Cover Page

Official Study Title: Three Approaches to Maintenance Therapy for Chronic Insomnia in Older Adults

NCT Number: NCT03774810

Date: 06/01/2021

Three Approaches to Maintenance Therapy for Chronic Insomnia in Older Adults (R01AG054521)

Principal Investigator	Michael Perlis Department of Psychiatry Suite 670, 3535 Market Street 215-746-3577 or 585-737-2531 mperlis@upenn.edu
Regulatory Sponsor **[If applicable]**	This work is supported by a NIA R01 R01AG054521
NIH Grant Number	R01AG054521
Investigational Product: *[If applicable]*	N/A
Protocol Number: *[If applicable]*	This study is a follow up study to our NCCAM funded grant NCCAM R01AT003332
IRB Number:	Prior IRB # 808978 (Flexible Dosing in Insomnia)
IND/ IDE Number: *[If applicable]*	*N/A*
ClinicalTrials.gov Number	*NCT03774810*
Title	Three Approaches to Maintenance Therapy for Chronic Insomnia in Older Adults
Short Title	Partial Reinforcement II

IRB Number	Prior study's number was 808978 (Flexible Dosing in Insomnia) Present number is 831801
Protocol Number	831801
Study Summary	Medication is FDA approved. The present study is a further evaluation of the behavioral pharmacotherapeutic strategy (i.e., partial reinforcement following the obtention of treatment response with standard treatment) with a particular focus on 1) how low a dose may be used (dose = frequency of active medication) and 2) how long low frequency dosing may be used to maintain treatment response.
	<u>See Study Diagram for a schematic of the protocol</u> (Last Page)
Methodology	
Study Duration	12-14 months

Study Center(s)	One site only: Penn Behavioral Sleep Medicine Program
Objectives	Phase-1. Assess for group differences for percent treatment responders. Phase-2. Assess for group differences with respect to relapse. Phase-3. Assess for group differences with respect to relapse.
Number of Subjects	We will enroll and complete 200 subjects in Phase-1 and randomize 25-50 subjects per condition for Phase-2. See study diagram.
Main Inclusion and Exclusion Criteria	Subjects. Subjects will be between the ages of 40-85 years old and have a stable sleep/wake schedule (no shift work) with a preferred sleep phase between 9:00 PM and 9:00 AM. Inclusion Criteria. Older adults ($\geq$ 40 years of age) with chronic insomnia who meet DSM-5 criteria for Insomnia Disorder and ICSD-3 criteria for Psychophysiologic insomnia. In addition, all subjects will have a sleep initiation and/or a sleep maintenance complaint ($\geq$ 30 min. to fall asleep and/or $\geq$ 30 min. of wakefulness during the night) with a problem frequency $\geq$ 3 nights/wk and problem duration $\geq$ 3 mo. This profile must be evident at both intake (based on retrospective reports) and as an average profile from the two weeks of baseline diaries (based on prospective sampling). Exclusion Criteria for All Subjects. In brief, the exclusionary criteria are: currently in treatment for insomnia, unstable medical or psychiatric illness, a history of treatment failure with zolpidem, discontinuation of zolpidem owing to side effects, and/or current experience, or history, of parasomnias (within the last 5 years).
Investigational Product (drug, biologic, device, etc.)	Zolpidem tartrate (trade name Ambien), 5mg and 10 mg doses.
Duration of administration (if applicable)	Phase-1: one month. Phases-2: three months. Phase-3: nine months
Reference therapy	The study has standard treatment arm (5mg or 10mg zolpidem [qhs]) for the duration of the study.

Statistical Methodology	The primary outcome for Phase-1 is percent of treatment responders. The primary outcomes for Phase-2 and Phase-3 are: percent of subjects that relapse, time to relapse, and average sleep continuity in non-relapsers. Inferential statistics will also be conducted using contingency analyses, survival analysis, ANOVAs and related statistics.
Safety Evaluations	Daily diary assessments of side effects, weekly symptom checklists, and interviews on a monthly basis to monitor the health status of subjects (upon disbursement of medication) and if deemed to be appropriate and necessary by the medical team - physicals. The monthly assessments will be performed by a Nurse Practitioner and will utilize a side-effect check list based on the package insert for zolpidem.
Data and Safety Monitoring Plan	We will establish a Data and Safety Monitoring Board (DSMB) to ensure the proposed study's safety and efficacy. The goal will be to have the DSMB consist of: 1) an expert in psychopharmacology or sleep medicine who is not part of the Behavioral Sleep Medicine program team (this person will chair the committee); 2) two faculty with clinical training (i.e., a psychologist, a nurse practitioner, or psychiatrist); and 3) a biostatistician. The DSMB will receive reports from the study team every six months with information about the progress of recruitment, the demographic characteristics of participants, adverse events, the number of dropouts, and participants' reasons for dropping out, and any protocol amendments. The DSMB will then prepare a formal report, which will be returned to the investigators and to the Penn IRB. The DSMB chair will be notified of any serious adverse events that occur, regardless of whether they are thought to be study-related, within 24 hours of project staff learning of their occurrence.

BACKGROUND AND STUDY RATIONALE

The promise of the behavioral pharmacotherapeutic strategy (i.e., partial reinforcement following the obtention of treatment response with standard treatment) is that it offers a means to maintain treatment gains over extended periods of time with less frequent medication use.

In our first study (PMID: 26298795), the behavioral pharmacotherapeutic strategy was assessed in middle aged subjects with chronic insomnia. The medication evaluated was zolpidem (10mg). As a first trial, a conservative approach was adopted using a 50% partial reinforcement rate. Four treatment maintenance conditions were evaluated: nightly dosing with 10 mg or 5 mg (QHS-10 and QHS-5), intermittent dosing with 10 mg (IDS-10 [3–5 days weekly]), and partial reinforcement dosing with 10 mg (PRS-10 [nightly pill use with 50% active medication and 50% placebos]). It was found that the group of subjects that received placebos interspersed with active medication had comparable outcomes with respect to relapse and average sleep continuity with the groups that received active medication nightly. Interestingly, the subjects in the intermittent dosing group exhibited poorer average sleep continuity and tended to exhibit worse side effect profiles.

The follow-up R01 is to re-assess the application of this paradigm in older adults using a low and high rate of partial reinforcement. The rationale for focusing on older adults is that chronic insomnia occurs most

commonly in individuals over 40 years of age and that this group is most likely to be managed with medication. The proposed study will be conducted in three phases and in 4 groups. Phase-1 is a conditioning/priming phase where all subjects receive 5mg or 10mg (as is age and sex appropriate) of zolpidem on a nightly basis for one month. Phase-2 is a 3-month experimental phase where Phase-1 treatment responders are randomized to one of four maintenance conditions: nightly (QHS); two low frequency partial reinforcement conditions (1 or 3 active doses per week with 6 or 4 placebos interspersed between the active doses [PRS1 and PRS3]); and a low frequency Intermittent dosing condition (1 to 3 active doses per week PRN [IDS]). Phase-3 is an extension phase to assess, over 9 months' time, the long-term durability of the various approaches. In Phase-3, treatment responders will remain in same maintenance condition they were originally randomized to. The primary goal of the study is to assess relative efficacy of the two partial reinforcement conditions as compared to nightly and intermittent dosing conditions over two time intervals (first 3 months of treatment and an extension phase with 9 months of treatment). The secondary goal is to explore how placebo coverage of non-medication nights compares to active pill use nights and to no-pill use nights.

