Pimavanserin for Insomnia in Veterans with Posttraumatic Stress Disorder (PIP)

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Protocol (includes Statistical Analysis) – version approved 08.20.2021

Informed Consent Form – version approved 08.20.2021

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The Feasibility of Pimavanserin for Insomnia in Veterans with Posttraumatic Stress Disorder

Abbreviated Protocol – version 08/20/2021

Background Information:

Posttraumatic stress disorder (PTSD), a common and disabling condition in Veterans, is frequently accompanied by sleep disturbances that have grave consequences. In the general population, lifetime prevalence of PTSD is 8%.[1] Rates of PTSD in military Veterans are even higher, as nearly 25% of former Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) servicemembers are affected.[2] In PTSD patients, in general, sleep disturbances are the most common complaint, with 50-70% of patients having co-occurring sleep disorders.[3] The most frequently reported sleep-related symptom in patients with PTSD is insomnia: impaired initiation and maintenance of sleep affect an estimated 41% and 47% of patients, respectively.[4] Posttraumatic nightmares, which occur in 70-90% of patients, are associated with greater disability and suicide risk.[5] Patients with PTSD also frequently report disruptive nocturnal behaviors, such as running, kicking, and punching during sleep that result in violence and injury.[4,6]

Current interventions are inadequate for PTSD-related sleep disturbances, which further confound response to otherwise effective treatments of PTSD. For example, sleep complaints in patients with PTSD persist even after completion of an evidence-based psychotherapy for PTSD.[7] Cognitive Behavioral Therapy for Insomnia (CBT-I) is a first-line treatment, but requires a trained clinician, which is not always available, and has high drop-out rates.[3] Pharmacotherapies for insomnia, e.g., benzodiazepines, nonbenzodiazepine receptor agonists, atypical antipsychotics, and trazodone,[8] all cause daytime sleepiness and other undesirable side effects due to their non-selective mechanisms of action. The addiction potential of benzodiazepines and nonbenzodiazepine receptor agonists further limits their use, and pharmacotherapy for nightmares has limited efficacy.[9] Finally, antidepressants commonly prescribed for PTSD may exacerbate dream enactment behaviors in susceptible individuals.[10] Engagement in PTSD-specific psychotherapies could benefit from a pharmacological intervention that improves nocturnal sleep without causing adverse daytime effects and also avoids putative pathogenic risks associated with second-line pharmacotherapies used to treat PTSD and its specific symptoms, e.g., antidepressant and antipsychotic medications.

Pimavanserin, a 5-HT2A inverse agonist approved by the FDA for Parkinson's Disease psychosis, is a promising candidate for the treatment of insomnia and other sleep disturbances. 5-HT2A receptors are distributed in several brain regions known to regulate wakefulness, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep.[11] In healthy volunteers, pimavanserin increases the amount of slow wave sleep without causing daytime sleepiness.[12] Similarly, 5-HT2A receptor antagonists increase deep slow-wave sleep, decrease the duration of wake after sleep onset (WASO), and decrease the frequency of arousals and awakenings from sleep.[13] Furthermore, studies on patients with Parkinson's disease treated with pimavanserin 34mg reported improved sleep, with effects greatest in those with baseline sleep impairment and psychosis.[14]

In patients with PTSD, we propose that pimavanserin will improve insomnia and other sleep disturbances by promoting slow-wave sleep and improving sleep maintenance. While PTSD lacks a polysomnographic "signature," a meta-analytic review of 20 polysomnographic studies found increased stage 1 sleep and decreased slow wave sleep in patients with PTSD relative to those without PTSD.[15] Evidence that pimavanserin selectively increases slow-wave sleep without causing daytime sleepiness suggests it would improve insomnia symptoms without causing the next-day hangover and other unwanted side effects of current pharmacological treatments for insomnia.[12-14]

Other potential benefits of inverse agonism of 5-HT2A receptors include reduced intensity of nightmares, disruptive nocturnal behaviors, and overall PTSD symptomatology. 5-HT2A agonists are known to exert dream-like hallucinations that are similar in nature to affectively-laden and bizarre dreams.[16] 5-HT2A partial agonism may reduce the severity and intensity of nightmares in the same manner that it improves visual hallucinations. The pathophysiology of dream enactment behaviors reported by patients with PTSD are not completely understood but are similar in phenomenology to rapid eye movement sleep behavior disorder (RBD), a parasomnia known to be unmasked or exacerbated by serotonergic medications.[10] As a 5-HT2A inverse agonist, pimavanserin may be a safer option for these patients, but the effects of such a medication on

these disruptive nocturnal behaviors is unknown. Finally, as slow-wave sleep is required for memory consolidation and emotional processing,[17] pimavanserin's effects on sleep may improve overall PTSD severity.

To address the critical need for pharmacotherapy targeting sleep disturbances in patients with PTSD, we propose a clinical trial of pimavanserin 34mg at bedtime for 6 weeks for insomnia in adult male and female Veterans with PTSD. We first propose a pilot, feasibility study to ensure adequate recruitment and retention rates prior to conducting a randomized, double-blind, placebo-controlled trial. The primary endpoints of this initial study are the feasibility of recruitment, defined as the average number of subjects recruited into treatment per month, and the percentage of subjects who complete the protocol in its entirety. We also aim to preliminarily examine the effect of pimavanserin on sleep architecture as a possible therapeutic mechanism; the safety and tolerability of pimavanserin in our population; and the completion rates of key outcome measures of insomnia. Exploratory aims of this feasibility study are to preliminarily assess the change from baseline to week-6 in subjective and objective measures of insomnia; overall PTSD severity; disruptive nocturnal behaviors; and nightmare severity. The results of this study will inform on the feasibility of objective and subjective insomnia severity measures, as well as on the potential therapeutic mechanisms of pimavanserin on sleep, for a future double-blind, placebo-controlled trial.

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Purpose and Objectives

Primary Objectives:
To determine the feasibility of pimavanserin 34mg at bedtime for 6 weeks in Veterans with PTSD and insomnia, as measured by subject recruitment and retention rates.

Secondary Objectives:
1. Explore the effect of pimavanserin on the duration of slow wave sleep as a possible, therapeutic mechanism.
2. Preliminarily examine the tolerability and safety of pimavanserin 34mg at bedtime in non-elderly Veterans with PTSD and insomnia.
3. To investigate the completion rate of subjective and objective measures of insomnia to inform on their feasibility in a definitive trial.
4. Synthesize key outcome measures to assist with sample size estimation for a future, definitive trial.

