

# BMJ Open Protocol for a placebo-controlled, within-participants crossover trial evaluating the efficacy of intranasal oxytocin to improve pain and function among women with chronic pelvic musculoskeletal pain

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## ABSTRACT

**Introduction:** This protocol presents the rationale and design for a trial evaluating the efficacy of intranasal oxytocin in improving pain and function among women with chronic pelvic musculoskeletal pain. Oxytocin is a neuropeptide traditionally recognised for involvement in labour, delivery and lactation. Novel evidence suggests that oxytocin decreases pain sensitivity in humans. While oxytocin administration has been reported to lower pain sensitivity among patients experiencing chronic back pain, headache, constipation and colon pain, no research has evaluated the association between intranasal oxytocin and chronic pelvic musculoskeletal pain. The association between oxytocin and pain may differ in women with chronic pelvic musculoskeletal pain relative to other chronic pain conditions because of the abundance of oxytocin receptors in the uterus.

**Methods and analysis:** This is a prospective, randomised, placebo-controlled, double-blind, within-participants crossover trial. 50 women with chronic pelvic musculoskeletal pain will be recruited through a local chronic pain centre and gynaecology clinics. Women will complete baseline measures and be randomised to an experimental or control condition that involve 2 weeks of self-administering twice-daily doses of 24 IU intranasal oxytocin or placebo, respectively. Women will then undergo a 2-week washout period before crossing over to receive the condition that they had not yet received. The primary outcome will be pain and function measured using the Brief Pain Inventory-Short Form. Secondary outcomes include emotional function, sleep disturbance and global impression of change. This trial will provide data on the 14-day safety and side-effect profile of intranasal oxytocin self-administered as an adjuvant treatment for chronic pelvic musculoskeletal pain.

**Ethics and dissemination:** This trial was granted approval from Health Canada and the University of Calgary Conjoint Health Research Ethics Board, and is registered online at ClinicalTrials.gov (#NCT02888574).

## Strengths and limitations of this study

- Methodologically rigorous randomised controlled trial.
- High internal validity, including control over menstrual cycle hormone fluctuations.
- Inclusion criteria may create a sample that does not generalise to all patients with chronic pelvic musculoskeletal pain (eg, results from a sample of women may not generalise to men with chronic pelvic musculoskeletal pain).

Results will be disseminated to healthcare professionals through peer-reviewed publications and to the general public through press releases.

**Trial registration number:** NCT02888574; Pre-results.

## INTRODUCTION

Oxytocin is produced in the supraoptic and paraventricular nuclei of the hypothalamus.<sup>1</sup> It is released peripherally into the bloodstream via the posterior pituitary, and into the central nervous system via paraventricular neurons.<sup>2</sup> While traditionally recognised for involvement in labour, delivery<sup>3</sup> and lactation,<sup>4</sup> novel evidence suggests that oxytocin is a safe method for decreasing sensitivity to pain with a low risk of adverse effects.<sup>5 6</sup> A systematic review of 38 randomised controlled trials (RCTs) reporting on more than 1500 participants concluded that central administration of 18–40 IU doses of oxytocin produced minimal, non-detectable side effects compared with placebo.<sup>7</sup>

There are three mechanisms through which oxytocin may decrease pain sensitivity.<sup>5</sup>

First, a direct hypothalamo-spinal projection originating from the paraventricular nucleus transports oxytocin to the dorsal horn (Lamina-I, II and IV),<sup>2</sup> an area involved in pain modulation. A subset of neurons in the dorsal horn (~35%) contain oxytocin receptors that influence glutamatergic neurons which, in turn, activate GABAergic neurons, resulting in an inhibition of pain-carrying A $\delta$ -fibres and C-fibres.<sup>8–10</sup> Second, evidence suggests that oxytocin binds to opioid receptors and may stimulate endogenous opioid release in the brain. An opioid system located in the periaqueductal gray activates a series of descending controls that prevent spinal cord transmission regarding injury.<sup>11</sup> Oxytocin administered to the periaqueductal gray results in antinociception that can be blocked by the administration of an opioid antagonist.<sup>12–13</sup> Further, analgesic effects of endogenous and exogenous oxytocin can be blocked by the opioid antagonist naloxone.<sup>14</sup> The final mechanism involves improving mood, decreasing anxiety and mitigating the stress response. In an informative controlled trial, intranasal administration of oxytocin in men resulted in greater calmness, less anxiety and a trend towards lower cortisol during the Trier Social Stress Test.<sup>15</sup> Given that negative emotion inductions (eg, anxiety, sadness, anger) are associated with greater pain,<sup>16–18</sup> along with concomitant heightened autonomic responses,<sup>17</sup> oxytocin may decrease pain sensitivity by improving mood and anxiety, and buffering the stress response.

