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

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Summary

Chronic heavy drinking in alcohol use disorder (AUD) results in psychological and physical distress during abstinence, including anxiety, irritability, and general discomfort, which increases the urge to drink to relieve these symptoms. The goal of this study is to modify the perception of such inner bodily sensations of distress using noninvasive vagal nerve stimulation (nVNS), a low risk form of neuromodulation, and consequently to reduce the drive to drink for relief. We hypothesize that nVNS will be well received by Veterans as a novel treatment option for AUD, and that it can improve alcohol-related functional disability and quality of life.

Specific Aims

Aim 1: The primary aim is to establish feasibility and acceptability of using nVNS as a rehabilitative treatment for AUD in Veterans within the VA San Diego Healthcare System (VASDHS).

Aim 2: The secondary aim is to evaluate the effectiveness of nVNS in improving functional outcomes and quality of life, as well as in reducing distress, and alcohol craving.

Aim 3: The final aim is to alter neural activation patterns in brain regions subserving perception and awareness of emotional and physical distress using nVNS.

Design and Methods

Approach: We plan to use noninvasive vagal nerve stimulation (nVNS; handheld device) in Veterans with AUD to downregulate interoception of emotional and physical distress and craving, in addition to reducing alcohol-related functional impairment and improving quality of life. Veterans with current AUD (with at least one functional disability due to alcohol use and current alcohol craving based on DSM-5 criteria), will be included in the study.

Subjects will be asked to come in for a total of two study visits (baseline and follow-up) and self-administer nVNS/sham twice a day for a period of 7 days in between these visits. During both visits, subjects will be asked to complete behavioral assessments and to participate in an fMRI scan. If subjects are unable to come in for their follow-up person, they will be given the option to complete the questionnaires remotely (via telehealth, phone, or mail). Procedures for this are detailed under "Covid-19 adaptations". Please see figure below for a schematic and chronological presentation of the research components. Subjects will be randomly assigned to receive nVNS or sham stimulation prior to performing a well-validated fMRI task designed to assess the neural correlates of

physical distress (pain processing via heat stimulus). During each scan (baseline and follow-up), nVNS or sham stimulation will be administered once for 120 seconds. Subjects will remain in the same condition (sham/nVNS) assigned at baseline and be instructed to self-administer nVNS/sham at home for 7 days and return for a follow-up visit (treatment adherence and adverse events will be measured with a daily log and interview). Behavioral assessments of functional disability, quality of life, psychological and physical distress and craving will be administered at baseline, after stimulation, and at follow-up (post 7 days of nVNS/sham self-administration). After completion of the study visit, subjects will be evaluated for any side effects from stimulation and sent home. The patient will be instructed to carry out stimulation (sham or nVNS) twice a day for the following 7 days. Subjects will be instructed to drink “as usual” during the 7-day treatment window, with the intention to observe whether nVNS leads to reduced alcohol use, and will be asked to abstain again for 24 hours prior to their follow-up study visit on day 9 (allowing subjects to administer nVNS/sham on day 8 ad lib). Drinking behavior during the trial (as well as at baseline and follow-up) will be quantified with the Timeline Follow Back. Treatment acceptability will be assessed at follow up. We previously established feasibility of applying nVNS/sham in healthy individuals (Lerman et al., 2019) and have completed similar work with Veterans. However, this work has not been done in heavy drinkers.

Subjects will be asked to refrain from drinking alcohol for 24 hours prior to each study visit as symptoms of anxiety, irritability, and physical distress due to the cessation of heavy drinking typically occur during this time frame (Caputo et al., 2020). A breathalyzer will be used to at each study visit to ensure subjects are not intoxicated. Subjects who test positive will be rescheduled for a later session and monitored until BAC returns to safe levels. During the 7-day window between study visits, subjects will be asked to abstain from drinking for 24 hours prior to each visit. The timeline-followback (TLFB) will be used to quantify alcohol consumption prior to each visit. The TLFB is a self-report measure.

