



BMJ Open Evaluating the efficacy of intranasal oxytocin on pain and function among individuals who experience chronic pain: a protocol for a multisite, placebo-controlled, blinded, sequential, within-subjects crossover trial

Joshua A. Rash ¹, Tavis S. Campbell,² Lynn Cooper,³ David Flusk,⁴ Aaron MacInnes,⁵ Maryam Nasr-Esfahani,^{6,7} Anastasia A. Mekhael ¹, Patricia A. Poulin,^{8,9,10} Magali Robert,^{6,7} Yanqing Yi¹¹

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For numbered affiliations see end of article.

Correspondence to

Dr Joshua A. Rash;
jarash@mun.ca

ABSTRACT

Introduction Current treatments for chronic pain (eg, opioids) can have adverse side effects and rarely result in resolution of pain. As such, there is a need for adjuvant analgesics that are non-addictive, have few adverse side effects and are effective for pain management across several chronic pain conditions. Oxytocin is a naturally occurring hormone that has gained attention for its potential analgesic properties. The objective of this trial is to evaluate the efficacy of intranasal oxytocin on pain and function among adults with chronic pain.

Methods and analysis This is a placebo-controlled, triple-blind, sequential, within-subject crossover trial. Adults with chronic neuropathic, pelvic and musculoskeletal pain will be recruited from three Canadian provinces (British Columbia, Alberta and Newfoundland and Labrador, respectively). Enrolled patients will provide one saliva sample pretreatment to evaluate basal oxytocin levels and polymorphisms of the oxytocin receptor gene before being randomised to one of two trial arms. Patients will self-administer three different oxytocin nasal sprays twice daily for a period of 2 weeks (ie, 24 IU, 48 IU and placebo). Patients will complete daily diaries, including standardised measures on day 1, day 7 and day 14. Primary outcomes include pain and pain-related interference. Secondary outcomes include emotional function, sleep disturbance and global impression of change. Intention-to-treat analyses will be performed to evaluate whether improvement in pain and physical function will be observed posttreatment.

Ethics and dissemination Trial protocols were approved by the Newfoundland and Labrador Health Research Ethics Board (HREB #20227), University of British Columbia Clinical Research Ethics Board (CREB #H20-00729), University of Calgary Conjoint Health Research Ethics Board (REB20 #0359) and Health Canada (Control # 252780). Results will be disseminated through publication in peer-reviewed journals and presentations at scientific conferences.

Trial registration number NCT04903002; Pre-results.

Strengths and limitations of this study

- The effect of oxytocin will be evaluated across different chronic pain presentations (ie, musculoskeletal, pelvic and neuropathic pain), and clinically relevant outcomes will be measured as recommended by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials.
- Two doses of oxytocin will be administered, to evaluate a dose-response relationship.
- The effect of oxytocin will only be evaluated over a 2-week period, precluding longer-term assessment.
- The 48 IU dosing is the last course of treatment in both trial arms, which may introduce expectancy effects due to incomplete blinding at this dose.
- Saliva samples will be collected to measure basal oxytocin levels and polymorphisms of the oxytocin receptor gene as potential moderators of treatment effect.

INTRODUCTION

In 2011, the Institute of Medicine concluded that chronic pain, defined as pain that persists longer than 3 months or beyond the expected duration of healing,¹ is a public health concern and should be treated as a disease itself.² Nationally representative data indicates that 20% of Canadians over 18 years of age³ and 15% of children⁴ suffer with chronic pain. The prevalence of chronic pain increases with age. Approximately 65% of community dwelling seniors and 80% of older adults living in care facilities experience chronic pain.⁵

Currently available treatments for chronic pain rarely result in complete resolution of symptoms,⁶ and often do not produce

concomitant improvements in physical and emotional functioning.⁷ For example, a 2018 meta-analysis reported that 1 in 8 patients respond to opioid medication with a mean 6.9 mm (on a 100-mm Visual Analogue Scale) reduction in pain, small improvement in physical function and no improvement in mental function.⁸ Moreover, current pharmacological treatments for pain, including opiates, are often addictive, associated with adverse effects,^{9,10} and have limited effectiveness in areas such as neuropathic pain. Given the gap between suffering and adequate pain management, there is a need for analgesics that are safe, non-addictive, have low adverse effect profiles and offer effective relief for a variety of painful conditions.

