Non-invasive Vagal Nerve Stimulation to Improve Functional Outcomes in Veterans With Alcohol Use Disorder

NCT05226130

May 8, 2023

VA | U.S. Department of Veterans Affairs	**Agreement to Participate in Human Subject Research** IRB Protocol #: **H210046**
Study Title: Non-invasive Vagal Nerve Stimulation to Improve Functional Outcomes in Veterans with Alcohol Use Disorder	
Principal Investigator: Ruth Klaming Miller, Ph.D.	
VA Facility: VA San Diego Healthcare System	
Participant Name:	Date:

STUDY SUMMARY

You are being asked to participate in a research study. This section summarizes key information about this study to assist you, or your legally authorized representative, in understanding the reasons why you may or may not want to participate in the research. Your participation is voluntary. You may refuse to participate or withdraw at any time. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer. Carefully review this section and the detailed information that follows before you agree to participate.

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

This study is about how non-invasive vagal nerve stimulation (nVNS) may or may not affect drinking behavior, brain activation, as well as feelings of anxiety, pain, and distress. It is being funded by the Department of Veterans Affairs (Career Development Award and Center of Excellence for Stress and Mental Health; CESAMH). By doing this study, we hope to learn about potential effects of nVNS on drinking behavior and mood.

WHAT DOES THE STUDY INVOLVE AND HOW LONG WILL IT LAST?

You will be asked to complete questionnaires, clinical interviews, functional magnetic resonance imaging (MRI) scans, and self-administer nVNS at home twice a day for 2 minutes for one week. Your participation in this research will last about 1 week, including two visits each lasting about 3 hours. The purpose of this research is to gather information on the safety and effectiveness of nVNS, which has been FDA-approved for cluster headache and migraine pains.

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

There are no direct benefits to you for participating in this study. However, you help the researchers learn more about how nVNS may affect drinking behavior and feelings of distress.

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

Some reasons why you might not want to participate in this research includes temporary emotional or physical discomfort while participating in clinical interviews or neuroimaging scans due to unpleasant questions or images or heat pain, which will be applied to your leg, temporary side effects from nVNS such as muscle twitches, pain, dizziness, or skin irritation, or fatigue from filling out questionnaires. A complete description of risks is included in the Research Details Study Risks section. Participation is voluntary and the only alternative is not to participate.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of the study is Dr. Ruth Klaming Miller of the VA San Diego Healthcare System. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study her contact information is: [redacted].

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RESEARCH DETAILS

WHO IS CONDUCTING THIS RESEARCH AND WHY?

Ruth Klaming Miller, PhD and her colleagues are asking for your consent to this research. This study is being sponsored by the Department of Veterans Affairs. The purpose of the research is to find out more about how nVNS may or may not affect drinking behavior, brain activation, as well as feelings of anxiety, pain, and distress. You are being asked to participate because you are a Veteran who consumes alcohol on a regular basis. Approximately 20 people will take part in this research at this facility. nVNS has not been FDA-approved for the treatment of alcohol-related symptoms.

FOR HOW LONG WILL I BE IN THE STUDY?

Your individual participation will take approximately 3 hours each time you come to the VA hospital, and you will be asked to come to the VA 2 times (with one week between visits). During this week, we ask you to self-administer nVNS twice a day for 2 minutes. Some parts of the study may be done remotely (from home) in case you are unable to come to the VA hospital in person. The entire study will take five years.

WHAT WILL HAPPEN AND WHAT CAN I EXPECT IF I TAKE PART IN THIS STUDY?

If you agree to be in the study, the following will happen to you:

1. You will be asked questions about your **medical history, alcohol consumption, and mental health** including questions about symptoms of anxiety and other psychological distress that you may have experienced. You may skip any question(s) you that make you uncomfortable or that you wish not to answer. These questions will be asked during a clinical interview and with a series of questionnaires. This portion of the study will take approximately 2 hours.
2. You will be asked to complete a short **neuropsychological assessment battery**. This includes paper and pencil tests, administered by study staff, to measure cognitive functions. Portions of the assessments may be audio-recorded for scoring purposes. Audio recording is optional and does not affect your enrollment in the study.
   Please mark one of the options below to indicate your choice:
   _____ I agree to having a portion of the neuropsychological assessment audio recorded
   _____ I do NOT agree to having a portion of the neuropsychological assessment audio recorded
3. You will also be asked to participate in a **functional Magnetic Resonance Imaging (fMRI) scan**, which is a non-invasive test that can detect changes in brain activity. During the fMRI scan, you will be placed in a large donut-like machine and your head will be placed in a helmet-like holder that allows us to take images of your brain. The scan will take approximately 1 hour. Prior to the scan, you will undergo a safety screen to ensure there are no MRI contraindications.
4. We will measure your skin conductance during the fMRI scan by attaching two small patches to your left index and middle fingers. We will also ask you to lie down on a bed for 10 minutes while we measure your heart rate variability using a wrist watch.

