A pragmatic randomized comparator trial of eszopiclone and brief behavioral therapy for insomnia in CPAP non adherent Veterans with PTSD and complex insomnia

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Unique Protocol ID: NURB-008-18F
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VHA Western New York Healthcare System
[Course title]

Research Informed Consent Document

Department of Veterans Affairs
VA Western New York Healthcare System, Buffalo, New York

PRINCIPAL INVESTIGATOR:	Ali El Solh, MD, MPH
TITLE OF RESEARCH STUDY:	A pragmatic randomized comparator trial of eszopiclone and brief behavioral therapy for insomnia in CPAP non adherent Veterans with PTSD and complex insomnia

SUMMARY OF KEY INFORMATION ABOUT THIS STUDY

WHAT IS THE STUDY ABOUT AND WHY ARE WE DOING IT?

We are asking you to choose whether or not to volunteer for a research study being funded by the Veterans Health Administration how best to treat Veterans with post-traumatic stress disorder (PTSD) who have both insomnia and sleep apnea. This summary is intended to give you key information to help you decide whether to participate. Ask the research team questions. Taking part in this study is completely voluntary.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

The study involves approved treatments for both insomnia and sleep apnea. By doing this study, we hope to learn whether the combination of a brief cognitive behavioral therapy and an approved US Food and Drug Administration (FDA) sleeping aid, eszopiclone, can improve your quality of sleep and help you to use the CPAP machine longer than brief cognitive behavioral therapy alone. Your participation in this research will last about 6 months.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. Taking part in this study will help doctors to learn more about the best approach to treat both insomnia and sleep apnea at the same time. This may help you and others with your health problem in the future*. For a complete description of benefits, refer to the Detailed Consent.*

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

As the combination of brief cognitive behavioral therapy and sleeping aid has not been tested before in patients with PTSD who have both insomnia and sleep apnea, it may not help your health problems, which may stay the same or might get worse. *For a complete description of risks, refer to the Detailed Consent and/or Appendix.*

Your Study Doctor will discuss with you any other treatments which may include other prescription sleep aids that may be available and will also discuss their risks and benefits. For a complete description of alternate treatment/procedures, refer to the Detailed Consent.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

It is important to tell the study team if you are taking part in another research study.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of the study is Ali El Solh, M.D. of the Western New York Healthcare System (VAWNYHS). If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his/her contact information is (716) 862-7392.

DETAILED CONSENT

WHAT IS THE PURPOSE OF THIS STUDY?

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You are being asked to take part in a research study at the VAWNYHS because you indicated that you have been diagnosed with PTSD and you have both insomnia and sleep apnea. Patients with insomnia can have difficulty tolerating CPAP because it can prevent them from falling asleep. As a result, these patients have poor sleep quality and are constantly falling asleep during the day. Previous studies have indicated that brief cognitive behavioral therapy and eszopiclone, an approved FDA sleeping pill, are both effective in treating insomnia. With this research we hope to learn whether the combination of a brief cognitive behavioral therapy and an approved US Food and Drug Administration (FDA) sleeping aid, eszopiclone, can improve your quality of sleep and help you to use the CPAP machine longer than brief cognitive behavioral therapy alone.

During the study, you will receive treatments and procedures that are standard of care for patients with your medical conditions.

HOW LONG WILL I BE IN THE STUDY?

This research study is expected to take approximately 4 years. Your individual participation in the project will take 6 months. This includes the enrollment visit, two face-to-face visits, two telephone-based interviews, an end-of-treatment session, and an end-of-study follow-up at 6 months. Each visit will last between 45 minutes to one hour. During these visits, we will assess any new health problems or side affects you may have experienced since your last study visit and your overall well-being.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 52 people will participate in this research study at the VA Western New York Healthcare System.

WHAT WILL HAPPEN AND WHAT IS EXPECTED IF I TAKE PART IN THE STUDY?

If you decide to take part in this study, it is important that you agree to:

- Attend all scheduled study visits. As soon as you know that you will not be able to go to a study visit, please contact your Study Doctor or the study staff to schedule a new visit.
- Truthfully answer any questions from your Study Doctor or the study staff when asked about any changes in your health, side effects, visits to other doctors or hospital admissions, or changes in your medication, including prescribed medications, over the counter medications, herbal remedies, and vitamins.
- You must not take part in any other studies while you are taking part in this study
- Tell the Study Doctor or study staff if you believe you may be pregnant
- Tell your Study Doctor or study staff if you change your mind about taking part in the study.