Introduction

1.1 Background and Relevant Literature

The present proposal builds upon findings from a study recently completed by our group (R01AT003332). In this prior study (PMID: 26298795), it was found that treatment responses obtained with one month's treatment (nightly dosing with standard dosages) could be maintained with any of the four strategies evaluated. The strategies included: nightly dosing with 5 or 10mg zolpidem (QHS-10 and QHS-5), intermittent dosing (IDS-10 [3-5 nights/week with 10mg zolpidem]), and partial reinforcement (PRS-10 [50% active medication and 50% placebo]). The proposed investigation is one of two avenues of research we intend to pursue. One avenue seeks to define a lower limit for this experimental / alternative strategy. That is, whether treatment response, in this case in older adults, can be maintained with 1 to 3 doses of active medication per week without placebos (intermittent dosing strategy; IDS) or with placebos interspersed between the active doses (partial reinforcement strategy; PRS). It is hypothesized that one and/or three doses of active medication per week with placebos interspersed between the active doses, will be comparable to nightly dosing and significantly differ from the intermittent dosing conditions with respect to rate of relapse (primary outcome), latency to relapse, average sleep continuity, and number and severity of side effects. This work will be pursued by resubmitting a R01 application on this subject. The other avenue, as noted above, is to explore the mechanisms of partial reinforcement (i.e., Behavioral Pharmacotherapeutics): (1) the effectiveness of intermittent dosing given the interspersion of placebos on non-medication nights (Phase 1); (2) the effectiveness of intermittent dosing with placebos given a priming phase; 1 month of full dose treatment prior to the use of partial reinforcement (Phase 2); and (3) the consequences of patient awareness of which doses (pills) are standard or variable dose (Phase 3).

If, over the course of multiple investigations, it is shown that the behavioral pharmacotherapeutic approach has similar outcomes to full dose strategies (and is reliably superior to intermittent dosing), this has both practical and theoretical implications. The practical implications are:

- effects of pharmacotherapy can be extended (i.e., increased resistance to habituation);
- side effects that occur with the use of medication can be minimized; and
- costs of long-term therapy can be reduced.

1.2 Name and Description of the Investigational Product

Zolpidem tartrate (trade name Ambien), is a non-benzodiazepine hypnotic available in 5mg and 10mg tablets for oral administration at bedtime. The 5mg and 10mg dosages are recommended, lower doses for individuals over 60 and for women. Zolpidem's primary indication is for sleep initiation problems, though it has also been found to reliably affect sleep maintenance. Zolpidem interacts with the GABA-BZ receptor complex, appears to bind selectively to the BZ1 receptor, is metabolized by the human liver cytochrome P450, has a Tmax of 1.6 hours, and a T1/2 of 2.6 hours. The pharmacokinetic profile of zolpidem, along with the absence of active metabolites, makes it unlikely that there are accumulation effects with multiple doses over days. See the attachment for a copy of the package insert for zolpidem.

Zolpidem will be purchased through, and managed by, the Investigational Drug Services of the University of Pennsylvania. An over encapsulation technique will be used to ensure that the drug doses and placebo formulations appear identical. Over encapsulation will be accomplished by using green and yellow capsules. Treatment will consist of 5mg to 10mg doses of zolpidem or one or more of inactive ingredients in zolpidem tablets (e.g., hydroxypropyl methylcellulose, lactose, cellulose, polyethylene glycol, etc.). All subjects will be instructed to take the medication or placebo 30 minutes prior to bedtime. Medication will be packaged in birth control style packs which contain 32 pills per pack and are enumerated for both week and day of the week. In the case of the partial reinforcement, the placement of active medication will be randomly assigned to 3 days per week. The placement of the active doses will differ from week to week. Placement of medication will be coded per pack (so as to allow for the post hoc assessment of which nights of the week were medication and which were placebo). Blister packs will be returned once a month when subjects are evaluated on-site and provided the next month's medication supply. The study CRC will dispense and receive the foil packs. The pattern of used and unused data will be coded.

1.2.1 Nonclinical Data

The Behavioral Pharmacotherapeutic/partial reinforcement strategy (PRS) has been evaluated in animal models. Such data support the concept that a mechanism of action for the PRS may indeed be related to classical conditioning (i.e., that the vehicle of a medication can become a conditioned stimulus for pharmacotherapeutic effects). Two such studies are listed below:

> Bovbjerg D, Ader R, Cohen N. Acquisition and extinction of conditioned suppression of a graft-vs-host response in the rat. J Immunol. 1984 Jan;132(1):111-3. PMID: 6606662.
>
> Ader R, Cohen N, Bovbjerg D. Conditioned suppression of humoral immunity in the rat. J Comp Physiol Psychol. 1982 Jun;96(3):517-21. PMID: 7096686.

1.2.2 Clinical Data to Date

Two clinical trials have been conducted to date with the Behavioral Pharmacotherapeutic/partial reinforcement strategy. One is summarized above (based on our NCCAM R01AT003332 grant and published in Sleep Medicine in 2015 PMID: 26298795). The other trial was conducted in patients with psoriasis and was published in Psychosomatic Medicine in 2010 (PMID: 20028830).

In brief, the psoriasis study was a two site, double-blind study, conducted in 46 patients with psoriasis (PMID: 20028830). The sites were in New York (NY) and California (CA). It was hypothesized that psoriasis subjects treated with corticosteroids (acetonide triamcinolone) using a conditioning and partial

reinforcement regimen would exhibit better clinical outcomes (less severe symptoms and fewer relapses) than subjects given the same amount of drug under standard conditions. Initially, lesions were treated with 0.1% acetonide triamcinolone under standard treatment conditions (conditioning phase of the study). Thereafter, subjects were randomized to one of three conditions (experimental treatment phase of the study): 1) a standard therapy group (n=18), 2) a partial reinforcement group (n=15), and 3) a dose control group (n=13). Standard therapy consisted of the use of a full dose of the corticosteroid on all treatment occasions. Partial reinforcement therapy consisted of a full dose of the corticosteroid on 25% to 50% of all treatment occasions, with placebos interspersed between the full dose administrations. Dose control patients received 25-50% of the initial dose on all treatment occasions.

