnia studies rarely had resolved symptoms at the time of their second screening because, as expected, they would not come to be screened for another study if their symptoms had resolved.

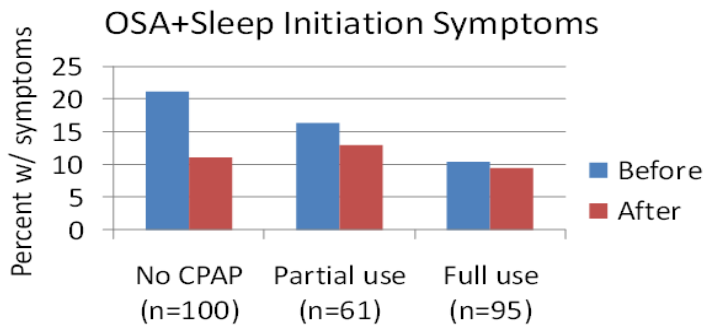
1.3.2. Temporal pattern of insomnia by presence or absence of OSA

We are currently conducting a longitudinal study of OSA and insomnia in a cohort of older adults first identified from 1995-1998. Follow-up data after approximately 14 years has been obtained on the first 15 subjects using the PSQI (Figure 1). Those without OSA (n=9, average AHI 1.3, +/- 1.7 events/hr) at baseline tended to have improvements in sleep latency and sleep maintenance insomnia symptoms, while those with OSA (n=6, AHI 10.6, +/- 3.9 events/hr) had persistence or worsening of their sleep maintenance symptoms. PSQI scores for both groups tended to worsen over the fourteen year follow-up period, with a more prominent increase in study participants with OSA.



1.3.3. Long term effects of CPAP on insomnia symptoms





The longitudinal effects of CPAP have been assessed in a 2-year follow-up study of patients from Iceland collected by Dr. Thorarinn Gislason, an Adjunct Professor at the University of Pennsylvania, and colleagues (unpublished data). Of 280 potential study participants, 256 returned for a follow-up visit. Persistence of insomnia was assessed in comparison to CPAP adherence and insomnia phenotype. These preliminary results suggest that sleep maintenance symptoms are more common in patients with OSA (30-50%) than sleep initiation symptoms (10-20%)—note difference in y-axis. Sleep maintenance symptoms are also more likely to

respond to CPAP therapy than sleep initiation symptoms: CPAP adherent patients with sleep maintenance insomnia are more likely to improve their insomnia symptoms than CPAP adherent patients with sleep initiation insomnia symptoms. Furthermore, sleep maintenance symptoms are more likely to persist without CPAP treatment, while sleep initiation symptoms are more likely to resolve spontaneously. Sleep maintenance symptoms are therefore potentially due to OSA, while sleep initiation symptoms may be independent of OSA.

1.3.4. Effects of CPAP on daytime symptoms in OSA patients with insomnia

To gather preliminary data on the effects of CPAP treatment on OSA patients, we conducted a pilot, open-label study in which OSA patients were treated with CPAP for a one month period. Nine patients with a diagnosis of OSA based on an out-patient clinical diagnostic polysomnography were identified, and five met study criteria, including the presence of a well-defined insomnia phenotype (either predominantly sleep initiation insomnia or sleep maintenance insomnia). Of these five patients, there were two in the sleep initiation group, and three in the sleep maintenance group. Study outcome measures included the Insomnia Severity Index (ISI), self-reported sleep onset latency (SOL, minutes) and wakefulness after sleep onset (WASO, minutes), Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleepiness Questionnaire (FOSQ) scores and CPAP usage (in minutes). Change scores comparing pre-CPAP and post-CPAP values for these measures are presented in Table 1. These findings suggest that patients with sleep initiation symptoms tended to do worse with CPAP therapy for their OSA relative to those with sleep maintenance symptoms as suggested by increases in their WASO (i.e., on-CPAP WASO was higher than pre-CPAP WASO, resulting in a negative value for the sleep initiation group), less CPAP adherence, and worsening of ESS. Changes for the FOSQ, ISI and SOL were essentially similar between the two groups.

Table 1: Change scores (pre-CPAP minus on-CPAP) after 4 weeks of CPAP therapy.