Of 33 animal investigations that have assessed the relationship between oxytocin and pain, 29 reported that exogenous oxytocin administration and higher endogenous oxytocin levels decreased pain.<sup>5</sup> However, an association between oxytocin and pain is less clear in the human literature due to a paucity of methodologically rigorous trials. Thus far, oxytocin administration has been reported to lower pain sensitivity among patients experiencing chronic back pain,<sup>19</sup> headache,<sup>20</sup> constipation<sup>21</sup> and colon pain.<sup>22</sup> It has been difficult to draw firm conclusions about the association between oxytocin and chronic pain in humans from these trials due to methodological limitations, including the lack of an adequate control condition,<sup>20</sup> use of a delivery method with a high likelihood of confounding pain assessment (eg, intrathecal punch),<sup>19</sup> peripheral administration<sup>22</sup> or the recruitment of a sample size that was inadequately powered to detect meaningful effects.<sup>21–23</sup> To date, no research has evaluated the association between intranasal oxytocin and chronic pelvic musculoskeletal pain.

Women report more pain, in more body areas, with greater frequency, and for longer duration than men.<sup>24</sup> Chronic pelvic pain accounts for 1 in 10 gynaecology outpatient visits<sup>25</sup> and the prevalence in general practice is similar to that of migraine, back pain and asthma (monthly prevalence of 21.5/1000).<sup>26</sup> The association between oxytocin and pain may differ in women with chronic pelvic musculoskeletal pain relative to other chronic pain conditions because of a potential

peripheral oxytocin-pain pathway. There is an abundance of oxytocin receptors in the uterus, and oxytocin is a potent uterogenic agent that is clinically used in large doses to stimulate uterine contractions and induce labour.<sup>2</sup> While oxytocin does not cross the blood–brain barrier, the central administration of intranasal oxytocin increases central and blood-plasma oxytocin concentrations.<sup>27</sup> Thus, intranasal oxytocin administration may be associated with decreased pain through central and peripheral pathways among women with chronic pelvic musculoskeletal pain.

This manuscript details the rationale and design of an RCT evaluating the efficacy of intranasal oxytocin versus placebo in improving pain and function among women with chronic pelvic musculoskeletal pain.

## METHODS

### Research questions and objectives

This research is a pilot study of the efficacy of intranasal oxytocin for improving pain and function among women with chronic pelvic musculoskeletal pain of primarily musculoskeletal origin.

The primary objective is to evaluate the efficacy of intranasal oxytocin for reducing pain.

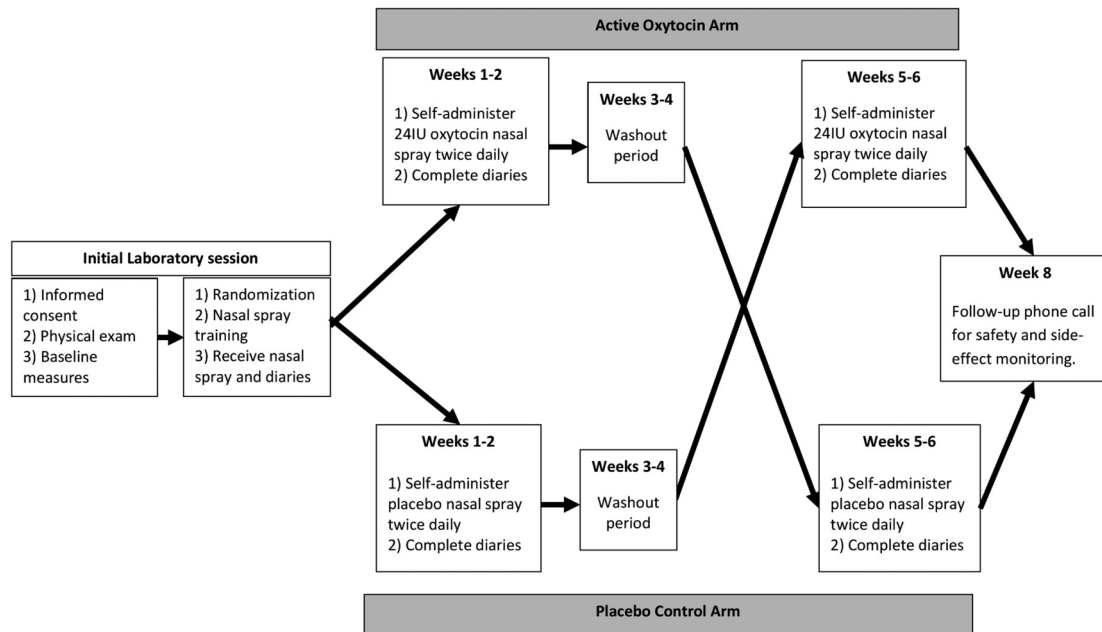
Secondary objectives are to evaluate the efficacy of intranasal oxytocin for improving mood, emotion function, physical function and sleep.