Design/Procedure:

This is an open-label, feasibility, fixed-dose design of pimavanserin 34mg at bedtime for 6 weeks in Veterans with PTSD and insomnia. After an initial screening visit, participants will complete 7 days of actigraphy monitoring and sleep diaries. Screening and baseline polysomnograms will be completed prior to receiving the study drug. Participants will then receive a fixed dose of pimavanserin 34mg (the recommended dosing for adults) at bedtime for 6 weeks. A duration of 6-weeks was chosen based on the pivotal, phase 3 study of pimavanserin in patients with Parkinson ls Disease psychosis, where a statistically significant improvement in sleep was not seen until week-4 and week-6 of the study. Safety will be assessed via questionnaires completed in-person at the baseline, midpoint, and end of the study. Between in-person visits, safety will also be assessed via phone calls from a research coordinator using the same questionnaires. Actigraphy and sleep diaries will again be performed during the final week of the study. A final polysomnogram and exit visit will conclude the study.

Inclusion Criteria:
1. Male and female Veterans, aged 18-64;
2. Determined to meet criteria for current PTSD, as per a total score of ≥ 33 on the PTSD Checklist (PCL-5) and Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) criteria for PTSD;
3. At the initial enrollment visit, meets DSM-5 standards of chronic insomnia disorder, as follows: a. Complains of dissatisfaction with nighttime sleep in the form of difficulty falling asleep (subjective sleep onset latency ≥30 minutes), difficulty staying asleep (subjective time awake after sleep onset ≥30 minutes), and/or awakening earlier in the morning (≥30 minutes before scheduled wake time and before a total sleep time of 6.5 hours) than desired. b. Insomnia frequency of ≥3 times per week c. The duration of the insomnia complaint is ≥3 months d. Associated with complaint of daytime impairment;
4. Insomnia Severity Index total score ≥15 (moderate insomnia);
5. Willing and able to comply with all aspects of the protocol;
6. Willing to not start a concurrent behavioral or other treatment program for insomnia, PTSD, or other psychiatric disorders during the participation in the study.
7. It is required that women of child-bearing potential who are sexually active agree to use two methods of contraception for the duration of the study and extending to 30 days after the last dose of study drug. The two methods should include: 1) A barrier method (e.g., condom with spermicidal gel, diaphragm with spermicide, intrauterine devices, cervical cap), and 2) One other method, including hormonal contraceptives (e.g., oral contraceptives, injectable

contraceptives, contraceptive implant) or another barrier method.

Exclusion Criteria:

1. Current or a history of a primary psychotic disorder (i.e., schizophrenia, schizoaffective or bipolar disorder);
2. Active suicidal or homicidal ideation requiring crisis intervention;
3. Current moderate or severe alcohol or marijuana/cannabis use disorder, or other illicit use disorder of any severity;
4. A history of moderate or severe traumatic brain injury or other neurological illness (i.e., stroke, epilepsy, multiple sclerosis);
5. Caffeine use that is deemed excessive and is contributing to the insomnia per the opinion of the investigators (i.e. caffeinated beverages consumed after 18:00 3 times/week or more and/or that correlates with the timing of the insomnia complaints);
6. Tobacco use before bedtime that is contributing to the insomnia per the opinion of the investigators or that would interfere with completing an overnight polysomnogram;
7. Previous diagnosis of periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, narcolepsy, RBD, or other sleep disorders (except obstructive sleep apnea) that may confound, per the opinion of the investigators, the assessment of insomnia;
8. Previous diagnosis of moderate to severe obstructive sleep apnea (defined as an AHI ≥ 15);
9. Participants deemed to be at high risk of moderate to severe obstructive sleep apnea per the Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, and male Gender questionnaire (STOP-BANG). Subjects with a STOP-BANG score of ≥ 5 or STOP score of ≥ 2 plus (body mass index greater than 35 kg/m2 or male or neck circumference greater than 40 cm), are considered to be high-risk and will be referred to clinical treatment;
10. Participants identified as having moderate to severe obstructive sleep apnea during the screening polysomnogram. These participants will be referred to clinical treatment;
11. Periodic limb movement arousal index ≥15 or other sleep disorders captured during the screening polysomnogram that may confound, per the opinion of the investigators, the assessment and treatment of insomnia;
12. A prolonged QT interval, corrected for heart rate (QTc), at the screening electrocardiogram. A prolonged QTc is defined as 470 milliseconds for males and 480 milliseconds for females;
13. Engagement in an evidence-based psychotherapy for 1- week prior to enrollment that in the opinion of the investigators, may confound the assessment of insomnia (ex. CBT for insomnia);
14. Current evidence of clinically significant cardiac, respiratory, gastrointestinal, renal, neurological, hepatic, and/or chronic pain that in the opinion of the investigator(s) could affect the participant's safety or interfere with the study assessments;
15. Females who are breastfeeding or pregnant at screening;
16. Females of childbearing potential who are not practicing acceptable pregnancy prevention methods (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal or have been sterilized surgically);
17. Patients with cardiac conditions that in the opinion of the investigators may increase the risk of torsades de pointes and/or sudden death (ex. symptomatic bradycardia, congenital prolongation of the QT interval).

Permitted medications:

1. Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, and anticonvulsants (excluding strong CYP3A4 inhibitors or inducers) for 1 month prior to enrollment;
2. Medications taken for other medical conditions (i.e., hypothyroidism, diabetes) at doses stable for 1 month prior to enrollment.

Prohibited medications:

1. Hypnotics or other sedating medications that are being taken at bedtime for sleep (ex.

melatonin, melatonin receptor agonists, zolpidem, eszopiclone, benzodiazepines, trazodone, mirtazapine, low-dose tricyclics, antihistamines, opioids, muscle relaxants) must be discontinued for 1 week prior to enrollment;
2. Antipsychotics and antidepressants with known 5HT2A antagonist activity (ex. quetiapine, olanzapine, mirtazapine, trazodone) must be discontinued for 1 week prior to enrollment;
3. Strong CYP3A4 inhibitors (ex. itraconazole, ketoconazole, clarithromycin, indinavir) that may increase the levels of pimavanserin;
4. Patients taking strong CYP3A4 inducers (ex. rifampin, carbamazepine, phenytoin, St. John's wort) that may reduce the levels of pimavanserin;
5. Concurrent use of medications known to increase the QT interval, such as Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin).