Intranasal oxytocin has gained increasing attention in recent years as a promising analgesic.^{11–14} Oxytocin is a neuropeptide that is produced in the hypothalamus,¹⁵ and released into the peripheral and central nervous system through independent pathways.¹⁶ Evidence from several sources, including our team, suggests that oxytocin may be a safe and effective method for pain management.^{12, 13} Oxytocin may decrease pain sensitivity through three mechanisms¹²: (1) oxytocin is transported to an area involved in pain modulation, Laminae I, II and IV of the dorsal horn, through a hypothalamic–spinal projection.¹⁶ Approximately 35% of neurons in the dorsal horn contain oxytocin receptors that act to inhibit pain-carrying Aδ-fibres and C-fibres^{17–19}; (2) oxytocin binds to opioid receptors, and results in analgesic effects when administered to the periaqueductal grey, and effect that can be blocked with an opioid antagonist.^{20, 21} Furthermore, analgesic effects of endogenous and exogenous oxytocin can be blocked by the opioid antagonist naloxone²²; and (3) oxytocin may decrease pain sensitivity by improving mood, reducing anxiety and buffering stress given that the induction of negative emotions are associated with heightened pain^{23–25} and autonomic arousal.²⁴ In an informative controlled trial, intranasal administration of oxytocin in men resulted in greater calmness, less anxiety and a trend toward lower cortisol during the Trier Social Stress Test.²⁶

Preliminary evidence suggests that oxytocin may be an effective adjuvant analgesic that is applicable to a broad patient population. Our team published a systematic review of the effect of oxytocin on pain in animals and humans.¹² Oxytocin had a reliable effect as defined by increasing pain tolerance in 29 out of 33 animal studies reviewed. This effect was large (standard mean difference=2.28), and persisted across central and peripheral modes of administration and various noxious stimuli (eg, heat, electric and chemical).¹² Results from research into the association between oxytocin and pain in humans have been variable due to methodological heterogeneity. For example, two studies have assessed associations between oxytocin and pain using experimental pain procedures in healthy adults, reporting a decrease in pain sensitivity to finger prick,²⁷ and no difference in pain unpleasantness to electric shock.²⁸ Interpreting these results is difficult due to methodological concerns, including insufficient sample size, one-dimensional pain measurement²⁸ and use of a poorly described finger prick pain procedure.²⁷ Our team conducted the first methodologically rigorous

placebo-controlled, blinded, within-subjects crossover trial evaluating the effect of intranasal oxytocin on acute pain.²⁹ We observed clinically meaningful effects of oxytocin on pain, particularly neuropathic indicators. With regard to chronic pain, individuals experiencing chronic back pain,³⁰ headache,³¹ constipation³² and colon pain³³ have reported lower sensitivity to pain following the administration of oxytocin. Confidence in the association between oxytocin and chronic pain has been difficult to discern due to limitations in study designs, including selection of an insufficient control condition,³¹ use of an intrathecal punch delivery method that likely confounded pain assessment,³⁰ administration of oxytocin peripherally without verification of influence in the central nervous system³³ or inadequate statistical power to detect meaningful effects.^{32, 34} Furthermore, no trial to date has assessed all clinically relevant outcomes endorsed by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT)—an international group of experts that develop recommendations to improve the design, execution and interpretation of clinical trials of treatments for pain.³⁵

Given the heterogeneity of extant trials, we propose a methodologically rigorous trial evaluating the efficacy of intranasal oxytocin on pain and function among men and women with chronic pain that evaluates clinically relevant outcomes endorsed by the IMMPACT.³⁵ Potential mediators and moderator of treatment effects will be assessed using basal oxytocin levels and polymorphisms of the oxytocin receptor gene measured using salivary assays given that: (1) chronic pain patients exhibit low basal oxytocin levels relative to controls,^{30, 36, 37} and may reflect underlying abnormality in the oxytocinergic system¹² and (2) relative to those with an rs53576 A allele, individuals with a rs53576G/G oxytocin receptor genotype show reduced amygdala,³⁸ neuroendocrine²⁶ and stress reactivity across a range of contexts,^{39, 40} and report greater benefit from social support⁴¹ following oxytocin administration. This represents a movement toward precision medicine.

Research questions

We will evaluate the efficacy of intranasal oxytocin when used as an adjuvant treatment (ie, in addition to usual therapies) for improving pain and function (physical and emotional) among men and women with chronic neuropathic, musculoskeletal or pelvic pain.

Primary hypotheses

Relative to placebo, patients will report greater improvement in: (1) pain intensity and (2) physical function measured using the Brief Pain Inventory–Short Form (BPI-SF) following a 2-week course of twice daily 24 IU or 48 IU intranasal oxytocin administration.

Secondary hypotheses

Patients will report improvement in emotional function, sleep and global impression of change following intranasal oxytocin administration relative to placebo.

Exploratory questions

Potential mediators and moderator of treatment effects will be assessed using basal oxytocin levels and polymorphisms of the oxytocin receptor gene measured using salivary assays. This represents a movement toward precision medicine.