Subjects with severe alcohol withdrawal will not be included in the study. Therefore, no management of alcohol withdrawal symptoms will be needed during the study. In order to ensure subject safety and prevent medical complications due to acute withdrawal syndrome, two measures will be put in place: 1) During the screening process, subjects will be asked if there has been a time in the past where they did not drink for 48 hours and if they experienced any symptoms or complications during that time, and 2) subjects with a score higher than 9 on the Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) will be excluded from the study and immediately referred to the hospital as it may not be safe for these individuals to abstain from alcohol without medical supervision.

Study outline:

Baseline Visit

1. Behavioral assessments (see below)

2. fMRI scan
- nVNS/sham (during scan)
- Scans: Anatomical, Heat pain task

7 day interval: at home
nVNS/sham self-administration (2 x day for 7 days)

Follow-up Visit

1. Behavioral assessments (see below)

2. fMRI scan
- nVNS/sham (during scan)
- Scans: Anatomical, Heat pain task

Description of nVNS device: The gammaCore® is a multi-use device designed for intermittent external stimulation of the vagus nerve, capable of delivering multiple (up to 150) 90-second vagal nerve stimulation with a 30-second margin for set-up and operator adjustment of the stimulation intensity (the stimulation automatically stops 120 seconds after the device is powered on). The user applies conductive gel to the stimulation surfaces and then holds the gammaCore® device on the skin over the vagus nerve of the neck (between the trachea and the sternocleidomastoid muscle, over the carotid pulse). The gammaCore® device produces a proprietary, low voltage electric signal that generates an electric field in the vicinity of the vagus nerve when the device is placed in the intended location. The sham stimulation is comprised of very low voltage direct current (DC) as opposed to alternating current used in the nVNS device.
For self-administration, the subject will undergo transcutaneous electrical stimulation over the neck in with the gammaCore device. Prior to stimulation, the subject will place gel on the device contacts and then place the device to the neck, after which the thumbwheel is turned to increase the stimulation intensity until the subject feels a buzzing sensation. This sensation will occur for 2 minutes after which the device automatically turns off. This will be repeated 1 time during visit #1 and #2. Between visit #1 and visit #2, stimulation will be carried out at home once daily for 7 days.

There is discernable difference in stimulation of sham vs. nVNS in that nVNS does cause muscle contraction (Platysma). To minimize any Placebo or Nocebo effects, all devices (nVNS and sham) will have an identical appearance and all subjects will undergo identical training paradigms. Both sham and active nVNS treatment produce reliable sensation on subject skin (sham device delivers a low dose DC voltage signal that results in paresthesia and prickling like sensation) and in our preliminary survey, subjects are unable to differentiate sham from active nVNS device ($p>.1$). Written home instructions are provided for use of both devices. Both devices are handheld and easily applied to the neck (over the carotid artery) for a treatment of two minutes (once daily for seven days). The nVNS device produces a low-voltage electrical signal (5-kHz sine wave series that occurres for 1 ms and repeated every 40 ms [25 Hz]). The sham device is identical in appearance, and carries out the same period of stimulation but differs in stimulation parameters with a slowly varying direct current(DC) signal(0.1 Hz) that produces a slight skin tingling sensation. In both the nVNS and sham device, there is an initial 30-sec ramp up period, resulting in a total of 90 sec of actual stimulation per two-minute stimulation session. There is a knob on both sham and nVNS device that is turned to the on position. As stated above, the stimulation occurs for 2 minutes time after the knob is turned on. For sham device the intensity is titrated (via the rolling knob) until there is actual sensation on the skin. For active nVNS device the intensity is increased until there is muscle (platysma) contraction. Finite element electric field modeling show at this intensity (with muscle contraction) the electric field penetrates deep and activates the vagus nerve.
To minimize placebo or nocebo effects, devices (nVNS/sham) will have an identical appearance and all subjects will undergo identical training for self-administration. Both sham and nVNS treatments produce reliable sensations on the skin (sham device delivers a low dose DC voltage signal that results in paresthesia and prickling like sensations) and in preliminary surveys, subjects were unable to differentiate sham from active nVNS devices ($p>.1$). Dr. Simmons will be unblinded to the treatment condition and provide the sham vs. nVNS device to the research team. Both the research team involved in data collection and subjects will be blinded (i.e., double-blind study design).