### Study design

This study is a double-blind, placebo-controlled, within-participants crossover RCT adhering to CONSORT guidelines.<sup>28–29</sup> A crossover design offers two advantages over a parallel-group RCT: (1) the influence of confounding covariates are reduced because each participant serves as their own control; and (2) statistical power is higher and required sample size to detect meaningful effects is lower.<sup>30</sup> The trial is registered at ClinicalTrials.gov (#NCT02888574). **Figure 1** depicts a flow diagram of the study design. Participants will be screened for eligibility and, once confirmed, will be randomised to undergo a 2-week experimental or control condition. The experimental and control conditions will involve the twice-daily self-administration of a 24 IU dose of intranasal oxytocin or placebo, respectively. Women will then undergo a 2-week washout period before crossing over to undergo the condition that they did not initially complete. The washout period will ensure that women will be in the same phase of their menstrual cycle (ie, luteal phase) during each nasal spray administration. The primary outcome is self-reported pain. Secondary outcomes include mood, emotion function, physical function and sleep.

### Study setting

Women with chronic pelvic musculoskeletal pain will be recruited from the Calgary Chronic Pain Centre (CPC)



**Figure 1** Study flow diagram.

and gynaecology clinics in Calgary, Alberta, Canada. Assessments will occur at the Calgary CPC.

## Patient eligibility

### Inclusion criteria

Non-menopausal women with chronic (intermittent or constant) pelvic musculoskeletal pain (ie, pain exceeding 6 months in duration, ie, located primarily in the pelvic region and reproducible on palpation to the muscles spanning the pelvic floor) will be eligible to participate if they: (1) have regular menstrual periods (monthly within a 21–35 day range), given that pain varies across the menstrual cycle<sup>31 32</sup> and nasal spray administration will occur during the luteal phase; (2) use a permanent, hormonal, or barrier form of contraception, or abstinence in order to minimise the risk of pregnancy during the trial, given that oxytocin is a potent uterogenic agent; (3) can commit to not change their medication during the 6 weeks of this study; and (4) have a moderate amount of pain at baseline (ie, a pain score of 4–7 out of 10 on a numeric rating scale). A baseline pain score of 4–7 out of 10 was selected to prevent floor and ceiling effects and ensure that participants have room to change throughout the course of the study.

### Exclusion criteria

Exclusion criteria include: muscle pain as a result of systemic disease, scoring positive on a urine pregnancy test or contemplating pregnancy, concurrent use of another nasal spray, nasal pathology (eg, ears, nose and throat diagnosis), diabetes insipidus, previous or concurrent use of narcotics delivered intranasally (eg, cocaine) or sacroiliac instability as defined by the European

Guidelines.<sup>33</sup> Women will also be excluded if they have a primary diagnosis of endometriosis, dysmenorrhoea, interstitial cystitis, functional bowel disorder, fibromyalgia or neuropathic pain. Given that the heart contains oxytocin receptors,<sup>34</sup> that, when bound to, result in inhibitory effects on cardiovascular activity,<sup>35</sup> a review of medical chart will be performed and women prescribed antihypertensive medication and those with heart problems (eg, cardiomyopathy, history of myocardial infarction, arrhythmias, prolonged QT interval) will be excluded.