Procedure:

Prior to the baseline visit, additional screening for the inclusion and exclusion criteria will take place over the phone and via chart review. If eligibility is likely, participants will be evaluated at a screening visit. See Table 1 for a schedule of visits and procedures, as well as the estimated times to complete visits and phone calls, and Table 2 for the subject reimbursement schedule.

At the screening visit, participants complete questionnaires and a clinical interview to 1) confirm the presence of insomnia symptoms of sufficient severity and frequency to meet criteria for chronic insomnia disorder per the DSM-5 and 2) confirm the subject meets DSM-5 criteria for current PTSD. Subjects will undergo a complete history, including sleep history; vital sign measurement (heart rate, blood pressure, temperature, respiratory rate, weight and height for body mass index, neck circumference); screening laboratory tests (complete metabolic panel, complete blood count with differential, magnesium level, urine toxicology screen, pregnancy test where appropriate); and baseline electrocardiograms (EKG).

For those subjects with comorbid obstructive sleep apnea, PAP device adherence is confirmed via data card download. If subjects have not completed a semi-structured or structured psychiatric diagnostic interview within 30 days of the initial screening phase, the Structured Clinical Interview for the DSM-5 (SCID-5) will be performed to assess for comorbid psychiatric conditions.

Eligible participants wear an actigraphy watch on their non-dominant wrist and complete nightly sleep diaries for 7 days prior to receiving the study drug. The actigraphy watch provides objective, home-based data to compare with subjective and polysomnographic measures of insomnia. To interpret the actigraphy data, and in accordance with proposed research standards for insomnia, participants will complete nightly sleep diaries while wearing the actigraphy watch. Specifically, the Spectrum PRO (Patient Reported Outcome) actigraphy watch has the capability to remind participants to complete the sleep diary up to twice daily at a prespecified time set by the investigator. Summary variables generated from actigraphy include total sleep duration, sleep efficiency, and number of awakenings per night. The sleep diary collects self-reported information on bed and wake times, sleep onset, time awake after sleep onset, naps, actigraphy removal or other events.

Subjects then complete two consecutive polysomnograms prior to receiving the study drug. The purpose of the first polysomnogram is to screen out participants with confounding and untreated obstructive sleep apnea or periodic limb movement disorder, as well as to prevent the "first night effect" from confounding the assessment of insomnia and sleep architecture. Attended polysomnography is performed overnight at the MEDVAMC utilizing the standard montage recommended by the American Academy of Sleep Medicine (AASM). Subjects sleep in private rooms with video monitoring. Polysomnogram tracings are scored according to current AASM standards.

Subjects diagnosed with moderate to severe obstructive sleep apnea during the screening polysomnogram may undergo PAP titration, where possible, and are referred for clinical treatment. Subjects with sleep disorders that may, per the opinion of the investigators, confound the assessment and treatment of insomnia (e.g., periodic limb movement disorder, suspected narcolepsy) are excluded and referred to clinical treatment.

Following the baseline polysomnogram, subjects start open-label, fixed-dose pimavanserin 34mg at bedtime for 6 weeks. Although pimavanserin is usually taken in the daytime, we predict the medication half-life (57 hours) is sufficiently long enough to enable nighttime dosing. Safety and

medication adherence will be evaluated in-person via questionnaire at week-3 (midpoint visit) and week-6 (closeout visit). For the remaining weeks, safety and adherence will be assessed via weekly phone calls. To monitor treatment progress, measures of insomnia, PTSD severity, and mood are performed at the 3-week, treatment midpoint visit.

During the final week of the treatment phase, actigraphy and sleep-diary measures are repeated to compare to pre- treatment values. Participants will also complete a post-treatment polysomnogram to assess the effects of pimavanserin on the duration of stage 3 sleep from baseline to week-6 post-drug and to compare objective and subjective measures of insomnia. Where applicable, PAP data card download will be performed to re-assess adherence. At the exit visit, subjects will again complete questionnaires assessing insomnia severity, PTSD, and mood. At this time, pimavanserin will be discontinued, and subjects will be referred for clinical care if indicated. Subjects receive a follow up phone call 2 weeks after pimavanserin's discontinuation to re-assess subject safety and to refer for clinical care if indicated.

Sample Size/Data Analysis:

Sample Size

We hypothesize that pimavanserin 34mg at bedtime for 6 weeks is a feasible intervention for the treatment of insomnia symptoms in Veterans with PTSD. Specifically, we hypothesize that, after exits for exclusion criteria, a total of 6 participants will be enrolled into open-label treatment during the recruitment period, and that at least 75% of these participants (approximately n=5) will complete the study protocol. We estimate that 6 subjects enrolled into treatment will provide preliminary information on the feasibility of the protocol given budgetary constraints.

Data Analysis

Primary Endpoint 1. The feasibility of the protocol, as measured by the average monthly rate of subjects recruited into treatment and the percentage of participants completing the protocol in its entirety.

Secondary Endpoint 1. Mean change in duration of stage 3 sleep from baseline to week-6 polysomnogram; 2. The number of subjects who discontinue the protocol due to adverse effects; 3. Completion rates of key outcome measures, including sleep diaries, actigraphy, and attended polysomnography.

Statistical analyses will be conducted with an alpha level of 0.05. We will derive point estimates and 95% confidence intervals for the quantities of interest, such as the recruitment rate, retention rate, the mean change in duration of stage 3 sleep from baseline to week-6, and rates of treatment discontinuation and completion. Repeated measures analysis and paired t-tests using baseline and subsequent scores will be used to assess for within patient time effects. The underlying assumptions of all analytic procedures will be carefully examined. If violation of any assumption is detected, we will implement alternative robust procedures, such as the Wilcoxon's signed-rank test for the change from baseline to endpoint. As appropriate, McNemar's test or its generalized version will be used to compare categorical variables.

Consent Procedures:

All recruitment materials, consent forms, and Health Insurance Portability and Accountability Act of 1996 form will be approved by the MEDVAMC Research and Development Committee and the IRB prior to the beginning of the protocol. The study personnel will have certification of Human Subjects Research Training. Informed consent will be obtained prior to conducting any study procedures.