	ISI*	SOL*	WASO*	ESS*	FOSQ**	CPAP adherence
Sleep initiation symptom	2.0 (2.8)	0 (7.1)	-30.0 (14.1)	-1.0 (1.4)	0.1 (0.27)	215 (302)
Sleep maintenance symptom	1.7 (8.1)	-0.7 (4.0)	15.7 (14.0)	5.0 (4.6)	0.6 (0.9)	238 (204)

Mean value for change scores with standard deviations in parenthesis. *Higher change score values indicate improvement. **Higher change score values indicate worsening

1.3.5. Adherence with CPAP and sham-CPAP

Adherence rates for CPAP in insomnia patients have ranged from 40-50% in our prior research in older adults (60), with others noting adherence rates up to 60% for all adult age categories (11), and 74% for subjects aged 18-60 (61). Since our study will include study participants in any adult age category (age>18 years), we will use an anticipated 60% adherence rate for our sample size calculations. When comparing CPAP vs sham-CPAP adherence, we anticipate that it will be comparable based on data from an investigation of CPAP treatment in the elderly conducted at Penn (A. Pack, PI), a placebo controlled study of 6 wk duration employing the same sham-CPAP device. The active CPAP group used their devices 3.6 hrs vs 3.7 hrs for the sham-CPAP group, similar to other sham-CPAP studies (62-64). We have also effectively used sham-CPAP in a study of mild OSA in older adults (49).

1.3.6. Efficacy of CPAP+cognitive-behavioral therapy for insomnia vs pharmacotherapy

We have conducted a double-blind, placebo-controlled, randomized study in patients with insomnia and OSA that were starting CPAP therapy. This study examined the effects of ramelteon vs placebo in older adults and found no subjective improvement in insomnia symptoms and no improvement in CPAP adherence with ramelteon despite objective improvement in sleep latency (60). Since insomnia is defined primarily as a subjective complaint (65), the lack of subjective improvement prompted us to extend our work to consider other insomnia treatment options for the current study, such as CBT or zolpidem.

We reviewed sleep clinic records from the study PI (N.S.G.) over the past month and identified all patients with OSA and insomnia who underwent CBT (n=6) and another group who used sedative pharmacotherapy (zolpidem, n=5). The net improvement after 4 weeks were slightly larger for CBT: 1) sleep onset latency 13.8 +/- 20.5 min vs 8.4 +/- 14.5 min, respectively; 2) wakefulness after sleep onset 70.3 +/- 64.6 min vs 61.8 +/- 72.9 min, respectively. All patients reported adherence to their respective insomnia treatment regimens.

1.3.7. Summary of Preliminary Data

- Sleep initiation and sleep maintenance insomnia phenotypes remain stable, suggesting that these are distinct and identifiable phenotypes.
- These sleep maintenance symptoms are more likely to persist in patients with OSA, as compared to patients without OSA, whereas sleep initiation symptoms improved slightly over time in both groups.

- When considering CPAP effects, longitudinal observation data indicate that sleep maintenance symptoms are more likely to improve in adherent CPAP users than sleep initiation insomnia symptoms.
- Those with sleep maintenance symptoms generally showed a more favorable response to therapy than those with sleep initiation symptoms, particularly in terms of WASO and daytime functional outcomes. Adherence was also mildly higher in the sleep maintenance group.
- We have experience treating patients with OSA and insomnia using CPAP and monitoring compliance. We have also conducted research with sham-CPAP in which we have confirmed that it is a reasonable placebo for CPAP with similar adherence rates (49).
- CBT had similar efficacy rates to zolpidem in OSA patients with insomnia. Other pharmacotherapy options, such as ramelteon, did not improve subjective insomnia symptoms or CPAP adherence.

While these studies provide evidence in support of a beneficial effect of CPAP, they have not controlled for placebo effects and were unblinded. Additional research using a randomized controlled trial methodology with a credible sham-CPAP control arm is thus necessary to establish the effects of CPAP therapy on insomnia in the different phenotypes of insomnia.

1.4. Research Study: Approach

1.4.1. Study Overview

This is a pilot, randomized, double-blind, placebo controlled trial to assess if CPAP can differentially improve insomnia in 108 patients with OSA based on insomnia phenotype. One-half of the study participants will be recruited with OSA and sleep latency insomnia symptoms, while the other half will have OSA and sleep maintenance insomnia symptoms, thus study participant selection will be stratified by insomnia phenotype (insomnia phenotype criteria are defined in item 2 of Inclusion/Exclusion criteria below) (Figure 3). The study intervention will consist of randomization to CPAP+contact control, sham-CPAP+contact control, or CPAP+CBT for a 6 week period. At the end of the treatment period, study participants will undergo a repeat assessment to determine if their sleep continuity or OSA severity changed. Data from their CPAP (for the CPAP+CC and CPAP+CBT groups) or sham-CPAP (for the sham-CPAP+CC group) will be downloaded to confirm adherence. The data gathered from this preliminary study will be used to determine sample size, feasibility and covariates for a planned full-scale trial which is anticipated to be a refinement of the design and aims of this preliminary study.