## Procedure

### Patient screening, recruitment and enrolment

Fifty women with chronic pelvic musculoskeletal pain will be recruited from the Calgary CPC and directly from the gynaecology clinics of MR and MN-E. Women will be examined by a study gynaecologist (JFJ, MN-E, MR) trained to examine sacroiliac instability and myofascial pain. Chronic pelvic musculoskeletal pain will be confirmed through a physical examination. Any concerns of sacroiliac instability on physical examination will be further assessed by a pelvic physiotherapist. It is estimated that 15 women per month could meet inclusion criteria.

Women will visit the laboratory four times (baseline, 2, 4, 6 weeks). Vital signs (heart rate (HR) and blood pressure (BP)) and self-reported pelvic pain will be monitored at all visits. The first dose of each nasal spray (baseline and 4-week visits) will be supervised and vitals taken every 10 min for 30 min. Women whose HR and BP decrease by 15% within this period will be identified as sensitive to the effect of intranasal oxytocin and withdrawn from the trial due to safety concerns. Patient symptoms and side effects will be monitored during the

2-week, 4-week and 6-week laboratory visits and again over the phone 2 weeks after trial completion.

### Baseline assessment

Testing will occur during the luteal phase of the menstrual cycle (ie, days 14–28) as this is the phase during which women report the highest pain.<sup>32</sup> At ~day 14 of their menstrual cycle, participants will attend a baseline session at the Calgary CPC. The objectives of the trial will be explained by a study gynaecologist (JFJ, MN-E, MR) who will also obtain consent to participate. Women will then complete a urine drug and pregnancy test, be randomised to study condition and fill out baseline study questionnaires (refer to [table 1](#) for a schedule of assessments).

### Randomisation and blinding

A research assistant (RA) not involved in study recruitment will use Research Randomizer (<http://www.randomizer.org/>) to generate lists of randomly sequenced numbers, stratified by recruiter (MR, MN-E), for assigning patients to condition in a manner consistent with CONSORT.<sup>28 29</sup> Central randomisation will be performed using a 1:1 allocation schedule with random block sizes of 4, 6 and 8. The allocation sequence will be concealed from the researcher using sequentially numbered, opaque and sealed envelopes. In order to protect against expectation effects and biases, the RA completing baseline assessment and providing participants with their

nasal spray will be unaware of condition or nasal spray (oxytocin or placebo), participants will not know what condition they have been assigned to and an RA not affiliated with this study will complete the outcome assessment without being aware of nasal spray that participants are assigned to. Adequacy of blinding will not be formally evaluated, given the lack of evidence for, and concern against conducting such an assessment.<sup>29</sup>

### Experimental condition

During the experimental condition, participants will receive a 2-week course of intranasal oxytocin. Participants will self-administer 24 IU intranasal oxytocin (12 IU delivered to each nostril; Syntocinon, Novartis, Switzerland), two times per day (once in the morning and once in the evening). In order to ensure standardisation of nasal spray administration, participants will be trained in the self-administration of intranasal oxytocin in accordance with published recommendations for the standardisation of oxytocin nasal administration.<sup>36</sup> Two times per day dosing will ensure elevated central concentration of oxytocin throughout the day, given that salivary concentration of oxytocin was elevated for 7 hours following intranasal administration of 24 IU oxytocin.<sup>37</sup> Further, a 24 IU dose represents a safe and effective concentration for two times per day dosing (see Rash and Campbell<sup>38</sup>). Oxytocin nasal spray is well tolerated and doses ranging from 10 to 60 IU have produced no reliable side effects in humans relative to placebo.<sup>7</sup>

**Table 1** Schedule of assessments

Testing variables	Screening	Randomisation				
		Baseline	Daily diary	Day 7 of diary	Day 14 of diary	Laboratory follow-ups
Inclusion and exclusion criteria	X	X				
Sociodemographics		X		X		
Medical history		X		X		
Vitals		X				X
PCS		X				
MSPSS		X				
Pain						
BPI-SF intensity		X	X			
BPI-SF interference		X	X			
Pelvic pain NRS	X					X
Emotional function						
PANAS		X	X			
DASS		X		X	X	
Sleep						
MOS-S		X		X	X	
Global impression						
PGIC		X			X	
Expectancy						
CEQ		X				
Side effects						
SAS					X	

BPI-SF, Brief Pain Inventory-Short Form; CEQ, Credibility, Expectancy Questionnaire; DASS, Depression, Anxiety, Stress Scale; MOS-S, Medical Outcomes Study Sleep Scale; MSPSS, Multidimensional Scale of Perceived Social Support; PANAS, Positive and Negative Affect Schedule; PCS, Pain Catastrophizing Scale; PGIC, Patient Global Impressions of Change; SAS, Symptom Assessment Schedule.