METHODS AND ANALYSIS

Design and trial registration

This is a multisite, placebo-controlled, triple-blind, sequential, within-subject crossover trial evaluating the efficacy of intranasal oxytocin on pain and function among patients with chronic pain. This is a basket trial consisting of heterogeneous populations of chronic pain conditions from multisites across Canada. This trial will be conducted in compliance with the trial protocol, good clinical practice, institutional ethics boards and applicable regulatory requirements, and is registered on ClinicalTrials.gov. A sample informed consent form can be located in the supplementary file: 'OT and Pain – Consent MUN V1.2'.

Study settings

There is increasing recognition that most common chronic pain conditions are heterogeneous with a high degree of overlap and that most patients enrolled in clinical trials are not representative of community dwelling chronic pain patients.⁴² As such, there will be four participating sites across three provinces, each province recruiting a different primary neuromusculoskeletal (NMSK) pain population. Adults with chronic neuropathic pain were recruited from the Jim Pattison Outpatient Care & Surgical Centre Pain Clinic (JPOCSC-PC; Surrey) and the Initium Centre for Pain Management (ICPM; Abbotsford). The JPOCSC-PC is a multidisciplinary centre that accepts referrals from a catchment area of 2-million people. Two thousand patients are seen per month, of which approximately 20% present with chronic neuropathic pain. Consecutive women with chronic pelvic pain will be recruited from the Calgary Chronic Pain Centre (Calgary) and directly from the gynaecology clinics of MR and N-EM. The waitlist for an assessment of chronic pelvic pain is approximately 500 patients. Consecutive adults with chronic musculoskeletal pain will be recruited from the Carbonear General Hospital (Carbonear). Approximately, 40 patients with chronic pain are seen each week, of which approximately 60% present with primary shoulder, neck or back pain.

Patient eligibility

Intersite inclusion criteria

(1) Adult (>18 years) males and premenopausal women; (2) on stable medication for pain management for 3 months or more with no anticipated changes during 10 weeks of this trial; (3) moderate pain at baseline (ie, a score of 4–8 on a 10-point Numeric Rating Scale) to prevent floor and ceiling effects; and (4) can commit the

use of two forms of effective contraception (eg, barrier methods), or one highly effective method, including abstinence, intrauterine device, intrauterine system, vasectomy, tubal ligation or hormonal contraceptive (eg, combined oral contraceptives, patch, vaginal ring, injectables and implants).

Intersite exclusion criteria

(1) Positive urine pregnancy test or contemplating pregnancy; (2) concurrent use of another nasal spray; (3) nasal pathology (eg, ears, nose and throat diagnosis); (4) diabetes insipidus; (5) current diagnosis or history of cancer; (6) significant unmanaged psychopathology (eg, severe depression as indicated by a score ≥ 15 on the Patient Health Questionnaire 9⁴³ due to its inverse association with patient adherence to procedures)⁴⁴; (7) receiving hormone treatment for gender-related motivations; (8) documented cardiovascular event (eg, myocardial infarction); (9) known prolongation of the QTc interval; (10) known hypersensitivity to oxytocin; (11) known latex allergy or (12) known or suspected renal impairment. Exclusion criteria will be vetted through a review of patient medical records and self-report given the concordance between self-report and medical diagnosis.⁴⁵

Intra-site criteria

Men and women with primary neuropathic pain—pain arising as a direct consequence of a lesion or disease affecting the central or peripheral nervous system⁴⁶—will be eligible. Neuropathic pain will be screened for using a score of 3+ on the Douleur Neuropathique 4 Interview,⁴⁷ and confirmed on clinical assessment.

Calgary, AB

Women with chronic (intermittent or constant) pelvic musculoskeletal pain (ie, located primarily in the pelvic region and reproducible on palpation of the pelvic floor) who have not received a hysterectomy will be eligible. Women with a primary diagnosis of endometriosis, dysmenorrhoea, functional bowel disorder, interstitial cystitis, fibromyalgia or sacroiliac instability as defined by European Guidelines⁴⁸ will be excluded.

Carbonear, NL

Men and women with primary musculoskeletal pain of back, neck or shoulder origin will be eligible. Pain will be assessed using the BPI-SF and confirmed through physical examination.^{49 50}

Across sites

Adults with multiple chronic pain conditions will be eligible to participate so long as their primary pain complaint meets eligibility criteria. Recruiting different primary NMSK presentations will allow us to evaluate the generalisability of intranasal oxytocin across common chronic pain presentations typically observed within the community and may allow for improved optimisation of treatment in future work.

