Understanding the Mechanistic, Neurophysiological, and Antinociceptive Effects of Transcutaneous Auricular Neurostimulation for Treatment of Chronic Pain

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Consent Form

The University of Texas Medical Branch at Galveston
More Than Minimal Risk Consent Form

Protocol Title: Understanding the Mechanistic, Neurophysiological, and Antinociceptive Effects of Transcutaneous Auricular Neurostimulation for Treatment of Chronic Pain

IRB Number: 22-0187

Sponsor: National Institute of Neurological Disorders and Stroke

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Why am I being asked to take part in this research study?
You are being asked to take part in this study because (a) you have chronic pain, (b) you take an opioid (such as hydrocodone, tramadol, acetaminophen with codeine, and/or morphine) medication for pain, and (c) your doctor has recommended that you reduce the amount of pain medication you take. Your participation in this study is completely voluntary. You may refuse to participate or stop your participation in this research study at any time without penalty or loss of benefits and without jeopardizing your medical care at the University of Texas Medical Branch (UTMB).

Study Summary:
You should know the following things about this research study:

- The purpose of the study is to find out how a stimulation device (Sparrow Therapy System) worn on the ear works. This device is thought to stimulate nerves in the area around the ear to change the signals in your brain. The device has been shown to reduce pain and to reduce the symptoms of withdrawal. We will also investigate changes in the way you perceive sensations of pressure and heat.
    - If you chose to participate, you will be asked to reduce the amount of pain medication you take.
    - You will need to bring your own prescribed medication and check it into a locked cabinet. You will be given your medication doses.
    - You will spend several days and nights (approximately 76 hours) in the Clinical Research Center at UTMB in Galveston.
    - During that time, you will be monitored for withdrawal symptoms and will receive either active (e.g., "real") brain stimulation or sham (e.g., "fake") brain stimulation for three days (four hours each day).
    - At two times over the course of the study (before and after ear stimulation treatment), you will complete questionnaires about your pain score and how you are feeling, sensory testing, and you will undergo magnetic resonance imaging (MRI) of your brain.
    - We will collect the following information from your medical record: age, gender, medication history, medical diagnoses, recent vital signs, past doctor visits or hospital stays, and results of urine drug tests.
- Risks and discomforts from this study include the following:
    - Discomfort during pain medication reduction (e.g., withdrawal symptoms, pain, emotional distress).
    - Discomfort during ear stimulation (skin irritation, headache).
    - Claustrophobia during MRI.
    - Discomfort or pain during sensory testing
    - Loss of confidentiality.

- The study might potentially provide you with relief from pain and withdrawal symptoms.
- Taking part in this research study is voluntary. You do not have to participate and you can stop at any time.

Please take your time to read this entire form and ask questions before deciding if you want to take part in this research project.

DETAILED RESEARCH CONSENT

What is the purpose of this research study?

The purpose of the study is to test how this device reduces pain and opioid withdrawal during reduction in pain medicine dose. Specifically, we are interested in how stimulation of several nerves near the outside of your ear changes how your brain processes pain.

How many people will take part in this study?

Up to 60 participants will enroll and initiate the study, and enrollment will cease once 40 participants have completed the study.

What procedures are involved as part of this research study?

If you agree to take part, you will be asked to sign this consent form and have the following tests and procedures. Some of the procedures may be part of your standard medical care, but others are being done only because you are taking part in this research study. If you participate you will have one study visit at the Clinical Research Center that will last approximately 76 hours (e.g., three nights).

On Day 1 at the CRC, we will review the consent and if you agree to participate, obtain consent. We will reduce the amount of pain medication on the first day and continue for four days. The reduction in dose will be 10-30% of your daily pain medication dose. You will complete questionnaires, MRI, and sensory testing (heat and pressure pain).

- Women of child-bearing age will complete a urine pregnancy test and it must be negative.
- Urine Drug Test
- Brain Imaging training
- Brain Imaging (fMRI)
- Quantitative Sensory Testing (QST)
- Neurostimulation training
- Subjective Pain questionnaires
- Demographics questionnaire
- Opioid Withdrawal Severity questionnaires (COWS/SOWS)
- Depression and Anxiety Questionnaires
- Physical functioning, sleep, and substance use questionnaires

On Day 1, you will be randomly assigned to receive either active, (real) brain stimulation or sham (fake) brain stimulation. You have an equal chance of being assigned to either group (similar to flipping a coin). Sham brain stimulation will look and feel like active stimulation. You will not be able to tell which type of stimulation you received until you complete the study. Brain stimulation will be delivered on the second, third, and fourth days of the study for approximately four hours each day (e.g., four sessions of stimulation for one hour each day). You will also have your heart rate, blood pressure, and breathing rate measured; and will complete withdrawal symptom questionnaires and give a pain score every four hours from 8am to 8pm. The researchers will not disturb you at night.