Moreover, a recent study of 14 women with fibromyalgia reported that an 80 IU dose of intranasal oxytocin was well tolerated and had no differential side effects from placebo when delivered daily over a 3-week period.<sup>23</sup> Participants will be instructed to store nasal spray at room temperature (between 15°C and 25°C) and outside of range of children.

### Control condition

During the control condition, participants will receive a 2-week course of intranasal placebo (containing the same ingredients as the oxytocin nasal spray except for the active oxytocin) self-administered on the same schedule as the experimental condition. The bottles containing oxytocin and placebo will be identical in appearance, smell, texture and taste. Different coloured stickers will be applied to the bottles in order to distinguish oxytocin from placebo. Only the study coordinator will be aware of what colour signifies which nasal spray and blinding will only be broken should an adverse event occur.

### Washout period

The experimental and control conditions will be separated by a washout period of ~2 weeks to ensure that intranasal administration coincides with the same phase of the menstrual cycle. If women have regular menstrual cycles (by definition  $\leq 35$  days, and the luteal phase is the fixed component of the menstrual cycle), the washout phase may be extended by up to 7 days to ensure that all women receive treatment in the same menstrual cycle phase. This time frame will be 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 full clearance in 14–49 hours.

### Daily diaries

Participants will be provided with daily diaries to record their menstrual cycle, time of nasal spray administration, study assessments and side effects (refer to [table 1](#) for a schedule of assessments).

### Participant engagement

A multipronged approach will be used to encourage participant engagement in our trial. First, the timeline and demands of the trial will be explicitly discussed at the outset with participants, who will be asked to sign a behavioural contract to commit to trying to meet the requirements. Second, women will receive telephone reminders prior to each laboratory visit and again if they miss one visit. Third, expectations will be developed for participant attendance. We will ensure that participants know our research staff by name and will be made aware that their research associate has an appointment scheduled with them and will be awaiting their arrival. Fourth, participants who have difficulties attending sessions will be provided with a telephone-based motivational conversation during which ambivalence towards attending sessions will be openly discussed with the goal of securing

commitment to attend a session at a time that is convenient for them. Many of these strategies have been identified by Cochrane reviews as methods for improving patient recruitment<sup>39</sup> and retention.<sup>40</sup>

### Measures

[Table 1](#) shows the measures obtained during each phase of the trial.

#### Primary outcome

As recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT),<sup>41</sup> pain and functional impairment will be measured at baseline and daily using the Brief Pain Inventory-Short Form (BPI-SF<sup>42</sup>). The BPI-SF measures pain intensity, the impact of pain on seven daily activities (eg, activity, work, sleep) and analgesic use. The BPI was originally designed to measure cancer pain, but has been shown to be a reliable and valid instrument for measuring non-cancer pain.<sup>43–46</sup> Test–retest values for pain and interference typically range between 0.72 and 0.98, and data from studies in many countries have supported a two-factor solution of pain severity and interference.<sup>47</sup>

#### Secondary outcomes

As recommended by the IMMPACT,<sup>41</sup> secondary outcomes include emotional function, sleep disturbance and global impression of change.

*Mood* will be measured daily using the *Positive and Negative Affect Scale* (PANAS<sup>48</sup>). The PANAS comprises 10 positive affect words (eg, excited, proud) and 10 negative affect words (eg, distressed, upset). Participants are asked to rate how they feel ‘today’ using a 5-point Likert scale ranging from 1 ‘slightly or not at all’ to 5 ‘extremely’. The PANAS has excellent internal consistency (Cronbach  $\alpha=0.87–0.90$ ), moderate 8-week test–retest reliability ( $r=0.39–0.47$ ) and correlates strongly and in the expected directions with measures of mood, well-being, distress and psychopathology.<sup>48</sup>

