EVALUATING THE EFFICACY OF OXYTOCIN FOR PAIN MANAGEMENT: AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS

by © Anastasia Mekhael

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Abstract

Currently available treatments for chronic pain rarely result in full recovery, indicating the need for an analgesic that is non-addictive and effective. Oxytocin has recently gained attention for its potential analgesic properties. We searched Ovid MEDLINE®, Embase, PsycINFO and CINAHL (from January 2012 to February 2022) and the Clinicaltrials.gov website. Studies from 1950- 2012 were included from our published review (Rash et al., 2014). Comprehensive Meta-Analysis software was used where three or more studies reported on the same outcome. Narrative synthesis was performed for outcomes with less than three studies by calculating individual effect sizes. Searches returned 2,087 unique citations, 8 of which met inclusion criteria. 6 studies were included from Rash et al. (2014; N= 1,504). Three meta-analyses were conducted to evaluate the effect of exogenous oxytocin on pain, the association between endogenous oxytocin and self-reported pain ratings and the effect of exogenous oxytocin on self-reported depression. The effect of exogenous oxytocin on acute pain and emotional function, and the association between endogenous oxytocin and self-reported anxiety were narratively reviewed. There was a trend favouring oxytocin as an analgesic despite non-significant meta-analysis. Results from meta-analysis and narrative review were mixed and highlighted potential sex differences but heterogeneity in the included studies precludes definitive conclusions from being drawn. Future studies are imperative and should undertake more precise exploration of mechanisms of analgesic action to clarify inconsistency in the existing body of literature.

Keywords: Oxytocin, Chronic Pain, Systematic Review, Meta-analysis, Analgesia

General Summary

Approximately 20% of the world's population suffers from chronic pain while current treatments rarely result in full recovery or improvement in function. Oxytocin, a naturally occurring hormone is gaining traction for its potential use as a treatment for pain. The current study aims to condense and summarize results from studies published between 1950 – 2022 which evaluate the use of oxytocin for chronic pain to gain a comprehensive understanding of the relationship between oxytocin and chronic pain. Data was pooled across studies when three or more studies evaluated the same outcomes. When less than three studies evaluated an outcome, we summarized the findings narratively. Overall, our results were inconclusive but showed promising results for the use of oxytocin for pain sensitivity. Future studies should focus on using more consistent methods to make results generalizable.

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Definition and Prevalence of Chronic Pain

The Institute of Medicine provides the widely accepted definition of chronic pain – defined as pain that persists longer than 3-months or beyond the predicted duration of healing (Merskey, 1979). The definition provided by the International Association for the Study of Pain (IASP) task force is aligned with the aforementioned but includes six additional notes that were proposed to be included in the definition; these notes emphasize key concepts aimed at better understanding the implication of biopsychosocial factors in the experience of pain (Raja et al., 2020). These notes include: recognition that pain is a subjective experience influence by biopsychosocial factors; pain cannot be inferred only from sensory pathways; the concept of pain is learned through life experiences; self-reports of a person's pain experience should be respected; while pain is adaptive, it may have adverse effects of function and psychological well-being; and verbal descriptions of pain are only one of several behaviors that can be used to express pain and the inability to communicate does not negate the possibility of pain (Raja et al., 2020).

Using the National Health Interview Survey in 2019, the prevalence of chronic pain in the United States is estimated to be 20.5 % (Yong et al., 2022). Other studies have estimated that the prevalence of chronic pain is higher or that prevalence ranges are wide. For example, larger prevalence estimates were recorded in the UK as results from a systematic review and meta-analysis including 139, 933 adult residents yielded estimates ranging between 35.0 – 51.3 % (Fayaz et al., 2016). Similarly, studies included in a meta-analysis evaluating chronic pain in developing countries (i.e., countries in Latin America, Africa and Asia) placed estimates within a

wider range, between 13 – 51%, with significant heterogeneity explained by year of study publication (i.e., studies published from 2007-2010 reported higher prevalence of chronic pain; Sá et al., 2019). Canadian prevalence estimates on the other hand are contained within a narrower range (from 16% to 41%; Schopflocher et al., 2011), with consensus that approximately twenty percent of Canadians, ages 18 and above (Schopflocher et al., 2011), 65% of community dwelling seniors (Hadjistavropoulos et al., 2009) and 15% of children (Stanford et al., 2008) suffer from chronic pain. Overall, consensus lies in that approximately 20% of individuals worldwide experience some form of chronic pain (Schopflocher et al., 2011).

In a systematic review, Nickel and Raspe (2001) included 17 epidemiological studies and highlighted trends in the prevalence estimates for adults with chronic pain based on extracted demographic variables. Most notably, authors reported that the incidence of chronic pain increased with age, peaking between 45-65 years and was more frequent among women (Nickel and Raspe, 2001; Moulin et al., 2000; Bhattarai et al., 2007 ; Sa´ et al., 2019). Notably, a systematic review across 9 countries indicated that the prevalence of chronic pain did not vary by the definition of pain adopted (Gureje, 1998). Patterns of increasing incidence of chronic pain with age and in women are consistent in two Canadian studies (Moulin et al., 2000; Boulanger et al., 2004) that interviewed over 1500 adults each, using identical telephone survey methodology. Both studies reported that prevalence estimates increased with age, with the largest estimates observed in participants 55 years of age or older. Further, 29% (Moulin et al., 2000;) and 25% (Boulanger et al., 2004) of respondents reported intermittent or continuous pain lasting 6-months or longer while the average duration of pain reported was comparable between studies (i.e., 10.7 and 9.8 years respectively).

A 2016 report by the Centers for Disease Control and Prevention (n = 33,028) highlighted subgroup analyses of prevalence rates of chronic pain in the USA which reported that the prevalence of chronic pain was greater among women relative to men (Dahlhamer et al., 2018). Authors also noted higher rates in adults who achieved lower levels of education, those who were unemployed or did not have private health insurance, and those living in poverty and rural communities (Dahlhamer et al., 2018). Chronic pain is a complex condition that affects the population across the lifespan.

Burden of Chronic Pain

Chronic pain is a pervasive condition and has been reported as one of the most common (Mäntyselkä et al., 2001), and personally compelling reasons for seeking medical attention (Gureje, 1998). This highlights the severity of living with pain and the motivation that patients have to seek relief. Correspondingly, the effects of chronic pain are far-reaching and will be examined in terms of functional, emotional and economic implications for a patient's life and for the larger community.

Functional and Emotional Burden. The chronicity of chronic pain negatively impacts various social and interpersonal facets of patients' lives. Chronic pain impedes social engagement with about one-half of patients surveyed by Schopflocher et al. (2011) reported being unable to attend social or family events due to their condition. Turk and colleagues (2011) also touch on the social and functional impairment associated with chronic pain, reporting that adult patients were 1.63 times more likely to experience limitations in their activities of daily living, including sleep disturbance, work and household chores as well as leisure activities relative to healthy controls. The interconnectedness of chronic pain with function impairment is also highlighted in self-report measures of pain which routinely ask about pain-related

interference and difficulty completing activities of daily living as a means of assessing severity of the condition (Feeny et al., 1985; Gureje, 1998; Brevik et al., 2006).

Living with chronic pain also affects patients' well-being, including energy levels, intimacy and emotional functioning (Turk et al., 2011). More specifically, like other chronic non-communicable diseases, chronic pain is usually accompanied by mental comorbidities (Goldberg and McGee, 2011). A series of studies by the World Health Organization (WHO) that report that patients suffering from persistent pain in each of 15 primary care facilities across the world, were 4.14 times more likely to be diagnosed with a depressive or anxiety disorders using *ICD-10* diagnostic criteria relative to patients who do not experience pain (Gureje, 1998). In fact, research suggests that 40-50% of chronic pain patients suffer from depressive disorders (Banks and Kerns, 1996; Dersh et al., 2006).

The same increased prevalence of mental health disorders holds true for children and adolescent populations suffering from chronic pain; this was shown in the National Longitudinal Survey of Children and Youth which assessed 2488 10-11-year-old children up to five times at intervals of 2 years (Stanford et al., 2008). Higher rates of headaches, stomach-aches and backaches were observed in girls at every time point. In addition, youth with chronic pain reported higher levels of anxiety and depression on self-report measures and these mental health difficulties were also predictive of trajectories that indicated high levels of pain across time, and pain that worsened with age (Stanford et al., 2008).

In as much as the functional and emotional difficulties accompanying chronic pain affect the patient's life, so too does it compromise the lives of loved ones and significant others (Flor et al., 1987; Turk et al., 2011). For example, the notion that living with someone who experiences chronic pain increases the risk of psychological distress was suggested by authors who found

evidence of emotional distress among patients (Duckro et al., 1995) and their families, with 28% of spouses of people who live with pain reporting clinically significant depressive symptoms (Schwartz et al., 1991). Overall, social correlates and mental health implications qualify chronic pain as a medical condition which cannot be disentangled from social disparities and psychological issues.

Economic Burden of Chronic Pain. Chronic pain is also associated with substantial direct and indirect financial costs borne to the patient, health-care system, and society. Direct health-care costs refer to those incurred by health-care services or patients themselves, including costs of hospitalizations, rehabilitation (e.g., physiotherapy) and medication (Phillips, 2006). Indirect costs are distinguished from direct costs as they occur outside the healthcare sector, and are typically a result of lost productivity, disability payment (Turk et al., 2011) and absenteeism (Phillips, 2006).

A Canadian survey of 2012 chronic pain patients reported that patients missed an average of 9.3 days of work due to their condition within the last year (Moulin et al., 2002). In addition to absenteeism, people living with chronic pain were seven times more likely to quit their job relative to healthy controls (Erickson et al., 2003). Survey results from Häuser et al. (2014) reported that the rate ratio of days taken off due to sick leave was increased by 6.4 times among 2508 individuals suffering from disabling pain (i.e., chronic pain which interferes with activities of daily living) relative to individuals without disabling pain and healthy controls. The same survey of 4,360 individuals ages 14 and above in Germany suffering from chronic pain also highlighted that disabling pain is associated with an increase in risk of unemployment (Häuser et al., 2014). Financial reports also estimate that the total cost of chronic pain exceeds US$210 billion annually (National Research Council, 2001). Comparable estimates have been reported

globally, including in the United Kingdom (Maniadakis and Gray, 2000) and across countries around the world (Phillips, 2006). By 2011 the American Institute of Medicine (2011) estimated that chronic pain contributes approximately $560 billion annually in direct medical costs, disability programs and lost productivity. Notably, the Canadian Pain Task Force Report estimated that direct and indirect costs of chronic pain in Canada were between 38.2 – 40.3 billion dollars annually in 2019 (Canadian chronic pain Task Force, 2021). Overall, research around the costs of chronic pain to the healthcare system and the economy has converged on there being a salient societal and economic burden of the condition. The salience and attention that this burden has gained, coupled with it's being claimed to be a threat to quality of life worldwide have justified it as a public health priority (European Federation of the International Association of Pain Chapters, 2014; Goldberg and McGee, 2011).

Biopsychosocial understanding of Chronic Pain

Although development is complex, research in the past few decades has made advancements in understanding the etiology, assessment, and treatment of chronic pain (Gatchel, 2004a, 2004b, 2005; Turk and Monarch, 2002). The biopsychosocial model of pain regards pain as an adaptive human experience involving the interaction of neurophysiological, genetic, cultural, cognitive and emotional factors. The following section will examine hypothesized biopsychosocial mechanisms that contribute to chronic pain. In particular, the field of neuroscience has contributed substantially to the delineation of the mechanisms behind pain processing (Gatchel et al., 2007). Differential models have been proposed for the mechanisms involving inflammatory pain, neuropathic pain, and cancer pain; these models carry with them implications for clinical practice and the understanding of condition-specific aetiologies (Gatchel et al., 2007). Generally, research suggests that chronic non-cancer pain can develop as a result of

damage to the central or peripheral nervous systems, (e.g., spinal cord injury, post-stroke pain; Cohen and Mao, 2014). chronic pain has also been described as caused by continuous changes to, or stimulation of, nociceptors as a result of localised tissue damage from injury or disease (Turk et al., 2011). In chronic pain caused by inflammation of tissue, inflammatory mediators influence pain states by potentiation or stimulation of nociceptive transduction at peripheral nerve terminals causing hypersensitivity (Levine and Reichling, 1999), thereby increasing the likelihood that subsequent stimulation be perceived as painful. Neuropathic pain on the other hand results from damage to the nervous system (e.g., spinal cord, peripheral nerves). Symptoms of neuropathic pain which distinguish it from inflammatory pain include: spontaneous pain, hyperplasia (i.e., exaggerated response to a somewhat painful stimulus) and allodynia (i.e., pain caused by a typically non-painful stimulus). Neuropathic pain may also spread to other areas of the skin enervated by the injured nerve resulting in a sensation of shooting, burning or electric shock (Gatchel et al., 2007).

Dysregulation of the Hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system have also been proposed as factors contributing to the development of chronic pain wherein pain acts as a stressor that will tax the system causing prolonged activation; this in turn generates the breakdown of bone and muscle tissue resulting in pain and putting the body in a cycle of pain-stress-reactivity (Gatchel, 2004b).

The field of genetics has also contributed to our understanding of the idiosyncrasy of chronic pain. Genetic predisposition and signal transduction have been linked to pain transmission (Diatchenko et al., 2005). For example, singe-nucleotide polymorphisms of certain genes have been reported to contribute substantially to basal pain sensitivity to noxious stimuli (Kim et al., 2004). While more research is being done in the epigenetic field (Laumet et al.,

2015), preliminary work links epigenetic mechanisms to the development and mechanisms of chronic pain states (Denk and McMahon, 2012). Future research in genetics is promising as Gatchel and colleagues (2007) assert that it should provide clarity and insight into the aetiological mechanisms that account for individual differences in the development of diverse chronic pain conditions (Diatchenko et al., 2005).

While the development of chronic pain has been explained by primarily physical origins, individuals' experiences of pain are multi-dimensional. Cognitive, emotional, behavioural, and socioeconomic factors interact to mediate and moderate the experience of pain. As such, the biopsychosocial model of pain has become widely accepted as the most holistic approach to understanding the aetiology of chronic pain. Further, advances in neuroscience also lend to our understanding of the comorbidity between chronic pain and psychiatric disorders in so far as they share pathogenic mechanisms (Polatin, 1991). For example, affective and nociceptive activation in the brain occur simultaneously and implicate shared neurotransmitters (i.e., norepinephrine and serotonin; Polatin, 1991). Researchers also warn that individuals experience pain idiosyncratically in that they are influenced by socioeconomic and psychological factors, coping styles and personal histories. These factors can then interact with physical pathologies to complicate and alter patients' reports of symptoms and disability (Gatchel et al., 2007). For this reason, the treatment of chronic pain can be complex and require a holistic approach that pays attention to several areas of life affected by pain (Turk, et al., 2011).

