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Investigating Intranasal Oxytocin as a Treatment for Women's Chronic Pelvic Pain: A Feasibility Study

by

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Abstract

Chronic pelvic pain (CPP) affects approximately 5.7-26.6% of women in the general population and has limited treatment options. Administration of oxytocin (OT) has been associated with reductions in pain in other chronic pain conditions. The current feasibility study was the first to investigate the OT-pain association in women with CPP. The aims were: 1) determine if a clinically significant change in pain intensity (1-centimeter improvement on a 10-centimeter visual analogue scale) could be detected following intranasal OT administration; 2) identify challenges in treatment and study protocol implementation. Women with CPP (N=18) were recruited from chronic pain and gynecology clinics for this randomized, double-blind, within-subject crossover trial (Registration#NCT02888574). Exclusion criteria included pregnancy, primary diagnosis of endometriosis, dysmenorrhea, interstitial cystitis, functional bowel disorder, fibromyalgia, or neuropathic pain. Currently, 11 women have completed the trial (2-weeks OT, 2-weeks washout, 2-weeks placebo, with random order of OT and placebo). Women recorded symptoms of pain at baseline and in daily diaries. One participant dropped out due to headaches following placebo administration, one did not complete daily diaries, and two were randomized despite having pain only during intercourse, leaving seven women in the analyses. Clinically significant change was reported for average and current pain following OT and placebo administration. Self-reported treatment adherence was near perfect. Participants viewed the treatment as credible, anticipating improved pain. Daily diary adherence was good. Challenges with protocol implementation highlight the need for more systematic eligibility assessments and recruitment strategies, and moving daily diaries to an online platform. Overall, a clinically significant change was detected on pain and the treatment protocol was feasible, though some adjustments to the study protocol are warranted before a subsequent trial is completed.

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Investigating Intranasal Oxytocin as a Treatment for Women's Chronic Pelvic Pain: A Feasibility Study

Chronic pelvic pain (CPP) is most commonly defined as pain that is cyclical or non-cyclical; experienced in the lower abdomen or pelvis; occurs for at least six months' duration, continuously or intermittently; and limits activities of daily living or causes functional disability (Daniels & Khan, 2010; Howard, 2003). Estimates indicate that CPP affects 5.7% to 26.6% of women in the general population, depending on how CPP is defined (Ahangari, 2014). Some estimates may underrepresent CPP's prevalence as surveys have reported that up to a third of women with CPP do not seek care from medical professionals (Pitts, Ferris, Smith, Shelley, & Richters, 2008; McGowan, Luker, Creed, & ChewGraham, 2007), and there is a paucity of population-based prevalence studies for CPP (Ahangari, 2014).

CPP can be a symptom, but it may also be considered its own syndrome when underlying pathology has been ruled out as a cause of pain (Daniels & Khan, 2010). Possible pathological causes of CPP include endometriosis, irritable bowel syndrome, and interstitial cystitis (Latthe, Mignini, Gray, Hills, & Khan, 2006; Beard, 2001), though, no obvious pathological cause for pain will be identified for up to 54% of women (Daniels et al., 2009; Howard, 1993). Miscarriage, previous caesarean section, heavy periods, pelvic pathology, abuse, and psychological comorbidities have been identified as predisposing factors associated with a higher risk of non-cyclical pain (Latthe et al., 2006). It has been proposed that CPP is best viewed from a biopsychosocial perspective, in which causes of CPP are multifactorial, with organic pathology, coping skills, social interactions, and beliefs contributing to the etiology of the condition and women's experiences of pain (Engel, 1977; see Moore and Kennedy (2000), Moore and Kennedy (2005) for reviews). One such perspective is the Fear-Avoidance (FA)

Model of Chronic Pain (Vlaeyen, Kole-Snijders, Boeren, & Van Eek, 1995). Patients' interpretations of pain are at the core of the FA model: non-threatening interpretations of pain typically allow patients to resume their daily activities, whereas when pain is interpreted as catastrophe, patients may experience excessive fear of pain and associated physical activities assumed to exacerbate their pain. Avoidance resulting from catastrophic interpretations of pain limits an individual's opportunities to adjust their expectations of painful experiences, leading to an overestimation of future pain and its associated negative consequences. While not included in the original FA model, the role of attentional processes (e.g., hypervigilance; Crombez, Van Damme, & Eccleston, 2005) and motivational factors (e.g., ignoring pain and goal-persistence; Crombez, Eccleston, Van Damme, Vlaeyen, & Karoly, 2012) have subsequently been acknowledged as important components of the pain experience within the FA model. Importantly, women's experiences of CPP extend beyond the pain itself. These women report lower general physical health than pain-free controls, describe social isolation and loss, and often experience a variety of comorbidities, including sleep disturbance and fatigue (Zondervan et al., 2001; Grace & Zondervan, 2006). CPP in women has also been associated with decreased work efficiency and poor quality of life (Reiter, 1990; Mathias, Kuppermann, Liberman, Lipschutz, & Steege, 1996).

Overall, the evidence-base for treatments for CPP is limited (see Speer, Mushkbar, and Erbele (2016) for a review). Moderate evidence supports progestogen treatment for CPP, though, among patients with pain of unknown etiology, this treatment is associated with short-term pain relief only, in addition to low patient satisfaction due to the treatment's adverse effects (Cheong, Smotra, & Williams, 2014). Opioids are an option for pain management, but their use in pain syndromes is controversial; the European Association of Urology (2017) recommends that use of

opioids in chronic pain management is considered only after all other reasonable treatment options have been tried without benefit. Research regarding the effectiveness of various other pharmacologic treatments (i.e., tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, anticonvulsants [e.g., gapapentin, pregabalin]) points to their usefulness in reducing symptoms among those with neuropathic pain only and this body of evidence is limited (Engeler et al., 2015; Sator-Katzenschlager et al., 2005). Pelvic floor physical therapy has shown promise as a treatment for CPP, though the current evidence is too limited to guide practice (Fitzgerald et al., 2013; Loving, Nordling, Jaszczak, & Thomsen, 2012). Following somatocognitive therapy – a hybrid of cognitive psychotherapy and physiotherapy – women with CPP reported reduced pain and psychological distress (Haugstad et al., 2008). However, evidence supporting somatocognitive therapy as a treatment for women's CPP is still preliminary (Haugstad, Kirste, Leganger, Haakonsen, & Haugstad, 2011). Surgical interventions, such as hysterectomies, are recommended only as a last resort due to high morbidity and limited benefit (Speer et al., 2016): only half of women who undergo a hysterectomy report improvements in physical and mental health post-surgery, up to 40% report persistent pain, and 5% report worse pain (Hartmann et al., 2004; Lamvu, 2011). Taken together, this reflects a need for additional effective treatments for women's CPP.

Oxytocin (OT) and Pain Sensitivity

Oxytocin (OT) is a neuropeptide produced in the supraoptic and paraventricular nuclei of the hypothalamus, released into circulation via neurons extending down to the posterior pituitary (Rash, Aguirre-Camacho, & Campbell, 2014; Viero et al., 2010). Traditionally, OT has been recognized for its role in labour and delivery (Fuchs, Fuchs, Husslein, Soloff, & Fernstrom, 1982) and lactation (Luhman, 1963). Additionally, evidence suggests OT decreases pain

sensitivity via three possible mechanisms (see Rash, Aguirre-Camacho, and Campbell (2014) for a review).

The first proposed mechanism involves spinal signalling. A direct hypothalamo-spinal projection originating from the paraventricular nucleus transports OT to the dorsal horn (lamina-I, II, and IV), a region well-known for its role in the modulation of pain (Gimpl & Fahrenholz, 2001). The dorsal horn is a site at which pain signals are modulated dynamically. A high concentration of nociceptors terminate in the superficial and deep dorsal horn: A-delta afferents terminate in the superficial lamina I, C-fibers terminate superficially in the lamina I and II, and A-delta afferents terminate in the deeper lamina V. The well-documented direct hypothalamo-spinal projection originating from the paraventricular nucleus also terminates in the dorsal horn (more specifically, lamina I, II, and IV) and contains an abundance of OT. Moreover, a subset – approximately 35% – of dorsal horn neurons in the lamina I and II contain OT receptors that influence glutamatergic neurons. In turn, these neurons activate GABAergic neurons, resulting in an inhibition of pain-carrying A-delta and C-fibers (Condes-Lara et al., 2009; Jo et al., 1998; Breton et al., 2008). The presence of a descending oxytocinergic pathway, coupled with the abundance of OT receptors in a region with a high concentration of nociceptive fibers, indicates the involvement of OT in pain signaling.