Recruitment will occur via referral from staff members and services at the MEDVAMC. The referring staff members will ask eligible subjects if they are interested in hearing more about this study. If the veteran agrees or expresses interest in the study,the PI or study coordinator will approach or contact the subject to explain, in detail, the characteristics of the study, including potential benefits and risks. Veterans will receive a brochure summarizing this information and describing the way in which Veterans may contact the research team. Brochures that describe the study and provide contact information for the research team will also be distributed to clinics and

staff members to be provided to interested veterans, who then may contact the PI or research coordinator.

We will also review the charts of patients enrolled in clinics at the Michael E. DeBakey Medical Center for eligibility, including the PTSD clinic, General Mental Health Clinic, post-deployment clinic, and sleep medicine clinics. Potentially eligible participants will be mailed a letter. If we do not receive a contrary response within 14 days, we will contact the patient by phone to inform them of the study. By pre-screening patients in CPRS, the research team can focus recruitment efforts on Veterans who are more likely to qualify for the study. Pre-screening involves reviewing the patient's medical record to check for inclusion/exclusion criteria. (Veterans who are referred or recruited through flyers may be pre-screened through CPRS chart review or over the phone. If pre-screening over the phone, a verbal consent script will be read before asking any questions).

VA RESEARCH CONSENT FORM

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: MELISSA JONES **VAMC:** _____

H-45799 - THE FEASIBILITY OF PIMAVANSERIN FOR INSOMNIA IN VETERANS WITH POSTTRAUMATIC STRESS DISORDER

MAIN CONSENT

Concise and Focused Presentation

PURPOSE

The purpose of this study is to see if pimavanserin 34mg at bedtime for 6 weeks is an acceptable and practical treatment for insomnia in Veterans with PTSD. We also want to learn whether pimavanserin increases deep sleep.

NUMBER OF PEOPLE PARTICIPATING IN THE STUDY This study will include men and women between the ages of 18 and 64 years old. Approximately 6 subjects will enter treatment and receive pimavanserin 34mg at bedtime for 6 weeks.

LOCATION OF THE STUDY All of your study procedures will be completed at the address: 2002 Holcombe Blvd, Houston, Texas 77030

ALTERNATIVES There may be other medications or alternative treatments for treating your condition. Please speak to your study doctor for other options.

SUMMARY OF THE RESEARCH The study consists of a screening visit (visit 1); a pre-treatment phase, which includes wearing an actigraphy watch and completing a sleep diary at home for 1 week, a screening overnight sleep study (visit 2), and a pre-treatment overnight sleep study (visit 3); a treatment phase, which includes weekly follow up phone calls and an in-person, mid-point follow up visit (visit 4); a post-treatment phase, which includes wearing an actigraphy watch and completing a sleep diary at home for 7 days during the last week of taking the drug, a final overnight sleep study (visit 5), and in-person exit interview at week-8 (visit 6); and a follow up phone call 2 weeks after stopping pimavanserin.

RISKS There are risks associated with pimavanserin, including changes to the rhythm of the heart, confusion, swelling, and allergic reactions. There are risks associated with the study procedures (wearing the actigraphy watch, electrocardiograms, sleep studies) and being asked personal questions. The potential risk section of the consent form will cover these in detail.

LENGTH OF PARTICIPATION

The total length of the study is 10 weeks (approximately 40 hours total, including all visits, sleep studies, phone calls, and sleep diary nights). You may discontinue from the study at any time for any reason and the participation is voluntary.

POTENTIAL BENEFITS The benefits of participating in this study is that your insomnia may improve. We may learn whether the study drug improves sleep in Veterans with PTSD, which may help others. The tests provided may help you learn about your general health. However, you may receive no benefit from participating.

Background

INTRODUCTION

You are invited to participate as a volunteer in a clinical research study. Your participation in this study is voluntary. You have the right to decide not to participate in it or to withdraw at any time without penalty or loss of benefits. During the study, you will be informed as soon as possible of any new information on

the study drug that might affect whether you want to continue participating in the study. The study doctor or a designated member of the study staff can also decide to withdraw you from the study, without your consent, if they judge that it would be better for your health, you do not follow the requirements of the study, or for any other reason. At the time of withdrawal from the study, you may be asked to undergo additional tests for your safety.

In total, there will be approximately 6 volunteers participating in this study, who will be recruited at the Michael E. DeBakey VA Medical Center. This Informed Consent Form is intended to give you an overview of this clinical research study and what it involves. It may contain words that you do not understand. Please ask the study doctor or a member of the study staff to explainany words or information that you do not understand.

If you decide to participate in this study, you will be asked to sign and date this Informed Consent Form. This will confirm that you have been informed of the nature of the study and what it involves but does not take away any of your legal rights.

GENERAL DESCRIPTION OF THE RESEARCH STUDY

This study involves a drug called pimavanserin, which is being studied as a potential treatment for insomnia in Veterans with Posttraumatic Stress Disorder (PTSD).

Insomnia is defined as difficulty falling or staying asleep. Insomnia may cause daytime fatigue, low energy, difficulty concentrating, and/or mood problems.

PTSD can occur in people who have experienced or witnessed a traumatic event, such as a natural disaster, war/combat, or other forms of violence. People with PTSD have intense, disturbing thoughts and feelings related to their experience that last long after the traumatic event has ended. They may relive the event through flashbacks or nightmares; they may feel sadness, fear or anger; and they may feel detached or estranged from other people. People with PTSD may avoid situations or people that remind them of the traumatic event, and they may have strong negative reactions to something as ordinary as a loud noise or an accidental touch.

Over a third of people with PTSD experience insomnia, and insomnia can worsen the symptoms of PTSD.

Pimavanserin is thought to have an effect on sleep. It has been approved by the US Food and Drug Administration (FDA) for the treatment of psychosis in Parkinson's Disease, but it is not known whether it may treat insomnia in Veterans with PTSD.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: MELISSA JONES **VAMC:** _____

H-45799 - THE FEASIBILITY OF PIMAVANSERIN FOR INSOMNIA IN VETERANS WITH POSTTRAUMATIC STRESS DISORDER

This research study is funded by the Michael E. DeBakey VA Medical Center Seed and Bridge Award ProgramThe Principal Investigator MELISSA JONES for this study:receives financial support for the conduct of the research project from the Michael E. DeBakey VA Medical Center Seed and Bridge Award Program

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: MELISSA JONES **VAMC:** _____

H-45799 - THE FEASIBILITY OF PIMAVANSERIN FOR INSOMNIA IN VETERANS WITH POSTTRAUMATIC STRESS DISORDER

Purpose

The goals of this study are:

1. To determine if pimavanserin 34mg at bedtime is a practical and tolerated treatment for insomnia in Veterans with PTSD;
2. To see if the study procedures, including the visits and sleep studies, are practical and tolerated by Veterans with PTSD and insomnia;
3. To determine the number of Veterans that qualify for the study and complete the study;
4. To better understand the types of sleep problems that are experienced by Veterans with PTSD and insomnia;
5. To see if pimavanserin improves deep sleep.

