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Oxytocin in Chronic Pain: From Analgesic to Biopsychosocial Adjuvant—An Opinion Paper

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Abstract

Chronic pain remains a major clinical challenge, with current treatments often providing insufficient relief. Oxytocin, classically recognized for its roles in reproduction and social bonding, has gained increasing attention for its potential involvement in pain modulation. Evidence suggests that oxytocin influences both nociceptive processing and broader dimensions of pain, including stress regulation, emotional appraisal, and coping. Despite this promise, clinical findings remain mixed. In this opinion paper, we summarize and discuss the rationale and current clinical evidence for the role of oxytocin in chronic pain (management), highlighting key research gaps and outlining future directions focused on: endogenous oxytocin system variability, biological modulators of its effects, dosing and timing strategies, and the role of psychosocial context. We propose that oxytocin should be reconceptualized not as a straightforward analgesic, but as a biopsychosocial adjuvant that strengthens resilience and coping. Positioning oxytocin within this framework may clarify for whom, when, and under what conditions oxytocin can be most effective, and ultimately guide its translational potential in chronic pain management.

Keywords: oxytocin; chronic pain; biopsychosocial framework

Introduction

Chronic pain remains one of the most pressing challenges in medicine, not only because of its sheer prevalence, but also because of the suffering it imposes on individuals and its vast socio-economic burden [1,2]. Despite advances in pharmacological, cognitive and behavioral therapies, many patients continue to experience inadequate relief [3]. The ongoing search for new strategies has drawn attention to oxytocin, a neuropeptide commonly known as the "bonding hormone", but also increasingly considered for its potential to modulate pain, raising the question of how oxytocin might help shape the way pain is processed and managed.

Oxytocin is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus [4]. From there, it is transported to the posterior pituitary, where it can be released into the bloodstream to exert peripheral hormonal effects, including uterine contractions and lactation [5]. Oxytocin also has documented anti-inflammatory and immunomodulatory properties, reducing the production of pro-inflammatory cytokines [6,7]. In addition to its peripheral roles, oxytocin is also released centrally, where it modulates neuronal activity through dendritic secretion and direct axonal projections [4]. This enables diffusion into multiple brain regions, where it plays a role in

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neurophysiological processes and supports a wide range of social functions including trust, empathy, social bonding, and the recognition of social cues [8–11].

Beyond its well-established reproductive, anti-inflammatory and social functions, oxytocin has been increasingly implicated in the modulation of pain [12,13]. Preclinical and some human studies suggest that oxytocin exerts analgesic effects by acting on both spinal and supraspinal levels [12,14–16]. At the spinal level, oxytocin modulates nociceptive input via projections to the dorsal horn, where oxytocin-receptors are expressed in dorsal root ganglia [15,17,18]. Oxytocin binding can suppress nociceptive signaling and inhibit sensitization, reducing pain transmission [16,19]. In supraspinal circuits, oxytocin modulates activity within regions central to pain perception and emotional appraisal, including the prefrontal cortex, anterior cingulate cortex, and amygdala [20–22]. Notably, oxytocin's role in thalamic modulation of sensory pain remains limited, suggesting its primary effects may be on cognitive and affective dimensions of pain processing [16].

Oxytocin's role in regulating stress and social behavior provides an additional mechanism through which it may impact pain perception. By promoting prosocial interactions, reducing stress reactivity, and enhancing coping mechanisms, oxytocin contributes to the biopsychosocial regulation of pain, **see** Figure 1 [10,23]. These findings align with the increasing recognition that chronic pain is best understood through a biopsychosocial framework, a perspective that views pain as the result of dynamic interactions among biological processes (such as tissue injury and neuroplasticity), psychological factors (including cognition, mood, and coping strategies), and social influences (such as support systems) [24,25]. This highlights the importance of addressing emotional and social factors alongside biological factors when assessing and managing pain.