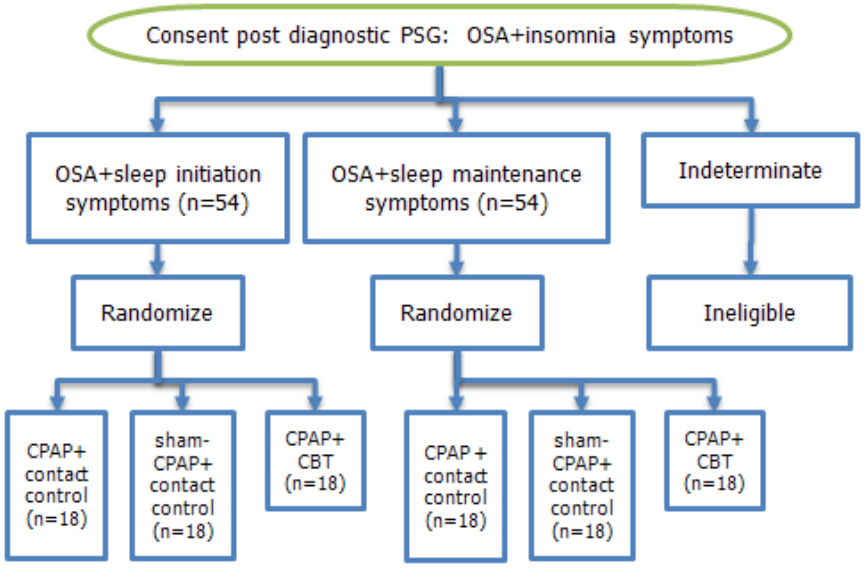


Figure 3: Study Diagram

1.4.2. Inclusion and Exclusion Criteria

Individuals must meet the following inclusion criteria prior to study enrollment:

1. Diagnosis of OSA: Established by an AHI ≥ 5 events/hr consisting of predominantly obstructive apneas and hypopneas on full-night in-laboratory polysomnography.
2. Insomnia symptoms: All study participants will be required to have significant insomnia symptoms, as defined by an Insomnia Severity Index score of >15, the commonly used threshold for clinical insomnia (66). We will enroll 54 patients with primary sleep latency symptoms and 54 patients with primary sleep maintenance symptoms. Question 1 of the Insomnia Severity Index, which asks about insomnia phenotype, will be used. The criteria for sleep latency insomnia will be a score 3 or 4 (severe or very severe) for “Difficulty falling asleep”, and a 0 or 1 (none or mild) for “Difficulty staying asleep” and “Problem waking too early”. The criteria for sleep maintenance insomnia will be the inverse: a score of 3 or 4 (severe or very severe) for “Difficulty staying asleep” or “Problem waking too early”, and a 0 or 1 (none or mild) for “Difficulty falling asleep”. Those who do not meet either criterion will be excluded as they represent an undifferentiated phenotype.
3. Age ≥ 18 years (see section 9, Inclusion of Children).

Individuals will be excluded from the study for the following reasons:

1. No sedative or psychoactive (including anti-depressant) medication use in the last month: Potential study participants who wish to enroll in the study will be asked to stop their medication for a period of four weeks prior to enrollment (will require approval of their primary physician to confirm safety).