The second plausible mechanism involves an indirect pathway for pain reduction. Evidence suggests that OT binds to opioid receptors and may stimulate endogenous opioid release in the brain. An opioid system located in the periaqueductal gray – another region known to play an important role in pain modulation – activates a series of descending controls that prevent spinal cord transmission regarding injury (Ge, Lundeberg, & Yu, 2002). OT administered to the periaqueductal gray results in the blocking of the detection of a painful or

injurious stimulus by sensory neurons, and this effect can be blocked by a subsequent administration of an oxytocin antagonist (Ge, Lundeberg, & Yu, 2002; Yang et al., 2011). This evidence suggests an interaction between oxytocin and opioids in the modulation of nociception (i.e., the nervous system's response to [potentially] harmful stimuli).

The third and final proposed mechanism by which OT may reduce pain is through its potential abilities to improve mood, decrease anxiety, and mitigate the stress response. In a placebo-controlled, double-blind study (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003), men administered intranasal OT prior to completing the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993). The TSST was designed to induce a state of stress among the individuals who complete it, consisting primarily of a 10-minute anticipation period and a 10-minute test period during which participants are required to deliver a free speech and perform mental arithmetic in front of an audience. The men who received intranasal OT prior to completing the TSST were calmer, less anxious, and displayed a trend toward having lower cortisol levels during the stress test (Heinrichs et al., 2003). Thus, it may be through mood-improving, anxiety-reducing, and stress-mitigating properties that OT improves pain.

Previous Studies on the OT-Pain Association

The influence of OT on pain in animals has been studied with various animal models. Methods (e.g., injecting OT, measuring OT concentrations in blood plasma, using mice with the genetic expression for OT removed) and nociceptive stimuli used to produce pain (e.g., electrical, mechanical, cold, heat, or a combination) in animal studies have varied widely (see Rash, Aguirre-Camacho, and Campbell (2014) for a review). Regardless of methodological variability, the majority of these studies (29 of 33) have reported support for an association between OT and pain. Both exogenous administration of OT and higher endogenous levels of

OT have been associated with decreased pain. In a recent study, intranasal OT attenuated chronic pain in a mouse model of mild traumatic brain injury (Meidahl, Eisenried, Klukinov, Cao, Tzabazis, & Yeomans, 2017). To date, the most reliable evidence suggesting that OT increases pain tolerance comes from studies employing animal models.

The nature of the OT-pain association in humans is less clear due to a lack of methodologically rigorous trials (see Rash et al. (2014) for a review). Higher endogenous OT concentrations have been associated with lower pain sensitivity in four of five studies that have assessed OT blood plasma concentrations in humans. A handful of studies have also examined OT administration in chronic pain populations. Yang (1994) investigated the OT-pain association among 165 patients experiencing lower back pain. Intrathecal OT injections relieved both acute (median effective dose: 0.121 micrograms/kilogram) and chronic lower back pain (median effective dose: 0.172 micrograms/kilogram). Louvel et al. (1996) investigated intravenous OT among patients experiencing chronic colon pain. OT dosed at 20, 30, and 50 milliunits/minute significantly increased the threshold of pain triggered by applying pressure to the colon. Two studies have investigated intranasal OT in individuals experiencing chronic headaches. Wang et al. (2013) reported a dose-dependent relationship, such that a larger proportion of patients reported complete relief of headache with each increased dose of intranasal OT (9/28 patients at 100 nanograms, 14/28 patients at 200 nanograms, and 20/28 patients at 400 nanograms); only two patients reported complete relief of headache with placebo, representing a statistically significant difference from all doses of OT. These studies are limited by lack of randomization (Wang et al., 2013), lack of placebo (Yang, 1994; Louvel et al., 1996), and confinement to one session in a laboratory setting (Wang et al., 2013; Yang, 1994; Louvel et al., 1996). More recently, patients with chronic headache who dosed intranasal OT over the course of a month

reported decreased pain and decreased frequency of headaches (Tzabazis et al., 2017). It is unclear if this study was randomized or placebo-controlled, and details regarding patients' intranasal OT dosing were not reported.

To date, there are only two double-blind, randomized, placebo-controlled studies investigating the OT-pain association among individuals with chronic pain. Ohlsson et al. (2005) randomized patients experiencing chronic constipation to intranasal OT (n=23) or a placebo nasal spray (n=26). Those administering OT were instructed to dose 40 International Units (IU) of OT twice daily for 13 weeks. Those in the placebo group administered a nasal spray without the active OT ingredient. All participants provided daily ratings of their abdominal symptoms. Only those administering OT reported decreased abdominal discomfort and a trend toward decreased abdominal pain, providing preliminary evidence that intranasal OT may reduce pain among patients with chronic constipation. Similarly, Mameli et al. (2014) investigated intranasal OT among 14 women with fibromyalgia in a double-blind, crossover, randomized trial. Women administered oxytocin or placebo daily for 3 weeks each, in a random order, and provided self-reports of pain severity. Contrary to the authors' hypotheses, administration of intranasal OT (80IU per day) did not result in reduced pain, though daily dosing of OT was determined to be safe and devoid of toxicity. The authors noted that the small number of patients recruited may explain the lack of therapeutic effects of OT nasal spray observed and concluded that further studies are needed to elucidate intranasal OT's potential usefulness as a treatment.

Gaps in the Current OT-Pain Literature

No research to date has evaluated the association between intranasal OT and CPP. Importantly, the OT-pain association may be different in women with CPP compared to other chronic pain conditions because of a potential peripheral OT-pain pathway. There is an

abundance of OT receptors in the uterus, and OT is a potent uterogenic agent used in clinical settings in large doses to stimulate uterine contractions and induce labour (Gimpl & Fahrenholz, 2001). While OT does not cross the blood-brain-barrier, central administration of intranasal OT increases central and blood-plasma OT concentrations (Gossen et al., 2012). Moreover, the administration of intranasal OT is safe: in previous studies, only mild side effects have been reported, and these side effects do not differ between placebo and OT (see MacDonald et al. (2011) for a systematic review). Thus, intranasal OT administration may be associated with decreased pain through central and peripheral pathways among women with CPP.

Developing OT as a Treatment for CPP

There are several frameworks and strategies for developing and evaluating interventions for chronic diseases (e.g., Obesity-Related Behavioral Intervention Trials [ORBIT] model, Czajkowski et al., 2015; Medical Research Council [MRC] framework, Craig et al., 2008; Multiphase Optimization Strategy [MOST], Collins, Murphy, Nair, & Strecher, 2005; Sequential Multiple Assignment Randomized Trial [SMART], Murphy, 2005). The ORBIT model is endorsed by the National Institutes of Health (NIH) and provides a framework for treatment development, as well as clinically meaningful milestones for each step of the process. The process outlined by this model begins with the identification of a significant clinical question, followed by four phases of research: Phase I Design (including Phase Ia "Define" and Phase Ib "Refine"), Phase II Preliminary Testing (encompassing Phase IIa "Proof-of-Concept" and Phase IIb "Pilots"), Phase III Efficacy, and Phase IV Effectiveness. While the model begins with developing a clinically significant research question and ends with effectiveness research to determine if the treatment works in real-world settings, the authors emphasize the bi-directionality of the treatment optimization process. That is, researchers may progress to a later

phase of the model or return to an earlier phase, dependent on the achievement of clinically significant milestones.

In the context of the OT-pain association in women's CPP, the significant clinical question has been identified, and Phase I Design studies have determined effective administration methods for OT (in line with "define" studies of the model; e.g., Van Ijzendoorn et al., 2012; Gossen et al., 2012) and safe and effective dosing of OT (in line with "refine" studies of the model; Rash & Campbell, 2014b; Mameli et al., 2014; MacDonald et al., 2011). The Phases II through IV of the ORBIT model have yet to be addressed in the context of OT as a treatment for women's CPP. Thus, the next appropriate stage of research is Phase II Preliminary Testing (often referred to as feasibility studies in research literature), specifically a Phase IIa Proof-of-Concept study. Phase IIa Proof-of-Concept studies focus on obtaining a clinically meaningful signal on the outcome of interest. These studies are also the initial test of a fixed treatment protocol. The results of Phase IIa Proof-of-Concept studies provide preliminary evidence regarding the treatment's ability to produce meaningful change in the population of interest, as well as information regarding the feasibility of the treatment and study protocols for both participants and investigators. Preliminary testing as outlined in the ORBIT model is essential to developing high-quality, rigorous, and appropriately implemented trials later in the research process.

The Current Study

The current study is a Phase IIa Proof-of-Concept study that investigated intranasal OT as treatment for women with CPP. The first aim of the study was to determine if a clinically significant signal could be obtained on women's self-reported pain following administration of intranasal OT. The second aim of the study was to determine the feasibility of a fixed treatment

and study protocol for investigators and participants. To this end, data on treatment expectations, drop-out rates, treatment adherence, study protocol adherence, adequacy of blinding, and side effects were collected and evaluated.