5. We will use the fMRI scanner to measure (and take pictures of) your brain activity while you receive the neck stimulation. You will be **randomized to either 1) placebo stimulation or 2) vagus nerve stimulation**. You will not know which condition you have been assigned to. During stimulation, we will apply gel to your skin above the vagus nerve (on the neck) and on the stimulation surface of the GammaCore device. A small amount of electrical signal will then be transmitted with the device to stimulate the vagus nerve. In case you receive the placebo device, the signal will not activate the vagus nerve, but the sensation will be nearly identical. You may feel tingling and tightness at the stimulation site.
6. We will use the GammaCore device for nVNS, which is FDA-approved for the use of cluster and migraine headache pain. You will be instructed on how to self-administed nVNS at home and be asked to apply the device to your neck twice a day for 2 minutes each, for a period of one week. During this week, you will also be asked to complete a diary of any side-effects you may experience. We ask that you keep the device safe for your use only and away from children. After one week, you will be asked to return for a follow-up visit and return the nVNS device to the research team.
7. While participating in this research study, do not take part in any other research project without approval from the investigators. This is to protect you from possible injury from things such as potential drug interactions. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other studies.
8. During the fMRI scan, you will be asked to complete computerized tasks. These tasks will include doing one or more of the following: (1) looking at a fixation cross (resting state), (2) looking at pictures of emotional faces or scenes (affective image task), and (3) you will receive a series of thermal stimulation ranging from warm to uncomfortable (hot) to your leg (thermal stimulation task).
9. During each study visit, you will be asked to take a breathalyzer test so we can ensure you are not intoxicated.
10. You will be asked if you are interested in the receiving information regarding additional research opportunities. If you are, you will be contacted by phone and given information about other studies. Whether or not you choose to participate in these studies is entirely your choice. Participation in other research studies will not affect your ability to continue in the current study. Please initial one of the lines below:
    _____ I am interested in getting information about additional research studies.
    _____ I am not interested in getting information about additional research studies.
11. Information from your medical record may be utilized as noted in the HIPAA Authorization.
12. **COVID-19:** During COVID-19, to minimize in-person interaction and maximize social distancing, studies will be comprised of remote and in-person activities. Activities such as consenting, answering questionnaires, and completing clinical interviews may be completed remotely via VA approved telehealth technology, mail and telephone. This means you may complete these aspects of the study from your home. In-person visits will involve an MRI scan and minimum day-of assessments (such an MRI safety screening form), and as necessary or preferred by volunteers, forms and questionnaires may be supplied and filled out in a private room, or outside (e.g., car, etc.). You will receive a COVID screening multiple times before attending your in-person visit in order to confirm that you are symptom free. If your screening is positive for COVID-19 symptoms or exposure, the study appointment will be postponed for a minimum of two weeks.
    During in-person visits, researchers will limit face-to-face interaction as much as possible. Parts of the visit might be conducted outside to provide better ventilation and dispersion of aerosol. For your protection and the

protection of others, you will always be required to wear a multi-layer face mask without respirator during your in-person appointment. Failure to do so at any point will result in the termination of the visit. You will be provided an MRI safe mask to wear during the scan.

WHICH PROCEDURE/S OR TREATMENT/S ARE DONE FOR RESEARCH?

All study procedures and treatments are done for research purposes.

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

Participation in this study may involve some added discomforts.

Risks of questionnaires and clinical interviews:

Temporary discomfort including restlessness, anxiety, or fatigue in some people while filling out questionnaires or during clinical interviews, temporary discomfort while being asked personal questions about anxiety, depression, and negative life experiences, and alcohol consumption. These experiences occur in a small portion of individuals and are generally mild.