2. Diagnosis of another sleep disorder in addition to OSA based on PSG or history (e.g., periodic limb movement disorder [≥ 10 limb movements/hour of sleep with arousal], central sleep apnea [≥ 50% of apneas on diagnostic PSG are central apneas], etc.) in accordance with ICSD-2 criteria.
3. Previous treatment for OSA (e.g., CPAP, oxygen, surgery, etc.).
4. A clinically unstable medical condition as defined by a new diagnosis or change in medical management in the previous 4 months (e.g., unstable angina, surgery, thyroid disease, Cheyne-Stokes breathing, acute psychosis, ventricular arrhythmias, or recently diagnosed cancer).
5. Night shift workers, recent jet lag, or irregular work schedules by history over the last 6 months.
6. Routine consumption of >2 alcoholic beverages/day by history or illicit drug use (urine drug screen).
7. Insomnia due to another disorder (aside from OSA): The intent of the current study is to establish a clearly identified phenotype of insomnia in OSA, thus study participants with insomnia that is secondary to another medical disorder, such as chronic pain, or a psychiatric disorder, such as depression, will be excluded. Psychiatric diagnoses will be assessed using the Mini-SCID, a structured clinical interview to diagnose psychiatric disorders for clinical trials (67).
8. Use of stimulants or excessive caffeine/tea (>2 drinks/day) as this may alter PVT findings.
9. Potential study participants for whom use of sham-CPAP may not be safe, including those with a) symptoms of excessive daytime sleepiness that represent a safety hazard, such as a history of falling asleep or feeling sleepy while driving; b) pregnant females (urine pregnancy test); and c) severe sleep apnea or hypoxia associated with nocturnal cardiac dysrhythmias, or nocturnal angina.
10. Inadequate OSA treatment with CPAP alone: Unable to be adequately treated solely with CPAP to a target AHI<5 events/hr and oxyhemoglobin desaturation nadir >90%.
11. Unable to perform tests due to inability to communicate verbally, inability to write and read in English; less than a 5th grade reading level; visual, hearing or upper extremity motor deficit (e.g., previous stroke that prevents patient from using CPAP treatment).
12. Cognitive impairment (Short Blessed dementia scale score <10)(68).

1.5. Specific Study Methods

1.5.1. Recruitment prior to starting CPAP

The Hospital of the University of Pennsylvania had approximately 2,400 new patient visits in 2010. Assuming that approximately 30% have insomnia complaints, and 40-50% are willing to participate in the research study protocol, we anticipate being able to readily recruit 108 study participants. Study participants will have already undergone an initial overnight diagnostic PSG as part of their regular clinical care. They will then be contacted after their baseline PSG, but prior to their CPAP titration PSG and are thus treatment naïve. Thus, they will not be able to distinguish CPAP from sham-CPAP (section 3.1.6).

Table 2: Clinical Data Collection Schedule

Item	**Study Days**					
Consent	-14					
Physician Sleep History/Exam	-14		14		42	72
Medication List Review	-14	7	14		42	72
Polysomnography (diagnostic)*	-14					
Efficacy Measures						
Wrist-actigraphy	-14 to 0				27-41	
Sleep Diary	-14 to 0	**	**	**	**	
Study questionnaires (ISI, FSS, SF-36)	0	7	14	21	42	72
Neurobehavioral Assessment Battery	0				42	
CPAP adherence monitoring by the internal CPAP monitor		**	**	**	**	
Study Intervention						
Randomization	Night of day 0					
Polysomnography with CPAP or sham-CPAP)	Night of day 0				42	
CPAP (for CPAP+CC & CPAP+CBT groups) or sham-CPAP		**	**	**	**	
CBT sessions (for the CPAP+CBT group only)	1^	7	14	21		
Contact-control sessions (for CPAP and sham-CPAP groups)	1^	7	14	21		
Safety Assessment						
Adverse Event Screening		7	14	21	42	72
Review concomitant therapy		7	14	21	42	72
Physician Exam	-14				42	72
End of study feedback						72

*Diagnostic sleep studies will be done as part of the potential study participant's standard clinical care
**Study participants will do this every day from study day 1 to study day 42.
^The first session will occur the morning after their sleep study

Study participant selection will be stratified by insomnia phenotype (sleep initiation or sleep maintenance) as described previously in section 3.4.2. The study can be divided into the following sections, which are described in more detail below: 1) pre-intervention baseline studies (days -14 to 0); 2) randomization (day 0); 3) study intervention (days 1-42); 4) treatment visits for CBT or CC (day 1 (post-polysomnography), 7, 15, 21); 5) end-of-treatment studies (day 42); 6) follow-up visit (day 72). The specific study assessments below are based on recommendations by a consensus panel for the standard research evaluation of insomnia (69,70).

1.5.1. Pre-intervention baseline studies (study days -14 to 0)

1.5.1.1 Physician History/Exam and OSA Education (day -14)

After completion of the consent form, potential study participants will undergo a physician history and exam, and OSA education/counseling. It is important to employ standardized procedures for the education and management of CPAP and sham-CPAP and to reduce variance in outcome measures resulting from varying degrees of exposure to the intervention. To ensure that this counseling is standardized across the entire study, it will be conducted by the study investigator team and will emphasize treatment specifics (71).