Treatment of Chronic Pain

Pharmacological Treatment. Historically, pain has been noted as one of the most difficult conditions to treat (Collier, 2018). Stemming the use of heroine and morphine for pain management in the 1900's, pain specialists began suggesting low incidences of addictive

behaviours associated with opioids (Collier, 2018). Inadvertently, this encouraged what authors describe as “prescription culture”, contributing to the now global opioid crisis (Collier, 2018). Pharmacological interventions continue to be commonly prescribed for chronic pain (Martin et al., 2008); these treatments include anti-inflammatory agents, opioid analgesics, adjuvant analgesics such as antidepressants or anticonvulsants and over the counter medications such as non-steroidal anti-inflammatory drugs (NSAIDs; Moulin et al., 2002). Most notably, the prescription of opioids—that is, a pain-relieving medication that interact with opioid receptors to produce analgesic effects, has dramatically increased over the last several decades. Opioids, commonly prescribed as an oral medication are altered to be taken by intravenous or intranasally to increase the intensity or latency of their effects (The National Academies Press, 2017). One study on prescription trends in the United States reported an increase of 176% from 1997 to 2006 (US Department of Justice, 2015). Similarly, in Canada, opioid over prescription has been linked to the increased rates of opioid related overdoses (Centers for Disease Control and Prevention, 2017; Strike and Watson, 2019). Moreover, up to 17%–20% of pediatric patients with chronic pain are prescribed opioid pharmacotherapy and face an increased risk of opioid misuse in adulthood (Richardson et al., 2021). While opioids carry considerable risk of misuse and adverse effects (Gregorian et al., 2010; Sostres et al., 2010) their effects on pain and function are modest at best. For example, one meta-analysis conducted by Busse et.al (2018) included 96 randomized controlled trials (RCTs) that reported on more than 26,000 participants and observed that only 1 in 8 chronic pain patients responded to opioid medication, with an average pain reduction of 6.9mm (on a 100mm analog scale), with limited to no improvement in social or emotional function. In another meta-analysis, it was reported that opioids alone are inappropriate for chronic non-cancer pain as weighted mean differences revealed an average of only a 12-point

reduction in pain (on a 100-point scale) using what authors categorized as "strong" opioids—the strongest opioids included in the analysis; as such, multimodal treatments were recommended (Reinecke et al., 2015). Overall, Treatment effectiveness seems to be inconsistent in the literature with patients undergoing treatment often showing little improvement in physical functioning, emotional functioning, and health-related quality of life (Martin et al., 2008; Turk et al., 2011); this points to the need for an analgesic that is non-addictive, has few adverse side effects and is effective at reducing pain across several chronic pain conditions.

Interdisciplinary Treatment. The emergence of the biopsychosocial model of chronic pain led to what Gatchel et al. (2007) refer to as the "most heuristic approach" to the management of chronic pain. The interdisciplinary management approach has been adopted to target the pervasive multi-modal effects of chronic pain and holds that comprehensive assessment and attention to different areas of a patient's life are necessary for treatment to be effective, given that the increase in risk for psychological disorders, maladaptive cognitions (e.g. pain catastrophizing; Burns et al., 2015) and nociceptive dysregulation (Dayer et al., 2019) are interdependent (Burns et al., 2003). Research has also shown that the perception of pain can influence physical and psychological adjustment to the condition (Turk et al., 1983). As such, a multi-disciplinary team integrates elements of cognitive behavioural therapy (CBT), medical management, and occupational and physical therapy to alter maladaptive perceptions and poor coping skills to mitigate pain and improve functioning (Jensen et al., 2001; Glare et al., 2019). Interdisciplinary treatment in the United States has been reported to be cost-effective (Gatchel et al., 2014) and highly endorsed in evidence-based clinical practice guidelines (Chou et al., 2009) while resulting in concomitant improvement across a range of domains (e.g. pain severity, interference; Gatchel et al., 2014; Oslund et al., 2009). Similarly, a systematic review of clinical

trials reported that interdisciplinary programs have outperform standard medical pain services (Scascighini et al., 2008) and demonstrated greater effectiveness that other common interventions like CBT and medication (Weiner and Nordin, 2010). A Cochrane review also demonstrated modest improvement (1-point out of 10) on self-reported ratings of pain and increased likelihood to return to work after multidisciplinary treatment for chronic pain (Kamper et al., 2014).

Other Treatment Options. Other treatment options for chronic pain include: surgical (Deyo et al., 2005; Chou et al., 2009), somatic (e.g. improving awareness of trauma to relieve tension; Meehan and Carter, 2020), psychological (Hoffman et al., 2007; Dixon et al., 2007; Morley et al., 1999) and alternative treatments (e.g., yoga or acupuncture) – all of which show limited to moderate efficacy for substantial or consistent reduction in pain (Turk et al., 2001). Given the evidence for only moderate chronic pain relief, promising results have been reported after lumbar spine surgery according to results from 422 patients, in that 44% reported a lot of improvement in chronic pain following surgery, while 17% reported complete improvement (Mancuso et al., 2017). The same study however noted that expectation pre-surgery had an influence on patients reports of improvement wherein patients reported less improvement in pain if, they expected greater improvement before surgery. Other controlled studies however have shown slight reduction in pain after radiofrequency facet joint denervation that was maintained for less that one month post-procedure (Leclaire et al., 2001). Additionally, one-year follow-up with chronic pain patients who received massage, acupuncture or self-care remedies reported modest improvements in pain of 48%, 28% and 38% respectively (Cherkin et al., 2001). It is noteworthy that interference with daily function is a crucial outcome to consider when describing

remission from chronic pain (Sadosky et al., 2016) and higher levels of pain intensity have consistently resulted in greater interference (Jensen et al., 2005; Jensen et al., 2006).

A unique line of research by deCharms et al. (2005) which provides us with insight into potential neural mechanisms behind pain management has attempted to teach patients to control the activation of localized regions associated with pain within the brain (e.g., the rostral anterior cingulate cortex; deCharms et al., 2005). This line of work is important as control over the endogenous pain modulatory system could provide insight into a unique mechanism for a clinical intervention for pain (deCharms et al., 2005). Chronic pain patients and healthy controls were taught four strategies for use in increasing/ decreasing brain activation and pain (e.g., attending toward and away from painful stimuli or attempting to perceive the stimulus as a neutral sensory experience) and were trained to use these strategies in a real time functional MRI scan. Participants then received continuous real time fMRI feedback while attempting to increase/ decrease activation in regions of interest. Decreased activation in certain brain regions was associated with a corresponding decrease in the perception of self-reported pain to a noxious thermal stimulus in pain patients and controls. These results indicate a potentially meaningful breakthrough for treating chronic pain by teaching patients to directly control the neurophysiological mechanisms that mediate pain (Gatchel et al., 2007), and may inform future work on the aetiology of chronic pain and how perception and physiology interact in the experience of pain. However, despite important improvements in the understanding of the neurophysiology of pain, the application of new therapeutic modalities and the dissemination of sophisticated diagnostic procedures, currently available treatments for chronic pain rarely result in full recovery or complete relief from symptoms (Turk, et al., 2011).

Oxytocin as a Treatment for Pain. In addition to standard pharmacological or interdisciplinary treatments, a novel intervention that has recently gained attention for its potential analgesic properties is Oxytocin, a naturally occurring hormone released during skin-to-skin contact, massage and lactation (Knobloch et al., 2012). More specifically, oxytocin is a neuropeptide, created in the paraventricular and supraoptic nuclei of the hypothalamus and released into the bloodstream through the central and peripheral nervous systems. Oxytocin that is released via magnocellular neurons that extend down the posterior pituitary (Uvnas-Moberg and Petersson, 2004) is thought to be responsible for the majority of peripherally-released oxytocin; this pathway is responsible for levels of oxytocin that can be measured from samples of blood and saliva (Carter et al., 2007). Oxytocin that is released by paraventricular neurons circulates through the Central Nervous System (CNS; Knobloch et al., 2012). This pathway delivers oxytocin to brain structures such as the Amygdala and the Striatum (Knobloch et al., 2012; Neumann and Landgraf, 2012) and can thereby affect behaviours such as fear, trust and social behaviour (Lee et al., 2009). The release of oxytocin through the CNS also projects oxytocin to the deep and superficial lamina of the dorsal horn (Todd, 2002), which is involved in the transmission of nociceptive signals (Jo et al., 1998).

This central route of oxytocin release is thought to be involved in pain modulation (Rash et al, 2014). Specifically, it is said that pain signals are modulated in the dorsal horn as there is a high concentration of nociceptors which terminate in the superficial and deep lamina of the dorsal horn (Todd, 2002). Additionally, a hypothalamo-spinal projection containing high levels of oxytocin (Gimpl and Fahrenholz, 2001) exists between the paraventricular nucleus (PVN) that terminates in the dorsal horn (Saper et al., 1976). Finally, a set of dorsal horn neurons exist that contain oxytocin receptors and influence GABA signalling (Jo et al., 1998). GABAergenic

interneurons result in presynaptic inhibition of pain transmitting Aδ- and C-fibers at nociceptive-specific and wide dynamic range (WDR) neurons (Breton et al., 2008). In summary, the high concentration of oxytocin receptors located among nociceptive fibres indicates the potential involvement of oxytocin in pain signalling (Rash et al, 2014).

There are also socioemotional theories regarding the processes by which oxytocin might mitigate pain. Notably, oxytocin has been reported to improve mood, decrease anxiety, and buffer self-report and physiological indicators of stress (Pedersen and Boccia, 2002; Brennan, 2009; Neumann, 2008; Heinrichs et al., 2003). Other recent studies have also suggested that oxytocin may be a viable option for decreasing the perception of pain with a low risk for adverse effects (Rash et al, 2014; Gonzalez-Hernandez, 2014; Rash et al., 2017). Given that oxytocin has been associated with biological processes (e.g. analgesia; Todd, 2002), social contexts (Pincus et al.,2010) and mood changes (Brennan, 2009; Neumann, 2008), it might also play a considerable role in understanding biopsychosocial mechanisms behind pain management; this aligns with recommendations to consider total biopsychosocial functioning in the treatment of chronic pain (Gatchel et al., 2007) and is therefore be a promising avenue for current research to explore.

Significance of the current study. Rash et al (2014) conducted the first systematic review of the literature on oxytocin and pain, including nine human and 33 animal studies published between 1950 and 2012. They reported that oxytocin increased pain tolerance in the majority of studies that met inclusion criteria, and that this effect was consistent across different modes of administration (e.g., intravenous, intranasal) and in response to diverse noxious stimuli (e.g., electric or heat). Authors concluded that the use of oxytocin as an analgesic for acute pain in animals was supported as it increased pain tolerance and reduced acute pain in rats and mice. Moreover, preliminary research was beginning to suggest that oxytocin could also decrease pain

sensitivity among humans. A call was made for additional methodologically rigorous research among human populations before definitive conclusions could be drawn regarding the effects of oxytocin on pain among humans (Rash et al., 2014). This systematic review will be the most current to evaluate the relationship between oxytocin and pain. The knowledge generated by this review will quantify the likelihood that oxytocin represents a novel potential analgesic, and may improve our understanding of pain pathways in the body. Lastly, this work has the potential to inform treatment among individuals who suffer with chronic non-cancer pain in clinical practice.

Objectives

An updated systematic review of the literature reporting on oxytocin and the management of chronic pain is necessary for several reasons. First, it is important to synthesize and organize the most current research on oxytocin and pain among humans in order to better understand and consolidate research findings in this area. This is especially important given a large body of mixed results exists around the effects of exogenous oxytocin (e.g., Ma et al., 2018; Grace et al., 2018; Bethlehem et al., 2013; Macdonald et al., 2013), as well as the association between oxytocin and pain (e.g. Valsted et al., 2017). The same contradictory findings exist in the literature evaluating the association between oxytocin and emotional functioning (Cochrane et al., 2013; Miwa et al., 2017). Moreover, there have been additional studies published after Rash et al. (2014) which would strengthen our understanding of the interplay between oxytocin and pain when analyzed in conjunction. More specifically, the nature of meta-analyses yields more robust and accurate conclusions (i.e., accurate pooled effect sizes) when results can be pooled across studies included in analyses (Viechtbauer, 2010). Secondly, an updated systematic review will function to identify gaps in the literature that will highlight areas for future research.

Methods

Protocol and Registration

The protocol was pre-registered on the Prospective Register of Systematic Reviews, PROSPERO (Registration CRD42021234926; Appendix 2).The protocol for this systematic review and meta-analysis was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocol (PRISMA-P) guidelines (Moher et al., 2015; Page et al., 2020; Appendix 3).

Study Eligibility Criteria

Population. Studies including human participants with a primary diagnosis of chronic non-cancer pain were flagged for inclusion (Treede et al., 2015). Studies which include chronic pain patients in addition to a healthy control group were also eligible for inclusion.

Interests. The present review represents an extension of our previous systematic review examining the relationship between oxytocin and pain (Rash et al., 2014). Our primary interest was to quantify the association between oxytocin and pain among those who experience chronic pain, and the effect of oxytocin administration on the experience of pain among chronic pain populations.

Comparison. Studies evaluating the association between oxytocin and pain, including controlled and observational studies were eligible for inclusion.

Outcomes. The primary outcomes of interest were pain and physical function. Secondary outcomes included emotional function (e.g., depressed, or anxious mood).

Design. Controlled, non-controlled, and observational studies were eligible for inclusion to gain a more comprehensive understanding of the effects of oxytocin on pain and to assess its efficacy as a potential analgesic. Interventions included those which administered exogenous

oxytocin peripherally or centrally. Interventions which did not administer oxytocin were included only observationally. Peer-reviewed studies that reported on original data were eligible for inclusion.

