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Title:	Evaluating the efficacy of intranasal oxytocin on pain and function among individuals who experience chronic pain: A multisite, placebo-controlled, blinded, sequential, within-subjects crossover trial.
Short Title:	Evaluating the efficacy of intranasal oxytocin on chronic pain.
Trial Sponsor:	Dr. Joshua A. Rash, PhD Memorial University of Newfoundland Phone: 709-864-7687 Email:jarash@mun.ca
Physician Lead:	Dr. David Flusk, MD
Research Coordinators:	Ms. Anastasia Mekhael & Ms. Laura Harris-Lane Memorial University of Newfoundland – Behavioural Medicine Centre Phone: 709-864-7686 Email: munbmc@mun.ca
Protocol Number	CIHR-PG#426528

Consent to Take Part in a Clinical Trial

This form is part of the process of informed consent. It should give you the basic idea of what this research is about and what your participation will involve. It also describes your right to withdraw from the study. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. Take your time to read this form carefully and to understand the information given to you. Please contact the researcher, Dr. Joshua Rash, if you have any questions about the study or would like more information before you consent.

Your participation in this study is completely voluntary. If you choose not to take part in this research or if you decide to withdraw from the research once it has started, there will be no negative consequences for you or change to your current care, now or in the future.

1. Why am I being asked to take part in this study?

We are inviting you to take part in this research because you experience chronic pain.

This research is being done to learn whether the use of a nasal spray that contains oxytocin improves pain and function when compared to a placebo (a nasal spray that looks like the study drug, but does not contain oxytocin). Participants will be asked to undergo three 2-week courses where they will use a nasal spray two times each day. Two courses of nasal spray contain oxytocin of different concentration while the third course of nasal spray is a placebo. The placebo is used to make the results more reliable and is not intended to have any effect on you. By taking part in this study you will help expand the body of knowledge towards improving the way that chronic pain is managed.

2. Can I participate in the study?

Individuals may be eligible to participate if:
1. Are 18 years of age or older
2. On stable medication for pain management with no anticipated changes during the 10 weeks of this trial
3. Generally have a moderate level of pain (i.e. a score if 4-8 on a 10-point scale)
4. For woman, are premenopausal and can commit to a method of effective contraceptive (e.g., abstinence, IUD) during the 10-weeks of this trial.
5. Experience persistent muscle or skeletal pain (e.g., in back, neck or shoulders).

In addition, individuals may not be eligible to participate if the following apply:
1. Are pregnant or contemplating pregnancy during the next 10 weeks
2. Are using another nasal spray
3. Have an ear, nose or throat diagnosis
4. Have been diagnosed with cancer or have a history of cancer
5. Have recently used or are using illicit drugs or narcotics delivered intranasally (e.g. cocaine)
6. Have significant, unmanaged mental health concerns
8. Are receiving hormone treatment for gender-related motivations

2b. What if I experience multiple chronic pain conditions?

If you experience multiple chronic pain conditions, you are still eligible so long as your primary pain complaint originates in the back, neck or shoulders.

3. What is being tested?

Oxytocin is a naturally occurring hormone that is released during skin-to-skin contact and massage. Synthetic oxytocin can be administered using a nasal spray to enhance natural levels. While originally administered using needle injections in very high doses to stimulate labor and delivery during childbirth, low doses of oxytocin delivered by a nasal

spray can have a calming effect that lowers stress, reduces anxiety, and enhances trust. Research suggests that low doses of oxytocin delivered using a nasal spray reduces the experience of pain.

We would like to learn whether the use of oxytocin nasal spray helps to improve your pain and function.

This study involves the self-administration of a nasal sprays that contain a 24 international unit or 48 international unit doses of the hormone oxytocin. This is a commonly used dose and method of administration that is well tolerated in humans.

4. How many people will take part in this study?

We plan to have 336 people from three Canadian provinces will take part in this study, including 112 people from Newfoundland and Labrador.

5. How long will I be in this study?

This study will span 10-weeks in duration.

6. What are the study groups?

Each participant will complete three study conditions that are assigned in a random order.

Condition 1:
This condition involves the administration of a nasal spray containing a dose of 24 international units of oxytocin twice daily over a period of 2-weeks.

Condition 2:
This condition involves the administration of a nasal spray containing a dose of 48 international units of oxytocin twice daily over a period of 2-weeks.

Condition 3:
This condition involves the administration of a placebo nasal spray twice daily over a period of 2-weeks.

All nasal sprays contain a water-based, sterile solution with a preservative.

