Cover Page

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

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UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT AND HIPAA AUTHORIZATON FORM

Protocol Title:	Three Approaches to Maintenance Therapy for Chronic Insomnia in Older Adults
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Why am I being asked to volunteer?

This consent form describes a research study and what you may expect if you decide to participate. You are encouraged to read this consent form carefully and to ask the person who presents it any questions you may have before making your decision whether or not to participate. You are being asked to participate in this research study because you have persistent trouble sleeping (insomnia) at night. This form describes the known possible risks and benefits of the study. You are completely free to choose whether or not to participate in this study.

You are being invited to participate in a research study. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

The purpose of this study is to determine whether insomnia symptoms can be managed with smaller amounts of medication than are commonly used among those who are treated with zolpidem.

How long will I be in the study?

Your active participation will last for a maximum of 54 weeks, including a 2-week baseline (no medication), 4 weeks of nightly zolpidem, 12 weeks of full dose (nightly), intermittent dosing (1-3 doses per week), or one of two forms of variable dosing, and 36 weeks of extended treatment.

How many other people will be in the study?

200 subjects from the local community are expected to complete this study. Recruitment will take place over 3-4 years' time.

What am I being asked to do?

If you decide to participate, there are a total of four study phases that you may be asked to complete. The four phases are described below.

Phase-1:

Initial Evaluation. This evaluation occurs at the offices of the Behavioral Sleep Medicine Program (Suite 670, 3535 Market Street Philadelphia, PA 19104) or via a virtual visit (via Blue Jeans) and lasts about 1 to 2 hours. Procedures include:

- Completing forms asking questions about your sleep, mood, alcohol use, medical history, your current medications, and background questions about your age, race, and education.
- The provision of your consent to contact your primary care provider to gain their assent (agreement) that you may participate in the trial safely.

The information obtained during the initial assessment will be used to see if you are eligible to participate in this study. If you are determined ineligible, you will not be able to continue in the study but will be provided with a referral if appropriate.

NOTE: This study will be using an Internet Data Portal (IDP) system to collect most questionnaire data. The IDP is a Research Electronic Data Capture and is a secure web application. It is a password protected site located on Penn's servers in which the data will live in a database online where only qualified research personnel can access it. During the initial evaluation you will be introduced to this system and provided with a username and password. The study staff will assist you in filling out the questionnaires using this IDP system.

Phase-2: Baseline Period. This phase lasts 14 days. Your participation includes:

- Completing daily sleep diaries at home. The online diary form requires about 5 minutes each day

to complete.

- Completing 6 to 7 forms asking questions about your medical symptoms, and sleep each week of the baseline period. These online questionnaires require about 15 minutes to complete.

- Abstaining from the use of any medication or over the counter product that is used expressly for the purpose of helping you fall or stay asleep (e.g. trazadone/desyrel, melatonin, nyquil, tylenol PM, Benadryl, etc.). If you choose to discontinue your current sleep medication to participate in our study, please do this in consultation with the clinician that prescribed your sleep medication. Please note that discontinuation of your current sleep medication will make it necessary to extend the baseline component of our study by at least two weeks.

Should the sleep diaries indicate that your insomnia is not of the type, severity, or frequency required for the study, you will not be able to continue in the study but will be provided with a referral. This referral will be for the Penn Sleep Disorder Center. If you or study personnel deem your two weeks to be unusual, you may be offered the chance to repeat the baseline period.

Phase-3: Sleep Lab Study (polysomnography) or Home Sleep Apnea Test (HSAT). You will undergo a polysomnography study or an HSAT to determine if you are eligible to continue in the study. During the pandemic all sleep tests will be administered at home. After the pandemic, the study investigators will decide which type of study you will receive. Both sleep assessments will last for 1 night.