Neuroimaging: MRI scans take approximately 1 hour. The protocol includes one structural scan (structural T1) and up to four functional scans.
Anatomical Scan: During the anatomical scan, participants are asked to remain as still as they can for approximately 8 minutes. Pleasant pictures may be put up on a screen for participants to enjoy while the anatomical scan is occuring.
Heat pain task: The pain paradigm includes two conditions: “heat pain” (i.e., brief thermal heat temperature that produces heat pain sensations), or “warm stimulus” (i.e., brief thermal heat that produces warm sensations). Each temperature is delivered for 5 sec. Thermal stimuli, experienced as heat pain and warm, are delivered in a pseudo-random and counterbalanced order through a 9-cm2 thermode (Medoc TSA-II, Ramat-Yishai, Israel) fastened to the subject’s left lower extremity (antero-medial ankle). Before scanning, subjects are pretested with several heat pain and warm thermal stimuli to ensure that temperatures are well tolerated. This setup is MRI safe and is currently used in Dr. Lerman’s study and has been used in our prior fMRI studies.

Behavioral assessments: After enrollment participants will complete self-report measures in a designated, secure space located at VMRF or the UCSD Keck Center for fMRI Data will be de-identified with a code and entered into a secure database on the VA server for future analysis. The code key will be kept separate from coded data and will not be available on the computers. No identifiable data will be stored with coded electronic research data. Assessment measures will be given at both baseline and follow-up visits. The research information that may be collected includes the following:

Questionnaires

Main outcome measures

Treatment Acceptability Questionnaire (TAQ). The TAQ will be used to assess acceptability of using non-invasive neuromodulation as a rehabilitative treatment for AUD. The TAQ uses a 7-point rating scale ranging from 1 to 7, with lower scores reflecting lower acceptability and a midpoint of 4 indicating neutral acceptability. A rating above the midpoint of the TAQ (i.e., score between 5 and 7) is the established criterion for "acceptable to highly acceptable" across several previous studies. Thus, a cut-point of ≥5 on the TAQ is selected as acceptable. This survey has good internal consistency and test-retest stability.

Substance Use Recovery Evaluator (SURE). The SURE assesses the following domains of AUD-related functional outcomes: self-care (mental and physical health), relationships, material resources (stability of housing and occupational resources), and outlook of life. The SURE has been developed for use in substance use disorder populations and was rigorously examined for sound psychometric properties.

WHO Quality of Life assessment (WHOQOL-BREF). The WHOQOL-BREF assesses quality of life across four domains (physical health, psychological, social relationships, and environment) with a total of 26 questions. The WHOQOL-BREF is a widely used instrument with strong psychometric properties.

Beck Anxiety Inventory (BAI). The BAI is a self-report instrument to measure the severity of anxiety and emotional distress. It takes approximately 5–10 minutes to complete with good test–retest reliability.

PROMIS Pain Interference. The PROMIS measures self-reported consequences of pain on relevant aspects of one's life, i.e., the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. The PROMIS is universal (not disease-specific), with good psychometric properties.

Alcohol Urge Questionnaire (AUQ). The AUQ is an internally consistent, reliable, and psychometrically valid 8-item scale that measures cognitive preoccupation with alcohol. This survey is commonly used in alcohol treatment research.

Alternative outcome measures

Sheehan Disability Scale (SDS). The SDS assesses functional impairment in three inter-related domains (work/school, social, family life) that directly overlap with five out of eleven DSM-5 diagnostic criteria for AUD. Completion takes approximately 10 min..

Inventory for Psychosocial Functioning (IPF). The IPF assesses functional limitations in interpersonal relationships, family, work, , parenting, education, and self-care) with good reliability and validity.

Screening questionnaires

Structured Clinical Interview for DSM-5 (SCID). This semi-structured interview will be used to establish a DSM-5 AUD diagnosis. Stem questions will be used to screen for inclusions/exclusions.

Alcohol withdrawal symptoms. The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) is a short form (5 min.) to assess physiological and psychological symptoms of alcohol withdrawal.