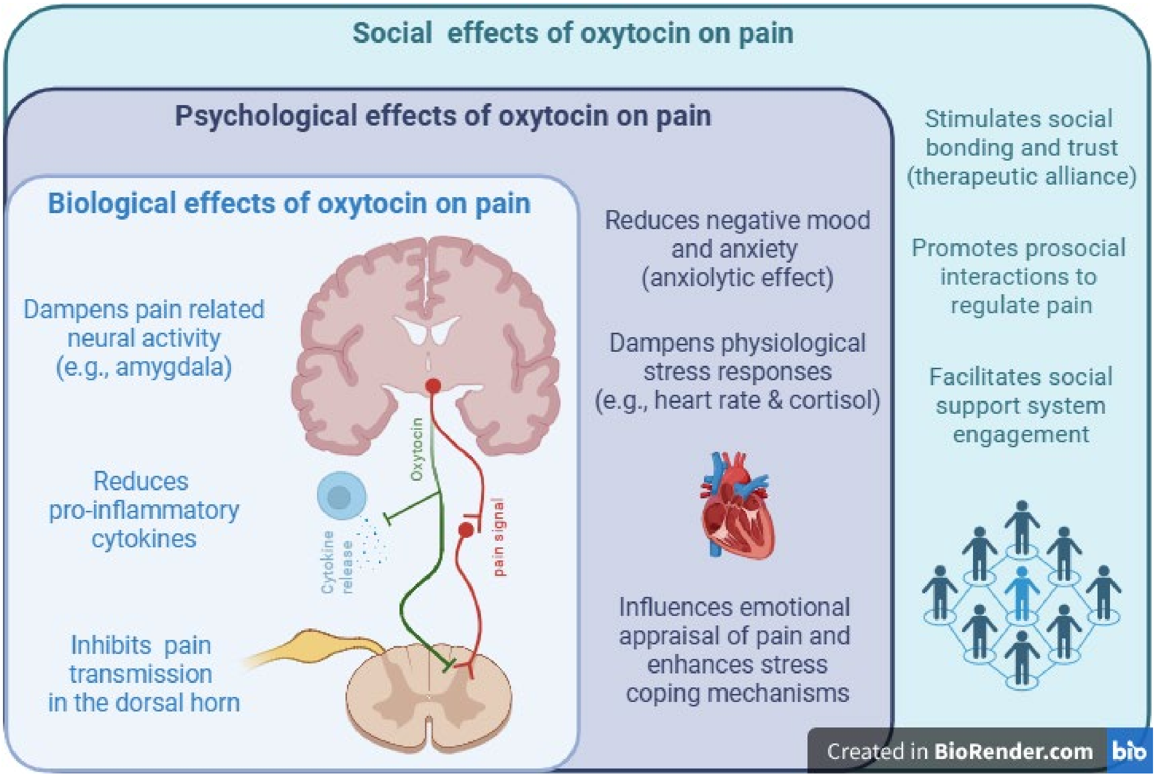

Figure 1. Oxytocin's role in the biopsychosocial framework of pain.

Clinically, interest has grown in exogenous administration of oxytocin, particularly through intranasal delivery, which is non-invasive, allows flexible dosing, and provides a potential pathway for central nervous system effects. However, only few studies to date have investigated the use of intranasal oxytocin in chronic pain conditions and these demonstrated mixed findings on efficacy [26,27]. Despite promising preclinical results, results from human studies remain inconsistent and endogenous oxytocin levels appear to vary across chronic pain conditions [13]. These inconsistencies

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do not necessarily undermine oxytocin's potential but rather highlight the complexity of the system: oxytocin not only dampens nociception but also shapes stress responses, emotional appraisal, and coping strategies [7,10,16]. Put differently, oxytocin may matter less for *blocking nociceptive signals* and more for *how pain is experienced and managed* [16].

Here we argue that oxytocin represents a biopsychosocial relevant candidate for chronic pain management. We summarize and critically discuss current clinical evidence, highlight key research gaps and outline directions for future research to clarify for whom, when, and under what conditions oxytocin may be most effective.

Current Clinical Evidence of Oxytocin's Role in Chronic Pain

Over the past decades, clinical studies exploring oxytocin in the context of chronic pain have yielded intriguing but often inconsistent findings. Investigations have examined both endogenous oxytocin levels and the effects of exogenous oxytocin administration across various chronic pain conditions. The following section highlights studies investigating the role of oxytocin in individuals with chronic migraine, chronic musculoskeletal pain, fibromyalgia, and chronic abdominal pain. A summary can be found in Table 1.