Procedure

Patient recruitment, screening and enrolment

Potentially eligible patients will be approached by a member of our study team during their regularly scheduled appointment at the clinic, and receive information about the objectives of the trial. Interested patients will undergo screening, including: (1) completion of a urine pregnancy test; (2) blood work to evaluate renal impairment (as defined by an eGFR <45 by the Cockcroft-Gault equation), if the history suggests any stage or renal insufficiency, including history of diabetes, inflammatory diseases, hypertension and no creatinine has been drawn in the last 2 years; and (3) ECG to evaluate prolongation of the QTc interval among anyone who may be at risk, including those prescribed antidepressant medication. Patients who meet all eligibility criteria will be randomised to study arm before completing a baseline assessment. Recruitment will begin in September 2021 until the target sample size is recruited, or March 2024.

Randomisation, allocation and concealment

The commercially available software, <https://app.studyrandomizer.com/>, will be used to generate a list

of randomly sequenced numbers for assigning patients to condition in a manner outlined in Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.^{51 52} As depicted in figure 1, patients will be randomised to one of two sequences: (1) 24IU oxytocin, placebo and 48IU oxytocin; or (2) placebo, 24IU oxytocin and 48IU oxytocin. Central randomisation stratified by province (British Columbia, Alberta and Newfoundland and Labrador) and performed using a 1:1 allocation schedule with permuted blocks of 4 and 6. Sex will be added as an additional stratification factor for sites in BC and NL. The lists will be uploaded on a web-based password protected randomisation system. When an eligible participant consents to the study, randomisation website will be contacted through a closed system and randomisation code will be assigned to the participant. Automated audit trails will document the patient allocation number and treatment sequence, and the date and time of transaction.

Blinding

This is a triple-blind study. In order to protect against expectation effects and biases, neither site investigators

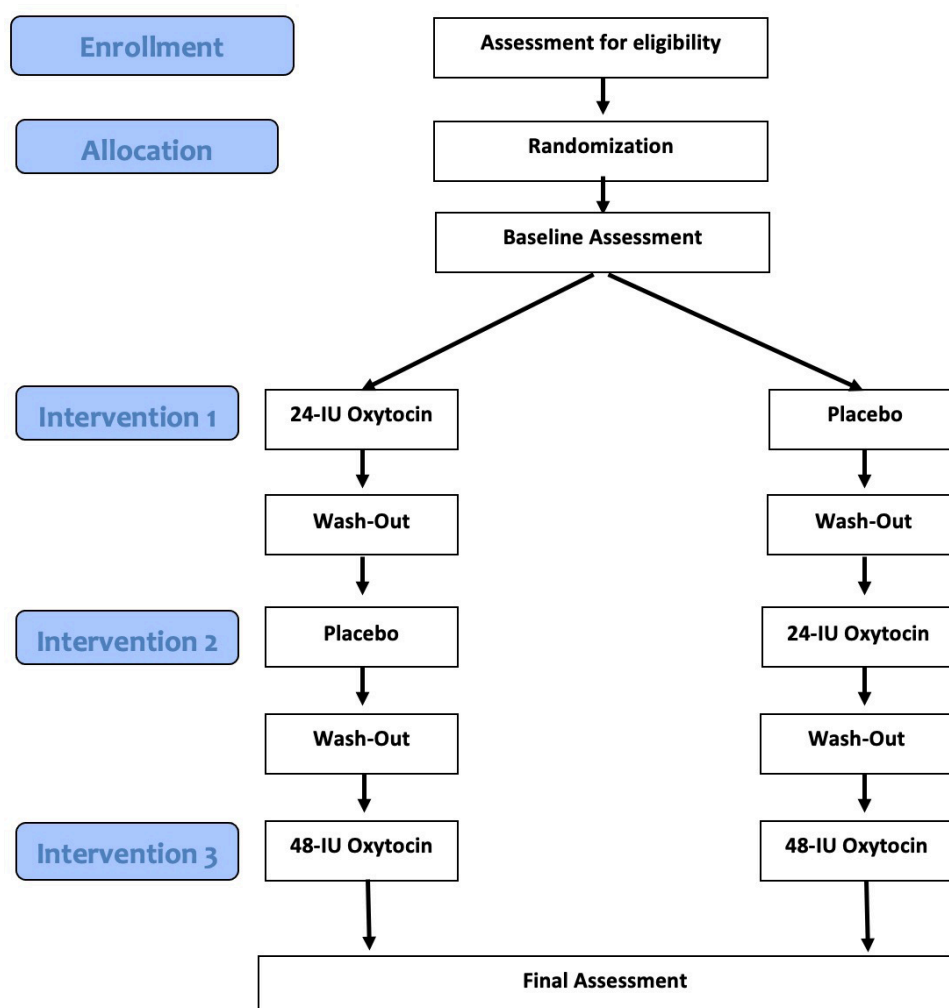


Figure 1 Flow chart of Randomized Controlled Trial design.