Damage to your personal reputation, ability to become or remain employed, or exposure to criminal or civil liabilities, or other unforeseen consequences, if your confidential information were to accidentally become public- e.g., whether you have used illegal substances. To minimize this risk, all your data will be anonymized and kept in locked cabinets or in databases with secured passwords. The study investigators have conducted this research for over 8 years and have not encountered such problems.

Risks of Magnetic Resonance Imaging:

Some people experience a 'closed-in' feeling due to the relatively restricted space within the MRI machine. You may not be able to have the MRI procedure if you have certain metal, surgical clips, or implants, including a brain aneurysm clip or a pacemaker, in your body, because during the MRI procedure metal can heat up and move, or clips and implants stop working. Dental fillings are not a problem. If there is any question about whether or not there is metal in your body, you may be requested to have an X-ray to determine this; the X-ray will become part of your medical record. You will need to remove all jewelry or clothing with metal before having the MRI. All of these precautions will be reviewed with you immediately before you have the MRI.

Other possible risks include muscle aches due to lying on your back for 1 hour in the scanner, emotional discomfort or agitation while in the scanner due to tasks that may be emotional in nature or challenging. You may terminate the scan if you become overly emotionally affected. You may experience discomfort due to banging noises that the MRI scanner makes while taking pictures. You will be asked to wear earplugs in order to minimize the risks of these loud noises to your hearing. You may experience muscle twitches during the scanning procedure. Sometimes over the course of a research study, research personnel may encounter incidental findings. An incidental finding is a previously undiagnosed medical or psychiatric condition that is discovered unintentionally. Research personnel are not trained to diagnose potential abnormalities. In such a case, a qualified medical professional will be consulted. If this condition requires further medical evaluation or treatment, you will be notified.

Risks of vagus nerve or placebo stimulation using the GammaCore device:

You might experience negative effects related to the stimulation or testing while participating in the study. All research participants taking part in the study will be watched carefully for any negative effects; however, the study team does not know all the potential effects that the treatment may have on you. You may experience application site discomfort, application site irritation/redness, local pain, face/head/neck area (including toothache), muscle twitching and/or contractions, face/head/neck area (including facial droop and/or lip pull), headache/migraine, metallic taste, dizziness, tingling, pricking or a feeling of "pins and needles" on the skin where the device is applied (paresthesia/ dysaesthesia). These side effects typically resolve immediately after the stimulation is complete and are very similar to side effects associated with a transcutaneous nerve stimulator or TENS unit. Occurrence of several of these events can be mitigated by the user repositioning the device on the neck and/or decreasing the stimulation intensity. Training on the positioning of the device and controlling the stimulation intensity is conducted at the time the device will be provided to you. In addition, the device is provided with detailed instruction for use.

Risks of thermal stimulation task and neurosensory testing:
The Thermal Sensory Analyzer has been approved by the Food and Drug Administration with Marketing Approval for sale in the United States. You will feel warm and heat sensations, as well as warm and hot pain. There is also a small risk of a sunburn-like burn from the heat application.

Risk from alcohol withdrawal:
As part of this study, you will be asked to not drink any alcohol for 24 hours prior to each study visit. Those who drink heavily on a regular basis, may experience potentially dangerous alcohol withdrawal symptoms. If you experience these symptoms or have experienced them in the past after you stopped drinking, it is not safe for you to participate in this study. If necessary, we will refer you to the hospital for medical treatment.

It is important that you report all symptoms, changes in your health, and side effects that you experience as soon as they occur, whether or not you think they are caused by the treatment. The telephone numbers for the study team are located at the end of this document.

COVID: Participating in on-site research activities during the COVID-19 pandemic may increase your risk of contracting COVID-19. This research study is taking extra precautions to keep participants safe during this time and mitigate this risk. To decrease risk of transmission, precautions such as wearing proper personal protective equipment, social distancing when possible, regularly cleaning research testing environments, hosting parts of visits outdoors, and altering visits to be partially completed remotely have been taken. Researchers and subjects will be screened (not tested) multiple times before in-person visits to ensure health and well-being. Screening will be provided by researchers and VA Employees located near the main entrance of the VA San Diego Hospital. Masks will be required for in-person visits; however, if you need one provided the VA will supply you with an MRI Safe Mask.