Table 1. Summary of the current clinical evidence of oxytocin's role in chronic pain.

PAIN TYPE	ENDOGENOUS OXYTOCIN FINDINGS	EXOGENOUS OXYTOCIN ADMINISTRATION FINDINGS
CHRONIC MIGRAINE	**Elevated oxytocin** in chronic migraine (♀/♂; aged 19-64; Wang et al., 2013), (♀; aged 22-65; Boström et al., 2019). **No significant difference** in plasma oxytocin, but trend toward elevation in migraine group (♀/♂; mean age 18.7; You et al., 2017).	**Intranasal oxytocin reduces headache frequency and pain** in dose-dependent manner; higher doses yield stronger relief (♀/♂; aged 19-64; Wang et al., 2013), (♀/♂; age not mentioned; Tzabazis et al., 2017).
CHRONIC MUSCULOSKELETAL PAIN	**Reduced plasma oxytocin** concentrations in chronic low back pain; **elevated oxytocin in cerebrospinal fluid** (♀/♂; mean age 47.3; Yang et al., 1994). Most studies focus on exogenous oxytocin only.	Intranasal and intrathecal oxytocin administration yields **pain reduction in chronic back pain and pelvic pain** (♀; mean age 38; Flynn et al., 2020), (♂; mean age 36.8; Boll et al., 2020), (♀/♂; mean age 47.3; Yang et al., 1994). **In women with chronic neck/shoulder pain, oxytocin may increase pain** (♀/♂; aged 18-60; Tracy et al., 2017). Dose/sex/context-specific responses are possible, but robust **pain attenuation** has been shown (♂; aged 18-65; Schneider et al., 2020), (♂; mean age 36.8; Boll et al., 2020).
FIBROMYALGIA	**Elevated oxytocin** in fibromyalgia, especially in those with high symptom burden (♀; aged 40-65; Otero et al., 2023). **No difference** to controls—greater variability observed (♀; aged 27-61; Anderberg et al., 2000).	**Intranasal oxytocin does not lead to significant pain reduction**; effect possibly masked by concurrent NSAID use and receptor desensitization (♀; aged 18-70; Mameli et al., 2014).
CHRONIC ABDOMINAL PAIN	**Reduced plasma oxytocin** in recurrent abdominal pain; lower oxytocin associated with ongoing	**Intranasal oxytocin increased pain thresholds and reduced pain sensitivity** (♂; aged 24-63) (Louvel et al. 1996).

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	pain (♀/♂; aged 6-17; Alfvén et al., 1994; Alfvén, 2004)	**Oxytocin showed no significant reductions in abdominal pain or discomfort** (♀; aged 20-70) (Ohlsson et al. 2005).

Chronic Migraine

In chronic migraine, evidence suggests an elevation of endogenous oxytocin in plasma, saliva, and cerebrospinal fluid compared to healthy controls [28,29]. These studies predominantly involved adults aged between 19 and 65 years, with a majority of female subjects, reflecting the higher prevalence of chronic migraine in women. This increase in oxytocin may reflect a compensatory response to neuroinflammation, supported by findings of elevated cytokines in migraine pathophysiology [30,31]. Experimental work indicates that inflammation can upregulate oxytocin-receptor expression on trigeminal neurons, raising the possibility that higher oxytocin levels represent a feedback mechanism aimed at dampening nociceptive activity [32,33].

Clinical studies of exogenous oxytocin administration in migraine—mostly conducted in adults—are limited, but some demonstrate reduced headache frequency or delayed pain relief after intranasal delivery [29,30]. However, replication has been scarce, sample sizes remain small, and variability in outcomes suggests that endogenous pain states, neuroinflammatory load, and patient-specific oxytocin biology may interact with each other to determine treatment efficacy.

Chronic Musculoskeletal Pain

In the context of chronic musculoskeletal pain, endogenous oxytocin levels have, to our knowledge, only been assessed in one study [34]. This study found that men and women with chronic low back pain exhibited significantly lower oxytocin levels in plasma compared to healthy controls, while simultaneously showing elevated oxytocin concentrations in cerebrospinal fluid [34]. These findings suggest a differential regulation or compartmentalization of oxytocin release between central and peripheral systems.