1.5.1.1 Out-patient sleep assessment (days –14 to 0)

1) Wrist-actigraphy monitor: The Actiwatch-2 (Philips Respironics, Inc., Sunriver, OR) is a wristwatch-sized device which monitors wrist activity using a miniaturized accelerometer (sensitive to 0.003 g). It can calculate several relevant sleep parameters (72-77). Study participants will be asked to wear it for fourteen days to capture data on sleep patterns at-home both during the week and weekend. It will provide secondary outcome variables for specific aim 1 (actigraphy sleep latency, wakefulness after sleep onset, and sleep efficiency)

2) Sleep Diary (Appendix A): The sleep diary is a 9-item log of sleep-wake habits that will be completed every morning and takes less than 5 minutes to complete. The sleep diary provides subjective information about at-home insomnia symptoms, an important consideration. It will provide secondary outcome variables for specific aim 1 (sleep diary sleep latency, wakefulness after sleep onset, and sleep efficiency).

Research conducted by our group has found that the combined diary and wrist-activity data can provide a complete, accurate sleep history because of their multimethod nature (78). Actigraphy has been found to have minimal degradation in accuracy in the presence of sleep apnea (79).

1.5.1.2 Survey instruments (study day 0) (Appendix A)

a) Insomnia Severity Index (ISI): A widely used measure of the severity of insomnia that can be used as an outcome assessment in insomnia treatment studies (66,69,70). Scores range from 0 to 30 with scores >15 indicating clinical insomnia. A 6-point reduction is considered to represent a clinically significant improvement (80). This will serve as the primary outcome variable for specific aim 1.

b) Fatigue Severity Scale (FSS): The FSS is a 9 item scale, with response options ranging from 1 to 7, that measures subjective perception of fatigue and correlates with insomnia severity (81,82). It is a recommended daytime outcome measure by an expert consensus panel on the standard research assessment of insomnia (70). This will serve as one of two primary outcome variables for specific aim 2.

c) Brief Symptom Inventory (BSI): A scale of self-reported psychological distress from anxiety, depression, hostility and other psychological factors, many of which may impact on sleep and adherence (83-86). The following subscales on the BSI are of particular relevance: Obsessive-Compulsive, Paranoid Ideation, Depression, Phobic Anxiety and Interpersonal Sensitivity because we have found that these are different in insomniacs relative to non-insomniacs based on prior research that we have conducted (unpublished data).

d) Cumulative Illness Rating Scale (CIRS): A reliable, standardized instrument for health status which can identify severity of comorbid illness in 14 different systems and provides a global comorbidity measure (87).

e) RAND Medical Outcomes Study Short Form (SF-36): The SF-36 assesses functional quality of life and has been widely used in sleep research as well (88-92).

1.5.1.3 Objective Testing (evening day 0)

1) Neurocognitive testing: A modified Neurobehavioral Assessment Battery (NAB) will be used to measure daytime alertness and vigilance before the sleep study (93). This will be repeated at the end of the study to determine if study participants have any improvement after treatment. It takes an average of 20-30 minutes to complete and consists of cognitive performance tasks and assessments of subjective activation (94). The cognitive performance task will consist of a psychomotor vigilance task (PVT) that measures the capacity for sustained attention and vigilance performance (95). It was developed by the Unit for Experimental Psychiatry at the University of Pennsylvania, and is currently being used in ongoing research by Drs. Gooneratne, Kuna and Perlis. The PVT mean lapses will serve as one of two primary outcome variables for specific aim 2.

2) Treatment Polysomnography: On the night of day 0, study participants will have a CPAP titration or sham-CPAP “titration” polysomnography. We will be using a modification of the sham-CPAP design of Farré et al. to create a sham-CPAP placebo (96). They inserted an orifice resistor identical to the original exhalation port in the end of the CPAP tubing to load the blower with the same airflow resistance that occurs with active