Photographs or videotaping: There will be no photographs or video tapes made of you as part of this study.

UNFORESEEABLE RISKS

Because this is an investigational study there may be some unknown risks that are currently unforeseeable. You will be informed if the researchers learn of any change in the amount of risk to you.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

There are no personal benefits to you from your taking part in this research study. However, the information we get from this study helps the researchers better understand nVNS, which may help others in the future.

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

The VA will provide necessary medical treatment should you be injured as a result of participating in this study and following study procedures. You will be treated for the injury by the VA at no cost to you or your insurance but no additional compensation is available. If you should have a medical concern or get hurt or sick as a result of taking part in this study, call: Research Compliance Officer at [redacted]A Research Service at [redacted] VA Regional Counsel at [redacted] or the VASDHS Human Research Protection Program at [redacted]

DO I HAVE TO TAKE PART IN THIS STUDY?

Taking part in this research study is your decision. Your participation in this study is voluntary. You do not have to take part in this study, but if you do, you can stop at any time. You have the right to choose not to participate in any study activity or completely withdraw from continued participation at any point in this study without penalty or jeopardy to the medical care you will receive at this institution or loss of benefits to which you are entitled. For data already collected prior to the withdrawal, the investigator may continue to review the data already collected for the study but cannot collect further information, except from public records, such as survival data.

RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

If you decide that you no longer wish to participate in this study, please call [redacted]. Your participation in this study may be stopped if the investigator decides that stopping is in your best interest.

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

There will be no costs to you or your insurance for any procedures or testing done only as part of this research study. If you receive a bill for services that you think could be related to your participation in this study, you should contact Dr. Ruth Klaming Miller.

Medical care and services provided by the VA that are not part of this study (e.g., normal hospital and prescription expenses which are not part of the research study) may require co-payments if your VA-eligibility category requires co-payment for VA services.

WHAT COMPENSATION WILL I RECEIVE IF I TAKE PART IN THIS STUDY?

You will receive up to $200 for your participation in this study. You will be paid $100 for each visit completed. You will receive $30 if you arrive for your first visit and it is determined that you are not eligible to participate in the remainder of the study. The most common reason for this determination is that information comes to light which

renders it unsafe for you to continue (for instance, that it is not safe for you to participate in an MRI scan due to the presence of metal).

Participants who complete MRIs may request a digital image of their brain, which will be sent through VA encrypted software.

Each payment will be entered by our staff approximately one week after the visit, though additional processing time may be required before the funds are received in your account. The study payment will be made directly to your bank account using electronic funds transfer. If you currently have a debt to the Federal Government, your debt may be subtracted from your funds transfer payment for study participation.

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

If you have any questions, complaints, or concerns about the research or other related matters, you may contact the Dr. Klaming Miller's research team at [redacted] If you have any questions or concerns about your rights as a research subject, the validity of a research study, or research personnel you can contact the Research Compliance Officer at [redacted], VA Research Service at [redacted], VA Regional Counsel at [redacted] or the VASDHS Institutional Review Board at 858-642-6362. This is the Board that is responsible for overseeing the safety of human participants in this study.

HOW WILL MY PRIVATE INFORMTION BE PROTECTED?

Participation in this study may involve a loss of privacy, but information about you will be handled as confidentially as possible. We will use your SSN and name to review your medical record and determine if you meet criteria for this study. Your research records will be labeled with a code number. The list that matches your name with the code number will be kept in a locked file in the research team's office. Any research records that identify you will be kept only as paper records in a secure VASDHS location, or as files behind the secure VASDHS computer firewall. Identifiers might be removed from the identifiable private information that is 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.

We will keep confidential all research and medical records that identify you to the extent allowed by law. However, you should know that there are some circumstances in which we may have to show your information to other people. For example, the Federal Office of Human Research Protections, the General Accounting Office, the VASDHS R&D Committee, the VASDHS Institutional Review Board, the Food and Drug Administration, UCSD Keck Center, and federal compliance officers may look at or copy portions of records that identify you.

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.