This study will provide important information on how to best design a larger study testing whether pimavanserin is an effective treatment for insomnia in Veterans with PTSD.

The study is divided into several phases. The first phase is a screening phase, where you will not receive any study drug, but you will work with the study doctor (Principal Investigator) and the study staff at the site to evaluate your disorder and make sure you meet all the study criteria to receive the study drug.

If you qualify to continue in the study, you will enter the 1-week pretreatment phase, where you will wear an actigraphy watch and complete a sleep diary at home for 7 days. This is so we can better understand how your sleep is at home before starting pimavanserin.

The next phase is a screening polysomnogram (sleep study), which makes sure you do not have other sleep problems that are causing insomnia and to help you get used to being in the sleep lab.

You will then return to the sleep lab for a baseline, or pre-treatment, sleep study before starting the drug, so we can see how your sleep is structured and how much deep sleep you have before starting treatment.

During the treatment phase, you will take pimavanserin 34mg at bedtime for 6 weeks. During the 6th week of treatment, you will again complete a sleep diary and wear the actigraphy watch to see how pimavanserin changes your sleep at home. You will also repeat a sleep study to see how pimavanserin changes your sleep in the sleep lab.

Procedures

A total of 6 subjects at 1 institutions will be asked to participate in this study.
You will be one of approximately 6 subjects to be asked to participate at this location.

The small sample size is included in the consent form, although safeguards are in place to prevent loss of confidentiality.

The research will be conducted at the following location(s):
Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center.
Before you decide to be in this research study, you must be given the chance to ask questions. You will need to sign and date this informed consent document, and you then will be given a copy to take home with you.

If you agree to take part in this study, the following will occur:

Visit 1 Screening Phase (4 to 5 hrs)
The purpose of this visit is to find out if you should be in the study. After this visit, you may be asked to return or you may be told that you should not be in the study. The following will happen at this visit:
*You will be asked to complete questionnaires about how you are feeling, how you are sleeping, and your past medical and psychiatric history
*You will be asked questions about the severity of your insomnia, PTSD, medical history, psychiatric history, and medications.
*You will have blood samples drawn and tested to check your kidney function, liver function, salt levels in your blood (including magnesium and potassium). The total amount of blood during this visit will be approximately 30 mL (6 teaspoons).
*You will need to provide a urine sample for urine drug testing.
*If you are a woman of childbearing potential, a urine pregnancy test will be performed to confirm you are not pregnant before receiving any study drug.
*You will be measured for height and weight and have your vital signs taken (blood pressure, pulse rate, temperature, respiratory rate, weight, height, neck circumference).
*You will have an ECG, which tests the functions of your heart.
*Your study doctor will speak with you about any medications you can and cannot take while in the study, including any over the counter medication, vitamins, or herbal remedies which may not be allowed during the course of the study.
*If you have a history of sleep apnea, we will download your data card to see how often you are using your breathing device and if it is working properly.

At this time, if you qualify for the study, we will review how to perform a sleep diary, introduce you to the actigraphy watch, and schedule your sleep study.

During the Pre-Treatment Phase of the study, the following will occur:

*You will wear an actigraphy watch on your wrist all day for 7-days. The actigraphy watch is a wristwatch that collects real-time information on activity levels, light, and sleep.
*You will complete a sleep diary for 7 days, which allows us to interpret and verify the data from the actigraphy watch (for example, so we know when you were actually asleep);
*The actigraphy watch will send you two reminders per day asking if you completed your sleep diary

You will come back a week after the screening visit to complete a screening sleep study (Visit 2).

Visit 2: Screening sleep study (9 hours)
The sleep study requires that you sleep overnight in the sleep laboratory. Arrival time is 9 PM and the end time is 6 AM, but you will be allowed to sleep in longer if you need to.
Before going to sleep, you will:
*Hand-in your sleep diary from the past week;
*Download the data from the actigraphy watch.
During the sleep study, you will have:
*Your oxygen and breathing levels monitored
*Electrodes placed on your scalp to monitor your sleep;
*Electrodes on your arms and legs to monitor your muscle activity while you sleep;
*Electrodes on your chest to monitor your heart rate;
You will be video-taped to see if you have any abnormal behaviors or movements while you sleep

If you are found to have moderate or severe sleep apnea or another sleep condition that may interfere with the assessment of insomnia, you will be referred for clinical care. However, to help get you treated for sleep apnea as quickly as possible, the study staff may test out a breathing machine with you during this sleep study.

After this visit, you may be asked to return, or you may be told that you should not be in the study. If you qualify, you will return within 1 to 3 days for the baseline (pre-treatment) sleep study (visit 3).

Visit 3:Baseline sleep study (10 hours)
The sleep study requires that you sleep overnight in the sleep laboratory. Arrival time is 8 PM and the end time is 6 AM, but you will be allowed to sleep in longer if you need to. Before going to sleep, you will meet with a research staff member in order to:
*Complete questionnaires about your sleep, PTSD, and mood
*Review your medications and other medical history;
*Receive the first 3 weeks of pimavanserin 34mg at bedtime

During the sleep study, you will have:
*Your oxygen and breathing levels monitored

*Electrodes placed on your scalp to monitor your sleep;
*Electrodes on your arms and legs to monitor your muscle activity while you sleep;
*Electrodes on your chest to monitor your heart rate;
You will be video-taped to see if you have any abnormal behaviors or movements while you sleep

Treatment Phase:
From this point forward, you will enter the treatment phase. During this time, you will take one tablet of the study drug (pimavanserin 34mg at bedtime) every night before bedtime. If you have difficulty tolerating the study drug between visits you will contact the study staff. You will also receive phone calls in-between visits to check how you are tolerating the medication, as described below.