In the NY cohort, partial reinforcement corresponded to a greater reduction in lesion severity than the dose control condition and the partial reinforcement condition did not differ from standard therapy. In the CA cohort, the three experimental groups did not differ overall with respect to lesion severity during the experimental phase of the study. The site differences in outcome were likely attributable to the dose control conditions. In the NY Cohort, the continuous use of the fractional dose (following the initial treatment response) resulted in a worsening of psoriasis symptoms during the experimental treatment phase of the study. In the CA cohort, the fractional dose group exhibited a less robust response to initial treatment during the conditioning phase of the study, but the clinical gains were maintained over time with the ½ dose. As for relapse rates, the site trends were reasonably comparable. The overall incidence of relapse by group were as follows: standard treatment (22.2%), partial reinforcement (26.7%) and dose control (61.5%). Thus, while standard treatment and partial reinforcement yielded comparable outcomes, the ½ dose control resulted in significantly more relapses.

1.2.2.1 Human Pharmacokinetics N/A

1.2.2.2 Clinical Studies in Adults N/A

1.2.3 Clinical Studies in Children N/A

1.3 Dose Rationale (if applicable) N/A

2 Study Objectives

As noted above, the primary goal of the study is to assess relative efficacy of the two partial reinforcement conditions as compared to nightly and intermittent dosing conditions over two time intervals (first 3 months of treatment following initial treatment response using standard dosing and an extension phase with 9 months of treatment). The secondary goal is to explore how placebo coverage of non-medication nights compares to active pill use nights and to no-pill use nights.

2.1 Primary Objective(s)

Phase 1. Assess for group differences for percent treatment responders.
Phase 2. Assess for group differences with respect to relapse.
Phase 3. Assess for group differences with respect to relapse.

2.2 Secondary Objectives (if applicable)

n/a

3 Investigational Plan

Phase 1 (1 month): Single condition: Full Dose: Nightly 5mg or 10mg (as is age and sex appropriate). Subjects older than 60 receive 5mg. Women (regardless of age) receive 5mg. All other subjects will receive 10mg. Dose is fixed and will not be adjusted.
Phase 2 (3 months): Treatment responders continue in study. Subjects are randomized to one of four maintenance conditions for three months: a full dose condition (7 doses per week, no placebos); one of two low frequency partial reinforcement conditions (1 or 3 active doses per week and the rest placebos); or a low frequency intermittent dosing condition (1 to 3 active doses per week, prn, no placebos).

Phase 3 (9 months): Phase 3 will be an extension period to assess the long-term durability of the approaches. The outcomes for the study will be: rate of relapse, latency to relapse, average sleep continuity, number and severity of medical symptoms during treatment, and daytime function during treatment.

During all phases of the study, sleep continuity, depression and anxiety, alcohol use, pill use, and medical symptomatology (and medication side effects) will be monitored via online daily sleep diaries, weekly evaluation with a medical symptom checklist (52 symptoms where positive endorsements allow subjects to rate their average severity and number of days affected), Nurse Practitioner-administered monthly assessments by interview at each medication resupply, , and physicals on an as-needed basis . Note: The monthly assessments will also utilize a side-effect check list based on the package insert for zolpidem.

3.1 General Design

Double Blind, multi-phase study with a 3x4 mixed model design. Factor 1: Study Phases. Factor 2: Study conditions (4 dosing groups: QHS; PRS1, PRS3, and IDS1-3).

3.1.1 Screening

Interested individuals are directed to call our phone number (215-7-INSOM) or to visit our web site at www.sleeplessinphilly.com. If the individual wishes to pursue participation in a study, they are directed to complete the on-line consent form(s) and then to complete a screening questionnaire. Once the screening questionnaire is complete, this information will be used to determine which subjects are eligible for participation and which subjects should be further considered and scheduled for an in-lab intake interview.

Subjects will have a 60-90 minute screening interview to confirm their eligibility for study. This interview will be conducted by a clinical research coordinator and will include the administration of a variety of questionnaires in order to 1) rule out medical and psychiatric illness, and 2) to rule in insomnia disorder. The questionnaires to be used include a set of 9 measures that are validated and a set of 10 measures that are specific to our laboratory. Subjects that are still eligible after the intake interview will be instructed to obtain their PCP's assent to participate in the study. Subjects that do not have a PCP will be provided a HnP by our program (HnP conducted by a NP in collaboration with Dr. Michael Thase [study medical collaborator]).

Following the intake interview, all subjects that remain eligible for the proposed study will complete two more assessments prior to being enrolled in the proposed experiment. First, each subject will complete two weeks of daily sleep diaries to confirm 1) their retrospective estimates regarding the type, severity, and frequency of their insomnia and 2) that they are compliant with the daily task of completing the daily diaries. Second, each subject will undergo a PSG or Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study) study to rule out the presence of occult sleep disorders (sleep disorders for which the patient does not exhibit the typical signs and symptoms). This sleep study will be equivalent to the quality of a clinical PSG. These screenings will be conducted according to the Penn CSCN Sleep Research Laboratory's

standards. The recording montage consists of 14 electrophysiological signals. The basic montage includes 2 EOGs referenced to a single mastoid [LOC & ROC], 6 EEGs referenced to linked mastoids [F3,F4,C3,C4,O1,&O2,], 1 bipolar mentalis EMG, an EKG, 2 bipolar tibial EMGs, a nasal/oral airflow thermocouple, 2 respiratory effort sensors, and an oximeter measure of blood oxygen saturation. All 14 signals will be recorded with SD32 amplifiers and use Sandman v10 acquisition software to transmit data directly to the control room where the PSG can be monitored online and simultaneously recorded to PCs located in the control room. PSG data will be scored according to Rechtschaffen and Kales standards and the sleep continuity and sleep architecture variables will be calculated using lab standard definitions. Additionally, AI/AHI and PLMI indices will be calculated according to AASM criteria. Subjects with an AI (vs. AHI) of >10 and a PLMI of >25 (or who exhibit evidence of other sleep disorders) will be ineligible for the proposed study.

3.1.2 Study Intervention Phase
See section 3.0 – Investigation Plan.

3.1.3 Phase II (if applicable include and add details about open label study phase if appropriate)
See section 3.0 – Investigation Plan.

3.1.4 Follow Up Phase
See section 3.0 – Investigation Plan.

3.1.5 Allocation to Interventional Group
The study statistician and/or staff member of the Investigational Drug Services will execute the randomization procedures.

3.2 Study Endpoints
As noted above, the primary outcomes will be assessed in terms of treatment response (Phase 1) and relapse (Phases 2 & 3).

3.2.1 Primary Study Endpoints
As noted in section 3.2

3.2.2 Secondary Study Endpoints
Average sleep continuity in non-relapsers by study group.

3.2.3 Primary Safety Endpoints [if applicable]
As noted above, side effects will be assessed in several ways: daily assessments via the sleep diaries, weekly evaluation with a medical symptom checklist (52 symptoms where positive endorsements allow subjects to rate their average severity and number of days affected), Nurse Practitioner-administered monthly assessments by interview at each medication resupply, and physicals on an as-needed basis . Note: The monthly assessments will also utilize a side-effect check list based on the package insert for zolpidem.

4 Study Population and Duration of Participation
Subjects will be between the ages of 40-85 years old and have a stable sleep/wake schedule (no shift work) with a preferred sleep phase between 9:00 PM and 9:00 AM. The Phase-1 recruitment sample will be populated by 200 completed subjects. Phase-2 will complete 25-50 subjects per condition. Phase-1 will be one month, Phases-2 will be 3 months and Phase-3 will be 9 months. The study duration will be 12-14 months.