- Neurostimulation. Neurostimulation will be administered using the Sparrow device (active or sham) You will have training on the neurostimulation device on day 1. You will have administration of 4-hours per day for three days (Days 2, 3 and 4). Administration times will typically be broken into four 1-hour administrations, but participants can request alterations to this schedule if needed as

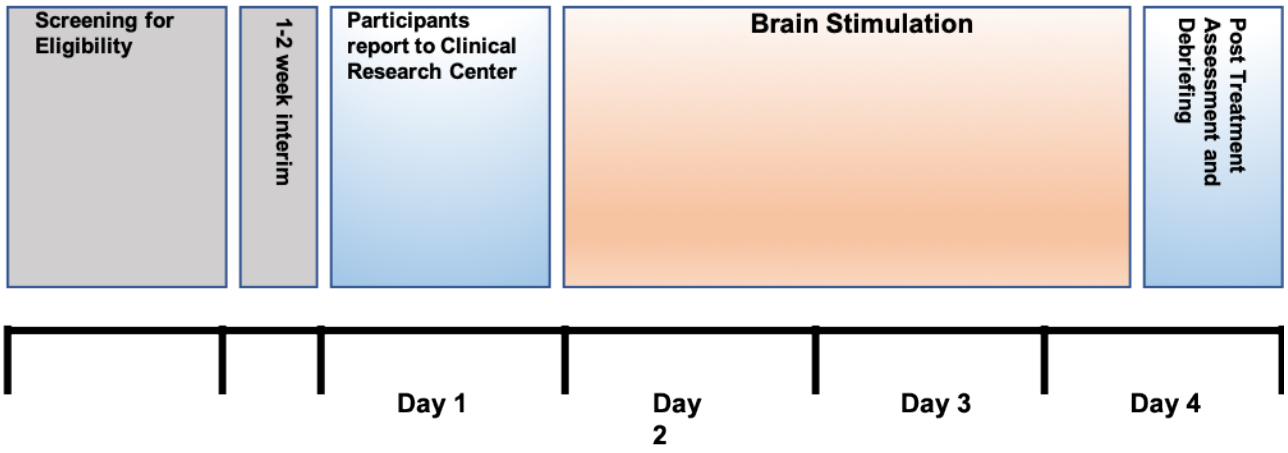
long as they receive four total hours of tAN.

- Subjective Pain Assessment. Subjective pain score will be assessed before and after each neurostimulation session using the questionnaire, from 8am to 8pm.
- Opioid Withdrawal Questionnaires. Study personnel will assess severity of opioid withdrawal symptoms using the Clinical Opioid Withdrawal Scale (COWS). Likewise, participants will provide their own ratings of withdrawal using the Subjective Opioid Withdrawal Scale (SOWS) three times a day from 8am to 8pm

On Day 4, you will complete questionnaires, fMRI, neurostimulation, and sensory testing.

- Neurostimulation for 4-hours
- Neurostimulation experience questionnaire
- Brain imaging (fMRI) will be conducted at post-treatment (evening of Day 4).
- Sensory testing of heat and pressure will be done in the same manner as on Day 2.
- Subjective Pain score questionnaires
- Opioid Withdrawal Questionnaires (COWS/SOWS)
- Depression and Anxiety Questionnaires
- Physical functioning, sleep, sham/active, and substance use questionnaires
- Debriefing Plan - Upon conclusion of the study, participants will be asked if they have any further questions or whether any adverse events occurred. They will be instructed to continue the current dose and to schedule a follow up appointment with their provider within two weeks.