CPAP. We have refined this design by placing a hidden leak in the connector between the mask and CPAP tubing and placing the resister (Lucite disc) within the tubing (96). Although this produces non-therapeutic pressure at the mask, pressure to the CPAP blower is maintained at the prescribed (and servo controlled) level. A distinct advantage of this design is that any mask can be used with this circuit, which is not true for designs inducing the leak at the mask (Appendix D). Having participants select masks that are comfortable to them is crucial to the application of the treatment as problems with mask interface occurs in 40% of CPAP users (97). We will create a pressure of 0.5-1 cmH_2O at the mask to generate sufficient airflow to convince the study participant that they are receiving treatment. Furthermore, inspection our sham circuit is indistinguishable from standard CPAP circuits. Since there is airflow and a similar degree of blower noise from both circuits, patients are provided with audible and tactile cues that do not differ between sham and CPAP and maintains blinding. The CPAP and sham-CPAP circuits, that will be labeled with the patient's identification number coded for intervention group, will be sent directly to the night Clinical Research Center for Sleep technician who is unblinded and will perform the sham-CPAP PSG and kept in a secure location unavailable to other Center personnel (Appendix C). The sleep technician will then program CPAP for study participants in the CPAP arm, and will arrange for a sham-CPAP unit for those in the sham arm. This will allow the research study participant, all research staff and Penn Sleep Center staff except for the Clinical Research Center for Sleep technician, to remain blinded to randomization assignments. The research study sleep technician must be unblinded to the study participants' randomization assignment because the sleep technician will be involved in titrating the CPAP pressure to treat the sleep apnea during the sleep study, and for the sham CPAP, the titration will be suboptimal to treat sleep apnea. It is important to emphasize that the sleep technician will have minimal contact with the other research staff, and will not be involved in any questionnaire or other outcome measures. This design has been successfully employed in several controlled studies evaluating CPAP efficacy including two NIH funded controlled studies of CPAP use in the elderly at Penn (A. Pack, PI, and T. Weaver, PI) (62,63).

Night time polysomnograms will be performed on study participants using our sham CPAP to document that sham CPAP has no effect on OSA severity with the sham-CPAP blower set at a pre-set level of pressure (this pressure is not transmitted to the study participant, but determines the blower sound) (96). This strategy ensures that individuals in both groups have identical procedures and blindness is maintained. The level of pressure for the blower of each sham-CPAP participant will be randomly selected by computer. Randomly varying the level of pressure of the sham-CPAP devices will contribute to maintaining the blindness of those interacting with the study participant, including the research coordinator who will use this same device to educate the study participant about CPAP use.

1.5.2. Intervention Phase (days 1-42)

During the study intervention phase, study participants will receive either CPAP+CC, sham-CPAP+CC, or CPAP+CBT. They will have treatment visits on days 1, 7, 14 and 21. For the CPAP+CBT groups, CBT will be administered by a psychologist from the Penn Behavioral Sleep Medicine Program (Dr. Perlis, study Co-I, is the director; described in section 6.1.1.8; protocol in Appendix E). The CPAP and sham-CPAP groups will have contact-control sessions by the psychologist (section 6.1.1.8; Appendix E) to minimize attention-bias effects and maintain blinding. Survey instruments will be re-administered, adverse events will be monitored and adherence promoted using standardized procedures to ensure consistent management (see Appendix B). During these visits, the device's internal data card will be sent to the Clinical Research Center for Sleep where data will be downloaded by the sleep technicians. CPAP (for both the CPAP+CC and CPAP+CBT groups) or sham-CPAP adherence and mask leak data will be abstracted from the card and provided to the research study staff. The machine-calculated AHI will NOT be provided to the research study staff since this value will be elevated for the sham-CPAP group and could result in unblinding (see Appendix C). Consistent with standard clinical guidelines, if a study participant's adherence is less than 4 hours/night and less than 5 nights/week, the following procedures will be used: 1) remedial education on the importance of CPAP; 2) alternate mask options will be provided; 3) any mask-specific or equipment specific concerns will be addressed (Appendix B). To monitor CBT adherence, a deviation score will be computed as the difference between prescribed and actual bed/wakeup times and will be used as a study covariate to assess treatment adherence for CBT.

1.5.3. End-of-Treatment visit (study days 27-42) consisting of the following:

1) Wrist-Activity/Sleep Diary measurements (study days 27-41). 2) Survey Instruments (day 42): These will be similar to the pre-intervention testing except that study participants will now be on the study intervention. 3) CPAP or sham-CPAP adherence data (day 42): The study participants will be asked to bring their CPAP or sham-CPAP machines, which records adherence, with them to the end-of-treatment visit. This adherence data will serve as the primary outcome variable for specific aim 3. 4) Physician Evaluation (day 42): To screen for adverse events. 5) Neurocognitive testing (evening of day 42 prior to polysomnography): Identical to the neurocognitive testing performed prior to starting CPAP+CC, sham-CPAP+CC or CPAP+CBT. 6)

Polysomnography (night of study day 42): Polysomnography will be used to reconfirm OSA severity while on treatment (in which OSA should be adequately treated based on AHI) or sham (in which OSA should persist and the AHI should be similar to that noted on the diagnostic PSG). All study participants will then be referred back to their sleep physician for management of their sleep disorders.