4.1 Inclusion Criteria

Patients with chronic insomnia will meet DSM-5 criteria for Insomnia Disorder, ICSD-3, and RDC criteria for Psychophysiologic Insomnia. In addition, all subjects will have a sleep initiation and/or a sleep maintenance complaint (> 30 min. to fall asleep and/or > 30 min. of wakefulness during the night) with a problem frequency $\geq$ 3 nights/wk and problem duration > 3 mo. This profile must be evident at both intake (based on retrospective reports) and as an average profile from the two weeks of baseline diaries (prospective sampling).

4.2 Exclusion Criteria

Use of medication expressly for the purpose of falling or staying asleep (e.g. trazadone/ desyrel, melatonin, Tylenol PM, Nyquil, Benadryl).

Hypersensitivity to zolpidem

Compromised respiratory function

Unstable medical or psychiatric illness
- Assessed with the patient Hx, PHQ-9, and the GAD-7
- Assessed with a History and Physical, an EKG, and a clinical chemistries panel
- To assure that the insomnia is not comorbid with unstable medical or psychiatric illness

Symptoms suggestive of sleep disorders other than insomnia
- Assessed with the Sleep Disorders Symptoms Checklist (SDS-CL).
- To assure that the insomnia is not comorbid with other intrinsic sleep disorders

Polysomnographic data indicating sleep disorders other than insomnia
- Assessed with PSG or Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study).
- Subjects w/ an AI of >10 or PLMI >25 are excluded from the study
- Subjects w/ an abnormal PSG or Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study) are excluded from the study
- Abnormalities include EKG arrhythmias, occult seizure activity, REM without atonia, etc.
- To assure that the insomnia is not comorbid with other intrinsic sleep disorders.

Evidence of active illicit substance use, abuse, or dependence
- Assessed with the patient Hx
- Assessed with the AUDIT and CAGE
- Assessed with the toxicology screens
- To assure that the insomnia is not comorbid with alcoholism or substance abuse

Use of CNS active medications that are for treatment of insomnia or are thought to have caused insomnia as a side effect
- Assessed by self-report and toxicology screen - obtained during the screening physical.
- To assure that the clinical effects observed in this study are not obscured by other medications

Inadequate language comprehension
- Assessed informally by the Clinical Research Coordinator during Intake Interview
- To assure the quality of self-report data as all the measures are in English.

Current experience, or history (within the last 5 years) of parasomnias
- Assessed with the SDS-CL, during the intake interview, and during the HnP
- To help assure that subjects do not experience parasomnias while taking zolpidem

No access to the computers, I-Pads, or the internet
- Since the primary recruitment methods are via the internet (ResearchMatch), this is likely to be a non-issue.

4.3 Subject Recruitment

A broad strategy will be employed to recruit subjects so that our annual recruitment goals can be met or exceeded. The primary methods will be use of our volunteer database (presently more than 3500 individuals), ResearchMatch, Craigslist, I-Connect (UPenn's CTRC recruitment system), MechanicalTurk (a platform where researchers can upload questionnaires and interested subjects respond), TurkPrime (a variation of MechanicalTurk specific to research), and an Electronic Medical Records query through the University of Pennsylvania Data Analytics Center and EXPRESSweekly (UPHS e-mail blast used to advertise studies). Additional strategies consist of enlisting the services of Postcard Mania (a postcard mailing company), Metro (Philadelphia's local newspaper), Nextdoor (similar to Craigslist), Study Scavenger (professional recruiting company that advertises through an app), professional recruiting companies (e.g., Clinical Trials, Paid Focus group, and Center Watch), automated telephone advertisement services (e.g., CallFire, One Call Now), and advertisements on social media (Facebook, Twitter, and Reddit). The online screening is a general form which will assist in identifying subjects who are in reasonably good health (please refer to protocol #809272 for details on this screening form). We will also use the services of PatientPoint, a company that displays health information on screens in select physician's offices throughout the Philadelphia area to display our TV advertisement. These strategies will be supplemented with local advertisements on cable TV, radio, city newspapers, local sleep centers, recruitment boards on Penn's campus, other community centers (e.g., senior citizen living centers), and places of business (e.g., restaurants). For an example of a TV advertisement, see www.med.upenn.edu/bsm/research_participate.html.

Additionally, a referral based lottery will be conducted to increase recruitment. Prior study participants who have given their permission for re-contact will be contacted to give them the opportunity to refer individuals to our study. For each individual referred, the prior participant will gain one entry into a lottery for three Amazon Gift Card prizes ($250, $150, $50). The referral period will last for three months and the lottery drawing will be at the end of the third month.

4.4 Duration of Study Participation

Screening will take about 1 month. Phase-1 will be 1 month, Phases-2 will be 3 months and Phase-3 will be 9 months. The study duration will be 12-14 months.

4.5 Total Number of Subjects and Sites

200 subjects recruited and completed Phase-1 at one site (Penn).

4.6 Vulnerable Populations:

The study does not involve any of the following populations:

- Pregnant women
- Fetuses or neonates
- Prisoners
- Children

No subjects, including the economically disadvantaged, employees, and/or students at Penn, will be unduly influenced, encouraged, or coerced into participating in this study. These populations will not be targeted or excluded. IF they are encountered and would like to participate, the appropriate measures will be taken in order to allow them the opportunity to provide consent.

5 Study Intervention (Study drug, device, biologic, vaccine, food etc.)

Zolpidem, 10mg and 5mg.

5.1 Description

Zolpidem tartrate (trade name Ambien), is a non-benzodiazepine hypnotic available in 5mg and 10mg tablets for oral administration at bedtime. The 5mg and 10mg dosages are recommended, lower doses for individuals over 60 and for women. The effect of zolpidem may be slowed if taken with or immediately after a meal. Zolpidem's primary indication is for sleep initiation problems, though it has also been found to reliably affect sleep maintenance. Zolpidem interacts with the GABA-BZ receptor complex, appears to bind selectively to the BZ1 receptor, is metabolized by the human liver cytochrome P450, has a Tmax of 1.6 hours, and a T1/2 of 2.6 hours. The pharmacokinetic profile of zolpidem, along with the absence of active metabolites, makes it unlikely that there are accumulation effects with multiple doses over days.

5.2 Intervention Regimen

Double Blind, multi-phase study with a 3x4 mixed model design. Factor 1: Study Phases. Factor 2: Study conditions (4 dosing groups: QHS; PRS1, PRS3, and IDS1-3).

5.3 Receipt

Zolpidem will be purchased through, and managed by, the Investigational Drug Services of the University of Pennsylvania.

5.4 Storage

Formulation and storage will be accomplished by Investigational Drug Services of the University of Pennsylvania.