The HSAT equipment will be shipped to your house. A member of the study team will contact you to go over proper use instructions. On the night of the test, you can go to bed at your regular bedtime. Prior to bedtime, you will attach the sensor(s) as instructed and start the test. Upon waking up, you will stop the test and remove the sensor(s). On the day immediately following the sleep test, you will ship the device back in the prepaid shipping envelope

Procedures for the polysomnography study are: you will be asked to arrive at the sleep lab located at the Hospital of the University of Pennsylvania (HUP) at the cross streets of 34th and Spruce by 7 P.M. for a polysomnographic study (PSG). Upon arrival, to ensure for accurate laboratory measurements, urine toxicology screens may be performed to rule out illegal substance use. These data are acquired to explain abnormal findings on the PSG. Following the sleep study, it will be determined whether a repeat study is necessary based on the findings both from the clinical chemistries and the polysomnography. If a repeat study is necessary, one of the project investigators will discuss the issue of substance use with you to: (1) determine if the clinical chemistries' finding was an error (for example poppy seeds led to a positive screen) or (2) gain your willingness to refrain from substance use for the second PSG and for the remainder of the study. If you screen positive a second time, your participation will be discontinued.

The specific procedure for a PSG requires that you have a set of sensors placed on your face, scalp, and body by a technician. All the sensors are attached with surgical tape, paste and glue. The sensors on your face are attached on your left and right temple, cheek bone and under your nose. The sensors on the temple and cheek bone measure eye movements associated with falling asleep and dreaming. The sensors under your nose measure airflow through your mouth and nose. The sensors on your scalp

measure brain waves during sleep. The sensors on the body are placed above the collar bones and over the calf muscles. The sensors over the collar bones measure heart muscle activity. The sensors over the calf muscles measure muscle activity from the legs. In addition, a strap will be placed around your chest and abdomen to measure respiration.

After you have been connected to the equipment, you are expected to stay in bed until final wake time the next morning, except for bathroom breaks. You will be visually monitored by the lab technicians by remote video. In the morning, you will be awakened by the technician (if needed), be unhooked from the equipment, and then allowed to shower, dress, and eat before leaving. You will be free to go about your normal schedule for the rest of the day.

If the in-lab PSG sleep or HSAT study finds evidence of a sleep disorder other than insomnia, such as sleep apnea, you will not be able to continue in the study but will be provided with a referral.

Phase-4: Standard Treatment. All participating subjects will receive *one month of standard nightly treatment*. If you have a positive treatment response you will remain in the study and be randomized to one of the following treatment conditions: nightly dosing, intermittent dosing (1-3 pills week, full dose), or one of two variable dose conditions (nightly pill use where any given pill is a variable dose). The assignment of condition will be accomplished by a process that is the same as the flip of a coin and neither you nor the study personnel will know which condition you have been assigned to (this is referred to as a "double blind" study). You will have an equal chance of being randomized to each of the 4 study arms. In the case of an emergency, the blind will be broken and the study doctor and clinicians associated with your care will be informed of which dosing condition you were assigned to.

Standard treatment will last for 4 weeks. The experimental phase will extend over two periods. The first period will last for 12 weeks. The second period will last for 36 weeks. Both periods include:

- Taking a pill 30 minutes prior to bedtime.

  In one case, this will involve taking 1-3 pills per week. In the remaining conditions, pills will be taken on each and every night. Depending on the specific group you are assigned to, you will either receive 10mg or 5mg of zolpidem (variable by age and sex) or a variable dose of zolpidem on a nightly basis (range from 0 mg to 10 mg per night).

Please note that the effect of zolpidem may be slowed if taken with or immediately after a meal.

- Completing a sleep diary each day;
- Completing 6 to 7 questionnaires each week;
- A monthly visit to Penn (or tele-visit) to return your medication foil packs and to receive a new foil pack with the next month of medication. During this visit, a Nurse Practitioner will ask questions regarding your mental and physical health as well as the effectiveness of the treatment so that we can optimally track your health and wellbeing.

If you do not experience a treatment response or (following a treatment response) you experience a relapse of insomnia, you will not be able to continue in the study but will be given the opportunity to be treated with Cognitive Behavioral Therapy for Insomnia (CBT-I) at no cost. Assessments of your clinical status (how your insomnia is responding to treatment) will be based on your daily sleep diaries and weekly questionnaires.

During Phase-4, you may be asked to undergo a physical if the nurse practitioner deems it to be appropriate and necessary. The physical will involve standard vital measures (e.g., temperature, blood pressure, height and weight, etc.) and, based on the judgement of the research clinician, may involve an EKG and/or blood and urine chemistries.

What are the possible risks or discomforts?