1.5.4. Follow-up visit (day 72)

During this visit, study participants will again be screened for adverse events, and they will complete the same survey questionnaires that they filled out pre and on-treatment to determine if there have been changes since concluding the study. Most will be on OSA therapy at this time as ordered by their physician.

1.6. Data and Statistical Analysis

1.6.1. Descriptive Comparisons Between Intervention Groups at Baseline

Descriptive analyses will be performed in order to characterize the three intervention groups (CPAP+CC, sham-CPAP+CC and CPAP+CBT) and to confirm that the randomization resulted in no clinically significant group differences at baseline in demographic, sleep, and other parameters. If the groups differ with regard to baseline variables and these variables are found to have significant associations with outcomes, secondary analysis of covariance will be used to investigate the degree to which estimated relative efficacy depends on these baseline differences.

1.6.2. Statistical Testing of Specific Aim 1 Primary Hypothesis

The primary outcome variable for Specific Aim 1 is the Insomnia Severity Index score. It will be evaluated to test if there is a significant effect by treatment (CPAP+CC, sham-CPAP+CC, vs CPAP+CBT).

1.6.3. Sample size calculations and study power: Relevance for future research studies

The stated purpose of the Program Announcement (PAR 10-005 NHLBI Clinical Trial Pilot Studies) is to fund research that will assist in the development of a larger clinical trial. As with all pilot studies, the current pilot study will not have adequate power to detect statistically significant differences (type II error) across the two factors (three study arms x two insomnia phenotypes) (98). However, the study sample size of 108 participants is within the approximate range needed to estimate parameters for larger multi-site trials as outlined below. This is necessary for calculating the required sample size for the larger study and is thus consistent with the goals of the R34 Program Announcement (98,104,105).

For standard deviation estimates, we will employ a conservative approach that will use an 80% upper one-sided confidence interval limit instead of the estimate itself as suggested by Browne (104). A sample size of n=10 per study arm will allow us to calculate standard deviation estimates which are within 5% of actual values for larger studies which may have n=50-200 per study arm, for example. In order to estimate the multiple covariate correlations, we will use the pilot data to derive multiple linear regressions with the dependent factor being the outcome of interest (e.g. Insomnia Severity Index score), and independent variables being the covariates of interest, such as age (106). The regression parameter coefficient will provide the covariate correlation parameter. In addition to adherence, particular focus will be placed on age-related effects to determine if the insomnia in OSA relationship is different in study participants <65 vs. >=65; age categories in 15-year increments will also be considered. Other planned analysis from the pilot data will examine the covariates of baseline OSA severity (measured as both AHI and time with oxyhemoglobin desaturation less than 90% (TST_{90}), gender, race/ethnicity, psychological comorbidities and socio-economic status (27,28,84,86,112-114).

Table 3: Parameters for sample size analysis which will be supplemented by standard deviation and covariate correlation data collected during the preliminary trial (106)

Primary Outcome Measure	Specific Aim	Meaningful change	Reliability*
Insomnia Severity Index (80,107)	1	6	0.65-0.83
Psychomotor Vigilance Task (10)	2	30 msec	0.8
Fatigue Severity Scale (108,109)	2	1.5	0.75
CPAP Adherence (110,111)	3	1 hour	0.77

*Correlation between repeat assessments

To allow for initial non-parametric analysis, we anticipate needing a 10% increase in the sample size (115), and to address drop-out/non-adherence (to CPAP, sham-CPAP or CBT), we will increase the sample size by an additional 40%, which results in n=18 per study arm. Of note, even study participants that are non-adherent will be informative for Aim 3.