Method

The current study – approved by the University of Calgary Conjoint Health Research Ethics Board (Ethics ID: REB16-0334) – was the initial test of the protocol for a double-blind, placebo-controlled, within-subject crossover RCT. The study protocol adheres to CONSORT guidelines (Moher et al., 2012; Schulz, Altman, & Moher, 2010).

Participants

Recruitment. Recruitment is ongoing: 11 women have currently completed the trial. In total, 18 women have enrolled to participate (refer to Figure 1 for participant flow diagram). Participants were recruited from chronic pain and gynecology clinics across Calgary, Alberta.

Inclusion Criteria. Women who were non-menopausal, with chronic pelvic musculoskeletal pain (i.e., pain exceeding six months' duration, located primarily in the pelvic region, and reproducible on palpation to the muscles spanning the pelvic floor) were eligible to participate if they: 1) had regular menstrual periods (i.e., on a monthly basis, within a range of 21-35 days), given that pain varies across the menstrual cycle (Pfleeger, Straneva, Fillingim, Maixner, & Girdler, 1997; Riley, Robinson, Wise, & Price, 1999), and nasal spray administration occurred during the luteal phase; 2) used a barrier or permanent form of contraception to reduce pregnancy risk during the trial, given that OT is a potent uterogenic agent (Gimpl & Fahrenholz, 2001); 3) committed to not changing their medications during the six weeks of the trial; and 4) were experiencing moderate pain at baseline (i.e., a score of 4-7 out of 10 on a numeric rating

scale). The baseline pain score of 4-7 out of 10 was selected to prevent floor and ceiling effects and to ensure that participants have room to change throughout the course of the study.

Exclusion Criteria. Women were not eligible to participate if they: 1) were experiencing muscle pain as a result of systemic disease; 2) produced a positive result on a urine pregnancy test or were contemplating pregnancy; 3) were concurrently using another nasal spray; 4) had nasal pathology (e.g., ears, nose, and throat diagnosis); 5) had diabetes insipidus; 6) had previously used or were concurrently using narcotics delivered intranasally (e.g., cocaine); 7) had sacroiliac instability; and/or 8) had a primary diagnosis of endometriosis, dysmenorrhea, interstitial cystitis, functional bowel disorder, fibromyalgia, or neuropathic pain.

Measures

Measures were selected based on recommendations by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT; Dworkin et al., 2005). The times at which participants completed each measure are outlined in Table 1.

Clinically Significant Signal. Pain was measured at baseline and in daily diaries using the Brief Pain Inventory – Short Form (BPI-SF; Cleeland & Ryan, 1994). The BPI-SF measures pain intensity, pain's impact on daily activities (e.g., work, sleep), and analgesic use. This measure was originally developed to assess cancer pain, but it has since demonstrated reliability and validity for measuring non-cancer pain (Kapstad, Rokne, & Stavem, 2010; Keller et al., 2004; Mendoza, Mayne, Rublee, & Cleeland, 2006; Tan, Jensen, Thornby, & Shanti, 2004). Test-retest reliabilities for pain and pain interference generally range between .72 and .98, and the two-factor structure of pain severity and pain interference has been supported with data across many countries (Cleeland, 2009).

Treatment Acceptability.

Treatment expectations. Participants reported treatment expectations at baseline and at the end of each 2-week phase of nasal spray (both OT and placebo) through the Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000). This 6-item questionnaire measures two factors: cognitively-based credibility of treatment and affectively-based expectancy of treatment effectiveness. The CEQ has demonstrated strong internal consistency (Cronbach α = .84-.85) and good test-retest reliability (r = .75-.82; Devilly & Borkovec, 2000).

Side effects. Side effects were assessed at the end of each 2-week phase of nasal spray (both OT and placebo) using open-ended prompts in addition to the Symptom Assessment Schedule (SAS; Kristjanson et al., 1999). This method is recommended for trials of chronic pain (Katz, 2012). In the current study, the SAS was supplemented with additional symptoms (i.e., headache, euphoria, dizziness, and nasal irritation) that were identified in a recent trial evaluating intranasal OT in a sample of 14 women with fibromyalgia (Mameli et al, 2014).

Protocol Feasibility. Participants' adherence to the treatment protocol (i.e., self-reported missed doses), investigators' adherence to the study protocol, and missing data were used as indicators of feasibility.

Additional Measures. The current study aimed to assess the feasibility of including these measures in the trial protocol rather than assessing participants' responses over time.

Demographic information. Demographic information was collected during the baseline assessment with a questionnaire including questions about participants' age, ethnicity, medical comorbidities, and current medications (see Appendix A).

Mood. Mood was measured at baseline and in daily diaries with the Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988). The PANAS contains 10

positive affect words (e.g., excited, proud) and 10 negative affect words (e.g., distressed, upset). Participants are asked to rate how they feel today on a 5-point Likert scale, with 1 representing "slightly or not at all" and 5 representing "extremely." The PANAS has demonstrated excellent internal consistency (Cronbach α = .87-.90) and moderate 8-week test-retest reliability (r = .39-.47), and the PANAS correlates strongly, in the expected directions, with measures of well-being, mood, psychopathology, and distress (Watson et al., 1988).

Emotion function. The Depression Anxiety Stress Scale (DASS-21; Lovibond, 1995) was used to measure emotion function at the end of each 2-week phase of nasal spray (both OT and placebo). The DASS contains 21 items and three scales. Each scale – Depression, Anxiety, and Stress – contains seven items. Participants are asked to reflect on the past week and rate items from 0, representing "did not apply to me at all" to 4, representing "applied to me very much, or most of the time." The scales are intended to reflect facets of diagnostic categories, with the Depression scale reflecting mood disorders, Anxiety reflecting panic disorder, and Stress reflecting generalized anxiety disorder (Brown, Chorpita, Korotitsch, & Barlow, 1997). Favourable psychometric properties of the DASS have been reported in numerous studies using clinical samples (Brown et al., 1997) and older patients in primary care (Gloster et al., 2008). The DASS has shown construct validity and strong internal consistency (Cronbach α = .68-.96) in chronic pain samples specifically (Sarda, Nicholar, Pimenta, & Asghari, 2008; Wood, Nicholas, Blyth, Asghari, & Gibson, 2010).

Sleep disturbance. Sleep disturbance was measured at baseline and at the end of each 2-week phase of nasal spray (both OT and placebo) with the Medical Outcomes Study Sleep Scale (MOS-S; Hays & Stewart, 1992). This 12-item self-report was designed to assess important dimensions of sleep, including initiation, maintenance, quantity, perceived adequacy, respiratory

problems, and somnolence. Support for the MOS-S has been observed in samples of individuals with chronic illness (Katz & McHorney, 2002). The MOS-S has also demonstrated reliability and validity (e.g., moderate to strong internal consistency among its subscales, Cronbach α = .63-.83; good test-retest reliability, r = .67-.87) in large studies of individuals with neuropathic pain (Hays, Martin, Sesti, Spritzer, 2005; Rejas, Ribera, Ruiz, & Masrramon, 2007).

Global change. Global change was measured at the end of each 2-week phase of nasal spray (both OT and placebo) with the Patients' Global Impression of Change scale (PGIC; Hurst & Bolton, 2004). This measure consists of one item that asks participants to rate their improvement with treatment during a clinical trial on a 7-point scale, ranging from "very much improved" to "very much worse", with a midpoint of "no change." The PGIC has been widely used in chronic pain trials (Dunkl, Taylor, McConnell, Alfano, & Conaway, 2000; Farrar, Young, LaMoreaux, Werth, & Poole, 2001).

Subjective social status. Subjective social status was measured during the baseline assessment using the MacArthur Ladder. For this measure, participants are given an image of a ladder meant to represent social status rankings and they are asked to mark an 'x' on the rung they believe best represents their social ranking (Adler, Epel, Casellazzo, & Ickovics, 2000).

Concern over pain. The Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995) was used to assess concern over pain during the baseline assessment. This 13-item questionnaire asks participants to reflect on their past painful experiences (e.g., "I worry all the time about whether the pain will end") and then rate the degree to which they have experienced each of the 13 feelings or thoughts during painful experiences, from 0, representing "not at all", to 4, representing "all the time." A total score and three subscale scores (rumination, magnification, and helplessness) are obtained from the PCS. The PCS total score has

demonstrated excellent internal consistency in undergraduate, community, and outpatient pain samples (Cronbach α = .93-.95), and the PCS subscale scores have demonstrated good internal consistencies in undergraduate and outpatient pain samples (Cronbach α = .75-.95; Osman et al., 2000; Osman et al., 1997; Sullivan et al., 1995). The PCS has demonstrated convergent validity; its scores are positively correlated (r = .42) with a measure of negative thoughts in response to pain (Osman et al., 1997). The PCS has also been used to differentiate between community and outpatient pain populations (Osman et al., 2000). In a sample of chronic pain patients, total PCS scores have shown adequate test-rest reliability (Lame, Peters, Kessels, Van Kleef, & Patjin, 2008).