Risks associated with taking zolpidem. Zolpidem is an FDA approved medication for insomnia. You could experience some of the following side effects: dizziness, daytime drowsiness, headache, nausea, or vomiting. Rare cases of severe allergic reactions have been observed, and there have been reports of people performing complex behaviors such as preparing and eating food, making phone calls, or driving while not fully awake after taking zolpidem. These risks are more likely to happen when zolpidem is taken with alcohol or other medications that depress the nervous system, so alcohol should be used cautiously during the course of the study. Worsening of depression or suicidal thinking may occur. There is also risk of respiratory depression in patients with compromised respiratory function. Other unknown side effects could occur and all should be reported to study personnel. Please note that withdrawal effects may occur with rapid dose reduction or discontinuation.

Drug Interactions. Zolpidem may interact with the following drugs to cause additional side effects. If taken with imipramine, decreased alertness may occur. If zolpidem is taken with chlorpromazine, impaired alertness and psychomotor performance may occur. The combination of zolpidem and rifampin may lead to a decrease in the efficacy of zolpidem. Lastly, if taken with ketoconazole, the effect of zolpidem may be increased. Memory Problems. Sleep medicines may cause a special type of memory loss or "amnesia." When this occurs, a person may not remember what has happened for several hours after taking this medicine. This is usually not a problem since most people fall asleep after taking the medicine. Memory loss can be a problem, however, when sleep medicines are taken while traveling, such as during an airplane flight and the person wakes up before the effect of the medicine is gone. This has been called "traveler's amnesia." Memory problems are not common while taking zolpidem.

If side effects occur that are not controllable or that are too bothersome, you will be free to withdraw from the study and you will be referred to a staff physician and/or to your primary care physician for follow up care. As with taking any medication, your symptoms may stay the same or even worsen. Our staff physician will be available in the event that you have any questions or concerns.

Risks associated with taking zolpidem while pregnant and/or nursing. Because the effects of zolpidem on unborn children are currently unknown, you may not participate in this study if you are, or are intending to become pregnant, or if you are breast-feeding. If you are a woman, you must meet one or more of the following criteria.

1. Two or more years post-menopause.
2. Surgically sterile (bilateral tubal ligation, hysterectomy or have had both ovaries removed),

If the above does not describe you, then you should be using an effective method of birth control as determined by your physician. There are no requirements regarding the specific form of contraception that must be used. However, you must agree to continue to use this method of birth control during the entire course of the study. In addition, if you are able to have children, a pregnancy test (urine) must be negative prior to entering the study. The test will be administered during Phase 3, the sleep study visit, and at subsequent quarter annual history and physical exams during Phase 4 of the study. Contact the study coordinator right away if you suspect that you are pregnant.

Risks associated with taking doses lower than those indicated for the treatment of insomnia. Some participants will receive lower than normal doses of zolpidem during portions of the study. If you receive a lower than normal dose, this may result in no change in your sleep, you may experience some insomnia symptoms, or you may experience a level of insomnia that is comparable with, or (in rare cases) worse than, what you experienced prior to enrolling in this study.

Risks associated with the questionnaires. Answering some of the questions may make you feel uncomfortable. You do not have to answer any questions you do not want to.

Risks associated with polysomnography. Some people experience minor discomfort (dry skin, rash) from having the skin cleaned and sensors placed on the skin during the sleep studies.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

The detailed assessment of your sleep (including an in- lab sleep study) may result in the detection of factors, or the presence of other sleep disorders, that may account for your insomnia. In these cases, you will be provided with a referral and our assessment materials will, upon your request, be made available to you to give to your primary care doctor and/or to the specialist to whom you were referred. You may or may not experience relief from your insomnia via the treatment provided during the study.

What other choices do I have if I do not participate?

Your alternative to being in the study is to not be in the study. If you choose not to be in the study you may want to talk to your personal physician about treatments for sleep problems.

Will I be paid for being in this study?

- At the end of your intake visit, you will receive $25.
- For completing a history and physical (H&P), you will receive $25.

- For completing the sleep lab study, you will receive $100.
- For completing the diaries/questionnaires and taking the medication as prescribed you will be paid $25 for each monthly visit you complete ($300 total if you complete all 12 study visits).

