Cleveland Clinic
Consent to Participate in a Research Study

Study Title: Nitrous Oxide for the Treatment of Complex Regional Pain Syndrome: A Prospective Randomized Controlled Pilot Study

Sponsor: Reflex Sympathetic Dystrophy Syndrome Association

Principal Investigator: **Alparslan Turan, MD**
During office hours Phone #: **216-445-9857**
After Office Hours: **216- 217-2312**

Carefully review this consent document. The purpose of a consent document is to provide you with information to help you decide whether you wish to participate in research. Your decision is completely voluntary and will not affect your medical care if you choose not to participate. It is important for you to ask questions and understand the research risks, benefits and alternatives.

Please note:

- **You are being asked to participate in a research study**
- **Carefully consider the risks, benefits and alternatives of the research**
- **Your decision to participate is completely voluntary**

Your doctor may be an investigator in this research study, and as a research investigator, is interested in both your welfare and in the conduct of the research study. Before entering this study or at any time during this research, you may ask for a second opinion about your care from another doctor who is not involved with the research study. You are not under any obligation to participate in any research project offered by your doctor.

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1. INFORMATION ON THE RESEARCH

Why Are You Being Asked To Take Part In This Research?

You are being asked to participate in this research study because you have been diagnosed with CRPS (type I or type II).

Why Is This Study Being Done?

The purpose of this study is to determine if nitrous oxide can help treat chronic pain from CRPS. Nitrous oxide, also known as "laughing gas" is a safe, inhaled anesthetic. On the molecular level, nitrous oxide works similarly to ketamine, which is another pain medication used to treat pain from CRPS.

How Many People Will Take Part In The Study?

About 56 people will take part in this study.

What Is Involved In The Study?

Your participation in this study will involve a series of questionnaires about your pain and daily activities, as well as three breathing treatment sessions. We will also track your daily opioid medication use.

You will be randomized (like flipping a coin) to one of two study groups. Both groups will receive three breathing treatments. One group will receive 50% nitrous oxide mixed with 50% oxygen, and the other group will receive 50% oxygen. All patients will receive a small dose of intravenous midazolam, a mild sedative. This will require IV access for each breathing treatment sessions. As nitrous oxide is sedating, the purpose of the mild sedative (midazolam) is to prevent patients from determining which group of the study they are in. Because of the sedating effect of midazolam, you will need a driver to return home.

You will fill out a few brief surveys, and you will be randomized to one of the two study groups. You will not know to which group you are assigned to. You will also be given a 7 days opioid use log to record your usage of opioid pain medications.

One week later, you will come to Cleveland Clinic Main Campus for your first breathing treatment. You will have a breathing mask that will remain on for up to two hours in the recovery room. You will be monitored with vital signs every 30 minutes (heart, blood pressure, and oxygenation), and you will be monitored for any side effects, including nausea, vomiting, desaturation, sedation, respiratory depression, and dizziness. You will complete the two additional breathing treatments over the course of 1 week.

Demographic data will be collected and recorded for our data analysis: age, sex, duration of disease, extremity/extremities affected.

You will have two follow-up phone call appointments at 1 week and 1 month after the final inhalation treatment session. Patients will be instructed (and reminded) to record their daily opioid use during the week preceding each phone call appointment. During each phone call appointment, you will complete the same surveys that were completed at the start of the study and report your answers over the phone.

How Long Will You Be In The Study?

Your participation in this study will last up to 2 months following the final breathing treatment.

2. RISKS AND DISCOMFORTS

What Are The Risks Of The Study?

There are risks, discomforts and inconveniences associated with any research study. Your research doctor will pay attention to any signs of unanticipated distress or discomfort, and will be ready to help you with appropriate treatment.

There is minimal risk associated with participation in this study. Your discomfort associated with this study should be minimal.

Nitrous oxide has a long history and its side effect and safety profile are well-known. Side effects associated with nitrous oxide generally appear with frequent, weekly usage. Therefore, we do not anticipate any side effects from study participation, as nitrous exposure will be infrequent and limited. However, mild side effects may include:

- nausea and vomiting
- chest pain
- respiratory distress
- headache

Pregnant women, fertile females/males:

There may be unforeseen risks to an unborn child associated with nitrous oxide exposure. Therefore, if you are capable of giving birth to or fathering a child, you and your sexual partner should use adequate birth control measures while you are in the study. These measures may include abstinence, oral contraceptives (birth control pills), IUD, diaphragm, approved hormone injections, condoms, or documentation of medical sterilization. If you are unwilling to do this, we ask that you not participate in this study.