After you sign the informed consent, the following procedures will occur:

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1) **Eligibility assessments**: you will need to have the following screening exams, tests or procedures to determine if you can participate in the study:

   - **Clinical Interview**: You will meet with the study coordinator at the VA clinical research center who will ask you questions about your medical history, current health, medications, and sleep patterns. During the interview, you will be asked to complete a set of questionnaires regarding your degree of sleepiness, how bad your insomnia is, and other health related behaviors such as:
     - Depressed mood and anxiety,
     - Alcohol or Substance Use problems
     - PTSD symptoms

   - **Pregnancy testing:** Because we do not know for sure that eszopiclone is safe for fetuses, pregnant women may not participate in this study. If you are a woman able to bear children, you must have a negative pregnancy test as part of the screening procedures. If you become pregnant while in this study, you will immediately contact the study physician and will be counseled as to your possible alternatives. If you engage in heterosexual intercourse, you must be willing to practice appropriate birth control or abstain from sex for the duration of the study.

   - **Urine sample**: You will be asked to give a urine sample for laboratory tests to screen for drugs of abuse. This test is for screening purposes only to ensure that you are eligible to participate in the study. You must have a negative urine toxicology screen to participate in the study. Your samples will be identified by your subject number (as described below), and not by your name

If the screening exams show that you can continue to be in the study, and you choose to take part, you will have to complete the following steps:

2) **Pre-treatment assessments:** The study coordinator will explain to you the following procedures:

   - **Sleep Diary**: You will complete a sleep diary form every day for 7 days. Each morning you will record your estimated sleep time, and the number of times you woke after bedtime. The diary takes approximately 5 minutes total to complete.
   - **Activity Monitor:** You will wear a monitoring device, called an actigraph, that will measure your wrist movement during waking and sleep. You will wear this device on your wrist, like a watch, at all times for the duration of the treatment phase (4 weeks).

3) **Treatment phase:** The treatment phase will last 4 weeks. You will have a one in two chance of receiving either a brief cognitive behavioral therapy intervention or a brief cognitive behavioral therapy intervention along with a sleeping pill, eszopiclone, to take at bedtime. A computer program will place you into one of the groups. Neither you nor anyone from the study team can choose the group that you will be in. You will have an equal chance of being placed in either group.

   A. Brief cognitive behavioral therapy: if you are randomized to the brief cognitive behavioral therapy group only, treatment will be delivered over four consecutive weeks, and includes one individual in-person visit (45 min) at week 1, a second in-person visit at week 3 (<30

min), and brief telephone appointments during weeks 2 and 4 (<20 min each). At these appointments, you will cover the structured intervention material discussing physical and cognitive components of insomnia and ways to improve sleep and sleep hygiene. These sessions may be audiotaped for supervision and training purposes. Audiotapes will be kept in secure, locked cabinets within locked offices. Only the study investigators and study staff will have access to these audiotapes. They will be stored for the duration of the study and as required by VA policy.

B. Combined Cognitive behavioral therapy plus eszopiclone: if you are randomized to the combined brief cognitive behavioral therapy group and a sleeping pill, you will receive in addition to the brief cognitive behavioral therapy described above, eszopiclone 2 mg tablet to take at bedtime starting with the first session of cognitive behavioral therapy for a total of 2 weeks. The pharmacist will review potential side effects that could arise from the medication. You will be given the medication in a counted capsule bottle, so that medication compliance can be monitored. Should you have any questions or concerns regarding the medication, you will be given a contact information that provides emergency contact
numbers of the study physicians.

4) **End of treatment phase:** at week 5, you will meet with the study coordinator for approximately one hour. She/he will inquire about any change in your medical history or medications. She/he will ask you then to complete the same questionnaires you have filled at the beginning of the study. You will be asked to give a urine sample for drug testing if required. You will be reminded prior to your visit to bring the smartcard of your CPAP machine to calculate the number of hours you have been using the machine in the previous 4 weeks.

5) **End of study phase**: at 6 months, you will meet with the study coordinator for approximately one hour. She/he will inquire about any change in your medical history or medications. She/he will ask you to fill the same questionnaires you have done at the beginning of the study. During this visit, you will complete an additional questionnaire to assess satisfaction with the treatment. If indicated, you will be asked to give a urine sample for drug testing. You will be also reminded prior to your visit to bring the smartcard of your CPAP machine to calculate the number of hours you have been using the machine in the previous 4 weeks.

   At this visit, you will meet with your study doctor to discuss whether or not it is in your best interest to be prescribed the sleeping pill. Your study doctor will refer you back to your primary care doctor or psychiatrist for further prescriptions of eszopiclone or other medications if you decide to continue at that time.