Table 1 Schedule of assessments

	Randomisation					
	2-week diaries					
Testing variables	Phone screen	Baseline	Daily diary	Day 7 of diary	Day 14 of diary	Follow-up
Inclusion criteria	X					
Sociodemographics		X				
Medical history		X				
Vitals		X				X
Pain NRS	X		X			X
BPI-SF intensity		X		X	X	
BPI-SF interference		X		X	X	
Emotional function						
Mood		X	X			
DASS		X		X	X	
Sleep		X		X	X	
Global impression of change					X	
Expectancy		X				
Side effects					X	X

BPI-SF, Brief Pain Inventory–Short Form; DASS, Depression, Anxiety and Stress Scale; NRS, Numeric Rating Scale.

nor patients will know which nasal spray contains oxytocin or which sequence of conditions patients are assigned. The allocation sequence will be concealed from researchers using automated randomisation. The bottles containing 24 IU oxytocin, 48 IU oxytocin and placebo will be identical in appearance, smell, texture and taste, and only identifiable through a colour labelling system known to the site pharmacists and study sponsor. Each province's randomisation sequence will be accessed by the site pharmacist and bottles prepared accordingly. Neither the Research Assistant assessing outcomes nor the statistician performing analyses will be unaware of condition. Patient blinding can be broken in the case of an adverse event (eg, emergency department attendance). Patients will be provided a study card with a number to call to reach the central administrator who can de-identify condition in the unlikely case of an adverse drug reaction. The decision to unmask will be made on a case-by-case basis and will depend on potential risk.

Baseline assessment

Baseline assessments will involve: (1) completion of study measures, refer to [table 1](#); (2) collection of approximately 4 mL of saliva into cryovials using a standard unstimulated passive drool technique. Saliva samples will be frozen until shipped to Salimetrics for analysis of salivary oxytocin concentration and genetic polymorphism in the oxytocin receptor gene OXTR rs53576; and (3) training on procedures for nasal spray administration. Patients will be provided with the option of completing baseline assessments immediately following randomisation, or scheduling a convenient time within 2 weeks. Baseline

assessments for women will be scheduled to occur within close proximity to the start of the luteal phase of the menstrual cycle (ie, days 14–28) as this is the stage during which women report greatest pain.⁵³ Due to the impact of the global pandemic, patients will have the option of completing study measures virtually. Patients will attend clinic to provide a saliva sample, undergo nasal spray training and receive their assigned nasal spray. Clinic attendance will be scheduled in the afternoon to avoid diurnal fluctuation in saliva oxytocin. Patients will be asked to avoid foods with high sugar, acidity or caffeine 1 hour prior to visiting the clinic as these can confound saliva assays.

Trial interventions

The intervention will span three 2-week conditions (24 IU, 48 IU and placebo) and two 2-week wash-out periods for a total duration of 10 weeks.

Experimental condition

There will be two experimental conditions. Experimental condition 1: patients will self-administer a 2-week course of 24 IU intranasal oxytocin (4 IU per puff (12 IU delivered to each nostril); syntocinon, Novartis, Switzerland), twice daily (once in the morning and once in the evening). Experimental condition 2: patients will self-administer a 2-week course of 48 IU intranasal oxytocin (4 IU per puff (24 IU delivered to each nostril)), twice daily. Given that treatment adherence is crucial to treatment success, we will ensure standardisation of nasal spray administration by training patients in the self-administration of intranasal oxytocin in accordance with

published recommendations.⁵⁴ Intranasal administration of oxytocin is an effective method of administering the neuropeptide across the blood brain barrier.⁵⁵ Twice daily dosing will ensure elevated central concentration of oxytocin throughout the day given that salivary concentration of oxytocin remains elevated for 7 hours following intranasal administration.⁵⁶ Patients will be instructed to store nasal spray at room temperature (between 15°C and 25°C) after first use. The inclusion of two doses will allow us to determine the lowest effective dose (ie, 24IU or 48IU), which will inform future trials assessing long-term treatment optimisation. Doses of 24IU and 48IU were chosen because these are the most frequently used doses in studies with humans and have proven safe for long-term study.^{49 50}

Control condition

Patients will receive an intranasal placebo containing the same ingredients as the oxytocin nasal spray with the exception of active oxytocin. Administration schedule and procedure will be identical to that described in the experimental condition.