Social support. The Multidimensional Scale of Perceived Social Support (MSPSS; Zimet, Dahlem, Zimet, & Farley, 1988) is a 12-item scale that measures perceptions of availability and adequacy of emotional and instrumental social support (e.g., "There is a special person who is around when I am in need"). Participants completed this measure during the baseline assessment. Participants were asked to rate items using a 7-point Likert scale, ranging from 1 "very strongly disagree" to 7 "very strongly agree." The MSPSS has demonstrated good test-retest reliability and strong internal consistency among older adults (Stanley, Beck, & Zebb, 1998). Importantly, evidence suggests that social support interacts with intranasal OT to reduce stress (Heinrichs et al., 2003); further, social support and OT may interact to reduce pain.

Procedure

Refer to Figure 2 for a diagram of trial procedures.

Patient Screening, Recruitment, and Enrollment. Women with CPP were recruited from chronic pain and gynecology clinics. Gynecologists identified women who were both eligible and interested in participating in the current study, then coordinated baseline

appointments with the research assistant. The research assistant confirmed participant eligibility through completion of the screening questionnaire (Appendix B) at the baseline appointment.

Baseline Assessment. When possible, testing occurred during the luteal phase of the menstrual cycle (i.e., days 14 to 28) because this is the phase during which women tend to report the highest pain (Riley et al., 1999). After study gynecologists confirmed participants' eligibility, women attended a baseline session at the Calgary Chronic Pain Centre or their gynecology clinic. During the baseline assessment, the research assistant completed informed consent with participants, then randomized participants to study condition. Participants completed baseline questionnaires and were trained in nasal spray administration (see Appendix C for nasal spray administration guidelines). Participants then received a nasal spray administration schedule based on their randomization, both sets of nasal sprays, and two daily diaries.

Daily diaries. Participants were provided with daily diaries to record their menstrual cycle, time of nasal spray administration, study assessments, and side effects. Daily diaries were labelled with nasal spray colours for differentiation, and, in addition, participants were asked to date each page of the daily diaries to ensure correct matching of nasal spray administration and daily diary completion.

Randomization and Blinding. A research assistant not affiliated with the proposed study used Research Randomizer (http://www.randomizer.org/) to generate lists of randomly sequenced numbers for assigning patients to condition using a method consistent with CONSORT guidelines (Moher et al., 2012; Schulz et al., 2010). Central randomization was performed using a 1:1 allocation schedule with random block sizes of 4, 6, and 8. The generated randomization sequence was concealed in sequentially numbered envelopes. To protect against expectancy effects and biases, the research assistant completing the baseline assessment and

providing participants with their nasal spray was not aware of which nasal spray was OT or placebo, and participants were not aware of which nasal spray was OT or placebo. OT and placebo nasal sprays were in identical bottles; labels were removed and replaced with different coloured stickers to differentiate between the two.

Experimental Phase. During the experimental phase, participants received two weeks of intranasal OT. Participants self-administered 24 International Units (IU) of OT (12IU delivered to each nostril), twice daily (once in the morning and once in the evening). The twice daily dose of OT was selected to ensure elevated central concentration of OT throughout the day, given that salivary concentration of OT was elevated for seven hours following intranasal administration of 24IU OT (Van Ijzendoorn, Bhandari, Van der Veen, Grewen, & Bakermans-Kranenburg, 2012). Previous reports suggest that this dose is a safe and effective concentration for twice daily administration (Rash & Campbell, 2014b). OT nasal spray is typically well-tolerated, with doses ranging from 10IU to 60IU having produced no reliable side effects in humans compared to a placebo (MacDonald et al., 2011). Further, in a recent study of 14 women with fibromyalgia in which 80IU of intranasal OT was administered daily over three weeks, the intranasal OT did not differ in side effect profile relative to placebo (Mameli et al., 2014).

OT and placebo were purchased from Victoria Apotheke Zürich in Zürich, Switzerland. The active OT nasal spray provided to participants was Novartis Syntocinon, containing the active ingredient of synthetic oxytocin and the excipients propyl parahydroxybenzoate, methyl parahydroxybenzoate, and chlorobutanol hyemihydrate. OT nasal spray bottles contained 5ml Syntocinon, with 40IU OT per ml. The placebo nasal spray included the same ingredients as the OT nasal spray aside from the active OT ingredient.

Control Phase. During the control phase, participants received two weeks of a placebo nasal spray. The placebo was self-administered on the same schedule as the experimental phase.

Wash-Out Phase. The wash-out phase separated the experimental and control phases to ensure that intranasal administration of OT and placebo consistently coincided with the luteal phase of the menstrual cycle. The half-life of OT administered centrally via nasal spray is 2 to 7 hours, and 7 half-lives would be achieved for full clearance in 14 to 49 hours; thus, this time frame sufficed for clearance of intranasal OT.

Reminder Calls. To promote participants' adherence to the treatment protocol, the research assistant provided reminder calls and/or emails (participants were asked their preferred method of contact during the baseline assessment) at four time points. The day preceding a participant's start dates for the experimental and control phases of the trial, the participant was contacted with a reminder to begin nasal spray administration the next day. Three days into the experimental and control phases of the trial, the participant was contacted again and asked which nasal spray was being administered; this served as confirmation that participants were administering nasal sprays in the order to which they were randomized.

Follow-Up. Participants met the research assistant for a follow-up appointment in person immediately after completing the trial, at which time participants returned their daily diaries. Participants were asked 1) about their experiences with adverse side effects, 2) to provide an estimation of the number of missed doses over the course of the trial, and 3) which set of nasal sprays they believed contained OT. The research assistant also phoned participants two weeks after in-person follow-up to inquire about adverse side effects, for continued safety monitoring.

Safety Monitoring. All participants were provided with a number for Health Link (#811) in the event of adverse reactions. Health Link is a free, 24-hour service that participants can call

to receive health advice from a registered nurse. Participants were asked to carry a study card – stating that they were currently participating in a trial and may have been administering intranasal OT, with appropriate contact information to break blinding – for the duration of the trial.

Data Analysis

Descriptive statistics were used to analyze the data. Frequencies and percentages were calculated to determine the feasibility of enrolling and retaining participants, treatment adherence, and daily diary adherence. Clinically significant change was defined as a reduction of pain of 1 centimeter on a 10-centimeter visual analogue scale (as reported on the BPI-SF; Cleeland & Ryan, 1994; Dworkin et al., 2008). Mean change from baseline on pain intensity, as well as percentage of participants reporting a clinically significant reduction in pain, were assessed. An additional aim of this study was to identify challenges with implementing the study protocol.

Results

Recruitment, Enrollment, and Retention

Over the course of one year (July 2017 to July 2018), the study gynecologists identified 25 women who were both eligible for and interested in participating in the current study (refer to Figure 1 for a participant flow diagram). Two women declined to participate, reporting they were too busy; five women did not respond to the research assistant's attempts at contacting to schedule a baseline assessment. Eighteen women enrolled in the study and completed baseline assessments. Eleven participants have completed all phases and follow-up appointments of the trial. Two participants were incorrectly identified as eligible candidates for the current study and were randomized despite these women experiencing pain during intercourse only; they were

excluded from analyses. One participant dropped out of the trial due to side effects, and one participant was not adherent to the daily diaries. Thus, follow-up data are available for seven participants.

Demographics and Baseline Characteristics

Table 2 summarizes demographic information and baseline characteristics for the eligible women who have currently completed the trial (including the participant who dropped out; N=9). Most women (*M* age=35.2 years) in the sample are white (66.7%) and married or in a relationship (55.6%). On average, women had been experiencing chronic pain for 11 years, reported moderate pain interference, and mild symptoms on the depression, anxiety, and stress subscales of the DASS-21 (Lovibond, 1995).

Missing Data

Seventeen of 18 participants completed all measures at the baseline assessment. One participant did not complete the Credibility/Expectancy Questionnaire (Devilly & Borkovec, 2000). Less than 1% of baseline data was missing. Eight participants met eligibility criteria and completed all phases of the trial, six of whom (75%) completed all outcome measures. Two participants (25%) had missing follow-up data. One participant did not complete measures on any of the 28 days. Another participant did not complete measures on 3 days in one daily diary, but completed all 14 days in the other daily diary. Accounting for the participant who did not complete daily diaries, substantial daily diary data (13.83%) was missing.