7. Are there risks to taking part in this study?

This study involves the self-administration of nasal sprays that contain doses of 24 international units and 48 international units of the hormone oxytocin. These are commonly used doses and method of administration that are well tolerated in humans. While the risks are minimal, there is a possibility that you could experience side effects. Between 1/100 and 1/1,000 people who use intranasal oxytocin report experiencing headache, nausea, or nasal irritation. Further, between 1/1,000 and 1/10,000 people report experiencing lowered blood pressure or abdominal contractions. While rate of occurrence is unknown, there is potential cardiac risk in the form of QTc prolongation. Contact the study investigator if you experience adverse effects that may be related to the study medication (phone numbers provided below). In the event of a medical emergency call 911. In addition, some of the questionnaires may be sensitive in nature, as they

pertain to your mood; these might cause emotional discomfort to participants, in which case they may choose to skip over them. Contact the Mental Health Crisis Line at **1-888-737-4668** if you experience significant psychological distress.

- **Reproductive risks**
  a. **Women:** Risks associated with pregnancy and breastfeeding are unknown and women should not become pregnant or breast-feed while taking part in this study.
  b. **Men:** There are no known reproductive risks for men.

8. What will happen if I take part in this study?

In order to participate in this study you must commit to not altering your pain medication within the following 10-weeks. If you agree to participate, the following procedures will be done in addition to your usual care:

A) Completion of a urine pregnancy test (for women) before beginning participation.
B) Complete a pain rating questionnaire and undergo a screening to evaluate suitability to participate.
C) Provide one sample of your saliva at the beginning of the study. Your saliva is being collected so that we can assess your level of naturally occurring oxytocin.
D) Complete questionnaires about your pain, daily function, and emotional well-being 3 times during each 2-week course of nasal spray. The purpose of these questionnaires is to understand whether your pain, mood, and daily function is influenced by the administration of nasal spray. Questionnaires will take **approximately 15- 20-minutes to complete.** Some of the questions are personal; you may choose not to answer these if you wish. Some of these questions pertain to your mood and may be sensitive in nature. If you wish to skip over these questions, you may.
E) Answer four questions each day about timing of nasal spray administration, pain, mood, and daily function.
F) Self-administer a 2-week course of nasal spray on three occasions over a 10-week period.

9. What are the possible benefits of taking part in this study?

You may not experience direct benefit from participating in this study. Participation will allow you to engage in the scientific process and contribute to knowledge that may improve pain management in the future.

10. Are there other choices?

You will continue to receive the usual standard of care that you have been receiving if you elect not to participate in this study.

11. What happens at the end of the trial?

Intranasal oxytocin will be available through the study but only until your participation ends.

12. If I decide to take part in this study can I stop later?

It is your choice to take part in this study, participation is voluntary. You can change your mind at any time during the research study. The study team may ask why you are withdrawing for reporting purposes, but you do not need to give a reason to withdraw from the study if you do not want to. Withdrawal from the study will not have any effect on the care you will receive. If you decide to leave the study, you can contact the study doctor or investigator.

You have the right to request the destruction of your information or samples collected during the study, or you may choose to leave the study and allow the investigators to keep the information already collected about you until that point.

13. What about new information?

It is possible that during the study we will get new information about a more effective treatment or other information that may affect your willingness to remain in the study. If this happens, you will be notified about the new information in a timely manner. You will be asked whether you want to continue taking part in this study and you may be invited to sign a new consent form, if you decide to continue in the research study.

A description of this clinical trial will be available on clinicaltrials.gov as required by local and international laws and regulations. This website will not include information that can identify you. You can search this website at any time.

14. Are there other reasons why I might stop being in the study?

The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- Your study doctor feels that you are experience a side effect that is likely related to the use of the study drug.
- New information becomes available and the study is no longer in your best interest.
- You need treatment not allowed in the study
- If you plan to or become pregnant
- If the study is stopped by (sponsor), the Health Research Ethics Board (HREB), Health Canada.

If you are asked to leave the study, the reasons for this will be explained to you and you will have the opportunity to ask questions about this decision. If your participation in the study is stopped, your study doctor will provide information about how to stop safely. If this happens, it may mean that you would not receive the study intervention for the full period described in this consent form. Your study doctor will arrange for you to continue your care outside of the study.

15. Will it cost me anything?

You will not have to pay for any part of this study. Individuals will be given an honorarium of $20.00 per clinic visit (4 visits) totaling $80.00 for the duration of the study.

16. What about my privacy and confidentiality?

Protecting your privacy is one of our top priorities. Every effort will be made to protect your privacy, including: 1) removing any personal identifying information once your data

has been received (i.e., name, email address); 2) storing data in a locked and secured office; 3) securing online data with password encryption software; 4) **being contacted through your choice of phone or a secure platform that is compliant with the Public Health Information Act (PHIA; e.g. Zoom)**; 5) ensuring that all members of the study team undergo periodic training in best practices for data management; and 6) using a commercially available survey software with industry standard security features, **Qualtrics**, to collect survey responses.