Wash-out periods

Conditions will be separated by a wash-out period of approximately 2 weeks to ensure that oxytocin has fully cleared the system. This time frame is sufficient given that the half-life of oxytocin administered centrally using nasal spray is 2–7 hours and 7 half-lives will be achieved for clearance in 14–49 hours. A 2-week wash-out will also allow each course of intranasal administration to coincide with the same phase of women's menstrual cycle (ie, the luteal phase). This is relevant given that oestrogen has a priming effect on oxytocin synthesis, release and receptor expression.⁵⁷

Follow-Up

Patients will be contacted over the phone 2 weeks following completion of the trial (12 weeks following randomisation) to assess for potential adverse events.

Patient and public involvement

Patients with lived experience were consulted in the design of this project and assisted in preparation of study materials. Engagement will continue throughout trial conduction and be emphasised when preparing materials for dissemination.

Measures

Refer to [table 1](#) for schedule of assessments.

Primary outcome

The primary outcomes will be the between condition (24IU vs placebo; 48IU vs placebo) change in pain intensity and physical function from day 1 to day 14 measured using the BPI-SF.⁵⁸ The BPI-SF measures pain intensity, the impact of pain on seven daily activities (eg, activity, work and sleep) and analgesic use. It has been recommended for use in trials measuring pain across multiple chronic

pain conditions.³⁵ The BPI-SF was originally designed to measure cancer pain but has been shown to be a reliable and valid instrument for measuring non-cancer pain.^{59–62} Two week and 1-month test–retest values for pain and function typically range between 0.72 and 0.98.⁶³

Secondary outcomes

Secondary outcomes include emotional function, sleep disturbance and global impression of change. Emotional function will be measured weekly using the 21-item Depression, Anxiety and Stress Scale.⁶⁴ Scales for depression, anxiety and stress are considered to approximate facets of diagnostic categories, including Depression scale for mood disorders, Anxiety scale for panic disorder and Stress scale for generalised anxiety disorder.⁶⁵ Sleep disturbance will be assessed weekly with the Medical Outcomes Study Sleep Scale (MOS-S).⁶⁶ The MOS-S is a 12-item self-report measure designed to assess the important dimensions of sleep, including initiation, maintenance, respiratory problems, quantity, quality and somnolence. Global change across the course of study will be measured at the end of each 2-week course of nasal spray using the Patients' Global Impression of Change (PGIC) Scale.⁶⁷ There has been a wide use of the PGIC Scale in chronic pain trials,^{68 69} and data provide a responsive and readily interpretable measure of participants' assessment of clinical importance of treatment.

Daily diaries

Ambulatory assessments will be administered by way of REDCap. Patients will complete electronic diaries throughout each 2-week course of nasal spray administration. Patients will make daily recording of: (1) time of nasal spray administration; (2) average pain using a 0 'no pain' to 10 'pain as bad as you can imagine' scale; (3) the degree to which pain has interfered with enjoyment in life and general activity using scales with anchors at 0 'does not interfere' and 10 'interferes completely'. Validated measures will be completed during day 1, day 7 and day 14, refer to [table 1](#). Patients will be asked to guess whether the nasal spray administered contained oxytocin or placebo following each 14-day course of nasal spray administration.

Demographics and covariates

A demographic questionnaire will collect age, ethnicity, medical comorbidities, medications taken, employment status, marital status, obstetrical history, menstrual history, urinary symptoms, headaches, substance use and smoking status. Concern over pain will be assessed using the 13-item Pain Catastrophizing Scale.⁷⁰ Treatment expectations will be measured with the Credibility/Expectancy Questionnaire.⁷¹ Allodynia/hyperalgesia will be assessed using the Central Sensitisation Inventory^{72 73} and confirmed with Q-tip testing.⁷⁴

Side effects and safety monitoring

As recommended for trials of chronic pain,⁷⁵ side effects will be assessed using open-ended prompts (ie, have

you experienced any unwanted symptoms in the past 24 hours?) and the Symptom Assessment Schedule⁷⁶ supplemented with additional symptoms (eg, euphoria, nasal irritation and dizziness) identified in a recent trial evaluating the effect of intranasal oxytocin on pain in a sample of 14 women with fibromyalgia.³⁴

Sample size calculation

We based our sample size calculation on the number of patients needed to evaluate a clinically significant reduction in pain intensity and improvement in physical function of the primary outcomes: change in pain intensity and physical function from day 1 to day 14 that occurs between conditions (24IU oxytocin vs placebo; 48IU oxytocin vs placebo). The hypothesis tests are one sided and the trial is powered using a sequential, repeated-measures crossover design with one interim analysis to monitor the preliminary activity of the 24IU and 48IU doses of oxytocin relative to placebo (refer to section 3.2.1 for greater detail on the interim analysis).