5.5 Preparation and Packaging

An over encapsulation technique will be used to insure that the drug doses and placebo formulations appear identical. Over encapsulation will be accomplished by using green and yellow capsules. While over encapsulation may slow the absorption of study medication, this should not pose a risk to participants nor compromise the experimental design as the slower absorption is constant to condition. Treatment will consist of 5mg to 10 mg doses of zolpidem or one or more of inactive ingredients in zolpidem tablets (e.g., hydroxypropyl methylcellulose, lactose, cellulose, polyethylene glycol, etc.). All subjects will be instructed to take the medication or placebo 30 minutes prior to bedtime. Medication will be packaged in foil packs which contain 32 pills per pack and are enumerated for both week and day of the week. The placement of the active doses will differ from week to week. Placement of medication will be coded per pack (so as to allow for the post hoc assessment of which nights of the week were medication and which were placebo).

5.6 Blinding

Blinding will be accomplished by the Investigational Drug Services (IDS) of the University of Pennsylvania. As noted above, placement of medication will be coded per pack (so as to allow for the post hoc assessment of which nights of the week were medication and which were placebo).

5.7 Administration and Accountability

Blister packs will be returned once a month when subjects are evaluated on-site and provided the next month's medication supply. The study CRC will dispense and receive the foil packs. The pattern of used and unused medication will captured by xeroxing or photographing each foil pack.

5.8 Subject Compliance Monitoring

Pill use will be tracked per week via the AM sleep diary. These data will be compared to, and corroborated with, the foil pack data acquired at the monthly in-person evaluations.

5.8.1 Return or Destruction of Investigational Product

Blister packs will be returned once a month when subjects are evaluated on-site. Following the archiving of the pill pack (pill utilization pattern captured by xeroxing or photograph) the study CRC will return the foil packs and remaining capsules to Investigational Drug Services of the University of Pennsylvania for destruction.

6 Study Procedures

All subjects will receive medication on a monthly basis and complete daily sleep diaries and weekly questionnaires.

Does your study use MRI? (CAMRIS is the appropriate contact for all studies involving MRIs)

☐ Yes ☒ No

Check of all that apply:

☐ 1.5T MRI
☐ 3T MRI
☐ 7TMRI

Does the MRI use investigational sequences and/or coils?
(See Experimental Device Clause)

☐ Yes ☒ No ☐ Unsure

Does your study include pregnant women?
(See Pregnancy Clause and Justification)

☐ Yes ☒ No

Does the MRI require the use of Contrast Agents?
(See Contrast Risks)

☐ Yes ☒ No

Does your study involve the exposure to radiation, radiotracers and/or radiological imaging modalities?

☐ Yes ☒ No (If No, no RRSC review is needed)

Will any of the radiation exposure result from procedures that are or could be performed solely as a result of a subject's participation in the research protocol?

☐ Yes ☒ No

The following are examples of procedures involving ionizing radiation:

(Refer to appendix 17.3 for radiotracers, radiation use and 17.5 for nuclear medicine guidance and language)

- X-rays (examples: CT scan, chest x-ray, hand/wrist x-ray, abdomen x-ray, DEXA, pQCT, Fluoroscopy/Angiography)

- Nuclear Medicine scans (examples: FDG-PET, PET/CT, Tc-99m, SPECT, MUGA, bone scan)

If you are unsure please contact Will Davidson in EHRS (wed@ehrs.upenn.edu).

Ultrasound

☐ Yes ☒ No

If yes, there is no protocol specific language to include but please contact Susan Schultz susan.schultz@uphs.upenn.edu

Will your study be using CT Scans? (CACTIS is the appropriate contact for studies involving CT scans)

☐ Yes ☒ No

Check off all of the following procedures that will be performed in your research- each option you select will link to the template language document:

☐ *Apheresis/plasma exchange*
☐ *Leukapheresis*
☐ *Bone Marrow Biopsy or Aspirate*
☐ *Use of AP clinical specimens*
☐ *Biopsies- check those which apply*

☒ *Blood draw*

6.1 Screening

- Informed Consent
- 17 questionnaires (See Section 7)
- Two weeks of prospective assessment with sleep diaries
- **PCP assent or onsite HnP**
- In-Lab PSG study (standard clinical screening) or Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study)

6.2 Study Intervention Phase

See section 3.0 – Investigation Plan.

6.3 Rescue Therapy [if applicable]

In the event of treatment non-response or relapse, subjects will be provided in-person or tele-health based treatment with Cognitive Behavioral Therapy for insomnia (CBT-I).

6.4 Unscheduled Visits

All subjects may contact the study coordinator at any time by email or phone to make an appointment or to discuss questions or concerns.

6.5 Subject Withdrawal

"Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules, AEs, or due to medication use. The Investigator or the Sponsor (if applicable) may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. Subjects who withdraw early will have one final visit to collect investigational product and to follow up regarding adverse events".

6.5.1 Data Collection and Follow-up for Withdrawn Subjects

"Subjects who withdraw consent to participate in the study will be seen for one final visit to collect the investigational product. During this visit they will be asked for permission to have the study team look into their survival status via publically available means".

6.6 Early Termination Visits

See section 6.5.1

6.7 Subject Contact

Subjects will be contacted through phone, email, text messaging, and Blue Jeans video conferences. We will use text messaging via an app for scheduling and reminding participants of study visits. Identifying information, such as names, will not be used. An app will be used to generate texts so that personal cell phones are not used.

7 Study Evaluations, Measurements, and Schedule

TABLE 2
SCHEDULE OF INSTRUMENTS & PROCEDURES

Cluster	Measure	Acronym	Factor(s)	Schedule
SCREENING	Demographics Form †	DEMO	Demographics	At Intake Only
	Alcohol Use Disorders	AUDIT	Alcohol use	At Intake Only
	Physical Exam	PE	Physical	Once every 4 months
	Polysomnography	PSG	Sleep Disorder	At Intake Only
MEDICAL	Medical Hx Form †	MHF	Medical Hx	At Intake Only
	Medical Symptom Checklist †	MS-CL	Medical Symptoms	Weekly
SLEEP	Sleep Dx Symptom Checklist †	SDS-CL	Sleep Symptoms	Monthly (All Phases)
	Insomnia Severity Index	ISI	Insomnia Severity	Weekly (All Phases)
	Sleep Diaries †	DIARIES	Sleep Continuity	Daily (All Phases)
	Types of Insomnia Form †	TIF	Insomnia Type & Subtype	At Intake Only
	Insomnia Hx Form †	IHF	Insomnia Hx	At Intake Only
	Morin - Tx Acceptability Scale	MITAS	Tx Acceptability	At Intake Only
	Tx Expectancy & Evaluation Form †	TEEF	Tx Expectancy & Evaluation	Pre & Post Study
	Sleep Medication Hx Form †	SMHF	Sleep Medication Hx	At Intake Only
MOOD STRESS & DAYTIME FUNCTION	Patient Health Questionnaire-9	PHQ-9	Depression	Bi-Weekly (All Phases)
	Life Events Scale	LES	Life Events	Monthly (All Phases)
	Perceived Stress Scale	PSS	Perceived Stress	Weekly (All Phases)
	Generalized Anxiety Disorder	GAD-7	Anxiety	Bi-Weekly (All Phases)
	Epworth Sleepiness Scale	ESS	Sleepiness	Weekly (All Phases)
	Functional Outcomes of Sleep	FOSQ-10	Daytime Function	Monthly (All Phases)

7.1 Medical Record Review *N/A*

7.2 Physical Examination

The physical examination – when needed - will include a review of the self-report medical history inventory, the self-report medical symptoms checklist, vitals, and a standard review of systems to rule out any acute or unstable medical comorbidity at screening or to detect emergent medical conditions during the study. An EKG and/or clinical chemistries panel (blood and urine) may be ordered at the quarterly HnPs at the discretion of the medical evaluator (MD or NP). If significant abnormal findings are discovered, the subject will be referred to their primary care provider.