1.7. Potential Problems and Alternatives

1.7.1. Feasibility of study

We anticipate that this study burden is reasonable from a research participant and research staff perspective. We have recruited more than 500 research study participants for diverse studies conducted over multiple weeks involving numerous polysomnograms, at-home wrist-activity monitoring, and other tests using CPAP, sham-CPAP, CBT and CC. Our dropout rates have been less than 20%. We have thereby gained the experience to conduct complex sleep research studies and successfully retain research study participants. The protocol involves a total of five 30-60 minute out-patient visits over a ten week period after initiation of therapy; this is not an excessive study burden as many patients starting CPAP therapy in routine clinical settings will have 2-5 out-patient visits during the first three months of therapy for CPAP adjustment, etc. As stated in the Program Announcement, assessing study feasibility for a larger trial is an appropriate objective of applications.

1.7.2. Parallel vs Sequential vs Cross-over design to include CBT

The initial SRG review noted that a study limitation was the absence of treatment for sleep initiation insomnia, which we have addressed by adding CBT. We have elected to add a parallel CPAP+CBT arm as opposed to a sequential CBT intervention (i.e., study participants would be randomized to CPAP+CC, sham-CPAP+CC or CPAP+CBT that would run in parallel for six weeks instead of a sequential design in which they would be randomized to CPAP or sham-CPAP for six weeks, then all study participants with persistent insomnia would receive CBT or contact control (CC) for another six weeks). In the parallel design, there are three arms that will be stratified into sleep initiation and sleep maintenance groups (two facators: 3x2), leading to 6 cells, with n=10 per cell (when factoring in drop-out/non-adherence, we will need to enroll n=18 per cell). However, for the sequential design, the study would have 16 (2x2x2x2) possible cells as follows: 1) CPAP vs sham-CPAP, 2) sleep initiation vs sleep maintenance phenotype, 3) insomnia not resolved with CPAP (who could be randomized to CBT vs CC) vs insomnia resolved with CPAP (who would not be randomized), and 4) CBT vs CC. This would lead to cells with only 5 subjects or less, which is too few to accurately estimate parameters for a future trial. Cross-over designs are not possible with sham-CPAP or CC as study participants will immediately realize the difference between CPAP/sham-CPAP, or CBT/CC, leading to unblinding.

1.7.3. Use of an R34 mechanism

We have chosen an R34 mechanism for this study because several of the study goals are consistent with those outlined in the R34 program announcement: 1) There are no published studies on the effect of CPAP, sham-CPAP and CPAP+CBT in OSA patients with insomnia, thus there is a need to identify parameters for sample size calculations, one of the stated aims of this R34 program announcement; 2) The study has an exploratory component which is to identify other covariates of interest. If a covariate, such as age, is found to exert a large effect, then consideration will be given to modifying the design of the future definitive trial to include stratification by that covariate in the randomization allocation to ensure balanced representation of that covariate; 3) Feasibility and adherence to CPAP, sham-CPAP and CPAP+CBT in insomnia patients has not been conclusively established—our preliminary research suggests that CPAP can be used in patients with insomnia symptoms, but further research is necessary to confirm exact estimates for future large trials. This is also consistent with the R34 goal of determining whether adequate adherence to a treatment is achievable.

1.7.4. Hazards and Risk Management

Potential Risks: The risks involved with screening pertain to confidentiality. The main study risk is from untreated OSA during the 6 week study period for those randomized to the sham-CPAP arm. During this time, study participants will continue to experience symptoms of untreated OSA, included insomnia and daytime fatigue. Of note, sham-CPAP interventions have been used in previous studies for periods of up to 6 months. Furthermore, the average time to initiating CPAP therapy for routine clinical care after a diagnostic sleep study is approximately 10 to 27 weeks (116), thus most patients receiving standard care for their OSA will remain untreated for longer than the six week period of the proposed study.

Protection Against Risk: *Questionnaires:* Study participants experiencing distress, or indicating significant medical/psychiatric disorders during the screening process or study, will be referred for appropriate treatment. *CPAP/sham-CPAP:* To minimize mask discomfort, patients will be offered the option of several different mask types, and will receive detailed instructions and guidance related to proper mask fit and maintenance. *Untreated OSA:* As noted previously, the six week sham-CPAP period is shorter than the typical untreated period for study participants started on CPAP. To further minimize risk from untreated OSA, we will exclude study participants with severe symptoms that pose a safety risk (see Inclusion and Exclusion criteria, section 3.4.2). *Confidentiality:* This risk will be attenuated by the use of encrypted computer files, use of de-identified documents, and storage of all patient files in locked offices/cabinets. No verbal or written information concerning a study participant will be released without their express written consent.