Study Exclusion Criteria

Studies were excluded if they reported on patients with chronic pain related to cancer as the conditions may have different origins (Novy et al., 2005) and comorbidities, while treatment goals may differ depending on patient prognosis. Studies that report on labour and birth-related pain were also excluded as oxytocin is typically used to induce labour (Simpson, 2011) and may be present in higher-than-normal levels during childbirth (Arrowsmith and Wray, 2014). Studies that included participants who have had a portion of the brain removed were also excluded as these surgeries may have effects on pain perception that obscure potential relationships between oxytocin and pain (Rash et al., 2014). Finally, we excluded studies that delayed pain testing for longer than 3 hours after oxytocin administration to ensure maximum concentration upon measurement of pain given that central oxytocin concentration peeks between 30-60 minutes after exogenous administration (Neumann et al., 2013). A list of inclusion and exclusion criteria can be found in Appendix 4.

Specific Questions to be addressed

The current study aimed to address four specific questions: (1) Is there an association between oxytocin and pain among individuals with chronic non-cancer pain?; (2) Is there an association between oxytocin and function among individuals with chronic pain?; (3) Do observed associations differ between children and adults?; (4) Do observed associations differ between different chronic pain conditions?

Data Sources and Search Strategy

A preliminary search strategy was created with the guidance of a Research data management and public services specialist (AF). An independent information specialist then peer-reviewed the strategy prior to implementation using the Peer Review for Electronic Search Strategies (PRESS; McGowan et al., 2016) checklist. We searched four bibliographic databases: 1) Ovid MEDLINE® (2012 to February 14, 2022), excluding indexed citations for conference abstracts and posters; 2) Embase (2012 to February 14, 2022); 3) PsycINFO (2012 to February 14, 2022); and 4) CINAHL (2012 to February 14, 2022). The Clinicaltrials.gov website was also searched for ongoing studies of potential relevance. Studies published before 2012 that were identified in our previous systematic review by Rash et al., (2014) were eligible for inclusion if they met all inclusion criteria. Finally, records were obtained through hand searches. See Appendix B for an example search strategy used for Ovid MEDLINE(R) and Epub.

Data Collection and Analyses

Study Screening. Searches were conducted, duplicates removed, and results imported into the "Covidence" online citation manager for systematic reviews (Veritas Health Innovation, Melbourne, Australia). Two independent reviewers AAM, JEB screened search results against eligibility criteria using a 2-step procedure: 1) screening of title and abstract; and 2) potentially relevant papers were then retrieved and screened in full-text. Disagreements between reviewers were resolved through consensus, or mediation by JAR. Agreement between reviewers was calculated using percent agreement, and the Cohen's Kappa statistic (Cohen, 1960).

Data Extraction. Data extraction was completed using a predefined rubric that captured the following information during full-text review: 1) journal article information (author's names, country, journal, DOI, publication year); 2) Methodological information (i.e. design, method of

oxytocin administration or assessment, standardized and study-specific measures, duration, and potential shortcomings/limitations in the methodology, comparison type); 3) sample characteristics (i.e. sample size, age, sex, recruitment, unique sample characteristics, type of chronic pain, history with chronic pain); and 4) Results (e.g., means and standard deviations reflecting change in pain and function, correlation between oxytocin measurement and pain or function, missing data). Extractions was compared across raters to ensure accuracy. Discrepancies were resolved by consensus or arbitration by JAR. Study authors were contacted via email when additional information was required. Authors that did not respond were provided with two reminder e-mails before information was considered unavailable due to non-response.

Risk of Bias and Quality Assessment

Risk of bias for RCTs was assessed using the Critical Appraisal Skills Program (CASP) tool for RCTs. (Critical Appraisal Skills Programme, 2019a). The domains assessed include: appropriateness of design, randomization, blinding, attrition and handling of missing data, participant similarity pre-treatment, adequacy of statistical reporting, reporting precision of estimated effects, and potential impact. Non-randomized-controlled studies were assessed using this tool with items pertaining to randomization omitted. Risk of bias in observational studies was assessed using the CASP appraisal tool for cohort studies (Critical Appraisal Skills Programme, 2019b). Domains assessed include: adequacy of recruitment, accuracy of exposure, accuracy of assessing outcomes, identification and handling of potential confounds, adequacy of follow-up, reporting of results, precision of results, and potential impact. Methodological quality and risk of bias assessment was conducted independently by two reviewers AAM, JEB. As recommended by the developers, criteria were assessed as “Yes”, “No” or “Can’t tell.” Discrepancies were resolved by consensus or arbitration by JAR.

Approaches to evidence synthesis

Evidence was used to answer three substantive questions around the relationship between oxytocin and pain management among individuals who experience chronic pain: (1) what is the effect of exogenous oxytocin administration on self-report of pain among individuals who experience chronic pain?; (2) what is the effect of exogenous oxytocin administration on pain experienced during acutely painful tasks or procedures?; and (3) what is the strength of association observed between pain ratings and endogenous oxytocin levels?

Quantitative Synthesis. Meta-analysis was conducted using Comprehensive Meta-Analysis software (CMA; Borenstein et al., 2015) in cases where three or more studies reported on the same outcome measured in a similar manner using random effects meta-analysis (Valentine et al., 2010) using the dersimonian and laird estimation method (CMA; Borenstein et al., 2015). Studies included in a meta-analysis were categorized according to study design and outcome variables. Effect size calculations were performed using formulae reported in Lipsey and Wilson (2001) and Wilson (2021).

Mean Differences. The effect size convention for studies reporting on differences between means was the standardized mean difference. Differences between means were calculated for each trial arm (e.g., oxytocin or placebo) using raw means and standard deviations (SDs). When presented, median and interquartile ranges (IQR) were converted to means and SDs using formula recommended in the Cochrane Handbook (Mean ≅ Median and SD ≅ (IQR)/1.35; Higgens and Green, 2008). Standard deviations of mean differences were calculated according to the formula presented in the Cochrane Handbook (Higgens and Green, 2008; SD_{change} = $\sqrt{[SD_{baseline}^2 + SD_{final}^2 - (2 \times Corr \times SD_{baseline} \times SD_{final})]}$. Moderate correlations (i.e., $r = 0.3$) were used to calculate the change in standard deviation for each condition given

that sensitivity analyses with small, moderate and high correlations of 0.1, 0.3 and 0.5 respectively did not result in appreciable differences. Effect sizes were calculated such that positive values indicated an effect favoring oxytocin.

Association between oxytocin and pain. The effect size convention used for studies reporting on strength of association was quantified using Spearman's Correlation, *r*. We did not use Pearson's correlation as it works with exclusively linear relationships while the Spearman's metric can account for the rank order of the correlation as well as monotonic relationships between variables (Bonnet, 2017).

Assessment of heterogeneity. Heterogeneity was assessed using I^2 and prediction intervals. I^2 is a measure of the proportion of overall variability in the reported effect attributable to "true" differences between studies relative to the variation attributable to sampling error. I^2 has arbitrary benchmarks pertaining to small, moderate or high levels of heterogeneity, and for this reason has become prevalent in meta-analyses (Borenstein et al., 2017). Because this variable is often measured inaccurately for models with few studies (often resulting in the erroneous conclusion that there is no heterogeneity), confidence intervals were calculated around I^2 using the test-based method (Higgins and Thompson, 2002). Finally, prediction intervals (PI's) were calculated to indicate the degree to which the effect differs across included studies, and provide a measure of the range of effects expected if a well-powered study were to be conducted and included in the current model (Borenstein et al., 2017).

Assessment of Practical Significance. Methods to assess the degree to which findings are clinically significant is paramount as commonly used statistical procedures such as null hypothesis significance testing have limitations that prevent the interpretations of practical significance (Loftus, 1996; Osborne, 2008). Within the context of health research, pooled effect

sizes can indicate whether an intervention could produce clinically meaningful change and has implications for policy and practice (Odgaard and Fowler, 2010). Statistically, practical significance for group differences was estimated by evaluating the pooled effect size against the recommended minimum effect size representing a practically significant effect (RMPE) for social science data, $g = 0.41$ (Ferguson, 2009). Strength of association (i.e., correlational effect sizes) were also compared to the RMPE for social science data, $R = 0.2$—a cut-off chosen by specialists in the field as *r* and *d* can be converted at this level without changes to interpretation of practical significance (Ferguson, 2009).

Publication Bias. Publication bias in meta-analysis results in skewed conclusions being drawn stemming from the publication or non-publication of relevant studies depending on the direction of their results (Sedgwick, 2015). Most commonly referred to as the file drawer problem, studies that fail reject the null hypothesis are not published thereby skewing results in the positive direction (Dalton et al., 2012). Erroneous effects observed in studies using small sample sizes can be the result of publication bias (Egger et al., 1997), wherein treatment effects are inflated, and conclusions are distorted or exaggerated (Thornton and Lee, 2000). Evidence for publication bias was assessed through visual inspection of funnel plot symmetry (Salanti et al., 2014). Other methods for evaluating publication bias (e.g. Eggers Test or Beggs method) were not suitable due to the small number of effects (Borenstein et al., 2021). As such, inspection of funnel plots should also be interpreted with caution.

Narrative Synthesis. Narrative synthesis was performed for outcomes where quantitative synthesis was deemed inappropriate due to: 1) significant methodological heterogeneity (Ioannidis et al., 2008); 2) sample size of included studies precluded quantitative

synthesis (i.e., fewer than three studies; McKenzie and Brennan, 2019); and 3) effect estimates could not be calculated due to insufficient available data.

Outcomes from studies synthesized using narrative review were reported according to the Synthesis Without Meta-analysis (SWiM) guideline (Campbell et al., 2020). Results from narrative synthesis included a rationale for the grouping of studies to be synthesized and a standardized metric for intervention effects (i.e., individual effect sizes for each narratively synthesized study with it's 95% confidence interval; Lipsey and Wilson, 2001). The standardized mean difference (i.e., Cohen's *d*) was calculated for studies that compared means. Odds ratios were computed for studies that reported frequency data, and Spearman's correlation was computed as an effect size for degree of association. Heterogeneity was evaluated based on degree of methodological diversity (Achana et al., 2014; Ioannidis et al 2008), including outcomes of interest and modality of the intervention (McKenzie and Brennan, 2019).

Results

Study Identification

Once duplicates were removed, database and hand searches returned 2,087 unique citations, of which 2071 did not meet eligibility criteria and were excluded during abstract screening. It should be noted that an additional 4 articles were intended to move to full text review but were discovered to be published abstracts and were therefore were excluded before full-text review. Upon reviewing full manuscripts, 3 articles did not contain the outcome variables of interest (i.e. pain ratings or measures of pain perception were not reported or were only reported at baseline and not as outcomes; Schneider et al., 2020; Lohman et al., 2019; Lincoln et al., 2018). 12 studies reported on originally collected data while Pacheco (2017) and Lohman et al.(2017) used data from the same participants. As such, data from Pacheco (2017)

was classified as secondary and was excluded. One study was excluded for having the wrong design, as it administered a derivative of Oxytocin (i.e. the enzyme Oxytocinase and therefore we could not assume that this substance would have the same effects as Oxytocin; Martinez-Martos et al., 2019). Proportion of agreement between independent reviewers at this stage was 97.68%; Cohen's Kappa= 0.55, indicating moderate to substantial agreement (McHugh, 2012). Eight articles were included following full-text review. An additional 6 articles that were identified in our previous review by Rash et al. (2014) were included (i.e. Alfvén et al., 1994; Yang, 1994, Louvel et al., 1996; Anderberg and Uvnäs-Moberg, 2000;Alfvén, 2004; Ohlsson et al., 2005) for a total of 14 articles. Figure 1 presents a flow-diagram depicting citation screening.

Study Characteristics

Table 1 provides a summary of the included studies with relevant information related to sample characteristics, study design, methodology pertaining to pain and oxytocin assessment, and outcomes of interest. Sample sizes ranged between 12 and 608 participants; data from 1,504 participants in total. Five studies focused on adult women; two of which assessed fibromyalgia (Mameli et al., 2014; Anderberg and Uvnäs-Moberg, 2000), one chronic pelvic pain (Flynn et al., 2020), one chronic constipation (Ohlsson et al., 2005) and one chronic migraine (Boström et al., 2019). One study recruited adult males who experienced chronic low-back pain (Boll et al., 2020). Seven studies collected data from men and women with diverse chronic pain conditions (i.e., chronic neck and shoulder pain: Tracy et al., 2017; chronic low-back pain: Yang, 1994; Fibromyalgia: Clark et al., 2020 and Bazzichi et al., 2013; Irritable bowel syndrome: Louvel et al., 1996; Chronic migraine: Wang et al., 2013). The remaining two studies examined recurrent abdominal pain among boys and girls (Alfvén, 2004; Alfvén et al., 1994).

Of the 14 included studies, six were RCTs that involved the exogenous administration of intranasal oxytocin (Flynn et al., 2021, Boll et al., 2020; Tracy et al., 2017; Mameli et al., 2014; Wang et al., 2013; Ohlsson et al., 2005). Two studies administered exogenous oxytocin by intravenous infusion (Louvel, 1996; Yang, 1994) and one intrathecally (Yang, 1994). Outcomes of interest varied, such that three RCT's evaluated improvement in self-reported pain using visual analogue or numeric rating scales (e.g., fibromyalgia; Flynn et al., 2021; Mameli et al., 2014; Ohlsson et al., 2005). Two RCT's evaluated pain relief categorically by having participants rate whether they experienced complete, partial or no pain relief (Wang et al., 2013; Yang, 1994). Three studies assessed sensitivity to acute pain stimuli after exogenous oxytocin administration in patients and healthy controls (Boll et al.,2020; Tracy et al., 2017; Louvel et al., 1996). Finally, six of the included studies were observational (Clark et al., 2020; Boström et al., 2019; Bazicchi et al., 2013; Anderberg and Unväs-Moberg, 2000; Alfvén, 2004; Alfvén et al., 1994), and evaluated the associations between endogenous oxytocin and pain or emotional functioning. Note that Clark et al. (2020), Bazicchi et al. (2013) and Boström et al. (2019) conducted RCTs on interventions that did not pertain to oxytocin and were classified as observational studies in this review given that only baseline data was used (i.e., data from chronic pain patients, pre-intervention was used to evaluate the association between pain and endogenous oxytocin).

Mean duration of illness was only reported in 6 studies and ranged between 4.5-11.9 years (Flynn et al., 2020; Mameli et al., 2014; Bazzichi et al., 2013; Wang et al., 2013; Anderberg and Uvnäs-Moberg, 2000; Yang, 1994).