If you complete all phases of the study you will receive a total of $450 compensation. Compensation will be distributed via ClinCard, our participant payment system. Please note that in order to be paid, you are required to complete a W-9 form, which includes your social security number.If you receive more than $600.00 compensation in one year for participation in research studies at the University of Pennsylvania, you must report this as income to the federal government for tax purposes.

In addition to the above payments, a lottery will be conducted once each month and will work as follows. Each sleep diary you complete will be counted as an 'entry' into the lottery. At the end of each month, we will conduct a drawing 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). You are 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). Seven to eight subjects out of every 10 participants will win one or more awards over the course of the 12 month period of participation, assuming equal compliance across subjects. 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 through the random drawing. Please note that the use of the lottery has been approved by both NIH and the Penn IRB for prior studies by our group.

Will I have to pay for anything?

There is no cost to you to participate in this research study. Reimbursement for travel to and from our offices is offered as part of your study remuneration. The treatment is provided at no cost to you. You and/or your health insurance may be billed for the costs of medical care during this study if these expenses would have happened even if you were not in the study, or if your insurance agrees in advance to pay.

What happens if I am injured from being in the study?

If you have a medical emergency during the study you should go to the nearest emergency room. You may contact the Principal Investigator or Emergency contact listed on page one of this form. You may also contact your own doctor, or seek treatment outside of the University of Pennsylvania.

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them. There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form. If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has

been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

You have the right to drop out of the research study at any time during your participation. There is no penalty or loss of benefits to which you are otherwise entitled if you decide to do so. Withdrawal will not interfere with your future care. If you no longer wish to be in the research study, please contact the study coordinator, at 215-746-4378 or 215-573-5935 and provide in writing a statement that you no longer wish to participate in the study.

Who can see or use my information? How will my personal information be protected?

The research team will make every effort to keep all the information you tell us during the study strictly confidential, as required by law. Any documents you sign, where you can be identified by name will be kept in a locked drawer in Dr. Perlis's office. Other documents containing your study information will be identified by a unique code number. These documents will be kept confidential. The Institutional Review Board (IRB) at the University of Pennsylvania is responsible for protecting the rights and welfare of research volunteers like you. The IRB has access to study information. All the documents will be destroyed when the study is over. The answers to the questionnaires that you complete on the computer each day will be kept in a secure database that only the study investigators can access. Your email address is the only identifying information that will be kept in this file.

As a reminder of study appointments, some subjects prefer to have contact via email. Email privacy is based on the user agreement with your email provider. Please indicate if you are willing to have your email used for study contact. Yes No (circle one)

We also intend to contact you via text message to remind you of study appointments and procedures. Please indicate if you are willing to receive study contact via text message. Yes No (circle one)

Subject Initials: _____ Date: _____

Finally, you should understand that study staff is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

Electronic Medical Records and Research Results

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any information produced from your participation in this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Information related to your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.
Once placed in your EMR or in the CTMS, your information may be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

Additional Information Regarding your Health Information Privacy (HIPAA)

What information about me may be collected, used or shared with others?

As part of our study you will share the following information,

- Name, address, telephone number, date of birth, electronic mail addresses
- Social Security number for compensation purposes
- Personal and family medical history
- Results from a physical examinations, tests or procedures

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are also used to:

- do the research
- oversee the research
- to see if the research was done right
- to evaluate and manage research functions.

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- The study Principal Investigator, Michael L. Perlis PhD
- The study Co-Investigators, Michael Thase MD, Nalaka Gooneratne MD, Knashawn Morales PhD
- The study collaborators, coordinators, research assistants, and administration

  Ivan Vargas PhD
  Yoon Chang MD
  Mark Seewald BS (Coordinator)
  Waliuddin Khader BA (coordinator & programmer)
  Eileen Mergliano BA (research business administrator)
  Josh Giller BS (research assistant)
  Alexandria Muench PsyD (postdoctoral fellow)
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of the School of Medicine, might receive my information?

Our collaborator from Harvard University
Our program officer from NIH (NIA)

Oversight organizations
The Office of Human Research Protections
The study data and safety monitoring board

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.

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

Name of Subject (Please Print)	Signature of Subject	Date

Name of Person Obtaining Consent (print)	Signature of POC	Date