Phone Call #1 and #2 (Week 1 and Week 2 of taking study drug):
In between the baseline sleep study (visit 3) and the next visit (mid-point check in or visit-4), you will receive a phone call weekly from study staff. The phone calls will occur at week-1 and week-2 of taking the drug and will last around 20 minutes.

During these phone calls, staff will:
*Ask you about any symptoms or changes and any medications you have taken other than the study drug since your last visit. You will need to keep track of all drugs, including drugs that are over the counter, prescribed, vitamins, or herbal remedies, and report them to the study staff at each visit.
*Ask you about any side effects from the medication
*Ask you questions about your sleep, PTSD symptoms, and how you are feeling
*Check to see if you are taking the medication
*Schedule you for Visit 3.

Visit 4 (Mid-point check in) (1.5-2 hrs)
During this visit, you will return your study drug bottles (used and unused) to the study site.
The study doctor and study staff will:
*Ask you about any symptoms or changes and any medications you have taken other than the study drug since your last visit. You will need to keep track of all drugs, including drugs that are over the counter, prescribed, vitamins, or herbal remedies, and report them to the study staff at each visit.
*Ask you about any side effects from the medication.
*Ask you about sleep, psychiatric, and medical symptoms.
*Check your vital signs (heart rate, blood pressure, respiratory rate, temperature, weight, height)
You will also complete questionnaires about your sleep and psychiatric symptoms.
If the study doctor approves, you will be given another 3-week supply of the study drug, and the staff will schedule you for a final sleep study (Visit 5).

From this point forward, you will continue to take one tablet of the study drug (pimavanserin 34mg) every night before bedtime. If you have difficulty tolerating the study drug between visits or phone calls, you will contact the study staff.

Phone Call #3 and #4 (Week-4 and Week-5 of taking study drug):
In between the mid-point check in (Visit 4) and the next visit (the final sleep study or Visit 5), you will receive a phone call weekly from study staff. The phone calls will occur at week-4 and week-5 while taking the drug and will last around 20 minutes.
During these phone calls, staff will:
*Ask you about any symptoms or changes and any medications you have taken other than the study drug since your last visit. You will need to keep track of all drugs, including drugs that are over the counter, prescribed, vitamins, or herbal remedies, and report them to the study staff at each visit.
*Ask you about any side effects you may have from the medication
*Check to see if you are taking the medication
*Ask you about sleep, psychiatric, and medical symptoms.
*Remind you to complete sleep diaries daily for 1-week and wear the actigraphy watch during week-5 of taking the study drug.
*Schedule you for the final sleep study (Visit 5).

Visit 5: Final sleep study (9 hours)
The sleep study requires that you sleep overnight in the sleep laboratory. Arrival time is 9 PM and the end time is 6 AM, but you will be allowed to sleep in longer if you need to.
During the sleep study, you will have:
*Your oxygen and breathing levels monitored
*Electrodes placed on your scalp to monitor your sleep;
*Electrodes on your arms and legs to monitor your muscle activity while you sleep;
*Electrodes on your chest to monitor your heart rate;
You will be video-taped to see if you have any abnormal behaviors or movements while you sleep.
You will take your bedtime dose of pimavanserin as regularly scheduled.

You will continue to take pimavanserin 34mg at bedtime until the final visit (visit-6), which will occur either the next day in the morning or within 3 days of the final sleep study.

Visit 6 (Closeout visit) (3 hours):
During this visit, the study doctor and study staff will:
*Ask you to hand-in your sleep diary from the past week;
*Download the data from the actigraphy watch;
*Ask you about any symptoms or changes and any medications you have taken other than the study drug since your last visit. You will need to keep track of all drugs, including drugs that are over the

counter, prescribed, vitamins, or herbal remedies, and report them to the study staff at each visit.
*Ask you about any side effects from the medication.
*Ask you about sleep, psychiatric, and medical symptoms.
*Ask you to complete questionnaires about how you are feeling, your PTSD and sleep symptoms.
*Check your vital signs (heart rate, blood pressure, respiratory rate, temperature, weight, height)
You will be asked to return your study drug bottles (used and unused) to the study site.
If you have a history of sleep apnea, we will download the data card from your breathing machine to see how often you have been using it and if it is working properly

Once the treatment phase is over, you will no longer have access to pimavanserin for the purposes of the study and can discontinue it.

If you would like to continue to be treated for insomnia and/or PTSD, you will be referred for appropriate clinical care.

Phone call #5:
2-weeks after your closeout visit, you will receive a phone call from study staff lasting approximately 30 minutes and asking you about how you are feeling. You will be asked about sleep, psychiatric, and medical symptoms.
Although follow up visits are often part of the standard of medical care, the two-week post study phone call (required of all subjects after study drug use is completed for the trial) is being done for the purpose of the study only and is not part of routine care. The purpose of this call is to evaluate your overall health after an adequate time has passed once you completed treatment with the study drug. It is important that you still complete this visit as part of the overall study requirements and report any new symptoms, if any, during that period. If you would like to continue to be treated for insomnia and/or PTSD, you will be referred for appropriate clinical care.

Clinically Relevant Research Results

The results of the screening blood tests, urine drug screen, and EKG will be available in your medical record and can be accessed for clinical care. If you are diagnosed with sleep apnea during the screening sleep study and authorize the study staff to titrate you on a breathing machine, the diagnosis of sleep apnea and the recommended settings for the machine may be entered into your medical records for clinical use.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

Sharing and Future Research Studies with Identifiable Private Information
Your identifiable private information collected as part of this research, even if the identifiers are removed, will not be used or distributed for future research studies.

Sharing and Future Research Studies with Identifiable Biospecimens
Your identifiable biospecimens collected as part of this research, even if the identifiers are removed, will not be used or distributed for future research studies.

Confidentiality
The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology

findings, etc.

- Specific information concerning alcohol abuse
- Specific information concerning drug abuse
- Specific information concerning sickle cell anemia
- Specific information concerning HIV
- Specific information concerning psychiatry notes
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Full Social Security #
- Partial Social Security # (Last four digits)
- Identifiable biospecimens
- Other: Your social security number will be collected in order to access you medical record. We will also collect your phone numbers and address(es) in order to contact you. Your date of birth will be used to determine your age, which will be used for the study analysis. None of these identifiers will leave the Michael E. DeBakey VA Medical Center. The purpose of collecting information covered under 38 U.S.C. 7332 is to conduct scientific research and no personnel involved in this study will identify, directly or indirectly, any individual patient or subject in any report of such research.