*Emotional function* will be measured weekly using the *Depression Anxiety Stress Scale* (DASS-21<sup>49</sup>). The DASS is a 21-item measure consisting of 3 scales that each comprise 7 items—Depression, Anxiety and Stress. Items refer to the past week and scores range from 0 ‘did not apply to me at all’ to 4 ‘applied to me very much, or most of the time’. The scales 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.<sup>50</sup> Numerous studies have reported favourable psychometric properties of the DASS in clinical samples<sup>50</sup> and older patients in primary care.<sup>51</sup> In patients with chronic pain specifically, the DASS has shown construct validity (ie, was related to other measures of similar constructs) and strong internal consistency (Cronbach  $\alpha=0.68–0.96$ ).<sup>52 53</sup> The DASS has also

shown moderate to strong 3-month test–retest reliability ( $r_s=0.59–0.77$ ) in a sample of older adults.<sup>54</sup>

*Sleep disturbance* will be assessed weekly with the *Medical Outcomes Study Sleep Scale* (MOS-S<sup>55</sup>). The MOS-S is a 12-item self-report measure designed to assess the important dimensions of sleep, including initiation, maintenance, respiratory problems, quantity, perceived adequacy and somnolence. Preliminary support for the MOS-S was provided in the developmental sample of 3445 individuals with chronic illness.<sup>56</sup> Further support for the reliability and validity of the MOS-S was reported in a nationally representative sample of 1011 US adults and in a sample of 173 adults with neuropathic pain (eg, moderate to strong internal consistency among different subscales; Cronbach  $\alpha=0.63–0.83$ ).<sup>57</sup> Another large study of people with neuropathic pain ( $n=603$ ) reported a similar Cronbach  $\alpha$  ( $0.64–0.87$ ) as well as good test–retest reliability ( $r=0.67–0.87$ ).<sup>58</sup>

*Global change* across the course of study will be assessed at the end of each 2-week course of nasal spray using the *Patients' Global Impression of Change* scale (PGIC<sup>59</sup>). This measure is a single-item rating by participants of their improvement with treatment during a clinical trial on a seven-point scale ranging from 'very much improved', to 'very much worse' with 'no change' as the midpoint. There has been wide use of the PGIC in chronic pain trials,<sup>60 61</sup> and data provide a responsive and readily interpretable measure of participants' assessment of clinical importance of treatment.

### Demographics and covariates

*Demographic* information will be assessed using a demographic questionnaire, including age, ethnicity, medical comorbidities, medications taken, employment status, marital status, obstetrical history, menstrual history, urinary symptoms, headaches, substance use and smoking status.

*Subjective social status* is highly correlated with socioeconomic status and will be measured to characterise the sample using the *MacArthur Ladder*, an image of a ladder meant to represent ranks of social status, on which people mark an 'x' on the rung they think best represents their rank.<sup>62</sup>

Concern over pain will be assessed using the *Pain Catastrophizing Scale* (PCS<sup>63</sup>). The PCS is a 13-item questionnaire that instructs participants to reflect on past painful experiences (eg, 'I worry all the time about whether the pain will end') and indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain, on 5-point scales with the anchors of (0) 'not at all' and (4) 'all the time'. The PCS yields a total score and three subscale scores assessing rumination, magnification and helplessness. Internal consistency of the PCS total score is excellent (Cronbach  $\alpha=0.93–0.95$  in undergraduate, community and outpatient pain populations) and good for subscale scores (Cronbach  $\alpha=0.75–0.95$ ) in undergraduate<sup>63 64</sup> and outpatient pain samples.<sup>65</sup> Scores on the PCS are

positively correlated ( $r=0.42$ ) with a measure of negative thoughts in response to pain<sup>64</sup> offering support for convergent validity, and have been used to discriminate community and outpatient pain populations.<sup>65</sup> Finally, total PCS scores have demonstrated adequate test–retest reliability over a mean period of 52 days in a sample of chronic pain patients.<sup>66</sup>

*Social support* will be measured using the *Multidimensional Scale of Perceived Social Support* (MSPSS<sup>67</sup>). The MSPSS is a 12-item scale that measures the perceived availability and adequacy of emotional and instrumental social support offered by family, friends and significant others (eg, 'There is a special person who is around when I am in need'). Participants respond using a 7-point Likert scale ranging between 1 'very strongly disagree' and 7 'very strongly agree'. Empirical evidence suggests that intranasal oxytocin and social support interact to reduce stress<sup>15</sup> and social support and oxytocin may also interact to reduce pain. The MSPSS has demonstrated strong internal consistency and test–retest reliability among older adults.<sup>68</sup>