Pain

In interpreting pain intensity scores, clinically significant change was defined as 1-centimeter or greater improvement in pain on a 10-centimere visual analogue scale (VAS), as reported on the BPI-SF (Cleeland & Ryan, 1994). Previous research has identified a 1-centimeter

improvement in pain on a 10-centimeter VAS to be what chronic pain patients consider a "minimally clinically significant change" (Farrar, 2000). Defining outcomes in terms of their importance to chronic pain patients is consistent with IMMPACT recommendations (Dworkin et al., 2008) and defining outcomes in terms of their clinical significance is consistent with the ORBIT model (Czajkowski et al., 2015).

Table 3 summarizes average baseline, follow-up, and change from baseline scores following OT and placebo administration. Following OT administration, the mean change from baseline at 14-days follow-up was clinically significant for average pain and current pain, but not for worst pain or least pain. Following placebo administration, the mean change from baseline was clinically significant for worst pain and average pain, but not least pain or current pain. Participant change in pain was also assessed individually. Following OT, clinically significant improvements were reported by 2 of 7 (28.6%) participants for worst pain, 3 of 7 (42.9%) participants for least pain, 4 of 7 (57.1%) participants for average pain, and 1 of 7 (14.3%) participants for current pain. Following placebo, clinically significant improvements were reported by 3 of 7 (42.9%) participants for worst pain, 2 of 7 (28.6%) participants for least pain, 5 of 7 (71.4%) participants for average pain, and 2 of 7 (28.6%) participants for current pain.

Treatment Expectations

Participants' responses to each item on the Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000) were averaged to evaluate treatment expectations. The CEQ is divided into two parts: the first four questions evaluate cognitive-based expectations and ask participants to reflect on what they think will occur, while the final two questions evaluate affective-based expectations and ask participants to reflect on what they feel will occur.

Cognitive-based expectations. Participants endorsed that the treatment was logical (average response of 7.5, with the anchors of 1 representing 'not at all', 5 representing 'somewhat logical' and 9 representing 'very logical'). Participants reported thinking that the treatment would be somewhat useful in reducing their pain (average response of 5.5, with the anchors of 1 representing 'not at all useful', 5 representing 'somewhat useful' and 9 representing 'very useful'), anticipating an average 51.3% improvement in pain symptoms. Participants were somewhat confident in recommending the treatment to a friend who experiences similar problems (average response of 5.9, with the anchors of 1 representing 'not at all confident', 5 representing 'somewhat confident' and 9 representing 'very confident').

Affective-based expectations. Participants' average affective-based expectations were similar to their average cognitive-based expectations: they reported being somewhat confident recommending the treatment to a friend who experiences similar problems (average response of 5.5), and they anticipated an average 46.3% improvement in pain symptoms.

Treatment Adherence

At follow up, participants were asked to estimate the number of doses they missed over the course of the trial. Self-reported adherence to the treatment can be described as excellent. Five of 7 participants reported that they did not miss any doses. One participant reported missing two doses (3.6% of the 56 total doses prescribed) and another participant reported missing three doses (5.4% of doses), as noted in their daily diaries. On average, self-reported treatment adherence was 98.7%.

Side Effects

Side effects were assessed with a modified Symptom Assessment Schedule (SAS; Kristjanson et al., 1999). One participant dropped out of the study due to headaches following

placebo administration; this participant was randomized to placebo first and self-reported that she dosed this nasal spray twice prior to dropping out. Given that the SAS was completed at the end of each active phase of the trial, data on side effects are not available for this participant. Table 4 provides a summary of participants' reported symptoms. For OT, data are available for seven women. For placebo, data are available for six women, as one participant did not complete this measure. All participants reported difficulty sleeping, fatigue, and headache during both OT and placebo administration. As well, approximately the same number of women reported appetite problems, nausea, breathing problems, dizziness, and nasal irritation following both OT and placebo administration. Three women reported experiencing euphoria following placebo administration, while one woman reported this side effect following OT administration. All women reported bowel problems following OT administration; 66.7% of women reported this side effect following placebo administration.

Challenges

Recruitment. A significant challenge with the current study was recruitment. Collectively, the gynecologists encounter approximately 40 chronic pain patients per month, with up to 16 of these patients being new referrals. Prior to the study's commencement, the gynecologists estimated that approximately 15 women would meet eligibility criteria each month, based on the number of patients seen in their clinics. Though the gynecologists did not track reasons for ineligibility, they noted that a larger than anticipated percentage of women experienced pain only during intercourse. Further, the gynecologists noted the following two difficulties in recruiting eligible women to the study: 1) women did not want a medication-like treatment for their pain, and 2) women needed more education on oxytocin than anticipated, as some confused oxytocin with the opioid drug, oxycodone.

Protocol Implementation.

Participants. The participants who completed the study self-reported that their adherence to the nasal sprays was excellent (5 of 7 women reported missing no doses, with treatment adherence ranging from 94.6% to 100% of doses administered). Likewise, most participants (75%) demonstrated excellent (89% to 100%) adherence to recording outcomes in their daily diaries. However, one participant did not record any outcomes in her daily diaries, resulting in a substantial loss of follow-up data given the current study's small sample size. All participants expressed preference for completing questionnaires on an online platform instead of the pen and paper diaries provided in the current study. At the end of the study, participants were asked which nasal spray they believed to be the active OT spray: only 4 of 7 women responded correctly, suggesting adequate blinding.

Investigators. Given low recruitment, eligibility criteria were adjusted to allow women with irregular menstrual cycles. Thus, it was not always possible to ensure that nasal spray administration co-occurred with the luteal phase of participants' menstrual cycles; this aspect of the study protocol was not implementable for 8 of the 18 participants enrolled (45.5%).

The accidental inclusion of two ineligible women suggests an issue with screening for eligibility. A 10-point numeric rating scale for current pain was included in the screening questionnaire to address the eligibility criteria of moderate pain at baseline (i.e., a score of 4 to 7 on the 10-point scale). This criterion should have served as a means of screening out women who experience pain only during intercourse; however, both women who were accidentally included in the study endorsed a moderate level of pain on the screening questionnaire.

Following up with participants in-person at the end of the trial presented difficulties. Participants living a considerable distance outside the city were not always able to travel to study

sites for a follow-up appointment at six weeks. As such, the research assistant followed up with participants over the phone to ensure the participants' safety, then scheduled in-person follow-up appointments at the participants' earliest conveniences. Whenever possible, study appointments were coordinated with participants' other appointments at the study sites to alleviate participant burden. Participants who did not have future appointments at the study sites were given self-addressed envelopes and postage for daily diary return.

Discussion

The current study investigated intranasal OT as treatment for women with CPP. The first aim of the study was to determine if a clinically significant signal could be obtained on women's self-reported pain following administration of intranasal OT. On average, participants reported clinically meaningful change in current pain following OT, worst pain following placebo, and average pain following both nasal sprays. When assessed individually, most participants reported a clinically significant change on average pain following OT and placebo administration. Thus, both OT and placebo were associated with reduced self-reported pain. This result is not surprising given the well-documented role the placebo plays in pain perception (see Tracey (2010) for a review). Levine, Gordon, and Fields (1978) first demonstrated the role of the endogenous opioid system in the production of placebo-produced analgesia in their seminal study. Subsequent research has lent further support to the relationship between the endogenous opioids and the placebo effect in pain (e.g., Benedetti, Arduino, & Amanzio, 1999; Gracely, Dubner, Wolskee, & Deeter, 1983; Wager, Scott, & Zubieta, 2007; Zubieta et al., 2005). Moreover, the participants in the current study reported expectations of pain reduction following treatment, and evidence suggests that cognitive expectations produce placebo effects and trigger endogenous opioids (Amanzio & Benedetti, 1999). Participants' clinically significant responses

to the placebo may be indicative of the credibility of the placebo used in this study, given participants' expectations and corroborated by the fact that participants were not able to identify which nasal spray contained the active OT ingredient above chance.

Participants' reported reduction in pain following OT may point to OT's potential usefulness as a treatment for women with CPP, which would be consistent with previous studies demonstrating OT's potential in pain management (Rash, Aguirre-Camacho, & Campbell, 2014; Gonzalez-Hernandez, Rojas-Piloni, & Condes-Lara 2014; Tracy, Georgiou-Karistianis, Gibson, & Giummarra, 2015) and associations between OT and pain sensitivity among other chronic pain patients (Wang et al., 2013; Ohlsson et al., 2005; Yang, 1994; Louvel et al., 1996). However, the results presented for the current study are preliminary and future research is necessary before drawing conclusions regarding the OT-pain association among women with CPP.