The overall type I error rate will be 0.05 and the O'Brien and Fleming's method⁷⁷ will be used to control for the inflation of type I error due to the interim analysis. The interim analysis will be conducted when primary outcomes are available for half of the proposed sample. The Sidak method⁷⁸ will be used to adjust for multiple comparisons (ie, $\alpha=0.0127$ after adjusting for 4 comparisons: 24IU and 48IU doses of oxytocin compared with placebo for pain intensity and physical function). Based on previous research with chronic pain populations,⁵⁸ we assume a SD of 2.0 for pain intensity and physical function and a block-based symmetric correlation matrix under which the 2-week correlation within the same arm is assumed to be 0.8⁶³; the subcorrelation matrix of day 1 and day 14 pain intensity and physical function across two arms is comparable for any two arms; and the correlation of day 1 and day 1 on two arms equals that of day 14 and day 14. We anticipate that the correlation of day 1 and day 14 cross-arms will be lower than the correlation of the same day pain intensity/physical function. As a conservative measure, we assume the correlation of day 1 and day 14 is comparable to the same day correlation cross two arms and a better power will be achieved if the correlation between day 1 and day 14 is lower. The sample size is determined as the largest for two scenarios on whether the subcorrelation matrix of day 1 and day 14 is stable over phases or not.

For the scenario of stable subcorrelation matrix of day 1 and day 14, all phases data will be included in the analysis. Target power is 0.9 to detect a 0.5 SD difference in pain intensity/physical function, which corresponds to an effect size of 0.56 for the outcomes of change between day 1 and day 14 under the aforementioned assumptions on the covariance matrix. The required sample size is 41 per province to accommodate one interim analysis. If the subcorrelation matrix of day 1 and day 14 is unstable cross phases, only the first two phases data will be included in the analysis and the size for evaluating the efficacy of the

24IU and 48IU over the placebo is reduced to 2/3, where the two samples are independent ($\alpha=0.0127$ using Sidak). Under this scenario, the power is set as 0.8 for the same effect size and the required sample size is 54, which is increased to 81 accounting for abandoning the phase III data due to instability of the correlation. Therefore, the sample size of 81 per province will be used and this is the robust size to guarantee at least 80% power and an overall type I error of 0.05 with an interim analysis for different scenarios of the correlation matrix of pain intensity/physical function. The covariates of sex and province will be adjusted and the rule of 8 additional cases per covariate will be followed for the combined analysis on the efficacy of 24IU and 48IU oxytocin relative to placebo. Accounting for a potential attrition rate of 20% and the balance among the 2 sequences per province, a total sample of 336 patients (112 per province) is required.

Data analysis

An intention-to-treat (ITT) analysis will be performed,⁷⁹ in accordance with recommendations by CONSORT.^{51 52} ITT analyses provide an assessment of the practical impact of the treatment. Primary analyses: the hypotheses that improvement in pain and physical function will be observed following 2-week administration of oxytocin nasal spray relative to placebo will be assessed using BPI-SF average 24-hour pain intensity scores. Using linear mixed models in SAS, the analytic strategy will be a mixed models analysis of covariance with fixed effects (time (day 1 and day 14) and condition (24IU oxytocin, 48IU oxytocin and placebo)) and random effect (individual), and sex (male and female) as between-subject factor after adjusting for relevant covariates (ie, province, basal oxytocin at baseline, expectation, pain catastrophising and medical comorbidity). One interim analysis will be performed (see 2.17 for details). Based on previous literature, BPI-SF assessed pain is a relatively 'well-behaved' variable with respect to the assumptions of a general linear model.⁸⁰ Even so, prior to conducting any analyses, preliminary examination of the assumptions of the General Linear Model will be conducted.⁸⁰ Should the data indicate violation of assumption, we will perform appropriate transformations and/or consider the appropriate interaction term(s).⁸⁰ Missing data will be handled using multiple imputation⁸¹ in accordance to Harrell's guidelines.⁸² Secondary analyses: the effects of the intervention on change in emotional function, sleep disturbance and global impression of change between conditions will be evaluated in a manner analogous to that described above. Exploratory analyses will be performed to evaluate whether basal oxytocin concentration or polymorphism of the oxytocin gene receptor moderate or mediate treatment outcomes.

Frequency of analysis

An interim analysis will be conducted when complete data are available from half of the desired sample size. The interim analysis will be used to decide: (1) stop the

trial for efficacy if overwhelming evidence indicates that the 48IU dose of intranasal oxytocin is efficacious relative to placebo (p value <0.0083); (2) drop the 24IU dose for inefficacy if evidence supports a conservative test of the null hypothesis that 24IU oxytocin is equivalent to placebo if the conditional power is less than 0.2 if continuing the stage 2 data collection; or (3) continue the trial as planned. The O'Brien and Fleming's method will control the overall type I rate at 0.0127 with 0.0083 α spending at the interim, and the overall type II error rate at 0.1 with 0.029 spending at the interim for each of the 24IU and 48IU doses and primary outcome. Final analyses will commence after the follow-up has been completed for the final participant enrolled (eg, May 2024) and span 3 months in duration.