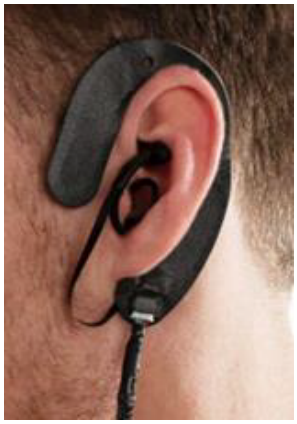
A visual timeline of the study is displayed below:



What extra tests and procedures will I have if I take part in this study?
You will be asked to complete questionnaires, sensory testing, and a brain MRI. Sensory testing will involve tests of thermal (heat) and pressure pain. Thermal pain is tested using a metal plate, attached to your forearm, which starts at body temperature and heats up. The temperature of the plate is well within a safe limit to not cause any harm to your skin. Pressure pain will be tested using a metal probe that is pressed against different areas of your body until you feel pain; this test will also not cause any harm. These tests are a part of the research study and are not a part of standard medical practice. The ear stimulation device and the reduction of pain medications are standard medical practice.

What are the possible risks for choosing to participate in this research study?
Because of your participation in this study, you are at risk for the following side effects. You should discuss these with the researchers.

Pain Medication Reduction: Reducing the dose of your pain medication can be uncomfortable for patients but is generally safe. Potential side effects include withdrawal symptoms (e.g., anxiety/restlessness, fast heart rate, stomach cramps, nausea, vomiting, diarrhea, sweating, tremor, yawning, bone/joint aches, goosebumps, and runny nose and/or nasal congestion). In very rare cases, fast heart rate can lead to abnormal heart rhythms or heart attack. We will monitor blood pressure and heart rate every four hours during the daytime (8am-8pm), in order to not disrupt sleep, in the CRC. However, when the reduction is done slowly with medical supervision, patients are less likely to experience adverse events, including intolerable withdrawal symptoms. You must also be ready and willing to reduce your pain medication dose.



Ear/Brain Stimulation: Ear stimulation, the type of brain stimulation we are studying, targets the vagus and trigeminal nerves as they pass near the ear. This treatment is cleared by the Food and Drug Administration for treatment of pain medication withdrawal symptoms and has been used safely in adults and babies. Some patients may experience skin irritation around the ear, such as tingling, earache, muscle twitching, allergic reaction, or other short-term discomfort. These discomforts typically disappear after stopping the device or turning down the intensity of stimulation. It is possible that ear stimulation could cause your heart rate to slow down, but this has not been observed in previous clinical studies. We will monitor your heart rate and blood pressure many times during stimulation and discontinue the treatment if any significant drop in heart rate occurs.

MRI: MRI is safe except for patients with implanted metal or who are currently pregnant. The only minor risk for other persons is the possibility of experiencing claustrophobia during scanning. To reduce this risk, participants will have time to get familiar to the MRI environment by spending time in a mock (pretend) scanner. The total amount of time for the complete MRI will be approximately 1 hour and 10 minutes.

Emotional Stress
Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions, take a break, or stop your participation in this study at any time.

Heat and Pressure Sensory Testing
You may experience discomfort or pain during sensory testing. If you are taking blood thinners, you may experience bruising.

Loss of Confidentiality
Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

What are the potential benefits for participating in this research study?
If you agree to take part in this study, there may be direct benefits to you. We hope the information learned from this study will benefit others with chronic pain and those who need to reduce their pain medication in the future. Potential direct benefits include reduction in pain and pain medication withdrawal symptoms.

Will I be paid for participating in this research study?
You will be reimbursed $2,000 dollars for the study visit including $100 for travel incidentals. You will be reimbursed at a rate of $25 per hour for each hour that you complete, even if you do not complete the overall study. In addition, each participant who lives greater than 50 miles from Galveston may receive travel related expences including mileage, flights, ground transportation, and hotel using standard rates. If a meal is needed the night prior or night after discharge, this will be reimbursed up to $20 per meal. This will be reimbursed up to a total of $300 per participant for extended travel. Participants who live within 50 miles, who need transportation may receive a Lyft ride to and from the CRC or a screening appointment. You will be issued a

UTMB Clincard, which is a debit card that your funds are loaded onto following completion of the study visit. When the study visit is completed, funds will be approved and loaded onto your card. The funds will be available within 48 hours and can be used at your discretion. You will be issued one card for the duration of your participation. If your card is lost or stolen, you can contact customer service at 1-866-952-3795. We will collect some information about you, including name, address, telephone number, date of birth, email address, if applicable, and your social security number (if a U.S. citizen) to issue the debt card. All information is stored in a secure fashion and will be deleted from system once the study has been completed and the funds on the card have been all used.