The second aim of the study was to determine the feasibility of a fixed treatment and study protocol for participants and investigators. Data on treatment expectations, drop-out rates, treatment adherence, side effects, and study protocol adherence were evaluated. Consistent with previous research, participants reported similar side effect profiles for intranasal OT and placebo administration (see MacDonald et al. (2011) for a systematic review). The one participant who dropped out of the study had been administering the placebo when she experienced chronic headaches. It is possible that the intranasal administration method itself was responsible for this symptom (MacDonald et al., 2011). Despite some side effects, most participants self-reported excellent adherence to the treatment for the duration of the study. In addition, participants endorsed intranasal OT as being a logical treatment, expected it to be useful in reducing pain, anticipated pain relief following treatment, and felt somewhat confident recommending

intranasal OT to a friend experiencing similar problems. Together, these observations support the feasibility of the treatment protocol.

Most participants completed all measures in both daily diaries, but one participant did not complete daily diaries at all. A possible solution to promoting daily diary completion is allowing participants to complete these measures through an online platform. Completing daily diaries online may improve adherence for two reasons: 1) investigators could implement a system of automated reminders to prompt participants to complete measures, and 2) all participants expressed a preference for completing measures online. Collecting data online would alleviate participant and investigator burden as in-person follow-up appointments would not be necessary, allowing follow-up to take place over the phone instead. Arranging in-person follow-up appointments with participants was identified as a challenge in the current study, highlighting the need to alleviate participant burden to obtain follow-up data. Thus, this adjustment to the study protocol may increase the acceptability of the study to participants.

Recruitment was also identified as a challenge. Aligning nasal spray administration with the luteal phase of participants' menstrual cycles was not possible in nearly half of the participants, as women with irregular menstrual cycles were included in the current study due to difficulties recruiting. Future studies may benefit from either removing the menstrual cycle criteria or implementing a different recruitment strategy. In the current study, gynecologists identified interested and eligible women from chronic pain and gynecology clinics, then coordinated baseline assessments with the research assistant. Low recruitment indicates a need for a broader and/or more systematic recruitment strategy.

The following recruitment strategy is proposed as a possible solution: 1) a flyer with information on the study and a sheet to leave contact information is provided to all women who

attend chronic pain clinics when they check in for their appointments, 2) a research assistant collects information on the number of women who received the flyer versus the number of women who left contact information, 3) the research assistant contacts interested participants to confirm interest and eligibility through a phone call screener, 4) reasons for disinterest and ineligibility that arise during the phone screeners are recorded, and 5) eligibility is confirmed with gynecologists to ensure participant safety (e.g., to ensure any potential participants do not have diseases or disorders encompassed by exclusion criteria). Considering that two women who did not meet eligibility criteria were randomized in the current study, the phone call screener in step 3) should include more specific questions about the nature of the woman's pain. In addition to providing a more structured recruitment strategy, the proposed solution may also address the gynecologists' reports that women needed more education regarding oxytocin than anticipated, as women were reluctant to take a medication for pain and some women confused oxytocin with oxycodone. As such, the information on the study provided to women at chronic pain clinics could be tailored to address these concerns.

Despite the identified challenges, most aspects of the treatment and study protocols were feasible for participants and investigators. Results of the current study lend empirical support to enhancing the recruitment strategy and/or removing synchronization with the luteal phase of the menstrual cycle to relax eligibility criteria, moving daily diaries to an online platform, and completing follow-up over the phone as opposed to in-person. No other aspects of the study and treatment protocols were identified as infeasible for investigators or participants. Importantly, participants' adherence to the treatment was excellent, and participants endorsed intranasal OT as being a logical treatment and anticipated it being useful in reducing pain.

Adhering to the ORBIT model (Czajkowski et al., 2015), the next step in trial optimization is to conduct a Phase IIb feasibility pilot, following adjustments to the study protocol, given that a clinically significant signal was demonstrated in the present study. A Phase IIb feasibility pilot has the following aims: 1) to determine if an intervention can demonstrate a clinically significant signal over the control, 2) to determine if a trial protocol is feasible, and 3) to obtain empirically-derived estimates to inform the design of an efficacy trial. A greater number of participants need to be recruited in order to address the first aim and systematic tracking of patient interest, eligibility, and enrollment is necessary to address the third aim. Additionally, the second aim would be investigated through the use of an adjusted study protocol, to determine if changes informed by the current Phase IIa proof-of-concept study (e.g., daily diaries changed from pen-and-paper to online; elimination of in-person follow-up appointments; implementation of a new recruitment and eligibility screening strategy) are acceptable and feasible.

Clinical Implications

The current study represents a meaningful contribution to the literature on OT and CPP by being the first to investigate intranasal OT's potential to reduce pain among women with CPP. In recent years, intranasal OT has been gaining increasing attention and findings have demonstrated its potential in pain management (Rash, Aguirre-Camacho, & Campbell, 2014; Gonzalez-Hernandez, Rojas-Piloni, & Condes-Lara 2014; Tracy, Georgiou-Karistianis, Gibson, & Giummarra, 2015), though only a handful of studies have evaluated the effect of intranasal OT on chronic pain in humans (see Rash, Aguirre-Camacho, and Campbell (2014) for a review). The association between pain sensitivity and OT may be different among women with CPP given the abundance of OT receptors in the uterus and the fact that OT is a potent uterogenic agent (Gimpl

& Fahrenholz, 2001), making this line of research especially important to conduct. The current study provides preliminary evidence for intranasal OT's analgesic effects among women with CPP, though future research is warranted to further investigate the OT-pain association in this context. Crucially, the current study lays essential groundwork for the implementation of future rigorous investigations of intranasal OT and pain in women with CPP, following best practice in treatment development (i.e., the ORBIT model; Czajkowski et al., 2015). This preliminary testing will help ensure that the conclusions drawn from future studies in this field will appropriately attribute results to the treatment's effects, rather than issues with treatment and study protocol implementation. This work is directly clinically relevant to CPP, as feasibility testing is demonstrating intranasal OT's promise in pain reduction, and CPP is a condition for which there is a limited range of empirically-supported treatments (Speer et al., 2016).

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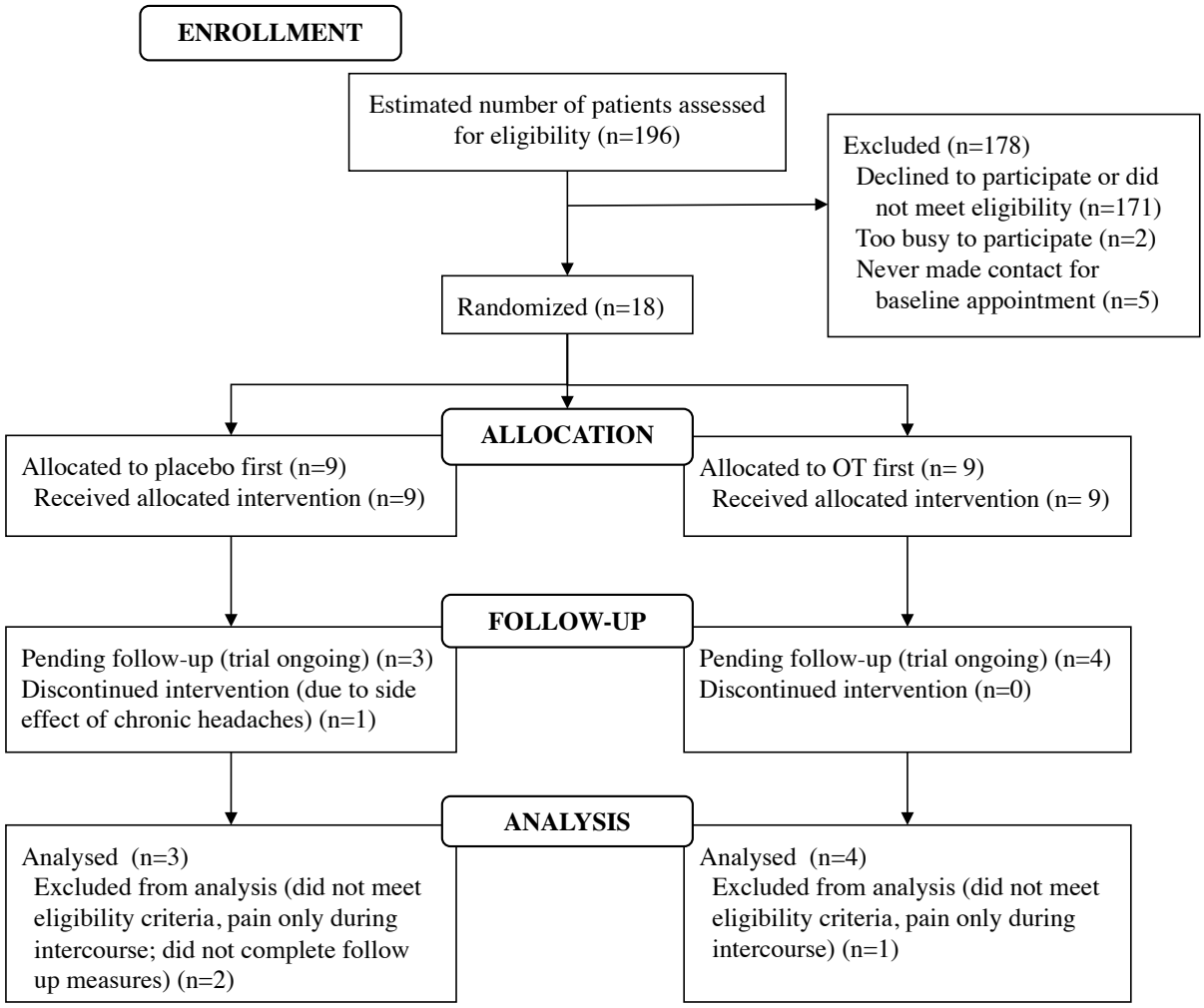

Figure 1. Participant flow diagram.