Use or Disclosure Required by Law

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality will not be used to prevent disclosure of child abuse, neglect, or harm to self or others to state or local authorities.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts

THE FOLLOWING ARE THE POTENTIAL RISKS OR SIDE EFFECTS OF TAKING PART IN THIS STUDY

Potential side effects of pimavanserin:

Please note that pimavanserin is approved by the Food and Drug Administration for the treatment of psychosis in patients with Parkinson¿s Disease. Psychosis means patients have difficulty telling the difference between what is real and what is in their imagination. Most of the information about the safety of pimavanserin comes from studies in elderly subjects (average age of 71 years old) with Parkinson¿s Disease and psychosis.

The most common side effects of pimavanserin are: Nausea, constipation, peripheral edema (swelling in legs), gait disturbance (problems with walking), hallucination (seeing, hearing, smelling, or feeling things that are not there), confusion, urinary tract infection, and fatigue.

Pimavanserin increases the QT interval, which is a change in the heart rhythm that increases the time it takes for the heart to recharge and beat again. If this heart rhythm becomes too long, it may increase the risk of serious, abnormal heart rhythms that may cause fainting, seizures, and even sudden death. Because of these risks, pimavanserin should not be taken by patients with a history of a prolonged QT interval, abnormal heart rhythms, and certain salt imbalances in the blood.

Other drugs that may increase the QT interval may not be taken in combination with pimavanserin. Medications that are prohibited during the study because they prolong the QT interval are: Quinidine, procainamide, disopyramide; amiodarone, sotalol, ziprasidone, chlorpromazine, thioridazine; gatifloxacin, moxifloxacin.

Certain medications may increase the breakdown of pimavanserin in the body, making the medicine less effective. Medications that increase the breakdown of pimavanserin are prohibited during the study. These drugs include: itraconazole, ketoconazole, clarithromycin, indinavir.

Certain medications may prevent the breakdown of pimavanserin in the body, which may cause levels in the body to be too high and even toxic. Medications that prevent the breakdown of pimavanserin are prohibited during the study. These drugs include: rifampin, carbamazepine, phenytoin, St. John's wort.

If you are taking any of these medications, please inform the Principle Investigator or research staff immediately. Also, you must inform the principle investigator or research team of any changes to your medications, even if taken over the counter, or if you develop any new health conditions throughout the trial.

Allergic reaction risks: With any medication, there is a small but real risk of allergic reactions that can be fatal. These reactions usually start shortly after taking the study drug. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are: Skin itching, redness or rash; difficulty breathing; dizziness and fainting; swelling around the mouth, throat or eye; a fast pulse; and/or sweating.

Blood collection risks: Pain, bruising, swelling at the site of blood collection, fainting, and very rarely, nerve damage or infection at the needle insertion site may occur with blood draws

Electrocardiogram risks: Electrocardiogram(s) (recording of the electrical activity of the heart or ECG) will be done during this study. Electrodes (small sticky patches) will be placed on your chest. There is no pain or risks related to an ECG. However, removing the electrodes may cause skin irritation. In some areas, it may be necessary to shave a small spot of body hair so the adhesive patches can be properly placed on your body.

Actigraphy watch risks: The watch may cause irritation to the skin or rash.

Sleep study risks: Electrodes (small sticky patches) will be placed on your body and head. However, removing the electrodes may cause skin irritation. In some areas, it may be necessary to shave a small spot of body hair, so the adhesive patches can be properly placed on your body. The electrodes, nasal cannula, oximeter and respiratory belts used to monitor sleep and breathing may be mildly uncomfortable and could potentially interfere with normal sleep. However, apart from the possibility of poor-quality sleep, no other important risk is anticipated. You may be sleepier than usual after participating, but you will have the opportunity to sleep without the electrodes and other monitors as long as you would like before driving home.

Risks associated with pregnancy and lactation:
There is not enough information to determine whether pimavanserin is safe to take during pregnancy or breast-feeding. It is unknown whether pimavanserin causes birth defects or miscarriages when taking during pregnancy in humans. There is no information on the amount of pimavanserin that enters breast

milk, what happens when the baby is exposed to pimavanserin through breast milk, or whether pimavanserin effects milk production. When animals were given high doses of pimavanserin during pregnancy and breast feeding in research studies, no birth defects occurred, but it was toxic to the pregnant animal, and exposed infants were less likely to survive or gain weight.
Because the risks of taking pimavanserin during pregnancy and breast feeding are unclear, you are required to avoid becoming pregnant while participating in this study. If you are not surgically sterile (for example, you did not have your ovaries or uterus removed), or if you are not post-menopausal (you did not stop having periods for at least 12 months), you must abstain from sexual activity or use acceptable methods of birth control to avoid pregnancy throughout the study and for 30 days after the last dose of the study drug. You must immediately inform the research staff or principle investigator if you may be pregnant or have stopped using acceptable birth control methods.

Personal Questions Risks: You will be asked questions about personal issues during this study. There may be questions about your psychiatric and medical history, upsetting events that may have occurred in your past, whether you are having thoughts of suicide, etc. These types of personal questions may make some subjects uncomfortable.

You must tell your study doctor right away if you have any thoughts about hurting yourself. If you are having thoughts of suicide, call the study doctor at the telephone number listed on the first page of this form. If you feel like you are in a crisis, you can call 911 and/or a Nationwide Suicide Hotline that is answered 24 hours a day with a skilled, trained counselor. One example is the National Suicide Prevention Lifeline at 1-800-273-TALK (8255).

OTHER IMPORTANT INFORMATION If you experience any new symptoms, contact the study doctor at the telephone number on the consent form. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study.

There may be unknown risks or discomforts involved. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits
The benefits of participating in this study may be: The benefits of participating in this study is that your insomnia may improve. We may learn whether the study drug improves sleep in Veterans with PTSD, which may help others. The tests provided may help you learn about your general health. . However, you may receive no benefit from participating.

Alternatives

The following alternative procedures or treatments are available if you choose not to participate in this study: You are being asked to take part in this study to help further our understanding of whether pimavanserin improves sleep. However, there may be other medications or treatments for treating your condition. Talk to the study doctor or your general practitioner about what those options may be to ensure you understand all the options for your condition..