Studies examining oxytocin administration in chronic musculoskeletal pain—including chronic back pain, pelvic pain, and neck/shoulder pain—typically involved adult participants aged 18 to 65 years, with sex distribution varying by condition; for instance, pelvic pain studies included mostly women, and back pain studies often had a higher proportion of men [20,26,27,34,35]. Intrathecal, intranasal, and systemic oxytocin administration have been associated with pain reduction in some contexts [27,34,35] but paradoxical pain enhancement in others, particularly in women with neck and shoulder pain [26]. Neuroimaging evidence further indicates that oxytocin administration in individuals with chronic low back pain modulates activity within key limbic regions such as the nucleus accumbens and caudate nucleus [20], regions known to integrate reward, stress regulation, and pain salience. Importantly, interindividual variability in pain-related brain responses to oxytocin was high, and psychological factors such as fear of pain and hypervigilance accounted for significant variance [20]. These findings underscore the possibility that oxytocin's effects are not uniform but instead shaped by ongoing emotional and cognitive appraisal of pain, aligning with oxytocin's broader role as a modulator of salience and social-emotional integration [8,10].

Fibromyalgia

Oxytocin research in fibromyalgia—a chronic disorder marked by widespread musculoskeletal pain, fatigue, and sleep disturbances—primarily involves adult women aged 18 to 70 years, reflecting its higher prevalence in females and older populations. Endogenous oxytocin levels do not consistently differ between fibromyalgia patients and controls [36,37]. Subgroup analyses reveal both elevated and reduced levels depending on symptom severity, comorbidities, and stress system dysfunction; for example patients with higher symptom burden show significantly lower oxytocin levels [36]. While Otero et al. [37] found that oxytocin levels were elevated in fibromyalgia-only patients compared to controls, with no difference when including those with comorbid chronic

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fatigue syndrome. Possibly, elevated levels of inflammatory cytokines in fibromyalgia may trigger an oxytocin increase as a compensatory anti-inflammatory response, especially within a disrupted hypothalamic-pituitary-adrenal (HPA) axis, as noted by the authors [37].

On the exogenous side, trials—almost exclusively in adult women—have produced largely negative or null results. For example, intranasal oxytocin often fails to reduce clinical pain or pain intensity scores [38]. Trial results may have been confounded by concurrent NSAID treatment, which could suppress oxytocin-receptor regulation by inflammatory signals [39]. Chronic elevations in endogenous oxytocin, as suggested in some patients, raise the possibility of receptor desensitization and diminished responsiveness to exogenous treatment [40]. A unifying theme emerging in fibromyalgia is the heterogeneity across patients, some show elevated baseline oxytocin possibly as a compensatory anti-stress signal [41], while others show reduced levels in relation to severe symptom burden. This variability complicates any straightforward therapeutic expectations.

Chronic Abdominal Pain

Studies on abdominal pain—including recurrent abdominal pain, irritable bowel syndrome (IBS) and inflammatory bowel disease—consistently report lower endogenous plasma oxytocin levels in affected individuals compared to healthy controls. For instance, Alfvén et al. [42] found that children with recurrent abdominal pain exhibited lower plasma oxytocin levels, a pattern that persisted after three months. Similarly, the same group reported decreased plasma oxytocin levels in children with recurrent abdominal pain or inflammatory bowel disease relative to controls [43]. These findings parallel the reduced oxytocin concentrations observed in chronic musculoskeletal pain populations and contrast with elevated oxytocin levels seen in chronic migraine and sometimes in fibromyalgia [42,43].

The administration of exogenous oxytocin, via intravenous, intranasal, or intrathecal routes, generally resulted in increased pain thresholds and reduced pain sensitivity in visceral pain models. Louvel et al. [44] demonstrated that continuous intravenous oxytocin infusions raised first sensation and pain thresholds during descending colon distension in IBS patients. However, clinical trials addressing daily abdominal pain and discomfort show mixed results. For example, Ohlsson and colleagues [45] observed no significant reductions in abdominal pain or discomfort with twice-daily intranasal oxytocin over 13 weeks, only a trend toward improvement. These results resemble the inconsistencies seen in fibromyalgia oxytocin trials and underscore that oxytocin's analgesic efficacy in chronic abdominal pain is highly context- and population-dependent [44,45].