7.3 Vital Signs

Vital sign measurements (i.e., systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], and body temperature [in centigrade]) will be obtained by a validated method.). Blood pressure will be measured using an automated BP device, the Omron HBP 1300 and body temperature will be measured using SureTemp PLUS, a digital oral thermometer. Blood pressure and pulse will be measured after the subject has been in a sitting position for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person. Validated methods will be used for all vital sign measurements, and values will be recorded. Height (cm; once only) and weight (lbs.) will also be measured.

When vital signs are to be obtained concurrently with blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

7.4 Laboratory Evaluations

The primary lab evaluation at screening is the in-lab PSG study Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study).

7.5 Pregnancy Testing

Urine pregnancy testing is required for all women who are pre-menopausal. Urine pregnancy testing will be completed at the sleep study visit. . Also, an effective method of birth control as determined by their physician is required for women who are pre-menopausal. There are no requirements regarding the specific form of contraception that must be used. Subjects must agree to continue to use this method of birth control during the entire course of the study. If a subject does become pregnant during the study, they will be disenrolled. Outcome data on incidental pregnancies will not be collected.

7.6 Other Evaluations, Measures N/A

7.7 Efficacy Evaluations

The primary efficacy evaluation is accomplished with on-line prospective sampling, e.g., daily sleep diaries.

7.8 Pharmacokinetic Evaluation N/A

7.9 Genetic Testing (only if applicable) N/A

7.10 Safety Evaluations

As noted above, side effects will be assessed in several ways: daily assessments via the sleep diaries, weekly evaluation with a medical symptom checklist (52 symptoms where positive endorsements allow subjects to rate their average severity and number of days affected), Nurse Practitioner-administered monthly assessments by interview at each medication resupply, and physicals on an as-needed basis .

Note: The monthly assessments will also utilize a side-effect check list based on the package insert for zolpidem.

8 Statistical Plan

As noted above, the primary plan is to calculate group effect sizes for relapse, time to relapse, and average sleep continuity in non-relapsers.

8.1 Primary Endpoint

The primary endpoints are percent treatment response and percent relapse per condition.

8.2 Secondary Endpoints

The secondary endpoints are time to relapse, and average sleep continuity in non-relapsers.

*8.3 Sample Size and Power Determination (*from the text of the grant)

Power was estimated using PASS-14. Based on our prior study, it is anticipated that at least 800 subjects will need to be screened to enroll 250 individuals into Phase-1 and to randomize 200 individuals into Phase-2. Of the 200 subjects (50 per maintenance treatment condition), it is estimated that 180 subjects (45 per group) will complete Phase-2 (either exhibit a relapse or complete the three month monitoring period). Taking into account drop out and relapse, it is estimated that between 50 and 80 percent of the subjects from Phase-2 will continue into the extension portion of the study (Phase-3).The power analysis for Aims 1 and 2 is based on four comparisons of two groups with longitudinal binary outcomes. Due to the four comparisons, the significance level was adjusted to 0.0167 using a Bonferroni correction. The correlation between observations on the same subject is assumed to be a conservative 0.8. With 45 participants per group expected to complete Phase-2 and 30 participants per group expected to complete both Phases 2 & 3, and with an estimated average of 170 daily measures per person across both phases, the study has 80% power to detect a minimum difference in relapse rate of 7.3-12.7% (OR=1.8-2.7) at the end of Phase-2 and 3.2-5.9% (OR=1.3-1.7) at the end of Phase-3 when the relapse rate ranges from 5%-25% in the reference group in a longitudinal model having a AR(1) covariance structure. Since Aims 3 and 4 are exploratory, these data are not presented here.

8.4 Statistical Methods

8.4.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

8.4.2 Efficacy Analysis (*from the text of the grant)*

General Approach**.** The first phase of the analyses will be descriptive. The sample will be characterized with regard to demographic variables and health status. Categorical variables will be summarized by frequencies, while continuous variables will be summarized by the mean and 95% confidence intervals, median, standard deviation and range. The results of randomization will be examined by comparing demographic variables and health status across the four treatment arms. If differences are found, these variables will be treated as potential confounders and included as adjustment variables in the final models. The second phase of the analysis will consist of model building and interpretation. Key issues when analyzing longitudinal data include: 1) prior status as a predictor of subsequent status (non-independence of assessments); and 2) management of missing data. Mixed effects logistic regression models will be used to account for the intra-individual dependence and allow the dependence of past responses. The model allows the conditional mean response to depend on both covariates and past responses that are treated as covariates. *The primary analysis will follow the intent-to-treat approach*

where individuals are considered part of their randomized group, regardless of compliance to treatment. Additional analyses, however, will follow seeking to adjust for departures from randomization arising from drop-out and non-compliance. Where possible and ideal, missing data will be managed using mixed effects models which assume that data are missing at random (i.e. missingness is dependent only on observed, past values of covariates and outcomes) and they use all available data, including the outcomes in early months from those patients who eventually dropped out. Sensitivity analyses will be performed to estimate the potential impact of missing data on overall program success assuming that those with no measurements were faring worse than those who remained in the study. To address the problem of non-compliance and to estimate the effect of treatment in the presence of full compliance, we will implement instrumental variable methods.

Approach by Study Aims. For Study Aims 1 and 2 the analysis for Phase-2 and 3 will be conducted jointly. The primary outcome will be a binary indicator of relapse at post-baseline time points. In adjusted analyses, the rate of relapse over time will be compared across the four treatment arms using mixed effect logistic regression models adjusting for any potential confounders identified in the preliminary analysis and baseline sleep continuity. The models will include a main effect for time, treatment group and the interaction between time and treatment group. A significant interaction term will indicate difference in the rate of relapse by treatment group over time. Contrasts at the end of each Phase testing 4 pairwise comparisons will be estimated. Results will be presented in terms of the odds ratio and 95% confidence intervals for the effects of QHS vs. (PRS-3, PRS-1, or IDS) . In the assessment of time to relapse, the time from the start of Phase-2 until relapse will be compared across the four treatment arms using a survival model for censored outcomes. QHS will serve as the reference group. Finally, an effect of treatment arm on sleep continuity, medical symptoms and side effects will be modeled individually similar to the approach for the primary outcome, using mixed effects models for continuous and count responses, as appropriate. The analysis for Aim 3 will be conducted jointly for Phases-2 and 3 and will be limited to the IDS group. Similar to above, we will apply mixed effects models for continuous and count responses where sleep continuity (SL, WASO, NWAK, TST, and SE%), medical symptoms and side effects are modeled as separate outcome measures. The independent variables of interest are a time dependent indicator of +/-Pill, time and the interaction between time and +/-Pill. A significant interaction term will indicate a difference in sleep continuity by type of pill over time. The analysis for Aim 4 will follow the same approach as Aim 3 adding in subjects from the PRS-1 and PRS-3 groups. Group indicators and all interactions between group, time and +/-Pill will be added to the model to examine whether sleep continuity and medical symptoms differ by type of pill and by treatment group over time.