Is there an alternative treatment/procedure?
You do not have to participate in this research to receive care for your medical problem. Instead of being in this study, you have the following options:

- If you are unsure about making changes to your pain medication regimen, discuss them with your doctor prior, and review your options.
- Discuss alternative strategies for reducing your pain medications with your doctor.

Please talk to the researchers or your personal doctor about these options.

If I agree to take part in this research study, can I be removed from the study without my consent?
Yes. The researchers may decide to take you off this study if:

- Your medical problem remains unchanged or becomes worse.
- The researchers believe that participation in the research is no longer safe for you.
- The researchers believe that other treatment may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Will my insurance provider or I be charged for the costs of any part of this research study?
No. Neither you, nor your insurance provider, will be charged for anything done only for this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring/Follow-up Procedures described above).

However, the standard medical care for your condition (care you would have received whether or not you were in this study) is your responsibility (or the responsibility of your insurance provider or governmental program). You will be charged, in the standard manner, for any procedures performed for your standard medical care.

What will happen if I am harmed as a result of taking part in this study?
It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Medical Branch at Galveston. If there are costs associated with an injury resulting from your participation, you or your insurance company or health care plan, will be billed and you will be responsible for any charges.

You will be responsible for paying any costs related to illnesses and medical events not associated with being in the study. There are no plans to provide other forms of compensation. However, you are not waiving any of your legal rights by participating in this study.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

How will my information be protected?
All results obtained in this study will be kept confidential and only available to the research study team. Your individual information will not be reported, only the results of all participants as a group. Data or specimens collected in this research might be deidentified and used for future research or distributed to another investigator for future research without your consent.

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

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

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

Clinicaltrials.gov Registration Information
A description of this clinical trial will be available on 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.

How will my privacy be protected?
We have rules to protect information about you. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form you provide your permission, called your "authorization," for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things 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. This could include information about HIV and genetic testing, or treatment for drug or alcohol abuse or mental health problems.

The research team will know your identity and that you are in the research study. Other people at UTMB, particularly your doctors, may also see or give out your information. We make this information available to your doctors for your safety. If you think this study might affect your clinical care, please inform your doctor.

People outside of UTMB may need to see or receive your information for this study. Examples include government agencies (such as the Food and Drug Administration), safety monitors, other sites in the study and companies that sponsor the study.

We cannot do this study without your authorization to use and give out your information. You do not have to give us this authorization. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form; however, people outside UTMB who receive your information may not be covered by this promise or by the federal Privacy Rule. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee that your information will not be re-disclosed.

The use and disclosure of your information has no time limit. You may revoke (cancel) your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing. If you contact the Principal Investigator by phone, you must follow-up with a written request that includes the study number and your contact information. The Principal Investigator's name, address, phone and information are on page one of this consent form.

If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your revocation (cancellation) would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

Finally, please specifically authorize the use of your private health information relating substance abuse, psychiatric information, or HIV/AIDS, if applicable, for the above-described purposes.

Initial: _____

Who can I contact with questions about this Research study?
If you have any questions, concerns or complaints before, during or after the research study, or if you need to report a research related injury or bad side effect, you should immediately contact Dr. Denise Wilkes at (281) 832-2450 or Dr. Kathryn Cunningham at(409 789-4999, if after normal office hours, Study personnel's mobile phone (832) 644-2121

This study has been approved by the Institutional Review Board. If you have any complaints, concerns, input or questions regarding your rights as a subject participating in this research study or you would like more information about the protection of human subjects in research, you may contact the Institutional Review Board Office via email irb@utmb.edu.

CONSENT TO PARTICIPATE:
The purpose of this research study, procedures to be followed, risks and benefits have been explained to you. You have been given the opportunity to ask questions, and your questions have been answered to your satisfaction. You have been told who to contact if you have additional questions. By signing this form, you are confirming that you have read this consent form and voluntarily agree to participate as a subject in this study.

_____ _____
Signature of Subject Date and time

Using language that is understandable and appropriate, I have discussed this project and the items listed above with the subject

_____ _____ _____

Signature of Person Obtaining Consent	Date and Time Consent Obtained

Printed Name of Person Obtaining Consent

A picture of the lead placement on your ear will record how we placed the lead for each day. The picture will only include your ear and the lead. It is very unlikely that someone can identify you from the picture.

CONSENT FOR PICTURE OF EAR

Signature of Subject	Date and time