Current Clinical Evidence of Oxytocin's Role in Chronic Pain—Across Studies

Taken together, clinical findings suggest that endogenous oxytocin profiles vary across pain conditions. In chronic migraine and fibromyalgia, elevated plasma oxytocin levels have been reported, possibly reflecting episodic flare-ups accompanied by inflammation that activates compensatory oxytocinergic mechanisms [36,37]. In contrast, chronic musculoskeletal pain has been associated with reduced oxytocin concentrations compared to healthy controls [34], possibly reflecting oxytocin system exhaustion due to the strain of persistent nociceptive input. Interestingly, recurrent abdominal pain has also been linked to lower oxytocin levels, but these findings are based on pediatric populations [42,43]. This raises the possibility that developmental factors play a role, since the oxytocin system is dynamic and known to fluctuate across the lifespan [46]. Indeed, oxytocin signaling appears to peak early in life, drop to lower basal levels during childhood and adolescence, rise again in adulthood, and later show altered receptor sensitivity with aging [46–49]. Considering these pain-condition and developmental variations, it is essential to account for heterogeneity in pain-related oxytocin outcomes.

Across studies, notable sex differences emerge in oxytocin's role in pain, likely influenced by interactions with estrogen, which primes oxytocin synthesis, release, and receptor expression, and fluctuates throughout the menstrual cycle [13]. Women generally show higher endogenous oxytocin levels than men, which may partly explain their differential responses to exogenous administration

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[13,50]. This variability is well captured by an inverted U-shaped dose–response model, where moderate increases are beneficial, but excessive levels, particularly in those with high baseline oxytocin, may result in diminished or adverse effects [51]. For example, Tracy et al. [26] reported that intranasal oxytocin increased pain in women with chronic neck and shoulder pain, illustrating how hormone–oxytocin interactions can lead to counterintuitive results.

In general, findings on exogenous oxytocin administration in chronic pain are indeed mixed, with some studies reporting pain relief (e.g., reduced headache frequency in migraine [29]) while others describe null or even paradoxical effects, such as increased pain sensitivity in women with musculoskeletal pain [26,30]. These inconsistencies likely reflect individual variability in oxytocin system function, including baseline endogenous level, as well as demographic factors such as age and sex, and the influence of psychosocial context. Importantly, several studies indicate delayed onset of analgesia, suggesting that single-dose oxytocin paradigms may overlook optimal therapeutic windows. Neuroimaging work further supports that oxytocin modulates stress- and salience-related brain circuits rather than acting as a direct analgesic. Accordingly, these patterns point to oxytocin's role as a contextual and modulatory agent, best considered within a biopsychosocial framework rather than as a stand-alone pharmacological treatment.

Research Gaps and Future Directions

Previous research on oxytocin and pain has yielded valuable insights. Clinical and preclinical studies have demonstrated that oxytocin can act at multiple levels of the nervous system, modulate affective and cognitive dimensions of pain, and interact with stress and social processes in ways highly relevant for chronic pain. However, despite this progress, critical mechanistic and translational gaps remain. Addressing these gaps is essential for refining therapeutic strategies and moving toward precision medicine. Below, we highlight key areas requiring attention, outline potential future directions, and propose hypotheses to guide this research.

Characterizing the Endogenous Oxytocin System Across Pain Populations

Most clinical studies investigated endogenous oxytocin within a single pain population, which limits direct comparison across conditions. As a result, meta-analytic findings remain inconsistent or even contradictory—some studies report elevated oxytocin concentrations in chronic migraine and fibromyalgia, while others find reduced levels in chronic musculoskeletal or abdominal pain populations [13]. Without between-condition comparison, it is unclear whether these discrepancies reflect true biological variation, methodological artifacts, or differences in pain type, duration, and extent. In particular, widespread pain conditions (e.g., fibromyalgia) may place different demands on the oxytocin system than more localized conditions (e.g., low back pain), and acute versus chronic pain may involve distinct trajectories of oxytocin signaling.