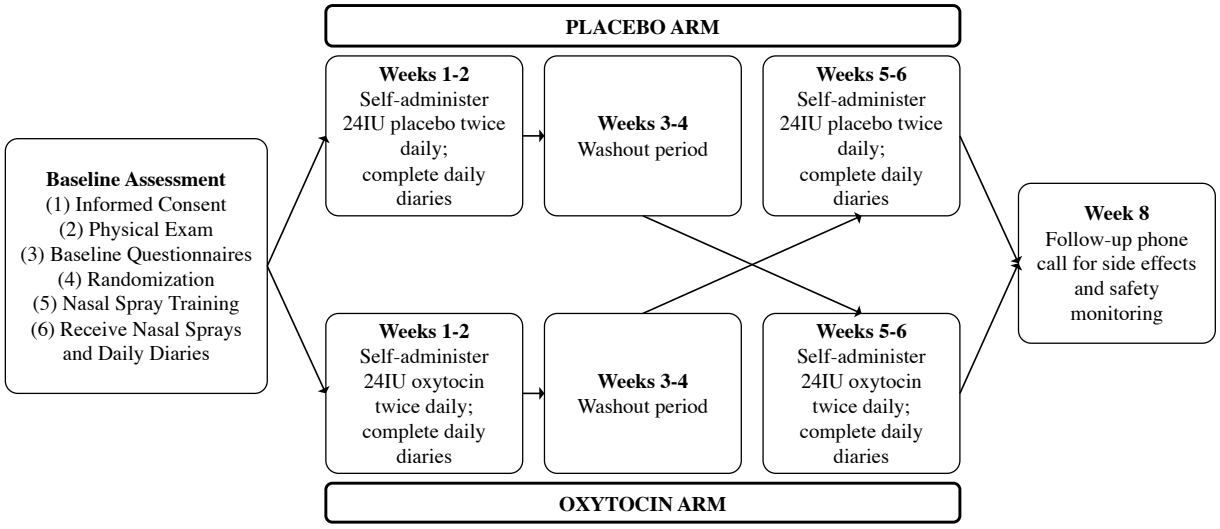

Figure 2. Trial procedures.

Table 1

Assessment schedule

	Time Completed		
Measure	Baseline	Daily	Following Experimental and Control Phases
Brief Pain Inventory – Short Form	x	x	x
Positive and Negative Affect Scale	x	x	x
Depression Anxiety Stress Scale	x		x
Medical Outcomes Sleep Study Scale	x		x
Patients' Global Impression of Change			x
Demographics Questionnaire	x		
MacArthur Ladder	x		
Pain Catastrophizing Scale	x		
Multidimensional Scale of Perceived Social Support	x		
Credibility/Expectancy Questionnaire	x		
Symptom Assessment Schedule			x

Table 2

Demographic and baseline characteristics (N = 9)

	N	*M*(SD)	Descriptive/ Response Range	Minimum - Maximum
Age (years)	--	35.22(9.28)	--	19.0 - 49.0
Pain duration (months)	--	131.56(110.24)	--	36.0 - 333.0
Ethnicity				
White	6	--	--	--
Métis	1	--	--	--
South Asian	1	--	--	--
Other (Afghanistan)	1	--	--	--
Marital Status				
Common-law/married	4	--	--	--
Single	2	--	--	--
In a relationship	1	--	--	--
Divorced/separated	2	--	--	--
Employment				
Full-time	3	--	--	--
Part-time	1	--	--	--
Unemployed	2	--	--	--
Other (Disability)	2	--	--	--
Other (Student)	1	--	--	--
Brief Pain Inventory-Short Form				
Pain Interference	--	5.67(2.66)	0 - 10	1.7 - 9.7
Pain Catastrophizing Scale				
Rumination	--	6.44(4.48)	0 - 16	0.0 - 15.0
Magnification	--	3.44(2.24)	0 - 12	1.0 - 8.0
Helplessness	--	9.44(5.64)	0 - 24	4.0 - 21.0
Total	--	18.33(10.67)	0 - 52	8.0 - 36.0
Positive and Negative Affect Scale				
Positive Affect	--	26.11(7.79)	10 - 50	16.0 - 40.0
Negative Affect	--	20.44(9.58)	10 - 50	11.0 - 36.0
Depression Anxiety Stress Scale				
Depression Subscale	--	10(12.69)	Mild	0.0 - 40.0
Anxiety Subscale	--	7.56(7.99)	Mild	0.0 - 24.0
Stress Subscale	--	16.25(12.44)	Mild	4.0 - 38.0
Multidimensional Scale of Perceived Social Support	--	5.65(1.09)	0 - 7	3.8 - 7.0
MacArthur Ladder	--	6.00(2.12)	1 - 10	2.0 - 9.0
Medical Outcomes Study-Sleep Scale				
Sleep Disturbance	--	42.78(30.14)	0 - 100	0.0 - 87.5
Sleep Adequacy	--	63.33(25.98)	0 - 100	20.0 - 100.0
Sleep Somnolence	--	38.52(28.44)	0 - 100	6.7 - 93.3

Table 3

Outcome measures at baseline, follow-up (14 days), change from baseline, and clinically significant improvement (N=7)

Outcome	Baseline *M*(SD) and range	Follow-up *M*(SD) and range	*M* change from baseline	n(%) with >1.0 pain reduction
Oxytocin				
Worst pain	7.36 2.00-9.00	6.41 2.80-8.00	-0.95	2(28.6)
Least pain	3.26 1.30-5.00	2.60 0.70-5.40	-0.66	3(42.9)
Average pain	5.54 2.00-8.00	4.20 1.00-6.60	-1.34*	4(57.1)
Current pain	5.61 0.00-7.50	4.61 0.70-7.30	-1.00*	1(14.3)
Placebo				
Worst pain	7.36 2.00-9.00	5.93 1.40-7.70	-1.43*	3(42.9)
Least pain	3.26 1.20-5.00	2.37 0.40-6.00	-0.89	2(28.6)
Average pain	5.54 2.00-8.00	4.06 0.40-7.00	-1.48*	5(71.4)
Current pain	5.61 0.00-7.50	4.66 0.50-7.40	-0.95	2(28.6)

Note. Participants reported pain on BPI-SF. Lower scores indicate lower pain intensity.

*Clinically significant improvement.

Table 4

Participants' reports of symptoms while administering nasal sprays

	Placebo (N = 6)		Oxytocin (N = 7)	
Symptom	Participants reporting symptom n(%)	*M*(range) severity	Participants reporting symptom n(%)	*M*(range) severity
Difficulty sleeping	6(100.0)	4.00(1-7)	7(100.0)	4.14(2-9)
Appetite problems	2(33.3)	6.50(5-8)	3(42.9)	4.67(1-9)
Nausea	3(50.0)	2.67(1-5)	4(57.1)	3.50(1-8)
Bowel problems	4(66.7)	3.75(1-7)	7(100.0)	3.86(1-10)
Breathing problems	2(33.3)	4.00(1-7)	1(14.3)	5.00*
Fatigue	6(100.0)	5.17(2-7)	7(100.0)	4.14(1-10)
Pain	5(83.33)	4.83(3-8)	7(100.0)	6.29(1-9)
Headache	6(100.0)	4.00(1-8)	7(100.0)	2.57(1-5)
Euphoria	3(50.0)	2.67(2-4)	1(14.3)	2.00*
Dizziness	3(50.0)	1.33(1-2)	2(28.6)	2.50(1-4)
Nasal irritation	4(66.7)	2.50(1-2)	5(71.4)	3.00(2-5)

Note. For severity ratings, 1 represents the least distress caused by the symptom's presence and 10 represents the most distress caused by the symptom's presence.