It is very important to remember that you have to attend all of the visits, including the final clinic visit. If you do not attend all of the visits, and the study staff is unable to contact you, they may need to find other ways to get in touch. For this reason:

- Please make sure you inform the study staff if any of your contact details change.
- Please make sure the study staff knows how to contact your family or next of kin if they cannot make contact with you.
- Please make sure that you or a member of your family informs the study staff if you are admitted to the hospital.

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Since this study involves asking you for further information about your sleep and mood, we want you to know that at any time if we are concerned about your safety, we will discuss it with you, if possible, or seek help from your primary care provider or other emergency services. At the discretion of the primary investigators, participants may be taken out of this study due to unanticipated circumstances, such as extreme distress. In other words, we may withdraw you from the study, should we judge your participation not to be in your best interest. At any time, you can choose to discontinue the entire study, including all assessment sessions.

WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur.

- Questionnaires: Responding to questions that are sensitive in nature (i.e., about distress associated with PTSD) during interviews may cause some minor discomfort. Examples of distress include anxiety symptoms (e.g., shortness of breath, fear) or feeling down. If you experience distress during the interview, please discuss this with your interviewer. You may decide to stop the interview or talk to the Study Doctor. The interviewer will discuss with you what to do if you experience distress after the interview, which will include calling the Study Doctor or the Veterans Crisis Line. In addition, there may be unknown or unforeseen risks associated with study participation. If, for any reason, you wish not to answer specific questions or you wish to terminate the session, you will be able to do so.

- Cognitive behavioral therapy: For the behavioral intervention, it is possible that some patients may find the assessments and intervention provided as part of the trial uncomfortable or emotionally sensitive. There is minimal risk that participation in this protocol will produce psychological distress (i.e., embarrassment, discomfort) when asked to share sensitive information about yourself with the research staff. Your therapist will discuss with you safety precautions to take if this does occur. Finally, your therapist will discuss with you steps to take to minimize any other distress that may occur.

- Eszopiclone: Most common side effects include daytime drowsiness, headache, unusual or unpleasant taste in your mouth, cold symptoms such as stuffy nose, sneezing, sore throat, acid or sour stomach, belching, and dry mouth. Less common side effects include lack of appetite, abnormal dreams, loss of interest or pleasure, memory problems.
  If you develop any of these effects: rash, allergic reaction, aggression, thoughts of hurting yourself, or hallucinations (hearing or seeing things), call the Study Doctors on the study contact sheet you were provided.

Unknown pregnancy risks

The safe use of *eszopiclone* in pregnant women and nursing mothers has not been established. Consequently, there may be risks to you (or to your embryo or fetus) if you are or may become pregnant that are unknown. Nursing mothers may not participate in this study.

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Female participants

- If you are of the age where pregnancy is possible or you are capable of becoming pregnant, the Study Doctor and/or study staff will ask you to take a urine pregnancy test to make sure that you are not pregnant.
- If you are between the ages of 45 and 60 and have not had a period for 12 months, you may still be required to take a urine pregnancy test to make sure that you are not pregnant.
- If you have the potential to become pregnant, you must use a reliable birth control method(s) during the study.
- If you do become pregnant while taking part in the study, you should let your Study Doctor know right away. Your Study Doctor will discontinue treatment with study drug but may continue other study procedures and follow-up will continue. Your Study Doctor will talk to you about the need for further medical attention if appropriate. The Study Doctor will ask you for permission to collect information about the outcome of your pregnancy.
- If you are breast-feeding, you must be willing to stop breast-feeding.

There is always a chance that any treatment can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect.

Risks of the usual care you receive are not risks of this study. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

Taking part in this study may or may not result in improvements in your sleep disturbance or PTSD symptoms. Your participation in any part of the study contributes to medical knowledge related to the treatment of sleep disorders and PTSD. Your participation may lead to knowledge that can be used to improve healthcare for other Veterans.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS STUDY?

You are free to choose not to participate in the study. You will not lose any of your regular benefits, and you can still get care from our institution the way you usually do. Your Study Doctor will discuss with you any other treatments or investigational drugs that may be available and will also discuss their risks and benefits. If you decide not to take part in this study, it will not affect your ability to receive medical care. You may discuss these options with your doctor.

HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

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Identifiers will be removed from the identifiable private information that are collected. After that removal, the information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

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

While this study is being conducted, you will not have access to your research related health records. This will not affect your VA healthcare including your doctor's ability to see your records as part of your normal care and will not affect your right to have access to the research records after the study is completed.

WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

You will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

WILL I BE PAID FOR PARTICIPATING?