Future research should adopt comprehensive, comparative designs that evaluate oxytocin across multiple pain populations within the same study framework. Such work should explicitly compare widespread versus localized pain, and acute versus chronic pain states, to determine whether the oxytocin system adapts differently depending on pain extent and duration. In addition, longitudinal designs are needed to track oxytocin dynamics during transitions from acute to chronic pain, clarifying whether oxytocin patterns predict recovery or chronification.

We hypothesize that pain duration and extent shape endogenous oxytocin profiles, with widespread and chronic pain being associated with blunted or depleted oxytocin signaling, whereas acute or episodic pain eliciting compensatory elevations. These oxytocin phenotypes not only distinguish pain populations but also predict clinical course and treatment responsiveness.

Characterizing the Endogenous Oxytocin System Across the Lifespan

Developmental stage introduces an additional layer of complexity. For instance, pediatric studies of abdominal pain show reduced endogenous oxytocin, whereas adult chronic pain patients

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sometimes present with elevated oxytocin levels. These age-related differences in oxytocin signaling are in line with research showing fluctuations of the oxytocin system throughout the lifespan [46]. Given that pain vulnerability and stress regulation also change across the lifespan, developmental dynamics in oxytocin may be a critical but underexplored determinant of clinical outcomes.

Lifespan-sensitive studies should examine the endogenous oxytocin system in pediatric, adolescent, adult, and aging pain populations, within comparable methodological frameworks. Longitudinal pediatric studies could clarify whether reduced oxytocin contributes to persistence of pain into adulthood, while research in older adults could determine whether age-related decline or receptor-desensitization exacerbate pain vulnerability. Ideally, such work would integrate repeated oxytocin sampling and pain assessments to capture dynamic regulation across development.

We hypothesize that the developmental stage determines oxytocin signaling capacity in relation to pain, with reduced signaling in youth contributes to vulnerability for recurrent pain, while altered receptor sensitivity in aging increases risk of pain persistence and diminished responsiveness to exogenous oxytocin.

Characterizing Biological Modulators of Oxytocin's Effect on Pain

Despite comprehensive preclinical research, mechanistic understanding of how oxytocin influences pain in humans still remains limited. While spinal and supraspinal actions are established, the contribution of biological modulators such as receptor-level dynamics, inflammation, and hormones (e.g., estrogen and cortisol) remains unclear. Chronic elevations of endogenous oxytocin may induce receptor desensitization [52,53], yet data on oxytocin-receptor expression and sensitivity in human chronic pain are scarce. Conversely, recent findings from children with autism suggest that oxytocin administration can stimulate the endogenous oxytocin system itself, potentially inducing epigenetic modifications of the oxytocin-receptor gene and creating a positive feed-forward loop that enhances long-term oxytocinergic signaling [54]. In parallel, inflammatory cytokines can upregulate oxytocin-receptor expression and promote oxytocin release [32], although these dynamics are still understudied within pain contexts. Sex hormones such as estrogen also shape oxytocin responses, possibly explaining sex-specific effects and paradoxical findings, with an inverted U-shaped dose–response curve suggesting that women with already higher baseline oxytocin levels may experience null or even adverse effects after exogenous administration (e.g., pain increase after oxytocin in women with neck/shoulder pain [26]). Finally, oxytocin and cortisol—a well-known stress hormone—are tightly interconnected as elevated cortisol appears to suppress oxytocin signaling, while oxytocin can attenuate HPA-axis activation and lower cortisol release [55,56]. For example, in healthy children, higher morning oxytocin predicted lower stress-induced cortisol in the afternoon—a protective feedback mechanism absent in children with autism, due to altered oxytocin dynamics [57]. In chronic pain, altered cortisol rhythms have also been described, with both hyper- and hypo-cortisolism linked to heightened pain sensitivity and impaired recovery [58]. This suggests that stress-axis functioning is a critical but still underexplored moderator of oxytocin's effects in pain.

Future research should adopt advanced multimodal approaches, including receptor quantification (PET ligands when available), and panels of inflammatory, hormonal, and stress biomarkers, combined with clinical phenotyping. Studies should stratify participants by pain phenotype, sex, hormone status, and stress reactivity (e.g., via stress-induction paradigms) to examine how these moderators influence oxytocin's efficacy.