Subgroup analyses

Subgroup analyses (eg, dose of oxytocin, province and sex) are built into the analytic plan. Secondary analyses include interactions between dose, pain type, sex and gender.

Risk management and safety monitoring board

A Data and Safety Monitoring Board (DSMB) has been established to perform (unblinded) analyses according to the DSMB charter. The DSMB is composed of three independent clinical experts, and a statistician with expertise in Randomized Controlled Trials. The DSMB will advise on any serious adverse event reported during the conduct of the trial. Moreover, safety and efficacy will be evaluated during the interim analysis. Early termination will only occur if the DSMB is unanimous in their conclusion of an unfavourable benefit-to-risk ratio.⁸³ Strict termination criteria were not established a priori given that: (1) rescue medication is not needed for intranasal oxytocin. The best method to resolve side effects is to discontinue use of the drug, which is our recommended course of action; (2) chronic NMSK pain is not a life-threatening condition; (3) study duration is brief; and (4) intranasal oxytocin has been extensively studied and side effects are rare and benign.⁸⁴ The advice of the DSMB will be sent to the study sponsor. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing medical research ethics committee, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

Ethics and dissemination

Results from this feasibility trial will be disseminated to the academic community through conference presentations and the publication of peer-reviewed manuscripts. Results will be posted to our website www.munbehaviour-medicine.ca and made available to patients, providers and the general public. Trial protocols were approved by the Newfoundland and Labrador Health Research Ethics Board (HREB #20227), University of Calgary Conjoint Health Research Ethics Board (REB20 #0359), University of British Columbia Clinical Research Ethics Board

(CREB #H20-00729) and Health Canada (Control # 252780).

Data management

Data will be collected, de-identified and stored. Electronic data will be stored on password-protected servers in encrypted files. De-identified data will be retained for 25 years and made available to members of the investigative team. Individual participant de-identified data (including data dictionaries) will be made available beginning 3 months after final follow-up data has been collected (anticipated September 2024) to researchers who provide a methodologically sound proposal for the purpose of achieving the aims of the approved proposal. Data sharing will be enacted with a data-transfer agreement between the sending and receiving institutions. Proposals should be directed to the corresponding author (JR).

Patient adherence

We will use a multi-pronged approach to encourage patient engagement. First, the timeline and demands of the trial will be explicitly discussed at the outset with patients, who will be asked to sign a behavioural contract to commit to trying to meet the requirements. Second, patients will receive telephone reminders prior to each laboratory visit and again if they miss one visit. Third, expectations will be developed for attendance. Patients will know our research staff by name and made aware that their research associate has an appointment scheduled with them and will be awaiting their arrival. Fourth, patients who have difficulties attending sessions will be provided with a motivational conversation during which ambivalence towards attending sessions will be openly discussed with the goal of securing commitment to attend sessions. We have successfully employed these strategies with some very challenging patient groups (eg, patients with cancer-related fatigue and obese patients attending exercise sessions). These strategies have been identified by Cochrane reviews as methods for improving patient recruitment⁸⁵ and retention.⁸⁶

Author affiliations

¹Department of Psychology, Faculty of Science, Memorial University of Newfoundland, St. John's, Newfoundland, Canada

²Department of Psychology, Faculty of Arts, University of Calgary, Calgary, Alberta, Canada

³Canadian Injured Workers Alliance, Thunder Bay, Ontario, Canada

⁴Anesthesia and Pain Medicine, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, Canada

⁵Anesthesiology, Pharmacology and Therapeutics, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

⁶Department of Anesthesiology, Perioperative and Pain Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

⁷Obstetrics and Gynecology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

⁸The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

⁹Department of Anesthesiology and Pain Medicine, University of Ottawa, Ottawa, Ontario, Canada

¹⁰The Ottawa Hospital Pain Clinic, Ottawa, Ontario, Canada

¹¹Community Health and Humanities, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland, Canada

Contributors All authors (JR, TC, LC, DF, AM, AAM, N-EM, PP, MR and YY) were involved in the conceptualisation and design of the trial, made significant intellectual contributions to the written protocol and have approved the submitted version.

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ORCID iDs

Joshua A. Rash <http://orcid.org/0000-0003-0927-0712>

Anastasia A. Mekhael <http://orcid.org/0000-0003-0620-3872>

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