Treatment expectations will be measured using the *Credibility/Expectancy Questionnaire* (CEQ<sup>69</sup>). The CEQ is a six-item questionnaire that measures two factors—cognitively based credibility of treatment and affective-based expectancy of treatment effectiveness. The scale has a strong internal consistency (Cronbach  $\alpha=0.84–0.85$ ) and good test–retest reliability ( $r=0.75–0.82$ ).<sup>69</sup>

*Side effects and safety monitoring.* As recommended for trials of chronic pain,<sup>70</sup> 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 Schedule* (SAS<sup>71</sup>) supplemented with additional symptoms (eg, euphoria, nasal irritation, dizziness) identified in a recent trial evaluating the effect of intranasal oxytocin on pain in a sample of 14 women with fibromyalgia.<sup>23</sup> Further, all participants will be provided with a number for Health Link (#811) in order to ensure participant safety. Health Link is a free service in Alberta, Canada, that participants can call 24 hours/day to receive health advice from a registered nurse.

*Risk management and discontinuation criteria.* Rescue medication is not required with intranasal oxytocin. The best method to resolve side effects is to discontinue use of the drug, which is our recommended course of action. Participants may voluntarily withdraw from the study at any point in time by informing the researcher that they wish to discontinue their participation. Participants are explicitly informed, verbally and in writing, that their decision to discontinue will not impact their future treatment by their physician. Given the limited drug interaction and rare, but non-fatal side effects, we have no a priori defined discontinuation criteria. In accordance with recommendations of the European Medicines Agency, a data monitoring committee is not needed, given that: (1) chronic pelvic musculoskeletal pain is not a life-threatening condition;

(2) study duration is brief; and (3) intranasal oxytocin has been extensively studied and side effects are rare and benign.<sup>7</sup>

## Data analysis

### Sample size calculation

We powered this study and based our sample size calculation on the number of patients needed to assess our primary outcome: change in self-reported pain between oxytocin and placebo nasal spray. In our previous work, intranasal oxytocin resulted in significant reductions in the report of acute pain (10–15% reduction in pain), with moderate to large effect sizes ( $\eta_p^2=0.11-0.13$ ).<sup>72</sup> This equated to a minimally clinically significant reduction in pain of 1 cm on a 10 cm visual analogue scale.<sup>73</sup> Given that our previous trial utilised a healthy sample, we powered this trial using a conservative estimate of a medium effect size. Setting power at 90%,  $\alpha=0.05$  and 2-tailed hypothesis testing, 44 patients would need to be recruited to detect a covariate adjusted medium effect ( $d=0.50$ ). Calculations were performed using GPower.<sup>74</sup> Fifty patients will be recruited in order to preserve power and account for potential attrition of 15%.

### Data management

Data from this study will be stored and protected in two ways: (1) electronic files will be password-protected and accessed only by the research team; (2) paper files will be stored in a locked filing cabinet within the study site, and will be accessible only to the research team. Data will be deidentified to protect participant confidentiality. An RA blind to study condition will perform data entry and a second RA will randomly sample 25% of entry values to ensure accuracy. Members of the investigative team will have access to the final trial data set.

### Statistical analysis plan

An intention-to-treat analysis will be performed,<sup>75</sup> in accordance with CONSORT guidelines,<sup>28 29</sup> to provide an assessment of the practical impact of a treatment. *Primary analysis:* Improvement in pain following oxytocin nasal spray relative to placebo nasal spray will be assessed using the BPI-SF. Using the linear mixed model function in SPSS, the analytic strategy is a mixed models analysis of covariance with time (baseline, 14 days) as the within-participant factor and treatment condition (oxytocin, placebo) as the condition factor after adjusting for relevant covariates. Given that randomisation is expected to eliminate selection bias and equate groups on relevant baseline characteristics,<sup>29</sup> an a priori decision was made to include only covariates with a strong empirically established association with the dependent variable, rather than include all possible covariates. Any missing data will be handled using multiple imputation in accordance with Harrell's guidelines.<sup>76</sup> *Secondary analyses:* The effects of the oxytocin nasal spray on change in mood, emotional function and sleep will be evaluated in a manner analogous to that described above.

## Dissemination

Important protocol modifications will be communicated to the CHREB, Health Canada and study participants. Results of this trial will be communicated through traditional channels (eg, conference presentations and peer-reviewed publications). To reach the general public via lay results, press releases detailing study results will be prepared and a study website will be created that details study results.