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During the course of your participation in this study, if there is any indication of suicidal ideation or that you may pose a threat to yourself, you will be contacted by a clinical member of the research staff. You will be asked questions regarding your intent to harm yourself and, at the discretion of the clinician, appropriate actions will be taken to ensure your well-being if it is determined that your immediate safety is in jeopardy. Questions regarding suicidal thoughts and actions are components of the self-report surveys that you will be asked to fill out, as well as parts of the clinical interviews that you will undergo. This information will be handled under the same privacy and confidentiality standards as the rest of your research data unless it is determined that immediate medical or mental health attention is required. Research staff is legally required to report known reasonable suspicion of abuse to a child, elder, or disabled adult. Staff is also legally required to report serious threats of physical violence against a reasonably identifiable victim or victims to law enforcement and the victims(s).

Any presentations or publications from this information will not identify you.

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

You have been informed that you do not have to take part in this study, and your refusal to participate will involve no penalty or loss of rights to which you are entitled. You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled.

The study research assistant has explained the 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. I also confirm that I have read this consent, or it has been read to me. I will receive a copy of this consent after I sign it.

I agree to participate in this research study as has been explained in this document.

_____ _____

Participant's Signature Date

_____ _____ _____

Signature of Researcher obtaining consent Name (print) Date

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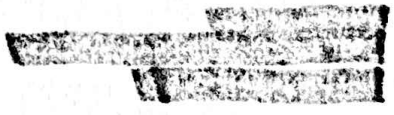

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Health Information Portability and Accountability Act (HIPAA)

There are rules to protect your private health information. Federal and state laws and the federal medical law, known as the HIPAA Privacy Rule, also protect your privacy. By signing this document, you provide your permission called your 'authorization,' for the access, use, and disclosure of information protected by the HIPAA Privacy Rule.

The research team working on the study will collect and use information learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records such as medical history, history of drug or alcohol abuse, or mental health treatment.

The research team may also need to share your health information and the information it collects to other entities as part of the study progress. Other VA entities may include the VA Office of Research Oversight (ORO), the VA Institutional Review Board, the General Accounting Office, and the VASDHS R&D Committee. Non-VA entities may include the Federal Office of Human Research Protections, the Food and Drug Administration, and the UCSD Keck Center. In addition, federal compliance officers may look at or copy portions of records that identify you. Your health information disclosed outside the VA as described in this authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the recipient.

You can revoke this authorization, in writing, at any time. To revoke your authorization, you may (a) write to the Release of Information Office at this facility; (b) ask a member of the research team to give you a form to revoke the authorization; or (c) send your written request to the Principal Investigator for this study at the following address:

If you revoke this authorization, Dr. Klaming Miller and her research team can continue to use information about you that was collected before receipt of the revocation. The research team will not collect information about you after you revoke the authorization.

While this study is being conducted you will not have access to your research-related health records.

Treatment, payment or enrollment/eligibility for benefits cannot be conditioned on you signing this authorization.

Unless you revoke (take back) your permission, your authorization to allow us to use and/or disclose your information will expire at the end of this research study.

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AGREEMENT TO AUTHORIZE USE AND RELEASE OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION

By signing this document below, I give my authorization (permission) for the use and disclosure of my individually identifiable health information as described in this document. This authorization has been explained to me and I have been given the opportunity to ask questions. If I believe that my privacy rights have been compromised, I may contact the VHA facility Privacy Officer to file a verbal or written complaint. I will be given a signed copy of this document for my records.

Participant's Signature	Last 4 of SSN	Date

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EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

You have been asked to participate as a subject in medical research.
You have the right to know:

1) The nature and purpose of the study.
2) The procedures in the study and any drug or device to be used.
3) Discomforts and risks reasonably to be expected from the study.
4) Benefits reasonably to be expected from the study.
5) Alternative procedures, drugs, or devices that might be helpful to you and their risks and benefits.
6) Availability of medical treatment should complications occur.
7) You may ask questions about the study or the procedure.
8) You may quit the study at any time without affecting your future care at the VA.
9) You should be given a copy of the signed and dated written consent form for the study.
10) Your consent to participate must be given freely, without being obtained through deceit, force, or coercion.

If you have any questions or concerns about your rights as a research subject please contact the VASDHS Research Compliance Officer at [redacted] or [redacted] You may leave an anonymous comment at the VASDHS research compliance hotline at [redacted]

REF: California HSC 24170-24179.5