Six studies reported measuring emotional functioning (Clark et al., 2020; Flynn et al., 2020; Boström et al., 2019; Mameli et al., 2014; Ohlsson et al., 2005; Anderberg and Uvnäs-Moberg, 2000). Yang (1994) reported insufficient data to calculate effect sizes for inclusion.

Risk of Bias and Quality Assessment

Table 2 depicts a summary of risk of bias assessment for the 8 included RCTs, and the 6 included observational studies. Overall risk of bias was low, with few studies being flagged for low methodical rigour. Most trials adequately reported on randomization (6/8), adjustment for attrition (6/8), blinding of patients (8/8), blinding of investigator (7/8), and baseline equivalency (6/8). No trials blinded outcome assessor (0/8), and few reported the precision of estimates in treatment effects (4/8). The six observational studies adequately reported on potential confounds, and designed outcome measures to minimize potential bias. All the studies also followed up with participants and results were deemed believable (6/6). It was inconclusive whether results were in line with other available evidence (4/6).

Quantitative Synthesis

Primary Outcomes.

Exogenous Oxytocin on Pain Intensity. The first meta-analysis included three RCTs in which exogenous oxytocin was administered as a treatment for chronic pain (i.e., Flynn et al., 2020, Mameli et al., 2014 and Ohlsson et al., 2005). As depicted in Figure 2, results from the random effects model yielded a non-statistically significant pooled effect, $g = 0.27$, 95% CI [-0.39, 0.91], 95% *PI* [-1.89, 2.48], $Z = 0.79$, $p = 0.43$, favoring oxytocin. Statistically significant heterogeneity was observed between effects, Q ($df = 2$) = 4.814, $p = 0.09$, $\tau^2 = 0.192$, $I^2 =$ 58.46%, 95% CI [0%, 88.17%]. Visual inspection of the funnel plot (Figure 3) showed

asymmetry in that RCTs with smaller sample sizes seemed to favour the use of oxytocin relative to placebo.

Association between pain-ratings and oxytocin levels. The second meta-analysis aimed to evaluate the pooled correlation between pain ratings and basal oxytocin levels. One study measured plasma oxytocin (Alfven, 2004) and two studies measured oxytocin in saliva (Boström et al. 2019; Clark et al., 2020). Results indicated that on average, there was no association between peripheral oxytocin levels and self-reported pain ratings, r_{pooled} = 0.04, 95% CI [-0.11, 0.20], 95% PI [-2.91, 0.48], p = 0.59, Z=0.543, refer to Figure 4. There was no evidence of statistical heterogeneity, Q (df =2) = 0.719, p =0.70, τ^2 = 0, I^2 = 0%, 95% CI [0%, 71.06%] and. Figure 5a depicts funnel plots for the correlation between basal oxytocin levels and self-reported pain-ratings, and visual inspection did not show visible asymmetry.

Secondary Outcomes.

Three studies provided sufficient data to conduct one meta-analysis evaluating the association between peripheral oxytocin levels and depressed mood (Clark et al., 2020; Boström et al., 2013; Anderberg and Uvnäs-Moberg, 2000). On average there was a small but non-statistically significant negative correlation between self-report measures of depressed mood and peripheral oxytocin concentration, r_{pooled} = -0.08, 95% CI [-0.432, 0.299], 95% PI [-2.03, 1.69], p = 0.697, Z = -0.389, refer to Figure 6. There was evidence of statistically significant heterogeneity, Q (df=2) = 7.378, p =0.025; I^2 = 72.89%, 95% CI [8.83%,91.94]. Figure 5b depicts the funnel plot for the correlation between basal oxytocin levels and self-reported ratings of depression. Visual inspection of the plot did not show substantial asymmetry despite one study near the border of the funnel.

Narrative Synthesis

Table 3 depicts studies that were narratively synthesized, grouped according to outcomes of interest.

Primary outcomes with computable effect sizes.

Effect of Exogenous Oxytocin on Acute Pain Sensitivity. Studies that used acute pain tasks to evaluate pain sensitivity (i.e., Boll et al., 2020, Tracy et al., 2017, and Louvel et al., 1996) were grouped for comparisons. Louvel et al. (1996) reported on pain threshold, and was grouped with Boll et al. (2020) and Tracy et al. (2017) who reported on pain intensity. These outcomes were evaluated together given that: 1) participants report an average of seven to eight out of 10 on a numeric rating scales of pain before reaching pain tolerance (Bowler et al., 2017); and 2) a validation study on pain severity and pain threshold among patient with chronic pain reported no significant differences in pain severity among patients with high or low pain-tolerance scores (Ankarali et al., 2018).

Specifically of the three included studies, Boll et al. (2020) used a finger-span device while a thermal stimulus was applied to the lower back via thermode. The results indicated a moderate effect size, $d = 0.57$, 95% CI [-0.02, 1.16], with oxytocin decreasing pain perception in chronic back pain patients. It is also noteworthy that authors reported a significant interaction of group by substance, in that oxytocin decreased pain perception in chronic pain patients but not in healthy controls. Similarly, Tracy et al. (2017) applied a noxious thermal stimulus to three different sites on the neck and shoulder region. The results showed a small effect size, favouring placebo, $d = -0.16$, 95% CI [0.72, -0.41]. Pain ratings were lower in the placebo condition for chronic pain patients, whereas pain ratings were lower in the oxytocin condition for healthy controls. Finally, Louvel et al. (2000) monitored pain threshold during isobaric distention at

different doses of oxytocin and placebo. A large effect size was computed d= 1.21, 95% CI [0.50, 1.29] at the median oxytocin dose (i.e., 20 mU/min) that favoured oxytocin. Overall, two of the three included studies that evaluated the effect of oxytocin on acutely painful procedures supported the use of oxytocin; results will be discussed further in light of study design to avoid vote-counting effect sizes (Borenstein et al., 2021).

Pain Relief. Odds ratios were calculated at the median dose of oxytocin for each route of administration using full-remission versus partial, or no remission to derive conservative estimates of effect. Patients with chronic low back pain who were administered the median dose (i.e.100 μg/kg) of oxytocin intrathecally were more likely to report complete remission than when administered a placebo with an odds ratio of 709.33, 95% CI [70.81, 7105.33] (Yang, 1994). There was difference in remission between oxytocin and placebo when administered intravenously, OR = 1, 95% CI [0.061, 16.521]. Patients who experienced chronic migraines were also more likely to report remission following the intranasal administration of a 200 ng dose of oxytocin relative to placebo with an odds ratio of 27.44, 95% CI [5.31, 141.82] (Wang et al., 2013). Results support the use of oxytocin for pain management when administered centrally.

Primary outcomes without computable effect sizes. Studies that compared plasma oxytocin levels in chronic pain patients versus healthy controls were grouped so long as the association was reported independent of oxytocin administration (Boström et al., 2019; Wang et al., 2013; Alfvén, 2004; Anderberg and Uvnäs-Moberg, 2000; Alfvén et al., 1994; Yang, 1994). Table 4 presents a comparison of Plasma oxytocin levels in healthy controls and chronic pain patients.

Endogenous Oxytocin Concentration comparisons. All studies reported significantly different ($p < 0.01$) basal plasma oxytocin levels between healthy controls and chronic pain

patients independent of pain condition. Wang et al. (2013) reported significantly higher mean plasma oxytocin levels in patients suffering from chronic migraine relative to healthy controls (See Table 4 for exact values). Boström et al. (2019) observed the same trend in basal salivary oxytocin concentrations in chronic migraine patients. It is noteworthy that only studies reporting on chronic migraine conditions observed this trend while all other included studies observed significantly lower oxytocin concentrations among chronic pain patients relative to healthy controls (Alfvén, 2004; Alfvén et al., 1994; Yang, 1994). Overall, across chronic pain conditions, three of the five included studies observed lower basal plasma oxytocin levels in patients when compared to age and sex matched healthy pain-free controls. While not reported in the manuscript, Anderberg and Uvnäs-Moberg (2000) asserted that the difference between plasma oxytocin levels in female fibromyalgia patients and healthy controls were not significantly different (p=0.55); however, the distribution of basal oxytocin levels in patients was larger than that of HCs as depicted in boxplots.

Other primary outcomes without corresponding effect sizes

Bazzichi et al. (2013) reported plasma oxytocin and pain-ratings at baseline, 2 weeks and 12 weeks after different mud-bath therapy and balneotherapy. Results were meaningful in that change in plasma oxytocin and self-reported pain were not observed to covary across time points.

Secondary outcomes with computable effect sizes.

Exogenous Oxytocin on Depressed mood. Three RCTs assessed symptoms of depressed mood through validated self-report measures and were considered similar. The administration of oxytocin in Flynn et al. (2020) resulted in small, non-statistically significant improvements in depressed mood relative to placebo, d= 0.218, 95%CI [-0.584, 1.021]. Results from Mameli et

al. (2014) favoured the use of oxytocin for depressed mood but was not statistically significant, *d*= 0.048, 95% CI [0.707,0.803] while Ohlsson et al. (2000) reported a small mean difference between oxytocin and placebo administration that favored placebo and was not statistically significant, *d*= -0.163, 95% CI [0.435, -0.760]. In summary, mixed findings were observed with respect to the effect of oxytocin on depressed mood.

Exogenous Oxytocin on Anxious mood. Three studies assessed the effect of exogenous oxytocin on self-reported anxious mood using validated scales (Flynn et al., 2020; Mameli et al., 2014; Ohlsson et al., 2000). Results from Flynn et al. (2020) associated the use of oxytocin with a small, non-statistically significant reduction in anxious mood relative to placebo, $d = 0.093$, 95% CI [-0.718, 0.883]. Mameli et al. (2014) reported that the intranasal administration of oxytocin resulted in a small increase in anxious mood relative to placebo that was not statistically significant, $d = -0.128$, 95% CI [-1.132, 0.391]. Similarly, Ohlsson et al. (2000) reported that using oxytocin resulted in a small increase in anxious mood relative to placebo, *d*= -0.147, 95% CI [-0.450, 0.745].

Association between plasma oxytocin and anxious mood. Two studies reported the correlation between plasma oxytocin concentrations and self-reported anxiety. Clark et al. (2020) reported no correlation between plasma oxytocin concentration taken during a resting state and anxiety-ratings using Spearman's correlation test, $r = 0.02$. Anderberg and Uvnäs-Moberg (2000) measured levels of anxiety via daily symptom ratings on a 10-point numeric scale for 28 days. Mean scores for each participant were used to calculate the correlation against mean plasma concentrations from two blood tests. Authors reported a statistically significant moderate, negative correlation using Spearman's correlation test, $r = -0.46$. Overall, findings for the correlation between plasma oxytocin and self-reported ratings of anxiety were mixed.

Discussion

The goal of this narrative review and meta-analysis was to evaluate the efficacy of oxytocin on pain, physical function, and emotional function among individuals who experience chronic pain. The most recent systematic review on oxytocin and pain was conducted 8 years ago (Rash et al., 2014). An update was merited given that the median time required for an update is approximately 5.5 years, and results from outdated reviews can mislead stakeholders (e.g. researchers, clinicians and policy makers; Higgins et al. 2020). A comprehensive review of the literature identified 14 studies that met inclusion criteria and provided insight into the association between oxytocin and pain among 1,504 individuals who experience chronic pain. Included studies provided evidence on six broad categories: (1) The effect of exogenous oxytocin on pain sensitivity; (2) The effect of exogenous oxytocin on sensitivity to acutely painful procedures; (3) The association between endogenous oxytocin and pain; (4) The effect of exogenous oxytocin on emotional functioning; (5) The association between endogenous oxytocin and emotional functioning; and (6) basal oxytocin levels among chronic pain patients relative to healthy controls.

Oxytocin and Pain

The effect of exogenous oxytocin on chronic pain sensitivity. The non-significant meta-analysis evaluating the exogenous administration of oxytocin, relative to placebo (Flynn et al., 2020; Mameli et al., 2014; Ohlsson et al., 2005) could reflect inherent heterogeneity in the observed effects, stemming from heterogeneity and lack of power in the included trial designs (e.g., different chronic pain conditions; See section on limitations of the included literature for further discussion). Stronger results favouring oxytocin seem to have been driven by individuals who reported lower baseline musculoskeletal pain severity (Flynn et al., 2020). Relative to those

who had no primary pain diagnosis, individuals with a diagnosis of IBS showed a reduction in abdominal pain in the oxytocin group (Ohlsson et al., 2005). Methodological shortcomings in Mameli et al. (2014) may have also contributed to weaker results observed, including incomplete reporting of administration procedures, no formal evaluation of patient expectancy effects (Kessner et al., 2013), and a small sample size (the interested reader should refer to the commentary by Rash and Campbell, 2014). The presence of psychological comorbidities among approximately 65% of patients in Mameli et al. (2014) may have also led to differential effects of oxytocin; this possibility comes in light of previous literature reporting that oxytocin differentially affects individuals with mood disorders compared to healthy controls (Pincus et al., 2010). These results are potentially important as they make salient the possibility that comorbid mood disorders may change the way that oxytocin functions in the central nervous system. Fibromyalgia may also represent a unique chronic pain condition, involving systems and pathways that may obscure the potential effects of oxytocin (Häuser and Tölle, 2015). It is noteworthy that physician evaluation of pain among patients contrasted self-report and favored beneficial effects of oxytocin (Mameli et al., 2014). Finally, the inclusion of larger sample sizes in each participant group (e.g. patients with mood disorders versus no mood disorders) is needed to delineate whether aspects related to methodology or participant characteristics are contributing to the strength and direction of the findings.

Two RCTs reported on remission from pain and were subject to narrative review, indicating that the exogenous administration of oxytocin using a route that enters the central nervous system was significantly more likely to result in remission of pain than placebo among adults with low back pain and migraine (Yang, 1994; Wang et al., 2013). Taken together, results are inconclusive yet promising, suggesting that additional rigorous trials are needed to determine

the unbiased effect of exogenous oxytocin administration on pain among individuals who experience chronic pain.