*When one participant reported the symptom, the sole severity rating is reported rather than the mean and range.

Appendix A

Demographics Questionnaire

Date:_____ Participant ID: _____.

Questionnaires
DEMOGRAPHICS

1. Your date of birth: _____/_____/_____
   Month / Day / Year

2. How would you describe your primary racial or ethnic group?

- ☐ White
- ☐ Black
- ☐ Latin American
- ☐ Japanese
- ☐ Metis
- ☐ Nonstatus Aboriginal
- ☐ Chinese
- ☐ Filipino
- ☐ Korean
- ☐ Arab
- ☐ Status Aboriginal
- ☐ Southeast Asian (e.g., Cambodian, Vietnamese, etc.)
- ☐ South Asian (e.g., East Indian, Pakistan, Sri Lankan, etc.)
- ☐ Other: _____

3. Which of the following best describes your employment status?

- o Unemployed
- O Full-time
- O Part-time
- O Stay at home caregiver
- O Other → Specify _____

4. Which of the following best describes your marital status?

- O Single
- O In a relationship
- O Living common-law or married
- O Divorced
- O Other → Specify _____

5. Approximately how long have you lived with chronic pain?

_____ Years _____ Months

6. Obstetrical History
   How many pregnancies have you had? _____
   Resulting in (#): ____Births ____Miscarriage/Abortion
   How many children were delivered: vaginally_____? Caesarean section _____?
   Operative vaginal delivery (vacuum or forceps) _____?

7. Menstrual History
   How old were you when your menses started?_____
   Are you still having menstrual periods? ☐ Yes ☐ No
   Are periods regular? ☐ Yes ☐ No

   Answer the following only if you are still having menstrual periods.
   Periods are: ☐ Light ☐ Moderate ☐ Heavy ☐ Bleed through protection
   What is the length of your cycle? _____
   How many days of menstrual flow? _____
   Date of first day of last menstrual period? _____
   Do you have any pain when your period starts? ☐ Yes ☐ No
   Does pain start the day flow starts? ☐ Yes ☐ No
   Or, pain starts _____ days before flow

8. Urinary symptoms
   Do you experience any of the following?
   Loss of urine when coughing, sneezing, or laughing? ☐ Yes ☐ No
   Difficulty passing urine? ☐ Yes ☐ No
   Frequent bladder infections? ☐ Yes ☐ No
   Blood in the urine? ☐ Yes ☐ No
   Having to void again within minutes of voiding? ☐ Yes ☐ No

The following questions help to diagnose irritable bowel syndrome, a gastrointestinal condition, which may be a cause of pelvic pain.

9. Do you have pain or discomfort that is associated with the following:
   Change in frequency of bowel movements ☐ Yes ☐ No
   Change in appearance of stool or bowel movements ☐ Yes ☐ No
   Does your pain improve after completing a bowel movement ☐ Yes ☐ No

The following questions help to diagnose painful bladder syndrome, which may cause pelvic pain

	0	1	2	3	4
1. How many times do you go to the bathroom **DURING THE DAY** (to void or empty your bladder)?	3-6	7-10	11-14	15-19	20+
2. How many times do you go to the bathroom **AT NIGHT** (to void or empty your bladder)?	0	1	2	3	4+
3. If you get up at night to void or empty your bladder does it bother you?	Never	Mildly	Moderately	Severely	
4. Are you sexually active? ☐ Yes ☐ No					
5. If you are sexually active, do you now or have you ever had pain or symptoms during or after sexual intercourse?	Never	Occasionally	Usually	Always	
6. If you have pain with sexual intercourse, does it make you avoid sexual intercourse?	Never	Occasionally	Usually	Always	
7. Do you have pain associated with your bladder or in your pelvis (lower abdomen, labia, vagina, urethra, perineum)?	Never	Occasionally	Usually	Always	
8. Do you have the sudden urge to urinate after voiding?	Never	Occasionally	Usually	Always	
9. If you have pain, is it usually	Never	Mildly	Moderate	Severe	
10. Does your pain bother you?	Never	Occasionally	Usually	Always	
11. If you have the sudden urge to urinate, is it usually		Mildly	Moderate	Severe	
12. Does your sudden urge to urinate bother you?	Never	Occasionally	Usually	Always	

GENERAL HEALTH

Please answer the following questions to the best of your ability

1. Please list any prescription medications you take regularly or occasionally

_____

_____

2. Birth control method: ☐ Nothing ☐ Pill ☐ Vastectomy ☐ Vaginal ring ☐ Depo provera ☐ Condom ☐ IUD ☐ Hysterectomy ☐ Diaphragm ☐ Tubal sterilization ☐ Other _____

3. Please list any over-the-counter medications (e.g., Tylenol) and supplements or homeopathic medications that you are currently taking.

_____

_____

4. Do you currently have any of the conditions listed below? (check yes, no, don't know)

	Yes	*NO*	*Don't Know*
Dysparunea (Painful intercourse)			
Irritable bowel syndrome			
High blood pressure			
Chest pains or angina			
Irregular heart beat (palpitations)			
Abnormal electrocardiogram (ECG)			
History of heart attack			
History of stroke/TIA			
Any other heart or circulatory problem			
Diabetes			
Asthma			
Respiratory disorder			
History of cancer or current diagnosis			

Gastrointestinal disorder			
Ulcer			
Allergies			
Arthritis or joint disorder			
Reproductive system disease or disorder			
Anemia			
High cholesterol			
Thyroid disease			
Depression			
Anxiety			
Other mental health disorder			
Drug dependency			
Other(s) Please Specify: _____			

The following questions will ask about your use of drugs and other substances for recreational purposes. The answers you provide are completely confidential.

1. How often do you exercise?
   O Rarely
   O 1-2 times weekly
   O 3-5 times weekly
   O Daily

2. How many cups of caffeinated beverages (coffee, tea or cola) do you typically consume in an average day? *(check one)*
   O None
   O 1 cup
   O 2-3 cups
   O 4-5 cups
   O 6 or more cups

3. How much alcohol (beer, wine and/or liquor) do you consume in a typical day?
   O None
   O Occasional drink
   O 1-2 drinks
   O 3-4 drinks
   O 5 drinks or more

4. What is your smoking status?
   O Current smoker
   How many cigarettes do you smoke per day? _____ For how many years? _____
   O Past smoker (smoked and quit)
   O Non-smoker (never smoked)

5. What is your use of recreational drugs?

☐ Never used ☐ Used in the past, but not now ☐ Presently using ☐ No answer

☐ Heroine ☐ Amphetamines ☐ Marijuana ☐ Barbiturates ☐ Cocaine

☐ Other_____

The following questions ask you about your experience with headaches.

1. Do you have light sensitivity with headaches?

   ☐ Yes ☐ No

2. Do you have impairments with headaches (e.g., difficulty working, socializing, exercising)?

   ☐ Yes ☐ No

3. Do you have any nausea with headache?

   ☐ Yes ☐ No

Appendix B

Screening Questionnaire

1. Is the participant currently prescribed anti-hypertensive medication?
   ☐ Yes ☐ No
2. Does the participant have a history of heart problems?
   ☐ Yes ☐ No
3. Does the participant have an irregular menstrual cycle (occurring outside a 21-35 day range)?
   ☐ Yes ☐ No
4. Is the participant pregnant?
   ☐ Yes ☐ No
5. Does the participant have nasal pathology?
   ☐ Yes ☐ No

Please rate your current pelvic pain:

1	2	3	4	5	6	7	8	9	10
No Pain									Pain as bad as you can imagine

I agree to use a contraceptive or remain abstinent while participating in this research study:

Participant Signature:_____

I agree commit not to change my pain medication regimen while participating in this research study:

Participant Signature:_____

Appendix C

Nasal Spray Administration Guidelines

Administering your nasal spray

Guidelines:

1. Keep your head upright, or in a comfortable position.
2. Do not administer if your nose is heavily congested and clear your nose from obvious obstruction before administering.
3. Prime the bottle with a test spray.
4. Close one nostril with one finger.
5. Insert the bottle about 1-cm into your nose and give 1 spray while inhaling gently through your nostril.
6. Alternate administrations (1-puff at a time) between nostrils allowing approximately 15-seconds between each re-administration to the same nostril.
7. Administer 3-puffs per nostril (6-puffs total).

Care for your nasal spray:

For best results, store your nasal spray bottle in the refrigerator until it is first opened. Once opened, store your nasal spray at room temperature. Please keep outside of the reach of children.

Each nasal spray bottle should provide you with 50-puffs. We ask that you administer 6-puffs on two occasions each day (12-puffs per day). Thus, each bottle should last you approximately 4-days.