## DISCUSSION

Data from this study will provide information about the efficacy of intranasal oxytocin to improve pain and function among women with chronic pelvic musculoskeletal pain. Intranasal oxytocin has gained increasing attention in recent years and is showing promising results for pain management,<sup>5 6 77</sup> though only a handful of studies have evaluated the effect of intranasal oxytocin on chronic pain in humans. Specifically, intrathecal injection of oxytocin in doses ranging between 50 and 400  $\mu\text{g}/\text{kg}$  were reported to reduce pain among adults with acute and chronic low back pain relative to a saline control.<sup>19</sup> Continuous intravenous administration of oxytocin has led to a dose–response decrease in reports of pain induced by inflating a barostat bag in the descending colon of 26 (11 women) patients with abdominal pain.<sup>22</sup> Relative to placebo, a single intranasal administration of oxytocin was reported to decrease headache in a dose-dependent manner in an otherwise healthy sample of Chinese participants.<sup>20</sup> The twice-daily administration of intranasal oxytocin over a 13-day period resulted in a significant reduction in abdominal discomfort and a non-significant reduction in abdominal pain in a sample of 49 women with daily abdominal symptoms and chronic constipation, relative to a placebo control.<sup>21</sup> Post hoc calculation indicated that 60–120 women would be required to detect an effect of oxytocin on pain. Finally, the daily administration of intranasal oxytocin over a 3-week period did not reduce pain in a sample of 14 women with fibromyalgia relative to a placebo,<sup>23</sup> though this trial had a number of limitations, including a small heterogeneous sample (refer to Rash and Campbell<sup>38</sup> for a commentary). This will be the first methodologically rigorous trial to provide data on the efficacy of intranasal oxytocin for use in women with chronic pelvic musculoskeletal pain. To the best of our knowledge, this will also be the first trial assessing the effect of intranasal oxytocin on pain that adequately accounts for important covariates such as stage of menstrual cycle. This is particularly relevant, given that oestrogen has a priming effect on oxytocin synthesis, release and receptor expression.<sup>78</sup>

Despite the recent proliferation of research, few trials evaluating associations between oxytocin and pain have extended from the laboratory into clinical practice where pain is often inadequately managed,<sup>79 80</sup> and the use of combination drug therapies is advocated as a

means to improve clinical outcomes and limit deleterious adverse effects by achieving similar therapeutic effects with two compounds, each at a lower dosage.<sup>81</sup> Oxytocin may be particularly amenable to combination drug therapies due to complimentary mechanisms of actions to opioids and non-steroidal anti-inflammatory drugs, and a low side-effect profile. This trial will provide data on the 14-day safety and side-effect profile of intranasal oxytocin self-administered as an adjuvant treatment for chronic pain.

The proposed trial will speak to the clinical importance of intranasal oxytocin in the treatment of chronic pain. It has been acknowledged that statistically significant results in pain research must be supplemented by consideration of clinical importance of change in a variety of outcomes.<sup>73</sup> Such information provides a basis for evaluating and comparing the impact of treatments on symptoms, functioning, well-being and overall quality of life. This trial represents the first methodologically rigorous investigation into the efficacy of intranasal oxytocin on chronic pain that adheres to IMMPACT recommendations for core outcome measures for chronic pain clinical trials.<sup>41</sup> The results of this investigation will speak to the clinical importance of intranasal oxytocin on pain, emotional well-being, physical well-being, mood and sleep. Moreover, the outcome measures selected for use in this trial will allow for direct comparison across clinical trials on women with chronic pelvic musculoskeletal pain.

Finally, an efficacy trial of this nature is a prerequisite before conducting effectiveness research. Intervention trials can be placed on a continuum with highly controlled efficacy trials on one end and 'real-world' effectiveness trials on the other.<sup>82</sup> Methodologically rigorous RCTs are ideal for efficacy evaluation because such designs minimise bias, enrol a homogeneous patient population, ensure that interventions are delivered in a highly standardised way (including timing and dose) and minimise issues of access, provider recommendation and patient adherence.<sup>82</sup> For these reasons, an efficacy trial can overestimate an intervention's effects when implemented in clinical practice. Thus, this trial will speak to the efficacy of intranasal oxytocin to manage pain among women with chronic pelvic musculoskeletal pain and support further efficiency trials.

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