The effect of exogenous oxytocin on acute pain sensitivity. Three studies evaluated the effects of exogenous oxytocin administration on acute pain sensitivity among chronic pain patients with two trials reporting effects that favored oxytocin (Boll et al., 2020; Louvel et al., 1996), and one trial reporting an effect that favored placebo (Tracy et al., 2017). Of the three studies it is notable that Boll et al. (2020) and Tracy et al. (2017) both evaluated noxious thermal stimuli in musculoskeletal pain conditions after the same dose of intranasal oxytocin. Robust findings in Boll et al. (2020) may have been driven by their entirely male sample—this suggestion comes in light of secondary findings from Tracy and colleagues who reported that oxytocin increased perceived intensity of noxious heat stimuli among female participants, but not in males with chronic neck and shoulder pain (d= 0.71; Tracy et al., 2017). These findings suggest that endogenous sex hormones may interact with oxytocin (Domes et al., 2010) to influence pain perception among individuals with chronic pain conditions, with oxytocin being a more efficacious analgesic in males(Tracy et al., 2017; refer to discussion on sex differences).

Association between endogenous oxytocin and pain ratings. We observed a small, non-significant pooled correlation between endogenous oxytocin levels and pain ratings in our meta-analysis. It should be noted that two of the included studies assayed salivary oxytocin concentration among adults (Clark et al., 2020; Boström et al., 2019) while one assayed plasma oxytocin concentration among children (Alfvén, 2004). While Clark et al. (2020) reported a small negative association and contained the largest sample size, Alfvén (2004) reported a moderate positive association and Boström et al. (2019) reported a large positive association. This heterogeneity raises the question of whether the chosen measures of oxytocin are

adequately correlated with pain (refer to discussion on central versus peripheral effects of oxytocin for detailed discussion).

Oxytocin and Emotional Functioning

The effect of exogenous oxytocin on emotional functioning. The present study examined two facets of emotional functioning: depressed mood and anxious mood. Inconsistent results from narrative review and meta-analysis will be discussed pertaining to both mood-states and which indicate a need for further research examining the associations between oxytocin and emotional functioning in those who suffer from chronic pain.

Depressed mood. Narrative review of studies that evaluated depressed mood after oxytocin administration yielded inconsistent results. The ways in which oxytocin acts to alleviate depressed mood may interact with elements of certain chronic pain conditions leading to these equivocal findings. This speculation is plausible given that depression implicates a heterogeneous cluster of symptoms that often overlap with symptoms associated with chronic pain, which can be difficult to disentangle. For example, the presence of hyperalgesias, fatigue and depressed mood which are typical in Fibromyalgia or irritable bowel syndrome often involve dysregulation in the dopaminergic, serotonin and oxytocin systems (Unväs-Moberg et al., 2000; Arletti et al., 1995) changing patients' response to exogenous oxytocin. For example, patients with fibromyalgia have been reported to have low levels of oxytocin (Frasch 1995; Anderberg and Uvnäs-Moberg, 2000). Severity of depressed mood may also be a consideration. For example, Muin et al. (2015) reported that oxytocin improved self-reported depressed mood among mildly depressed women, but not more severe presentations. A seminal fMRI study by Pincus et al. (2010) observed that oxytocin triggered differential patterns of neural activation in depressed patients versus healthy controls during a behavioural paradigm (Baron Cohen et al.,

2001). The relationship between oxytocin and depressed mood among individuals who experience chronic pain is complex and required further investigation.

Anxious mood. Three RCTs evaluated the effect of oxytocin on self-reported anxiety and narrative review produced ambiguous findings. Mixed results are consistent with other research that attempted to evaluate the efficacy of oxytocin for anxiety in humans (Neuman and Slattery, 2016), with reports of both anxiogenic (Macdonald and Feifel, 2013) and anxiolytic properties (Feifel et al., 2011). Moreover, it has been suggested that comorbid anxiety might moderate the effects of oxytocin on depression (Scantamburlo et al., 2007). Relatedly, it is possible that the doses of oxytocin administered were not strong enough to reach the necessary structures in the brain, the periphery or the CNS (Spengler et al., 2017; Liberez et al., 2020) that would result in a detectable improvement in mood. Overall, studies of the effects of oxytocin on anxiety and depression continue to yield novel findings and further research is needed to elucidate the mechanisms by which oxytocin acts in conjunction with complex pain diagnoses to affect depressed or anxious mood.

Association between endogenous oxytocin and emotional functioning. Results from meta-analysis indicated a small and non- statistically significant association between oxytocin levels and depressed mood with heterogeneity among included studies. High comorbidity between depression and anxiety (Kalin, 2020) renders their association with oxytocin comparable. Relatedly, a systematic review by Macdonald & Feifel (2013) asserted that direct correlations between anxiety disorders and oxytocin levels is minimal. The same study states that given the heterogenous nature of anxiety, more complex interactions such as recruitment of the HPA and serotonin systems could be involved in the association between oxytocin and anxiety.

Overall, results into the relationship between oxytocin and depressed as well as anxious mood appear to be equivocal.

Basal oxytocin in chronic pain patients relative to healthy controls. Oxytocin levels were observed to differ between individuals who experience chronic pain and health controls, and these differences appeared to depend on the chronic pain condition. Three studies looking at recurrent abdominal pain and low back pain observed lower oxytocin levels among patients with chronic pain (Alfvén et al., 1994; Alfvén, 2004; Yang, 1994) while the two studies on headache and migraine reported the opposite pattern; this suggests that different pain diagnoses may influence the oxytocinergic system differentially (refer to discussion on Central versus Peripheral Effects of Oxytocin).

Sex Differences and the Effects of Oxytocin

Sex differences have been reported in previous research evaluating the association between oxytocin and pain, and may explain heterogeneity in observed results. For example, research has reported consistent analgesia in healthy male volunteers after a singe-dose of oxytocin (Pfeifer et al., 2020; Zunhammer et al., 2015), including an RCT that reported results consistent with preclinical evidence for antinociceptive properties of oxytocin (Paloyelis et al., 2016). Mixed findings were reported in similar studies that included female participants (Pfeifer et al., 2020; Cepeda et al., 2003; Sarton et al., 2000), raising the question about whether women with primary pain diagnoses may be hypersensitive to painful stimuli (Zunhammer et al., 2016; Cepeda et al., 2003). More work needs to be done considering the suggestion that the association between oxytocin and pain may interact with endogenous sex hormones (Tracy et al., 2017) and that sex differences may be implicated in oxytocin mechanisms (Domes et all., 2010; Kirsch et

al. 2005), including oxytocin's profound regulation by estrogen in the brain and it's role in estrogen-dependent responses (e.g. sexual behaviour; McCarthy, 1995).

Central versus Peripheral Effects of Oxytocin

Most biologically plausible mechanisms linking oxytocin and pain involve central availability. This is complicated in two ways: 1) two pathways of endogenous oxytocin release exist (one centrally and one peripherally); and 2) oxytocin is a peptide molecule that does not cross the blood brain barrier (BBB; Ermisch et al., 1985). These factors have important implications for interpreting the results of this review. Specifically, research evaluating associations between oxytocin and pain relied on peripheral assays from saliva or plasma in all but one case. This is pertinent as the degree to which peripheral assays reflect central bioavailability is uncertain. The indices of endogenous oxytocin may also have influenced the reported levels as several studies used measures of plasma oxytocin, while others used salivary oxytocin. A systematic review and meta-analysis by Valsted and colleagues reported that blood plasma itself may not be an appropriate index of central oxytocin under resting conditions (Valsted et al., 2017). Despite the appeal of using peripheral indices of oxytocin, and the invasive nature of obtaining oxytocin concentrations from the cerebrospinal fluid (CSF), it is possible that levels of central oxytocin would vary more consistently with pain ratings. This is especially important given that Valsted et al. (2017) also suggest that the presence of pain conditions may bias the coordination of central and peripheral oxytocin, which if true, could explain the consistent mixed results (Amico et al.,1990; Rash et al., 2014; Valsted et al., 2017). Results from the same meta-analysis (Valsted et al., 2017) also indicated that there is a positive correlation between central and peripheral concentrations of oxytocin, but this association depends on the experimental context—that is, evidence existed for the positive correlation after

intranasal oxytocin administration but not during resting state, at which our results were measured. Definitive conclusions regarding the assumption that single measures of endogenous oxytocin can index release of oxytocin in the brain have yet to be obtained (MacLean et al., 2019). Our observation that centrally administered oxytocin yielded more robust pain relief (Yang, 1994; Wang et al., 2013) also support results from a recent experiment in which nasal oxytocin was applied in rats, after which high concentration of oxytocin was detected in the dorsal and ventral dura matter which are innervated by the trigeminal nerve afferent fibres, reported to play a critical role in migraine headache (Burgos-Vega et al., 2015); this finding cannot be ruled out as possibly contributing to strong findings favouring oxytocin in headache studies (Wang et al., 2013; Boström et al., 2018). Relatedly, exogenous oxytocin administered using a direct injection, or nasal spray can enter the CNS given that the BBB is incomplete at the nasal cavity (Daneman and Prat, 2015). Notably all but one included RCT (Louvel et al., 1996) administered oxytocin into the CNS, and this may not have had much impact on the results observed.

Another angle from which to examine central versus peripheral measures of oxytocin is in the evaluation of basal oxytocin in chronic pain patients relative to healthy controls; this analysis led to interesting findings. Most notably, Yang (1994) reported statistically significant differences between plasma oxytocin in patients compared to healthy controls, wherein individuals with chronic pain exhibited lower basal plasma oxytocin than healthy controls when assayed through cerebrospinal fluid. The finding that patients who experienced headache and migraine had higher basal oxytocin levels than healthy controls, when the opposite was observed for all other included pain conditions points to another avenue for exploration. The prerequisite for this finding to be valid (Wang et al., 2006) was explored in a pertinent paper by Martins and

colleagues (2020) who review the assumption that a single measurement of endogenous oxytocin in peripheral fluids at rest provide reliable estimates of basal levels of endogenous oxytocin in plasma or saliva. Their analyses lacked robust evidence, and thereby did not support the aforementioned assumption. A potential explanation by Szeto et al. (2011) suggests that potential contamination of assays with immunoreactive products other than oxytocin may have lead to erroneous results. Using radioimmunoassay, Martins et al. (2020) showed that single measures of basal oxytocin concentrations in saliva and plasma were not stable within the same individuals across different days; this raises the possibility that our observations are not valid trait markers of the physiology of the oxytocin system, but rather represent reliable state markers.

The reliability of peripheral assays to capture central oxytocin levels can also be debated when we are aiming to evaluate the relationship between measures of endogenous oxytocin and emotional functioning. For example, in a meta-analysis by Valsted et al. (2017), neither plasma oxytocin nor oxytocin in the CSF were associated with psychiatric disorder status with the exception of anorexia nervosa (Rutigliano et al., 2016).

Strengths and Limitations

Strengths. This review has several strengths in line with the AMSTAR checklist (Shae et al., 2017). Foremost, it meets the standards of methodological rigour necessary for meta-analyses and systematic reviews (Shae et al., 2017). For example, we included all the necessary components of a review according the PICO guidelines, rationale for study inclusion and exclusion, summary of studies included as well as adequate risk of bias assessments for the given literature. All deviations from the initially planned analyses are transparently stated with accompanying evidence allowing readers to make informed judgements pertaining the

implications of the current work. Moreover, the current review includes research from 1950 - 2022 providing readers with a comprehensive summary of the existing literature.

Limitations.

Limitations of the literature. The most prominent limitation of the included literature is the methodological heterogeneity between studies. Diverse chronic pain populations, measures used to assess pain-related and emotional functioning outcomes, different behavioural paradigms, and different methods of pain induction and endogenous oxytocin assays make the included studies difficult to compare and limit interpretability. It is also possible that associations between oxytocin and pain vary according to level of pain severity; this suggestion comes in light of unanalyzed findings from Anderberg and Uvnäs-Moberg (2000) who report that patients with severe pain had significantly lower plasma oxytocin concentrations than those who self-reported lower pain ratings. Finally, the heterogeneity in chronic pain populations may have skewed our findings—that is, the association between pain and endogenous OT concentrations may differ in certain chronic pain conditions. Most distinctly, research in headache and migraine have been highlighted as outliers in previous meta-analyses (Valsted et al., 2017), and have been flagged as reporting consistent findings favouring the use of oxytocin for migraine and containing unequivocal positive associations between oxytocin and pain (Tzabazis et al., 2016; Wang et al., 2013; You et al., 2017) compared to other chronic pain studies. More specifically, oxytocin has been shown to be preferentially deposited in the trigeminal system (Boll et al., 2018), whose dysregulation has been associated with migraine (Goadsby et al., 2017). It thereby stands that the inclusion of migraine and non-migraine studies may blur the differential associations between oxytocin and pain. Moreover, the included studies often lacked adequate data to calculate the magnitude of the effects for the effect sizes of interest; this precluded us

from investigating several outcomes of interest in meta-analysis and reduced the number of studies we were able to include in meta-analysis. In addition, some studies that evaluated the association between endogenous oxytocin levels and pain, and emotional functioning relied on endogenous concentrations using peripheral assays. Such methods have been reported to have limited associations with central oxytocin concentrations during resting states (Valstad et al., 2017). Moreover, two studies also used peripheral exogenous administration as a proxy for central bioavailability which may contribute to mixed findings regarding analgesic properties. In a review by Macdonald et al. (2013) authors assert that there are several factors that might influence individuals' responses to oxytocin such as gender, hormone status, genetic variations in the oxytocin system, and attachment history (Yang et al., 2022; Bartz et al., 2011) which could confound consistent results. This is important in that these pertinent confounds were not always considered in the included literature. Another concern is the small sample size recruited in several of the studies included. Under powered studies included in systematic review and meta-analysis may reduce our ability to detect true effects or the overestimation of effect sizes (Button et al., 2013), leading to difficulty interpreting meta-analysis. A final limitation is the scarcity of research which reports on pain-related interference or physical function as an outcome, given it's important in chronic pain management (Gatchel et al., 2014).

Limitations of the Review. The current review should be interpreted with caution in light of several limitations. Foremost, we included methodologically diverse studies with heterogeneous chronic pain presentations that were difficult to synthesize and draw meaningful conclusions. Similarly, heterogeneity impeded adequate or conclusive meta-analytic interpretation due to a lack of power—that is, the use of meta-analysis is more powerful when more studies are included as this increases the included sample size (Viechtbauer, 2010).

Another limitation of the current work is the lack of a robust method to assess publication bias when only three studies are meta-analyzed (Soeken and Sripusanapan, 2003); for this reason further studies would need to be included in order to ascertain whether publication bias has affected the results. Finally, searches of the grey literature could have been beneficial in light of the scarcity of the current body of research (Shae et al., 2017).