Subject Withdrawal from a Study

You are encouraged and have the right to ask questions at any time concerning potential and /or known risks of this study. Your participation in this study is voluntary. You have the right to decide not to participate in it or to withdraw at any time without penalty or loss of benefits. The study doctor will inform you of any new significant information, when it becomes available, which may affect your willingness to continue to participate in this study. This new information may mean that you can no longer participate in this research. It could also mean that the sponsor may suspend or prematurely end the study. If this occurs, the person(s) supervising the research will stop your participation.

Investigator Withdrawal of Subject from a Study

The investigator or sponsor may decide to stop you from taking part in this study at any time. You could be removed from the study for reasons related only to you (for example, if you move to another city, if you do not take your study medication, or if you have a serious reaction to your study medication) or because the entire study is stopped. The sponsor, investigator, Food and Drug Administration, or Institutional Review Board may stop the study at any time.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If you decide to withdraw from the study, or if the study doctor or a study designee decides to withdraw you from the study for safety reasons, for not following the requirements of the study, or for any other reason, the data collected up to the time of your withdrawal from the study remains part of the study database and may not be removed.

Subject Costs and Payments

You will not be asked to pay any costs related to this research.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: MELISSA JONES **VAMC:** _____

H-45799 - THE FEASIBILITY OF PIMAVANSERIN FOR INSOMNIA IN VETERANS WITH POSTTRAUMATIC STRESS DISORDER

Screening Visit (Visit 1) study compensation:
*Travel pay: $10
*EKG/Vitals/blood draw: $20
*Questionnaires: $10
*Clinical Interview: $10
*Total: $50

Screen sleep study (Visit 2):
*Travel pay: $40
*Sleep study: $90
*Sleep diary: $30
*Actigraphy: $30
*Total: $190
(You will only be compensated for this visit after the actigraphy watch is returned)

Baseline sleep study (Visit 3):
*Travel pay: $40
*Questionnaires: $10
*Sleep study: $90
*Total: $140

Midpoint Treatment (Visit 4):
*Travel pay: $10
*Questionnaires and interview: $10
*Vitals: $10
*Total: $30

Final sleep study (Visit 5):
*Travel pay: $40
*Sleep study: $90
Total: $130

Closeout visit (Visit 6):
*Travel pay: $10
*Vitals: $10
*Questionnaires: $10
*Actigraphy return: $30
*Sleep diary: $30

*Total: $90
(You will only be compensated for this visit after the actigraphy watch is returned)

You will be compensated via direct deposit after each visit. If you complete all visits and procedures of the study, you can make up to $630.

Research Related Injury

SAFETY INSTRUCTIONS, COMPENSATION, CONFIDENTIALITY, AND VOLUNTEERS RIGHTS
(a) Safety instructions
It is important that you respect all restrictions since it could affect the study results or haveconsequences on your safety. If you do not follow these restrictions, you should tell the study staff as soon as possible.

Before taking any medicine or before any medical procedure (for example, surgery), it is recommended that you tell your regular doctor, pharmacist and/or dentist that you are taking part in a clinical research study on a study drug called pimavanserin (trade name Nuplazid) that is being developed for the treatment of insomnia in PTSD.

Upon leaving the clinical facility, if you feel dizzy or drowsy, you should not perform activities requiring mental alertness, judgment and physical coordination such as driving or operating machinery until you feel secure and safe to do so.
You should not share study drugs and should keep them out of the reach of children.

(b) Study-related injury
In case of injury or disease related to your participation in this study, you will receive appropriate medical care.

In no way does signing this consent form waive your legal rights nor does it relieve the investigators, Sponsor or involved institutions from their legal and professional responsibilities.
Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: MELISSA JONES **VAMC:** _____

H-45799 - THE FEASIBILITY OF PIMAVANSERIN FOR INSOMNIA IN VETERANS WITH POSTTRAUMATIC STRESS DISORDER

Women of Childbearing Potential

It is possible that the medicines used in this study could injure a fetus if you or your partner becomes pregnant while taking them. Because of the potential risks involved, you or your partner should not become pregnant while you are participating in this study.

If you are sexually active or become sexually active and can get pregnant or can get your partner pregnant, you must agree to use the following form of birth control every time you have sex and for (1) months afterwards.

It is required that all women of childbearing potential who are sexually active use two methods of contraception for the duration of the study and 30 days after the last dose of study drug. The two methods for women of childbearing potential should include:

One barrier method, such as diaphragm with spermicidal gel, condom with spermicidal gel, cervical caps or intrauterine devices (IUDs) placed for at least four weeks before sexual intercourse;

AND one additional method. The other method could include hormonal contraceptives, such as oral contraceptive, injectable contraceptives, contraceptive implant, or second barrier method as listed above.

The Investigator will discuss the risks and benefits of each of the different forms of contraception available to you in an effort to provide you with the information necessary for you to make a fully informed decision as to which form of contraception you will use.

There is specific information available about the risks of each form of contraception and there is also information available about the "failure rates" of each form.

Should you become pregnant while on this study, you must immediately notify the study personnel.

The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can choose not to provide this information.

VA RESEARCH CONSENT FORM

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: MELISSA JONES **VAMC:** _____

H-45799 - THE FEASIBILITY OF PIMAVANSERIN FOR INSOMNIA IN VETERANS WITH POSTTRAUMATIC STRESS DISORDER

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, MELISSA JONES, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: MELISSA JONES at 713-794-8907 ext. 24747 during the day and 412-977-3389 after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.
Under Federal Regulations, the VA Medical facility shall provide necessary medical treatment to you as a research subject injured as a result by participation in a research project approved by a VA Research and Development Committee and conducted under the supervision of one or more VA employees. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. If you sustain an injury as a direct result of your study participation, medical care will be provided by the Michael E. DeBakey VA Medical Center. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. You do not waive any liability rights for personal injury by signing this form.

You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled. Your participation will not affect the way you now pay for medical care at the VAMC. If you would like to verify the validity of the study and authorized contacts, you may speak with the Michael E. DeBakey Veterans Affairs Medical Center Research Office at 713-794-7918 or 713-794-7566.

Department of Veterans Affairs

VA RESEARCH CONSENT FORM

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: MELISSA JONES **VAMC:** _____

H-45799 - THE FEASIBILITY OF PIMAVANSERIN FOR INSOMNIA IN VETERANS WITH POSTTRAUMATIC STRESS DISORDER

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Investigator or Designee Obtaining Consent	Date
Witness	Date