8.4.3 Pharmacokinetic Analysis **N/A**

8.4.4 Interim Analysis **N/A**

8.4.5 Safety Analysis

Side effects and adverse events will be assessed in several ways: daily assessments via the sleep diaries, weekly evaluation with a medical symptom checklist (52 symptoms where positive endorsements allow subjects to rate their average severity and number of days affected), Nurse Practitioner-administered monthly assessments by interview at each medication resupply, and physicals will be conducted on an as-needed basis .

An adverse event will be defined as 1) any behavioral or health complaint spontaneously reported during the study, 2) an above threshold score on the study clinical assessment instruments (ESS, PHQ-9, or GAD-7), and/or a 20% increase in the medical symptom check list scores (frequency or severity).

8.5 Subject Population(s) for Analysis

- All-randomized population.
- All-treated population
- Protocol-compliant population

9 Safety and Adverse Events (as stated in the IRB template)

9.1 Definitions

9.1.1 Adverse Event

"An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- *results in study withdrawal*
- *is associated with a serious adverse event*
- *is associated with clinical signs or symptoms*
- *leads to additional treatment or to further diagnostic tests*
- *is considered by the investigator to be of clinical significance"*

9.1.2 Serious Adverse Event

Serious Adverse Event

"Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- *fatal*
- *life-threatening*
- *requires or prolongs hospital stay*
- *results in persistent or significant disability or incapacity*
- *a congenital anomaly or birth defect*
- *an important medical event*

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events****."*

9.2 Recording of Adverse Events

"At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately."

9.3 Relationship of AE to Study

"The relationship of each adverse event to the study procedures will be classified in terms of the event's potential relationship to the study (definitely related, probably related, possibly related, unlikely or unrelated)."

9.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

"The occurrence of adverse events will be reported to the study's medical collaborators, DSMB chair, Penn IRB, and our NIA program officer.

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- *Study identifier*
- *Study Center*
- *Subject number*
- *A description of the event*
- *Date of onset*
- *Current status*
- *Whether study intervention was discontinued*
- *The reason why the event is classified as serious*
- *Investigator assessment of the association between the event and study intervention*

Additionally all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual and below."

9.4.1 Follow-up report

"If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The investigator will be responsible for ensuring that all SAE are followed until either resolved or stable."

9.4.2 Investigator reporting: notifying the study sponsor

Any study-related unanticipated problem posing risk to subjects or others, and any type of serious adverse event, will be reported to the study sponsor (NIA) by telephone and email within 24 hours of the event. Specifically, the SAE will be reported to our program officer. "*To report such events, a Serious Adverse Event (SAE) form will be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:*

Dr. Miroslaw Mackiewicz
GWY BG RM 3E400
7201 Wisconsin Ave
Bethesda MD 20814
Phone: 301-496-9350
Fax: 301-496-1494
E-mail: miroslaw.mackiewicz@nih.gov

Within the following 48 hours, the investigator will provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This will include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events will be provided promptly to the study sponsor."

9.5 Investigator Reporting: Notifying the Penn IRB

Penn IRB will be notified in accordance with the requirements and timelines as specified by the IRB.

9.5.1 Sponsor reporting: Notifying the FDA (applies only to Penn sponsor –investigator IND/IDE holders) N/A

9.5.2 Sponsor reporting: Notifying participating investigators N/A

9.6 Unblinding Procedures

In the event of an SAE, Investigational Drug Services of the University of Pennsylvania will unblind the subject's status with respect to treatment condition. This information will be provided to the subject, and with permission, the subject's clinical providers (or emergency care providers) within 24 hours or less.

9.7 Stopping Rules

The DSMB chair will be notified of any serious adverse events that occur, regardless of whether they are thought to be study-related, within 24 hours of project staff learning of their occurrence. The DSMB chair will decide, independent of the study investigators, whether the study should be discontinued.

9.8 Medical Monitoring

The medical monitoring will be accomplished by our collaborating physician, Dr. Michael Thase.

9.8.1 Data and Safety Monitoring Plan

See 9.9

9.9 Data Safety Monitoring Board

We will establish a Data and Safety Monitoring Board (DSMB) to ensure the proposed study's safety and efficacy. The goal will be to have the DSMB consist of: 1) an expert in psychopharmacology or sleep medicine who is not part of the Behavioral Sleep Medicine program team (this person will chair the committee); 2) two academicians with clinical training (i.e., a psychologist, a nurse practitioner, or psychiatrist); and 3) a biostatistician. The DSMB will receive reports from the study team every six months with information about the progress of recruitment, the demographic characteristics of participants, adverse events, the number of dropouts, participants' reasons for dropping out, and any protocol amendments. The DSMB will then prepare a formal report, which will be returned to the investigators and to the Penn IRB.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

In the case of the present study all self-report data will be acquired through RedCap. Files containing PHI (that is not stored in the EMR) will be stored on a secure shared drive on the Penn Network. Only authorized study staff will have access to this shared drive.

10.2 Data Collection and Management

All data will be collected via RedCap. Data download will only be available to the PI and/or his designates. Files containing PHI will be stored on a secure shared drive on the Penn network. Only authorized study staff will have access to this shared drive. All paper copies of data will be kept in a locked filing cabinet separate from both the list of subject names/ID numbers and the raw data. All in person encounters will occur at our offices at 3535 Market street. Subject encounters will occur in private offices or exam rooms. Additionally, all subjects will undergo screening sleep studies at the Penn Sleep Laboratory on 11 Gates at HUP. Subjects may be referred to the CTRC at Presbyterian 1 Mutch out-patient clinic or HUP 1 Dulles out-patient clinic for health and physical examinations. These facilities are regulated by the hospital and comply with all patient privacy protocols.

10.3 Records Retention

All electronic data will be maintained for a period equal to that required by the study sponsor. Longer term database management will occur but all subject identifiers will be removed.

11 Study Monitoring, Auditing, and Inspecting

The study materials and databases will be available to the study sponsor, the DSMB, and/or Penn IRB should a data audit be deemed necessary.

11.1 Study Monitoring Plan

See section 9.9

11.2 Auditing and Inspecting

"The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices."

12 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

"This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study."