Future Directions

Evidence is needed from rigorous trials that examine the effect of exogenous administration of oxytocin among diverse chronic pain populations to draw conclusions with greater precision and certainty. Our team is conducting an adequately powered, pre-registered, double-blind, placebo-controlled multi-site RCT investigating the effect of exogenous oxytocin administration on pain and pain-related interference among adults who experience chronic neuropathic, pelvic, and musculoskeletal pain (refer to Rash et al., 2021 for further details). The literature would also benefit from efforts to reducing risk of bias by reporting indices of precision of the estimate of the intervention or treatment effect to increase the interpretability of results. Finally, there is a need for future research to focus on two prominent areas of debate in the literature: (1) delineating sex differences which may confound results; and (2) investigating complexities, mechanisms and the intersection of central versus peripheral effects of oxytocin.

Conclusion

This updated systematic review and meta-analysis included 14 studies evaluating the association between oxytocin and pain that showed limited but promising evidence for the efficacy of exogenously administered oxytocin as an analgesic for chronic pain. Overall meta-analyses and narrative review of individually calculated effect sizes showed a tendency toward favouring oxytocin for pain severity and sensitivity. The same was not true of narrative review

of emotional functioning, with some studies favouring the use of oxytocin over placebo for depressed mood and anxious mood, while others favoured placebo. Moreover, oxytocin levels differed between chronic pain patients and controls, but directions differed and appeared to vary based on chronic pain condition. Specifically, current findings point to potentially disparate associations between oxytocin and analgesia in migraineurs relative to other chronic pain conditions. Potential sex differences were also observed when investigating several outcomes, indicating that oxytocin might increase pain sensitivity. While promising results were observed for the use of exogenous oxytocin administration to decrease pain severity and sensitivity among individuals who experience diverse chronic pain conditions, future studies are imperative and should undertake more precise exploration of mechanisms of analgesic action to clarify inconsistency in the existing body of literature.

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Tables

Table 1

Characteristics of Studies Included. Studies are arranged by similarity in outcomes and type of analysis undertaken.

First Author, Year	Type of Chronic Pain Assessed (Main Pain Outcome)	Method of Oxytocin Assessment	Method of Pain Assessment	Control	Sample size included in original analysis (Mean Age)		% Female	% Affected by mood disorder	Analysis of emotional functioning
					Controls	Treatment			
Randomized Controlled Trials (Included in meta-analysis)									
Flynn, 2020	Chronic Pelvic Pain (Improvement in pain and function)	Daily Administration of 24 IU intranasal OT for two weeks	Daily diaries of BPI-SF	Crossover arm, randomized to Placebo	PBO: 12 (37.7)*	12 (37.7)	100%	75%	Narrative Synthesis using the DASS
Mameli, 2014	Fibromyalgia (Improvement in pain)	Daily administration of 40 IU of intranasal OT for one week then 80 IU for two weeks	VASPI	Independent samples, Randomized to Placebo	PBO: 14 (51.9)*	14 (51.9)	100%	64.23%	Narrative Synthesis using Zung Self-rating Depression scale
Ohlsson, 2005	Chronic Constipation (Improvement in pain)	Twice daily administration of 24 IU of intranasal OT	GSRS	Crossover arm, randomized to Placebo	PBO: 26 (49)*	23 (47)	100%	23.08% PBO; 39.13% TRT	Narrative Synthesis using PGWB
Randomized Controlled Trials (Not included in meta-analysis)									
					Controls	Patients			
Boll, 2020	Chronic Low-back pain (Acute heat-Pain task)	Single administration of 24 IU intranasal OT	VASPI	Healthy controls recruited With a crossover design	HC: 22 (34.41)	22 (36.82)	0%	N/A	N/A

Lincoln, 2017	Chronic neck and shoulder pain (Acute heat-Pain task)	Single administration of 24 IU intranasal OT	Pain intensity rated on 11-point NRS	Healthy controls recruited. Crossover design	HC: 24(28.46)	24(28.46)	33% in each group	N/A	N/A
					Controls	Patients			
Louvel, 1996	Irritable Bowel Syndrome (Acute Pain Task)	Two consecutive intravenous administrations of 10, 20, 30 or 50μU/min OT (10-hours apart)	Pain Threshold during isobaric colonic distension	Repeated measures design	N/A	26 (45)	42.3%	N/A	N/A
Yang, 1994	Chronic Low-back pain (Improvement in pain). Basal plasma OT was also measured	Two Intrathecal (0, .1,.2,.4,.8,1.6μ/kg) or Intravenous (50,100,200,400μg/kg) administrations of OT	Complete, partial or no relief rated using self-report.	Healthy controls recruited for basal OT level comparison; subset of patients received placebo to control for OT effects	NR	608(47.2) $n_{OT(ith)}$ = 337 $n_{PBO(ith)}$= 77 $n_{OT(IV)}$= 151 $n_{PBO(IV)}$ = 43 Breakdown of age not reported	38.3% of patients	N/A	Examined but not reported in study
Wang, 2013	Chronic Headache and migraine (Improvement in pain). Baseline OT was measured from Plasma and CSF	Intranasal (100, 200 or 400μg/kg) administrations of OT	Complete, partial or. no remission rated using self-report.	Healthy controls recruited and placebo administered	HC:103(45.6)	112 (44.5)	59.22% (CTRLs); 56.25% (PTs)	N/A	N/A
				Observational Studies (Included in meta-analysis and narrative review)					
					Controls	Patients			
Anderberg, 2000	Fibromyalgia;	Fating morning Plasma levels of OT assessed twice (14-days apart)	Daily pain ratings correlated	Healthy Controls	HC:30(mean age controls not provided)	39(48.6)	100% in both groups	0 (HCs) 17 (PTs)	Correlations Examined qualitatively

			with levels of OT						
Alfvén, 2004	Pediatric chronic abdominal pain	Fasting morning Plasma levels of OT assessed	VAS ratings of pain intensity, frequency and duration correlated with OT levels	Healthy Controls	HC:79 (10.9)	n_{TOT} = 48 (9.6) $n_{RAP\text{-}P}$= 32 $n_{RAP\text{-}N}$=9 n_{FU}=25 n_{IBD}=15	62.03% (HCs) 75% (PTs)	N/A	N/A
Alfvén, 1994	Pediatric chronic abdominal pain	Fasting morning Plasma levels of OT assessed	Plasma OT levels compared across controls and patients	Healthy Controls	HC: 34(11)	40 (10)	55.88% (HC) 47.5% (PTs)	N/A	N/A
Clark, 2020 [a]	Fibromyalgia (Improvement in pain)	Measured Salivary Oxytocin levels pre and post animal assisted therapy or control therapy.	NRS taken pre and post treatment	Patients randomized to non-animal assisted therapy control group	PBO: 110(43.99)	111(43.03)	92.73% (CTRL); 91.89% (patients)	N/A	Correlations Examined qualitatively
Bazzichi, 2013 [a]	Fibromyalgia (Improvement in pain)	Measured plasma Oxytocin pre and post balneotherapy vs. mud-bath therapy.	VAS taken pre and post treatment	No healthy controls. Patients randomized to mud-bath therapy (i.e. not balneotherapy)	21 (52.81)	20 (54.00)	95.24% (CTRL); 95% (patients)	7 (CTRL), 4 (PTs)	N/A

Boström, 2019[a]	Treatment-refractory EM and CM (Improvement in chronic pain condition)	Measured salivary Oxytocin levels pre and post treatment (i.e. vagus nerve stimulation)	VAS taken pre and post treatment	Age and sex matched healthy controls	14 (46.9) Only 12 included in analyses	12 (47.6)	100% (CTRL); 100% (patients)	0 (CTRL), 9 (PTs)	Examined qualitatively

BPI-SF = Brief Pain Inventory-Short Form; CBP = Chronic Back Pain; CSF = Cerebrospinal Fluid; CTRL = Control; CM = Chronic Migraine; DASS: Depression Anxiety Stress Scale; EM= Treatment-refractory episodic migraine; FU=Follow Up; HC = Healthy Controls; IBD = Irritable bowel disease; ith = intrathecal; IV= intravenous; IU= International Units; N/A = Not Available (denotes information that was not reported); NRS = Numeric Rating Scale; NR = Not reported; OT = Oxytocin; PGWB = Psychological General Well-being Scale; PBO = Placebo; PT = Patients; RAP = Recurring abdominal pain; RAP-P = RAP of Psychosomatic origin; RAP-N = RAP non psychosomatic origin; TOT= Total. GSRS = Gastrointestinal Symptoms Rating Scale; VAS = Visual analogue scale; VASPI – Visual analogue scale of pain intensity;
An * indicates that the control group is the same as the treatment group and were randomized to placebo.
[a] indicates that the study was an RCT, but only data from observational assessments were included in this thesis.
Note. 40 IE of OT is equivalent to 24 IU.
Note. Percentage of participants affected by a mood disorder refers to a clinically significant/ diagnosed mood disorde

Table 2

Summary of the Results of Risk of Bias Assessment Using the CASP Checklist.

Item	
CASP for RCTs	
Did the study address a clearly focused research question?	
Was the assignment of participants to interventions randomised?	
Were all participants who entered the study accounted for at its conclusion?	
Were the participants 'blind' to the intervention they were given?	
Were the investigators 'blind' to the intervention they were giving to the participants?	
Were the people assessing/analysing outcome/s 'blinded'?	
Were the study groups similar at the start of the randomised controlled trial?	
Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?	
Were the effects of intervention reported comprehensively?	
Was the precision of the estimate of the intervention or treatment effect reported?	
Do the benefits of the experimental intervention outweigh the harms and costs?	
Can the results be applied to your local population/in your context?	
Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	
CASP for Observational Studies	
Did the study address a clearly focused issue?	
Was the cohort recruited in an acceptable way?	
Was the exposure accurately measured to minimise bias?	
Was the outcome accurately measured to minimise bias?	
Have the authors identified all important confounding factors?	
Have they taken into account of the confounding factors in the design and/or analysis?	
Was the follow up of subjects complete enough?	
Was the follow up of subjects long enough?	
Do the results of this study fit with other available evidence?	
Do you believe the results?	
Can the results be applied to the local population?	

Items answered as "Yes" are represented by green squares; Items answered as "Can't Tell" are represented by orange squares; Items answered as "No" are represented by red squares. 8 Randomized controlled studies were included, and 6 observational studies were included. Top row divides remaining space into 8 equal portions representing the 8 included RCTs. Only categorical items from the CASP checklist used to evaluate observational studies was included here.

Table 3

Grouping of studies for Narrative Synthesis.

First Author, Year	Outcome	Type of Effect-size	Effect Size [95%CI]
		Primary Outcomes	
Boll, 2020 Lincoln, 2017 Louvel, 1996	Pain-intensity (Boll, Lincoln) and pain threshold (Louvel)	Individual effect sizes	Boll: *d* = 0.57 [-0.02, 1.16] Lincoln: *d*= 0.16 [-0.72, 0.41] Louvel: *d*= 1.21 [0.50, 1.29]
Yang, 1994 Wang, 2013	Presence of pain relief	Odds ratio at the mid-level dosage of intravenous and intrathecal OT	Yang: Intravenous; *OR*= 1 [0.061, 16.521] Intrathecal; *OR* = 1646.21 [167.209, 16216.350] Wang:Intranasal; *OR* = 57.00 [6.655, 488.228]
		Secondary Outcomes	
Flynn, 2020 Mameli, 2014 Ohlsson, 2005	Change in depressed mood	Mean difference of the mean differences between depression ratings in OT and PBO (i.e. [postOT-preOT]- [postPBO-prePBO])	Flynn: *d* = 0.22 [-0.58, 1.02] Mameli: *d* = 0.05 [-0.71, 0.80] Ohlsson: *d* = -0.16 [-0.76, 0.44]
Flynn, 2020 Mameli, 2014 Ohlsson, 2005	Change in anxious mood	Mean difference of the mean differences between anxiety ratings in OT and PBO (i.e. [postOT-preOT]- [postPBO-prePBO])	Flynn: *d* = 0.09 [-0.72, 0.88] Mameli: *d* = -0.13 [-1.13, 0.39] Ohlsson: *d* = -0.147 [-0.45, 0.75]
Clark, 2020 Anderberg, 2000	Association between anxiety and OT levels	Separate correlations between self-reported anxiety ratings on a 10-point scale and OT levels in patients for each study	Clark:*r* = 0.02 Anderberg: *r* = -0.46

HC= Healthy Control; OT = Oxytocin; PBO = Placebo; Post = Self-report ratings of pain, anxiety and depression after Oxytocin administration; Pre = Self-report ratings of pain, anxiety and depression before Oxytocin administration; PT: Patient; r = Spearman's Correlation Coefficient; SMD (*d)* = Standardized mean difference (effect sizes calculated such that positive values favour the effect of oxytocin).

Table 4

Mean endogenous oxytocin concentrations in chronic pain patients versus healthy controls.

First Author, Year	Plasma OT Level (pmol/L)		Summary of Results
	Healthy Controls (Mean ± SD)	Chronic Pain Patients (Mean ± SD)	
Wang, 2013	9.43 ± 2.32	18.95 ± 4.83*	Higher Plasma OT levels in patients
Bostrom, 2019	20.4 ± 1.7	44.2 ± 10.1*	Higher Plasma OT levels in patients
Alfvén, 2004	45.00 ± 15.42	30.50 ± 17.17*	Lower Plasma OT levels in patients
Alfvén, 1994	63.00 ± 26 .00	24.00 ± 15.00*	Lower Plasma OT levels in patients
Yang, 1994	28.10 ± 4.10	8.80 ± 3.40*	Lower Plasma OT levels in patients
Anderberg, 2000	NR	NR	The difference between plasma OT levels in HCs and PTs was not significantly different (p=0.55). The distribution of plasma OT levels in PTs was larger than that of HCs.