You will be paid according to the following schedule via Visa debit card:

Visit	Amount
Enrollment	$100
Week 1 In person	$50
Week 3 In person	$50
End of treatment follow up	$100
End of study follow-up	$100
	$400

If you drop out of the study before completing all the *visits* you will be paid for the *visits* that you completed. If you complete all the scheduled *visits* you will have received a total of $400.00. An Internal Revenue Service (IRS) Form 1099 may be generated, which will use your Social Security Number. This payment is considered taxable income. If you owe money to the government, this payment may be garnished to satisfy the debt.

WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

The VA Western New York Healthcare System will provide necessary medical treatment to you if you are injured by being in a research study *in accordance with applicable federal regulations (38 CFR 17.85)*. This does not apply to treatment for injuries that occur because you did not follow study procedures, your injury was not deliberately caused, or the medical advice of the Study Doctor was not followed. Except in limited circumstances, the necessary care will be provided in VA medical facilities. Any expenses not covered by your insurance may be covered by the VA, consistent with applicable law, regulation, and policy.

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If you should have a medical concern or get hurt or sick as a result of taking part in this study, call: DURING THE DAY:

Dr. Ali El Solh, MD at (716) 834-9200 and the study coordinator at (716) 834-9200 x2653; AFTER HOURS: Dr. Ali El Solh, MD at (716) 834-9200.

Emergency and ongoing medical treatment will be provided as needed.

DO I HAVE TO TAKE PART IN THE STUDY?

Taking part in this study is entirely voluntary. You do not have to take part in this study. If you choose to take part and you change your mind later, you are free to take back your consent and to stop being in the study at any time without giving a reason. In that case, we ask you to tell your Study Doctor or study staff so that you can be withdrawn safely. If you choose to withdraw from the Study, Study Doctor will ask you if you would be willing to continue to provide information about your health status until the Study is over. Your choice to take part or to stop taking part in this study, will not affect your routine/regular treatment, your relationship with those treating you or your relationship with the place where you are getting treatment. You will still receive care for your condition and will not lose any benefits to which you are otherwise entitled.

If you decide to withdraw from the study, the research team may continue to review the data already collected for the study but will not collect further information, except from public records.

RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION (Include if applicable)

This study or the study treatment may be stopped without your consent. Reasons why the Study Doctor can stop your study treatment include:

- Continuing to take part in the study may be harmful to you
- You become pregnant during the study
- You are having a side effect from the intervention
- You are not coming to study visits and/or complying with study procedures
- You need to get other treatments for your medical condition that the study does not allow
- The study closes

WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

Dr. Ali El Solh or his designee has explained the study to you and answered all of your questions. If you have questions, concerns or complaints about the research, you have been told you can call Dr. Ali El Solh at (716) 834-9200 ext. 7392 during the day or (716)834-9200 after hours. You may also contact the study coordinator during the day at (716) 834-9200 x2653. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. If you have questions about your rights as a research participant, or if you think you have a research-related injury, you may contact the Chair of the Research & Development Committee at (716) 862-6528 or the Patient Advocate at (716) 862-8752. You may also contact the Patient Advocate (716) 862-8752 if

you have concerns, questions, or complaints and cannot reach the research team, or if you wish to talk to someone else.

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the Dr. Ali El Solh at (716) 834-9200 ext. 7392 during the day or (716) 834-9200 after hours if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

In case we learn about new findings during the course of the study that may affect your willingness to continue to participate, we will provide you with that information.

We may publish what we learn from this study. If we do, we will not let anyone know your name. We will not publish anything else that would let people know who you are

FUTURE USE OF DATA AND RE-CONTACT

Your data may be retained after the study for future research. The data will be stored at the VA WNY in the research building (20) in a locked cabinet in Dr. El Solh office. The data will be accessed by the research team only. You may be contacted in the future about participating in future VA research related to PTSD or sleep disorders.

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

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Dr./Mr./Ms_____ has explained the research study to me. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me. I have been given the chance to ask questions and obtain answers.

By signing this document below, I voluntarily consent to participate in this study and authorize the use and disclosure of my health information for this study. I also confirm that I have read this consent, or it has been read to me. In the future, if I decide that I no longer wish to participate in this research study, I agree that my information which were already collected, may continue to be used only for this research by removing all identifying information. However, identifiers may be stored separately and held in accordance with the VA records control schedule. A copy of this signed consent will also be put in my medical record.

I voluntarily consent to participate in this study. I have been told that I will receive a copy of this consent form.

I agree to participate in this research study as has been explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date
_____ Participant's DOB	_____ Participant's last 4 Social Security	

_____
Name of Person Obtaining Consent

_____
Signature of Person Obtaining Consent