Timeline follow-back (TLFB). The TLFB is a standard tool used to document number and types of drinks consumed per day during a specified time frame. The TLFB will be used to measure alcohol use (percentage days abstinent, amount consumption, length of use episodes, and current alcohol use pattern) use during the 90 days preceding baseline interview, during, and between interviews.

Human Subjects

The participants in this study will be 20 physically healthy male Veterans with current AUD. Subjects will be recruited via flyers posted in VA mental health and primary care, from advertisements in print and web-based media, and from VA substance use and other psychiatry clinics. Participants will be asked to refrain from drinking alcohol 24 hours prior to each study visit and will be randomly assigned to receive nVNS or sham stimulation (10 nVNS/10 sham) prior to performing a well-validated fMRI task designed to assess the neural correlates of physical distress (pain processing via heat stimulus). Subjects will then be instructed to self-administer nVNS at home for 7 days and return for a follow-up visit (same protocol will be repeated at follow-up). Behavioral assessments of drinking-related consequences, functional disability and health, psychological and physiological distress, and craving will be administered at baseline, after stimulation, and at follow-up (post 7 days of nVNS/sham self-administration).

Inclusion Criteria.

1. Male subjects between 21 and 65 years, any race or ethnicity. 2. Meet current DSM-5 diagnosis of AUD (Structured Clinical Interview for DSM-5 (SCID) interview 1) with at least one functional disability due to alcohol use, current alcohol craving, and current heavy drinking (>4 drinks on any given day within the last week OR more than 14 drinks per week). 3. Able to forgo consumption of alcohol for 24 hours without any serious discomfort including nausea/vomiting, visual/auditory/tactile hallucinations, or non-essential tremor. 4. Capable of complying with study schedule, procedures, and speaks English. 5. Able to provide voluntary written informed consent prior to initiation of visit 1; and be able to commit to the return visit at the end of the study.

Exclusion Criteria.

1. Clinical Institute Withdrawal Assessment of Alcohol Scale (CiWA) score >=9 on the day of the scan (symptoms judged to be due to co-existing anxiety conditions or headache disorders will not be counted toward the total). 2. Currently or recently (within last 90 days) enrolled in abstinence-based treatment program. 3. Evidence of a maladaptive pattern of substance use or abuse (based on the SCID) other than alcohol one month prior to the screening visit. 4. Significant mental illness, e.g. psychosis or

bipolar disorder based on SCID interview. We will not exclude for PTSD 5. At risk for suicide or homicide (based on BDI-2 screen and follow-up clinical interview). 6. History of neurological disorder that might be associated with cognitive dysfunction. 7. History of head trauma involving loss of consciousness >24 hours and post-traumatic amnesia of more than 1 week. 8. Chronic pain as defined by pain persisting beyond its ecological alerting function, and clinically defined as lasting longer than 3 months, and/or currently under the care of a chronic pain physician. 9. Clinically significant uncontrolled/unstable medical illness or clinically significant surgery within 1 month of the screening visit. 10. MRI-related exclusion criteria: cardiac pacemaker, metal fragments in eyes/skin/body, aortic/aneurysm clips, hearing aid, heart-valve replacement, copper intrauterine device, shunt (ventricular or spinal), neuro/bio-stimulators, inability to lie still on their backs for 60 minutes, piercings that cannot be removed. Any implants will be reviewed for safety. 11. Vagus nerve stimulation related criteria: history of carotid endarterectomy, severe carotid artery disease (e.g. history of transient ischemic attack (TIA) or stroke], congestive heart failure, cardiac arrhythmia, known severe coronary artery disease or recent myocardial infarction (within 5 years), or history of seizure or syncope (within the last 1 year), prior neck surgery.

Subjects with a score higher than 9 on the Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) will be excluded from the study and immediately referred to the hospital as it may not be safe for these individuals to abstain from alcohol without medical supervision.