NR = Results were not reported, not able to be calculated or obtained;
* statistically significant difference between OT levels in Healthy controls and Chronic pain patients ($p < 0.01$)
[a] denotes studies that used methods other than plasma to measure endogenous oxytocin

Figures

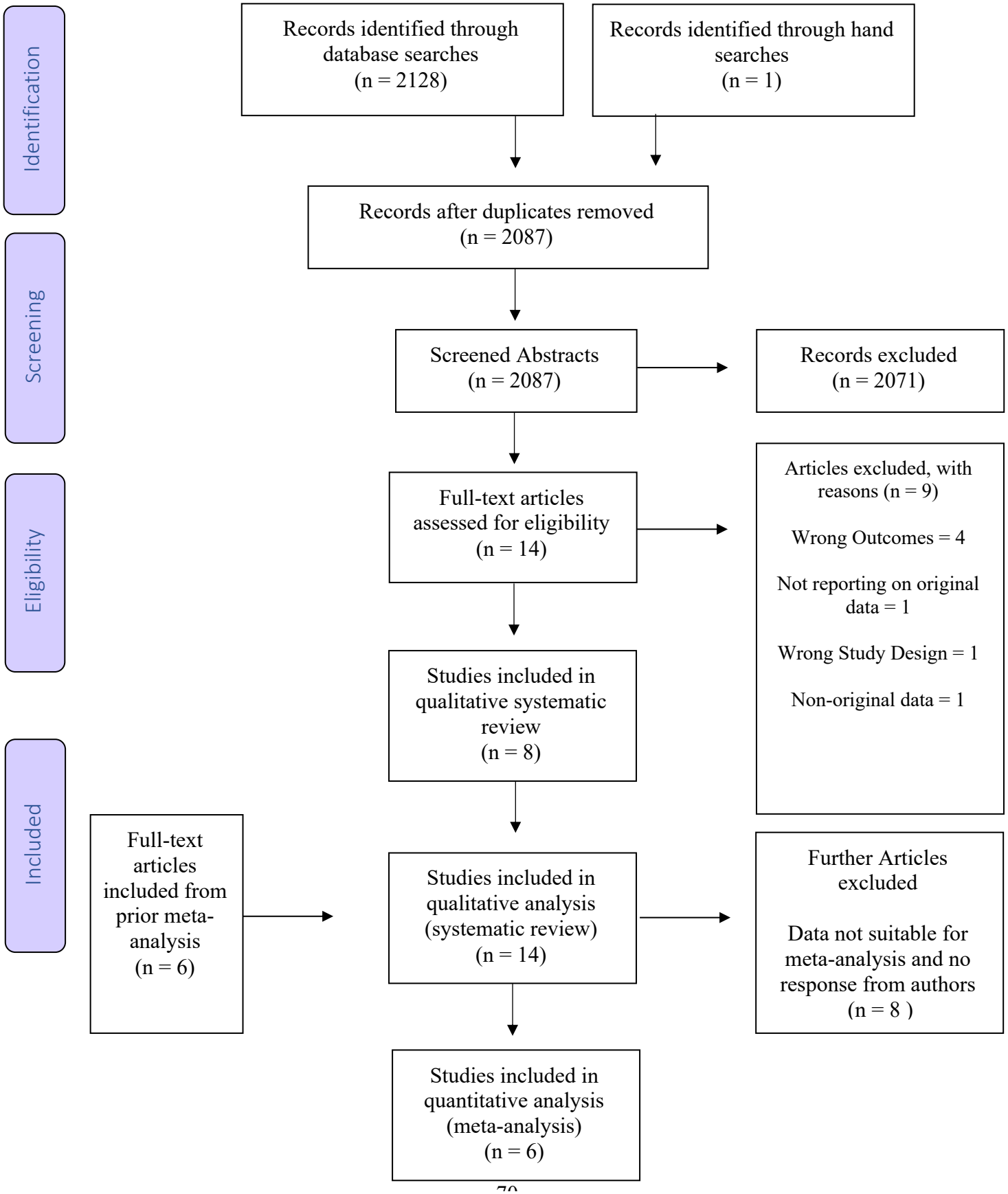


Figure 1. PRISMA flow chart of studies included and excluded throughout each phase of the systematic review.

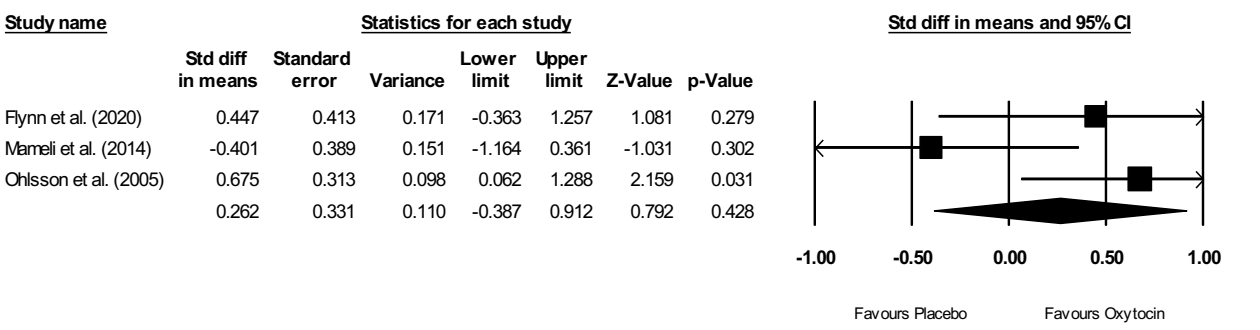


Figure 2. Change in self-reported pain ratings after oxytocin or placebo administration. Positive values represent a change favouring oxytocin.

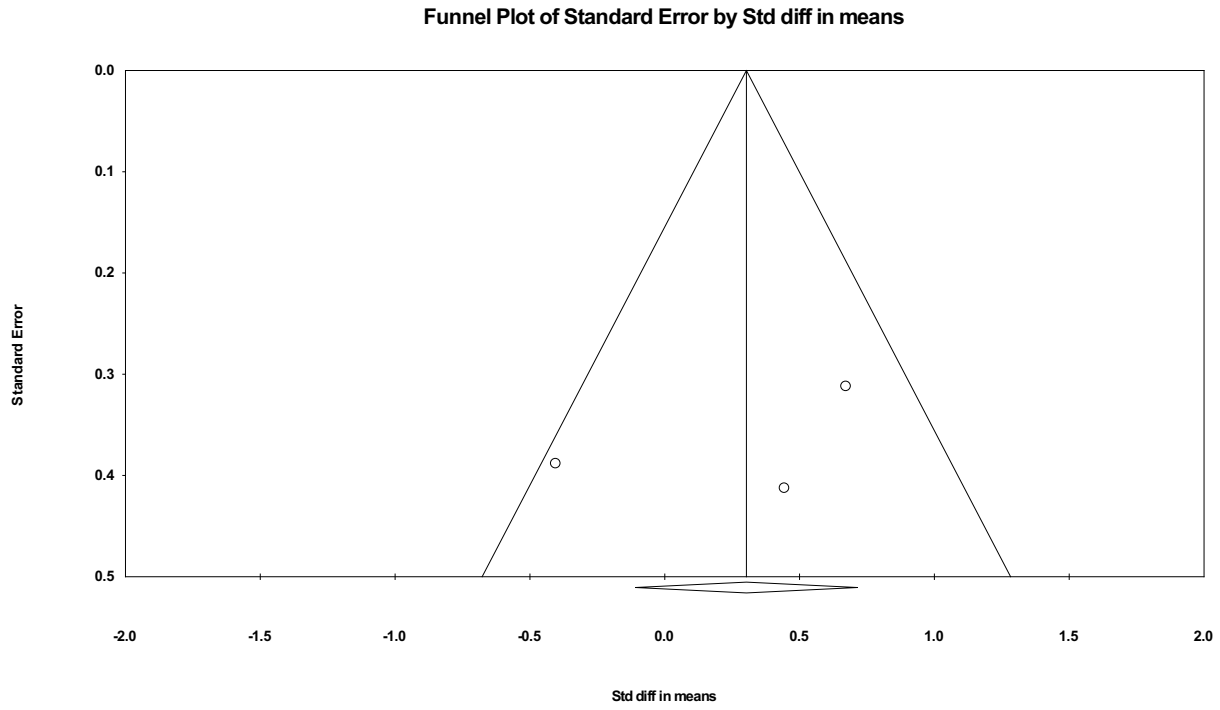


Figure 3. Funnel plot of standard error by the standardized mean difference for pain intensity ratings from pre to post treatment with oxytocin and placebo.

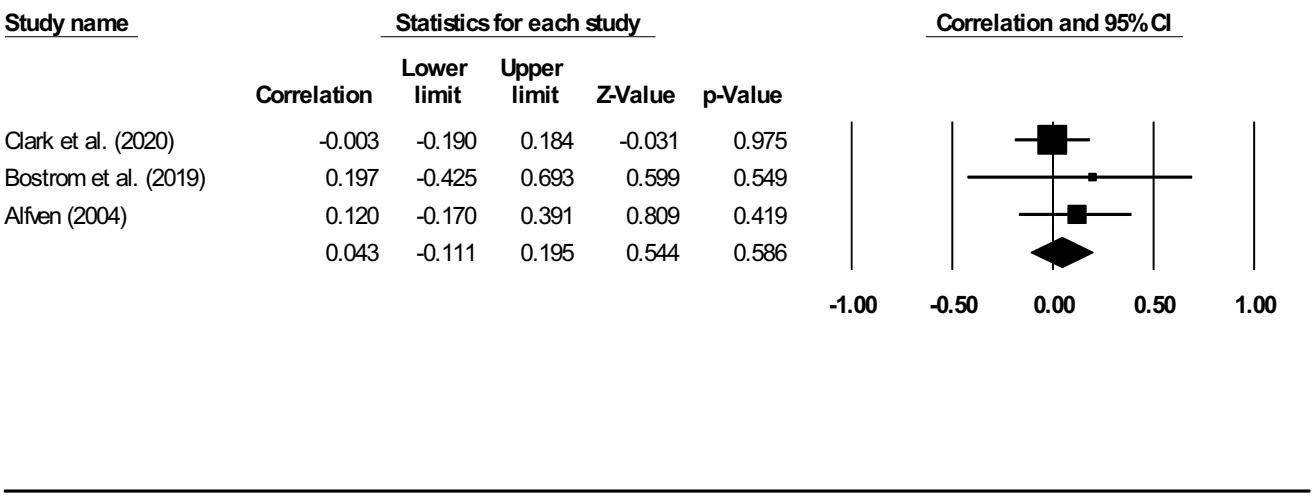
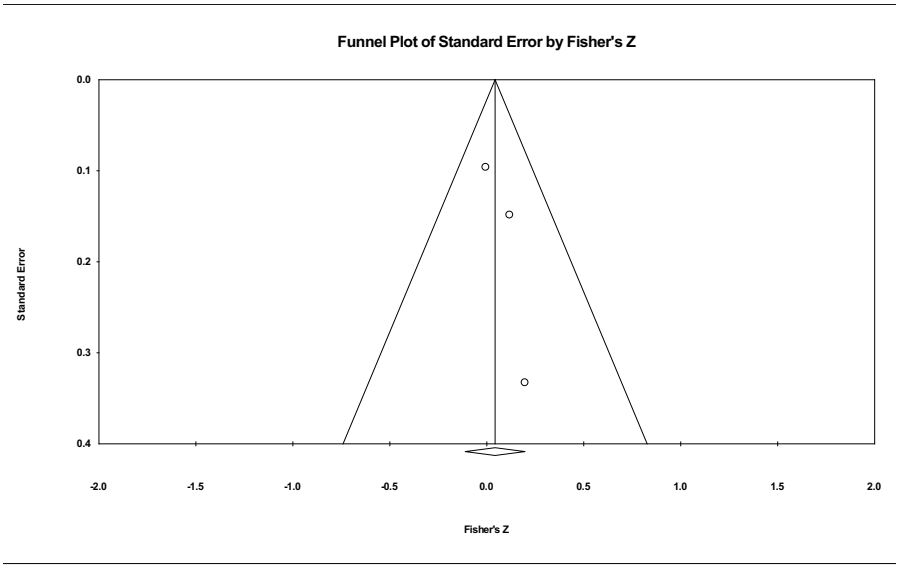


Figure 4. Correlation between self-reported ratings of pain intensity and basal oxytocin concentration.

a)



b)

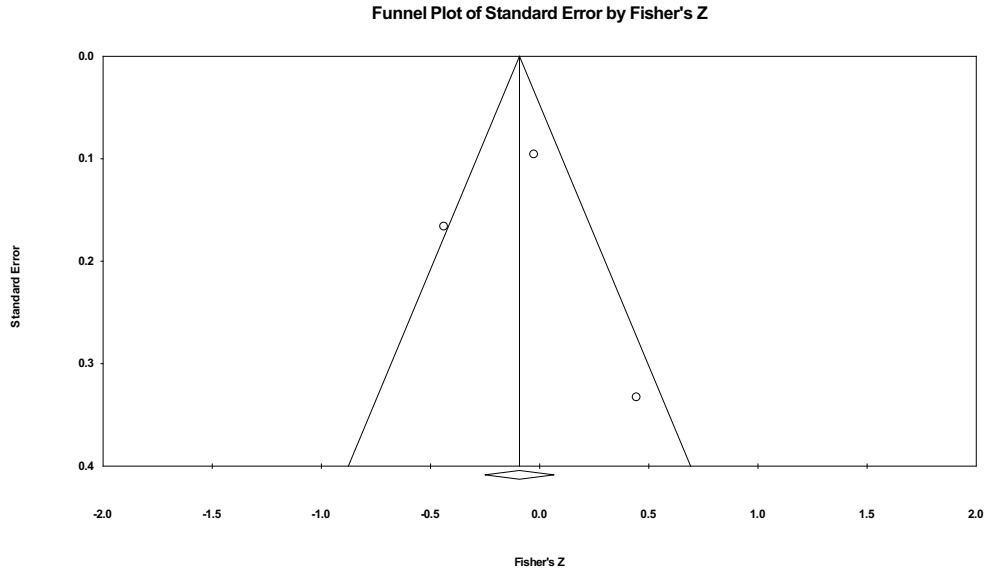


Figure 5. a) Funnel plot of standard error by Fisher's Z for the association between basal oxytocin concentrations and self-reported ratings of pain. b) Funnel plot of standard error by Fisher's Z for the association between basal oxytocin concentrations and self-reported ratings of depressed mood.