Pregnancy tests will be performed on all women of child-bearing potential before the first breathing treatment. If you or your spouse becomes pregnant while taking part in this study you must notify the study doctor immediately. If birth control methods must continue after the study drug is discontinued, this time period should be provided to subjects.

Questionnaire/Survey Research:

There is, however, the potential risk of loss of confidentiality. Every effort will be made to keep your information confidential, however, this cannot be guaranteed. 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 and you may take a break at any time during the study. You may stop your participation in this study at any time.

3. BENEFITS

Are There Benefits To Taking Part In The Study?

Participation in this study may help to improve your condition, but it is also possible, however exceedingly unlikely, that your condition may worsen. There is no guarantee that you will personally benefit by participating in this research study. Your participation in this study may provide information that may help other people who have a similar medical problem in the future.

4. ALTERNATIVES
What Other Options Are There?

The alternative for you is to not participate in the study. Choosing not to participate in the study will not result in any prejudice to your care.

5. PRIVACY AND CONFIDENTIALITY

Cleveland Clinic has rules and procedures to protect information about you. Federal and State laws also protect your privacy.

The research team working on the study will collect information about you. This includes your health information, data collected for this research study and personal identifying information including your name, address, date of birth and other identifying information.
Generally, only people on the research team will know your identity and that you are in the research study. However, sometimes other people at Cleveland Clinic may see or give out your information. These include people who review research studies including the Institutional Review Board and Research Compliance, their staff, lawyers, or other Cleveland Clinic staff.

People outside Cleveland Clinic may need to see your information for this study. Examples include government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study and the sponsor of the research and their agents. Cleveland Clinic will do our best to ensure your information is kept confidential and that only the health information which is minimally required to conduct the study is used or disclosed to people outside Cleveland Clinic; however, people outside Cleveland Clinic who receive your information may not be covered by this promise.

You do not have to give this permission to use and give out your information; however you will not be able to participate in this research study without providing this permission by signing this consent form. The use and disclosure of your information has no expiration date.

You may cancel your permission to use and disclose your information at any time by notifying the Principal Investigator in writing**,**

Alparslan Turan, M.D.
Outcomes Research
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If you do cancel your permission to use and disclose your information, your participation in this study

will end and no further information about you will be collected. Your cancellation would not affect information already collected in the study.

6. RESEARCH RELATED INJURIES

What Happens If An Injury Occurs?

In the event you are injured as a result of participation in this research, medical care is available to you. The costs of such medical care will be billed to you or your insurance company. There are no plans to provide compensation for lost wages, direct or indirect losses. The Cleveland Clinic will not voluntarily provide compensation for research related injury. You are not waiving any legal rights by signing this form. Further information about research related injury is available by contacting the Institutional Review Board at 216-444-2924.

7. COSTS

What Are The Costs?

There are no additional costs to you for participation in this research study. The cost for routine tests and services that would normally be performed even if you don't participate in the study will be billed to you or your insurance provider.

8. STIPENDS

You will receive a stipend of $50.00 for each study visit breathing treatment session that you complete, for a total of ($150.00). You will receive a check in the mail. The IRS requires CCF to report payments to an individual of $600 or greater (in a calendar year) on a Form 1099-MISC. Your name, address and social security number will be collected to track the payments made to you and, if you receive $600 or greater, will be used to process a Form 1099-MISC.

9. VOLUNTARY PARTICIPATION

What Are Your Rights As A Participant?

Taking part in this study is voluntary. You will be told of any new, relevant information from the research that may affect your health, welfare, or willingness to continue in this study. You may choose not to take part or may leave the study at any time. Withdrawing from the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to withdraw from the study you should discuss with your study doctor your decision to ensure a safe withdrawal.

10. QUESTIONS

Whom Do You Call With Questions Or Problems?

If you have any questions, concerns or complaints about the research, or develop a research-related problem, contact Alparslan Turan, M.D., at 216-445-9857 or after hours at 216-217-2312. If you have questions about your rights as a research subject, you should contact the Institutional Review Board at (216) 444-2924.

11. SIGNATURE

Statement of Participant

I have read and have had verbally explained to me the above information and have had all my questions answered to my satisfaction. I understand that my participation is voluntary and that I may stop my participation in the study at any time. Signing this form does not waive any of my legal rights. I understand that a copy of this consent will be provided to me. By signing below, I agree to take part in this research study.

_____
Printed name of Participant

_____ _____
Participant Signature Date

Statement of Person Conducting Informed Consent Discussion

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____
Printed name of person obtaining consent

_____ _____
Signature of person obtaining consent Date

_____ _____ _____
Signature of Witness Date Printed Name of Witness