Despite our best efforts, privacy cannot always be guaranteed. For example, we may be required by law to allow access to research records under exceptional circumstances. These circumstances usually involve random audits of health records where the focus is on appropriate record keeping by the investigators listed. Such audits may be conducted by Health Canada who is under legal obligation to respect your privacy.

When you give consent below you give us permission to

- Collect information from you and use de-identified information in the analysis of study data.
- Collect and store one saliva sample from you, for the purpose of this study. Saliva samples will be collected and stored in Newfoundland and Labrador until trial completion. They will then be shipped to Salimetrics located in California where they will reside under the care of Dr. Steve Granger and be analyzed for resting salivary levels and genetic structure of the oxytocin receptor gene. Please note that the saliva samples are collected in cryovials and are labeled only with a barcode (and no other participant-identifying information). As such, Salimetrics does not have access to identifying information about participants.

Access to records

We will not have access to your medical records.

Use of your study information

The research team will collect and use only the information they need for this research study. This information will include:

- Information from conversations had over telephone and video conference
- Information from study questionnaires
- Information from saliva sample

Your name and contact information will be kept secure by the research team at Memorial University in **Newfoundland and Labrador and only shared with Dr. Joshua Rash as required by Health Canada.**

As required by Health Canada, data obtained throughout the process of this trial will be retained for 25-years.

Information collected and used by the research team will be stored in a locked office in the Department of Psychology at Memorial University of Newfoundland. The security of this information will be safeguarded by Dr. Rash.

17. Who will see my medical information?

Representatives from the following organizations may come to the hospital/clinic and look at your personal health information under the supervision of the study staff to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines:

- Representatives of the Health Research Ethics Board
- Representatives of Health Canada, group of people who oversee the use of drugs in research in Canada.

Your access to records

You have the right to know what information is collected and may ask the study investigator to see the information that has been collected about you. This is a 'triple-blinded' study, which means that neither the research team members, nor the study doctor are aware of which nasal spray you are taking at any given time. Blinding will be broken in the case of a serious adverse event. You will be provided with a study card with a number to call to reach the central administrator, who can de-identify the condition that you are assigned to in the case of an emergency.

18. Reporting and the sharing of results with participants:

Please contact the researcher **after January 2024** if you are interested in the outcome of this study. Please note that we will be unable to provide you with your individual results because identifying information is not stored with your data. Individual participant results will not be reported in academic publications or presentations arising from this research – averages of responses across groups of participants will be reported instead. Results of this project will be presented on our website (www.munbehaviourmedicine.ca/).

19. What are my rights when participating in a research study?

You have the right to receive all information that could help you make a decision about participating in this study, in a timely manner. You have the right to ask questions about this study at any time and to have them answered to your satisfaction. You also have the right to withdraw from the study at any point in time.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

Signing this form gives us your consent to be in this study. It tells us that you understand the information about the research study. When you sign this form you do not give up any of your legal rights against the study doctor, sponsor or involved institutions for compensation, nor does this form relieve the study doctor, sponsor or their agents of their legal and professional responsibilities.

You will be given a copy of this signed and dated consent form prior to participating in this study.

20. Questions or problems:

If you have any questions about taking part in this study, you can meet with the investigator who is in charge of the study. That person is:

Dr. Josh Rash at 709 864 7687
jarash@mun.ca

Or you can talk to someone who is not involved with the study at all, but can advise you on your rights as a participant in a research study. This person can be reached through:

Ethics Office at 709-777-6974
info@hrea.ca

This study has been reviewed and given ethics approval by the Newfoundland and Labrador Health Research Ethics Board.

Please proceed to the next page.

SIGNATURE PAGE

	Please check as appropriate	
I have read the consent.	☐ Yes	☐ No
I have had the opportunity to ask questions/to discuss this study	☐ Yes	☐ No
I have received enough information about the study.	☐ Yes	☐ No
I understand that I am free to withdraw from the study • at any time • without having to give a reason • without affecting my future care	☐ Yes	☐ No
I understand that it is my choice to be in the study and that I may not benefit.	☐ Yes	☐ No
I understand how my privacy is protected and my records kept confidential.	☐ Yes	☐ No
I agree that the study doctor or investigator may read the parts of my hospital records which are relevant to the study.	☐ Yes	☐ No
I agree to take part in this study.	☐ Yes	☐ No

_____

Signature of participant Printed name Day Month Year

_____

Signature of person conducting the consent discussion Name printed Day Month Year

To be signed by the investigator:

I have explained this study to the best of my ability. I invited questions and gave answers. I believe that the participant fully understands what is involved in being in the study, any potential risks of the study and that he or she has freely chosen to be in the study.

_____

Signature of investigator Name Printed Day Month Year