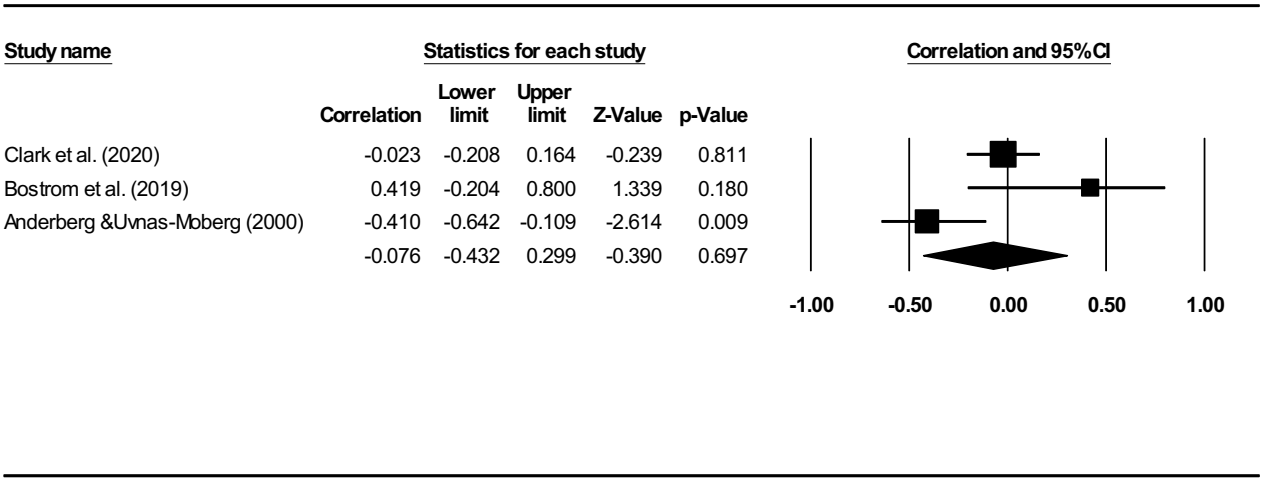


Figure 6. Correlation between self-reported ratings of depressed mood and basal oxytocin concentration.

Appendix 1. *Database Search Strategies*

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to February 23, 2021>
Search Strategy:

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1 exp Pain/ (405260)
2 Analgesia/ (20224)
3 Nociception/ (2859)
4 Pain Management/ (35715)
5 (pain or analgesia or nociception).tw,kf. (691951)
6 Oxytocin/ or Receptors, oxytocin/ (20986)
7 (oxytocin or syntocinon or pitocin).tw,kf. (24215)
8 1 or 2 or 3 or 4 or 5 (847035)
9 6 or 7 (28487)
10 8 and 9 (1396)
11 from 10 keep 1-24,28-46,48-565,567-568 (563). (this is Jan 1 2012 – Feb 23, 2021)

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Embase®

Embase Session Results

No.	Query	Results
#8	#5 AND #6 AND [2012-2021]/py	1,680
#7	#5 AND #6	3,605
#6	#3 OR #4	42,115
#5	#1 OR #2	1,732,917
#4	oxytocin:ti,ab OR syntocinon:ti,ab OR pitocin:ti,ab	28,507
#3	'oxytocin'/exp OR 'oxytocin receptor'/exp	37,947
#2	pain:ab,ti OR analgesia:ab,ti OR nociception:ab,ti	1,012,513
#1	'pain'/exp OR 'analgesia'/de OR 'nociception'/de OR 'hyperalgesia'/exp OR 'hypoalgesia'/exp	1,469,550

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MY

EBSCOhost

Wednesday, February 24, 2021 11:00:13 AM

#	Query	Limiters/Expanders	Last Run Via	Results
S9	S4 AND S7	Limiters - Publication Year: 2012-2021 Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	106
S8	S4 AND S7	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	210
S7	S5 OR S6	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	Display
S6	TI (oxytocin or syntocinon or pitocin) OR AB (oxytocin or syntocinon or pitocin)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	Display
S5	DE "Oxytocin"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	Display
S4	S1 OR S2 OR S3	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	Display
S3	TI (pain or analgesia or nociception) OR AB (pain or analgesia or nociception)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	Display
S2	DE "Pain Perception" OR DE "Analgesia" OR DE "Pain Management"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	Display
S1	DE "Migraine Headache" OR DE "Muscle Contraction Headache" OR DE "Trigeminal Neuralgia" OR DE "Pain" OR DE "Acute Pain" OR DE "Aphagia" OR DE "Back Pain" OR DE "Chronic Pain" OR DE "Headache" OR DE "Myofascial Pain" OR DE "Neuralgia" OR DE "Neuropathic Pain" OR DE "Somatoform Pain Disorder"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	Display

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EBSCOhost

Wednesday, February 24, 2021 10:51:02 AM

#	Query	Limiters/Expanders	Last Run Via	Results
S8	S5 AND S6	Limiters - Published Date: 20120101-20211231 Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	262
S7	S5 AND S6	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	468
S6	S3 OR S4	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	Display
S5	S1 OR S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	Display
S4	TI (oxytocin or syntocinon or pitocin) OR AB (oxytocin or syntocinon or pitocin)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	Display
S3	(MH "Oxytocin")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	Display
S2	TI (pain or analgesia or nociception) OR AB (pain or analgesia or nociception)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	Display
S1	(MH "Pain+") OR (MH "Analgesia") OR (MH "Pain Management")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	Display

Appendix 2. *Pre-registered PROSPERO protocol*

Evaluating the efficacy of oxytocin for pain management: An updated systematic review and meta-analysis

Joshua Rash, Anastasia Mekhael, Jennifer Bent, Alison Farrell

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided **here**.

Citation

Joshua Rash, Anastasia Mekhael, Jennifer Bent, Alison Farrell. Evaluating the efficacy of oxytocin for pain management: An updated systematic review and meta-analysis. PROSPERO 2021 CRD42021234926 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021234926

Review question

What is the association between oxytocin and pain among adults who experience chronic non-cancer pain. Specific Questions to be addressed:
1. Is there an association between oxytocin and pain among individuals with chronic non-cancer pain?
2. Is there an association between oxytocin and function among individuals with chronic pain?
3. Do observed associations differ between children and adults?
4. Do observed associations differ between various chronic pain conditions?

Searches

A preliminary search strategy was created with the guidance of an information specialist (Refer to Appendix A for a sample search). An independent information specialist then peer-reviewed the strategy prior to implementation using the Peer Review for Electronic Search Strategies (PRESS) checklist43. we searched four bibliographic databases: 1) Ovid MEDLINE® (2012 to February 25, 2021), excluding indexed citations for conference abstracts and posters; 2) Embase (2012 to February 25, 2021); 3) PsycINFO (2012 to February 25, 2021); and 4) CINAHL (2012 to February 25, 2021). The ClinicalTrials.gov website was also searched for ongoing studies of potential relevance. Studies before 2012 will be excluded as they have been included in the analyses of Rash et al., (2014)30, whose findings this study aims to extend, and not overlap.

Search strategy

https://www.crd.york.ac.uk/PROSPEROFILES/234926_STRATEGY_20210511.pdf

Types of study to be included

Controlled, non-controlled, and observational studies will be eligible for inclusion in order to gain a more comprehensive understanding of the effects of oxytocin on pain and to assess its efficacy as a potential analgesic.

Condition or domain being studied

Chronic non-cancer pain

Participants/population

Adults suffering with chronic non-cancer pain.

Intervention(s), exposure(s)

We will extend our previous systematic review examining the relationship between oxytocin and pain (Rash et al., 2014)30. Our primary interest was to quantify the association between oxytocin and pain, and the effect of oxytocin administration on the experience of pain.

Comparator(s)/control

Any study evaluating the association between oxytocin and pain, including controlled and observational studies.

Context

The following inclusion criteria will be applied, and studies will be included if they:
• Report on human subjects.
• Are Peer reviewed.
• Assess the association between oxytocin and pain.
• Report on original data.
• Include participants with a primary diagnosis of chronic non-cancer pain.

Studies will be excluded if they:
• Report on patients with chronic pain related to cancer
• Report on labour and birth related pain as oxytocin is often used to induce labour 44 and oxytocin might be present in higher-than-normal levels during childbirth.
• Include participants who have had a portion of the brain removed as these surgeries may have effects on pain perception and the potential effects of oxytocin.
• Delayed pain testing for longer than 3 hours after oxytocin administration to ensure maximum concentration upon measurement of pain as it has been reported that central oxytocin concentration peeks between 30-60 minutes after external administration.

Main outcome(s)

The primary outcomes of interest will be the association between oxytocin, pain and physical function.

Measures of effect

Standardized mean difference.

Additional outcome(s)

Secondary outcomes include emotional functioning (e.g., depressed mood).

Measures of effect

Standardized mean difference.

Data extraction (selection and coding)

Searches will be conducted, duplicates removed, and results imported into the "Covidence" online citation manager for systematic reviews. Two independent reviewers (one Master's level graduate student and a trained Undergraduate research assistant) will screen search results against eligibility criteria using a 2-step procedure: 1) screening of title and abstract; and 2) potentially relevant papers will be retrieved and screened in full-text. Disagreements between reviewers will be resolved through consensus, or mediation by an arbiter will be used. Agreement between reviewers will be calculated using the Cohen's Kappa statistic.

The study selection/exclusion process will be documented using a PRISMA flow chart. Data extraction will be completed using a predefined rubric. Interpreters will be recruited to translate non-English language studies as needed. The following information will be extracted from full-text review: 1) journal article information (author's names, country, journal, DOI, publication year); 2) Methodological information (i.e. design, method of OT administration or assessment, standardized and study-specific measures, duration, and potential shortcomings/limitations in the methodology, comparison type); 3) sample characteristics (i.e. sample size, age, sex, recruitment, unique sample characteristics, type of chronic pain, history with chronic pain); and 4) Results (e.g., means and standard deviations reflecting change in pain and function, correlation between OT measurement and pain or function, missing data). Extractions will be compared across raters to ensure accuracy. Discrepancies will be resolved by consensus or arbitration by a third reviewer.

Risk of bias (quality) assessment

Risk of bias for randomized- controlled studies will be assessed using the Critical Appraisal Skills Program (CASP) tool for randomized-controlled trials. The domains assessed include appropriateness of design, randomization, blinding, attrition and handling of missing data, participant similarity pre-treatment, adequacy of statistical reporting, reporting precision of estimated effects, and potential impact. Non-randomized-controlled studies will be assessed using this tool with items pertaining to randomization omitted. Risk of bias in observational studies will be the CASP appraisal tool for cohort studies. The domains include adequacy of recruitment, accuracy of

exposure, accuracy of assessing outcomes, identification and handling of potential confounds, adequacy of follow-up, reporting of results, precision of results, and potential impact. Questions pertaining to the above domains will be answered using, “Yes”, “No” or “Can’t tell”. Methodological quality and risk of bias assessment will be conducted independently by the same two reviewers. Discrepancies will be resolved by consensus or arbitration by a third reviewer. Quality of assessment will be depicted using a table and authors of studies assessed will be contacted for clarification when insufficient evidence is reported to assess risk of bias.

Strategy for data synthesis

Included studies will be categorized according to study design. Frequencies and percentages will be reported for categorical variables evaluated in the included studies. Means and standard deviations (SDs) or median and interquartile range will be reported for continuous data (e.g., ratings of pain). The effect size convention used for studies reporting on strength of association will be quantified using r. The effect size conventions for studies reporting on differences between means will be separately calculated using standardized mean differences. Effect size calculations will be performed using formulae reported in Lipsey and Wilson (2001). Random effects meta-analyses will be conducted for outcomes reported on by three or more studies. Meta regression will be performed for outcomes in which ten or more studies report and evaluate the following as potential moderators of effect: 1) Age; 2) Chronic pain condition; and 3) Risk Bias. Meta-analysis will be performed using Comprehensive Meta-Analysis software (CMA). Evidence for publication bias will be assessed through visual inspection of the funnel plots, and fail-safe Ns will be calculated using Orwin’s formula with the recommended criterion of effect size of 0.20.

Analysis of subgroups or subsets

Subgroup analyses will be performed by chronic pain condition using meta-regression should sufficient studies be identified.

Contact details for further information

Joshua Rash
jarash@mun.ca

Organisational affiliation of the review

Memorial University of Newfoundland

Review team members and their organisational affiliations

Dr Joshua Rash. Memorial University of Newfoundland
Ms Anastasia Mekhael. Memorial University of Newfoundland
Ms Jennifer Bent. Memorial University of Newfoundland
Ms Alison Farrell. Memorial University of Newfoundland

Collaborators

Dr Tavis Campbell. University of Calgary
Dr Jonathan Fawcett. Memorial University of Newfoundland

Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

01 April 2021

Anticipated completion date

31 August 2021

Funding sources/sponsors

This review is not funded.

Conflicts of interest

Language

English

Country

Canada

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

10 June 2021

Date of first submission

11 May 2021

Details of any existing review of the same topic by the same authors

Rash, J. A., Aguirre-Camacho, A., & Campbell, T. S. (2014). Oxytocin and pain: a systematic review and synthesis of findings. The Clinical journal of pain, 30(5), 453-462.

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

10 June 2021
10 June 2021

PROSPERO
This information has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. The registrant confirms that the information supplied for this submission is accurate and complete. CRD bears no responsibility or liability for the content of this registration record, any associated files or external websites

Appendix 3. *Prisma Checklist*

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	i
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	ii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	15
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	15
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	16
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	18
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	75
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	18
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	18-19
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	20-21
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	18
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	19
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	20-21
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	20,22
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	20
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	22
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed,	20

Section and Topic	Item #	Checklist item	Reported on page #
		describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	21
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	20
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	22
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	21
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	23, 69
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	23
Study characteristics	17	Cite each included study and present its characteristics.	61
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	25,65
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	26-29
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	26,27
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	26,27
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	26,27
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	26,27
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	31-39
	23b	Discuss any limitations of the evidence included in the review.	40
	23c	Discuss any limitations of the review processes used.	42
	23d	Discuss implications of the results for practice, policy, and future research.	42-43
OTHER INFORMATION			
Registration	24a	Provide registration information for the review, including register name and registration number, or state that the review was	16

Section and Topic	Item #	Checklist item	Reported on page #
and protocol		not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	16, 76
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	!!!!!!
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Appendix 4. *List of Inclusion and Exclusion Criteria*

Inclusion Criteria

1. Controlled studies or observational studies
2. Peer reviewed
3. Assess the relationship between OT and pain
4. Original data
5. Diagnosis of chronic pain

Exclusion Criteria

1. Patients with chronic pain related to cancer
2. Studies with participants who have had a large portion of the brain removed
3. Studies that delayed pain testing for longer than 3 hours after OT administration
4. Missing Info-no response from Authors
5. Wrong study design
6. Wrong patient population
7. Wrong outcomes
8. Wrong intervention