12.1 Risks

There are minimal risks associated with the acquisition of questionnaires. There is also minimal risk associated with PSG or Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study); affixing electrodes can be uncomfortable, and an allergic reaction or rash to the substance used to affix electrodes may occur. Sleeping in an unfamiliar place may be disorienting. The laboratory overnights may also result in being late to morning commitments. Additionally, there is minimal risk from the blood draw. Infection, bruising,

fainting and a small amount of bleeding are possible. Regarding the study medication, in general, there are minimal risks associated with nightly or intermittent use of ≤ 5 mg zolpidem. The most notable include low incidences (overall and relative to placebo) of dizziness, drowsiness and diarrhea. One additional consideration is the occurrence of parasomnias in individuals taking zolpidem (or more likely one or more substances that act at the GABA-BZ receptor complex). While there is not good evidence that zolpidem, in particular, or BZRAs, in general, are "parasomnogenic", this potential side effect is nonetheless highlighted here because of media coverage and public concern about this specific issue. Other risks, including angioedema and anaphylaxis have also been reported; do not re-challenge if such reactions occur. Worsening of depression or suicidal thinking may occur. There is risk of respiratory depression in patients with compromised respiratory function. Additionally, withdrawal effects may occur with rapid dose reduction or discontinuation. Finally, it should be noted there is a line of research that suggests that the use of sleep medication is associated with increased risk for accidents and injury, poor health, and mortality. These findings, while not without exception, underscore the need to develop and assess alternative strategies for maintenance therapy for insomnia. The proposed study is an example of such a study – the aim being to evaluate how treatment gains with standard medical approaches can be maintained with less medication over time. This said, information regarding the association of hypnotic use with increased risk for accidents and injury, poor health, and mortality will be included in the informed consent form.

12.1.1 Possible Drug Interactions

Possible drug interactions with zolpidem include:

- Imipramine: decreased alertness
- Chlorpromazine: impaired alertness and psychomotor performance
- Rifampin: combination use may decrease effect
- Ketoconazole: combination use may increase effect

12.2 Benefits

All subjects are provided, at no cost, a comprehensive evaluation during the initial phase of the study. This evaluation includes a thorough assessment of the subject's sleep problem, a psychiatric evaluation, a physical and clinical chemistries study, and a PSG or Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study) evaluation. These data may be useful to the extent that occult medical, psychiatric, or sleep disorders are identified and/or ruled out. Subjects that are randomized to medical treatment may benefit by the successful treatment of their insomnia. Subjects that do not experience improvements during the study may benefit to the extent that in-person or tele-health based CBT-I will be provided at no cost following the study.

12.3 Risk Benefit Assessment

As indicated in the research plan, the value of the proposed project is that it may provide an evidence based approach to the long term management of insomnia. The practical value of the "behavioral pharmacotherapeutic approach" is that it may provide a means by which the:

• effects of pharmacotherapy can be extended (i.e., increase resistance to habituation);
• side effects that occur with the use of medication can be minimized; and
• costs of long-term therapy can be reduced.

These potential ramifications are especially relevant for populations with high chronic disease burden (e.g., older adults). Not only will this approach likely extend the "efficacy half-life" of regular hypnotic use, reduce healthcare costs (both the expense of hypnotics and the emergent health care costs associated with untreated insomnia), it also may be helpful in diminishing the amount of medication needed for one or more of the individual's treatment regimens and may thereby reduce risk for drug interactions.

12.4 Informed Consent Process / HIPAA Authorization

Overview
Consent is done on an individual basis during the initial evaluation by a designated staff member. For the informed consent process, the details of the consent form are discussed and the subject is encouraged to ask questions about study participation and any other details described in the consent form. Once signed, the subject is provided a copy of the consent form to keep.

Children and Adolescents
N/A

Adult Subjects Not Competent to Give Consent
Only competent adults will be included in this study.

12.4.1 Alterations to Typical Consent Process (only include if applicable)
N/A

12.4.1.1 Waiver of Consent (In some cases for screening/portions of that study that qualify as minimal risk, a waiver of documentation of consent may be permissible per IRB SOPs)

N/A

12.4.1.2 Waiver of Written Documentation of Consent N/A

12.4.1.3 Waiver of Written Documentation of Consent where the research is subject to FDA regulations
N/A

12.4.1.4 Waiver of HIPAA Authorization *N/A*

13 Study Finances

13.1 Funding Source
This study is supported by an NIA Bridge funding award (R56AG050620).

13.2 Conflict of Interest
All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

13.3 Subject Stipends or Payments
Subjects will be provided payment for participating in this research project. They will be provided $50 for completing the initial intake evaluation, $100 for the screening PSG or Home Sleep Apnea Testing (HSAT, type 3 or 4 sleep study), and a study completion payment of $350 (prorated for $100 for phase-1 [4 weeks] and $250 for phase-2 [12 weeks], and another $100 for Phase-3 (12 weeks); total $600 per subject). In addition to the prorated payments, a lottery will be conducted once each month and will work as follows. Each sleep diary that a subject completes is automatically counted as an 'entry' into the lottery. Each subject accumulates entries over the course of the month. At the end of each month, a drawing will be conducted within excel where random ID's are "selected" for each of the following prizes: 4@$50 and 3@$100, 2@$500 and 1@$1000 ($2500 per month / $30,000 per year). Each subject is eligible to win one

prize per month and one prize of each dollar value over the year (total of 4 awards per person is possible. At the conclusion of the study, a final lottery will be conducted for all participants that have completed the study with twenty $500 prizes being awarded based on a random selection of participants through the excel. Please note that the use of the lottery has been approved by both NIH and the Penn IRB for prior studies by our group.

14 Publication Plan

While the primary intent of the study is to garner effect size data, if the inferential statistics are significant with 5-8 subjects per condition, the data will be summarized as a short report for the journal SLEEP or the Journal of Sleep Research.

15 References

Relevant references were placed in text (PMID numbers). Also below.

1: Perlis M, Grandner M, Zee J, Bremer E, Whinnery J, Barilla H, Andalia P, Gehrman P, Morales K, Thase M, Bootzin R, Ader R. Durability of treatment response to zolpidem with three different maintenance regimens: a preliminary study. Sleep Med. 2015 Sep;16(9):1160-8. PMID: 26298795.

2: Ader R, Mercurio MG, Walton J, James D, Davis M, Ojha V, Kimball AB, Fiorentino D. Conditioned pharmacotherapeutic effects: a preliminary study. Psychosom Med. 2010 Feb;72(2):192-7. PMID: 20028830;

3: Bovbjerg D, Ader R, Cohen N. Acquisition and extinction of conditioned suppression of a graft-vs-host response in the rat. J Immunol. 1984 Jan;132(1):111-3. PMID: 6606662.

4: Ader R, Cohen N, Bovbjerg D. Conditioned suppression of humoral immunity in the rat. J Comp Physiol Psychol. 1982 Jun;96(3):517-21. PMID: 7096686.

16 Attachments

- Sample Consent Form

16.1 Source Documents

The data is being acquired on-line. The original questionnaires are not retained, though they can be regenerated from the database data.

16.2 Case Report Forms (CRFs)

The data is being acquired on-line. The original questionnaires are not retained, though they can be regenerated from the database data.

STUDY DESIGN