Data analysis

Image analysis pathway: Image processing will be done with the AFNI software package (afni_proc.py). Specifically, the EPI timeseries despiked (3dDespike), slice time corrected (3dTshift), and co-registered, which will provide motion parameters (x, y, z, roll, pitch, yaw) for each EPI image's registration to the optimal base image (align_epi_anat.py:3dvolreg). Based on the distribution of these average motion parameters, subjects will be excluded if the average in any one of these parameters exceeds 2 absolute deviations from the mean. All EPI timeseries will be moved to MNI coordinates (align_epi_anat.py: 3dQWarp), blurred to 2x voxel width (to account for individual variations in the anatomical landmarks (3dBlurToFWHM), and converted to percent signal change (3dcalc). Preprocessed time series data for each individual will be analyzed using a multiple regression model. A multivariate regressor approach will be used to relate changes in EPI intensity to differences in task characteristics. Regressors of interest include: 1) Pain [i.e., what activates during pain stimuli], 2) Non-pain [i.e., what activates during non-painful stimuli], 3) Pain anticipation [i.e., what activates during anticipation of pain stimuli] and 4) Non-Pain anticipation [i.e., what activates during anticipation of non-painful stimuli]. To reduce the false positives induced by auto correlations of the time series, data will be fit using the AFNI program 3dREML. Statistical analysis of fMRI derived data will be obtained with standard statistical techniques.

Group analyses. Statistical analyses will be performed to evaluate treatment acceptability, if nVNS improves functional outcomes, quality of life, emotional and physical

distress, and alcohol craving in Veterans with AUD, and if nVNS alters neural activation patterns in brain regions involved in perception and awareness of distress. The family-wise error (FWE) rate will be set at p=.05 as we have limited power to more stringently correct for multiple comparisons. We will examine correlations between dependent variables and potentially confounding factors, such as age, AUD severity, or level of depression and anxiety, and covary for these factors if necessary. In addition, we will covary for TLFB data (i.e., days since last drink, number of drinks, percent days drinking, etc.).

Aim 1: The primary aim is to establish feasibility and acceptability of using nVNS as a rehabilitative treatment for AUD in Veterans within the VA San Diego Healthcare System (VASDHS).

To test hypothesis 1: Recruiting 16 subjects within 12 months as well as treatment adherence and retention rates of >75% will be considered feasible. A mean group score for treatment acceptability (TAQ) will be calculated for the nVNS group and a value of ≥5 will be considered an acceptable treatment (17).

Aim 2 (exploratory): The secondary aim is to evaluate preliminary effectiveness of nVNS in improving functional outcomes and quality of life, as well as in reducing distress and alcohol craving.

To test hypothesis 2a: We will use linear mixed effects (LME) models to assess the impact of treatment group on Substance Use Recovery Evaluator (SURE) and WHOQOL-BREF scores. Specifically, we will test group (nVNS/sham) by time (baseline/7 days FU) interactions.

To test hypothesis 2b: We will use LME models to assess the impact of treatment group on Beck Anxiety Inventory and PROMIS Pain Interference Scale scores. Specifically, we will test group (nVNS/sham) by time (baseline/7 days FU) interactions.

To test hypothesis 2c: We will use LME models to assess the impact of treatment group on Alcohol Urge Questionnaire scores. Specifically, we will test group (nVNS/sham) by time (baseline/7 days FU) interactions.

Aim 3 (exploratory): The final aim is to alter neural activation patterns in brain regions subserving perception and awareness of emotional and physical distress using nVNS.

To test hypothesis 3: We will use linear mixed effects models to assess the impact of treatment group (nVNS/sham) by time (baseline/7 days FU) in a 2-way interaction on insular activation. Exploratory voxel-wise analyses will also be performed to examine effects of group on amygdala, anterior cingulate, and striatum. The MNI transformed percent signal change from the functional data will be contrasted in a voxel-based linear mixed effects model (AFNI 3dLME), with group and time factors entered as primary contrasts. In addition, subject will be entered as a random factor. A threshold adjustment method based on Monte-Carlo simulations will be used to guard against identifying false positive areas of activation. These simulations will use a 2-parameter model fit calculated in the 3dFWHMx (ACF) function using a measured blur and requiring a voxel-based threshold at .001 and cluster level thresholding at .01 or with 22 for group and time effects for the whole brain analysis.