We hypothesize that oxytocin's effects on pain are shaped by multiple interacting biological modulators. At the receptor level, intermittent administration or moderate oxytocin dosing may stimulate receptor sensitivity, while sustained high levels risk desensitization. Inflammation is expected to act as a critical trigger, with cytokines promoting oxytocin release and engaging compensatory anti-nociceptive mechanisms. Sex hormones, particularly estrogen, likely influence baseline oxytocin levels and exogenous efficacy: individuals with lower oxytocin levels may benefit most, while those with higher levels may show paradoxical or null responses. Lastly, cortisol may play a dual role, with oxytocin dampening HPA-axis activation during acute stress, while chronic stress and persistently elevated cortisol could blunt oxytocinergic signaling.

Characterizing Dosing and Timing Effects of Oxytocin Administration

The optimal dosing and timing for oxytocin administration still remains unclear. One study in chronic migraine found a delayed analgesic effect, with significant pain reduction emerging only 2–4 hours after administration, pointing to the advantage of multiple-dose administration [30]. However, to date almost all oxytocin trials in pain employ single-dose paradigms. If there is to be a transition towards the therapeutic use of oxytocin administration, there is a critical need for studies on multiple-dose administration. When looking at oxytocin research outside the pain-field, it is apparent that repeated dosing enhances efficacy [54,59,60]. A recent clinical trial in autism suggests that intermittent oxytocin dosing, followed by positive social interaction, can optimize therapeutic effects and minimize the risk of desensitization, supporting the use of less frequent dosing schedules in clinical practice [61]. Furthermore, chronic intranasal oxytocin has been shown to exert anxiolytic effects, reducing neural responses to threat in a dose-frequency-dependent manner [62]. These findings reinforce the idea that not only the dose, but also the timing and context of oxytocin administration are critical for maximizing its therapeutic potential.

Future clinical trials should evaluate multiple-intermittent and context-sensitive dosing schedules. These should be paired with monitoring of stress reactivity, inflammatory and hormonal markers, as well as pain phenotype.

We hypothesize intermittent multiple-dose and context-integrated oxytocin administration (e.g., over weeks in combination with stress-coping interventions) produces more durable analgesic and affective benefits than acute dosing.

Integrating Psychosocial Dimensions of Oxytocin in Pain Management

Most clinical studies treat oxytocin primarily as a stand-alone analgesic, yet growing evidence suggests that its role in pain is more indirect, operating through stress regulation and emotional appraisal. Oxytocin has been shown to attenuate cardiovascular stress responses, reduce negative mood, and dampen anxiety, mechanisms that can indirectly contribute to pain relief [63,64]. Neuroimaging and animal studies further indicate that oxytocin acts on brain regions central to the cognitive and affective dimensions of pain (e.g., amygdala and prefrontal cortex) supporting the view that its analgesic effects may arise in part from reducing anticipatory anxiety and negative affective states [16]. Importantly, psychosocial factors including pain hypervigilance, pain catastrophizing, anxiety and fear strongly modulate treatment responsiveness in clinical chronic pain populations [65], underscoring that oxytocin's effects are not uniform but context dependent [20,66]. These findings align with oxytocin's broader functions in stress buffering and coping, situating its relevance within a biopsychosocial rather than purely nociceptive framework. Building on this, social context emerges as a critical determinant: oxytocin enhances processes of bonding and affiliation, and supportive interpersonal environments may therefore amplify its therapeutic potential [67]. Yet, few pain studies have systematically accounted for this dimension, highlighting an important gap in translational research [68].

Therefore, future studies should integrate oxytocin administration with behavioral interventions such as cognitive-behavioral therapy, mindfulness, or stress-coping training. Randomized controlled trials should examine whether oxytocin enhances the learning of adaptive coping skills and strengthens therapeutic alliances by leveraging its roles in salience processing, social bonding, and anxiolytic effects. Neuroimaging and autonomic measures could be employed alongside clinical assessments to elucidate how oxytocin modulates brain circuits underlying both pain and psychosocial resilience.

We hypothesize that exogenous oxytocin does not primarily reduce nociception directly but enhances psychosocial resilience, amplifying the effectiveness of behavioral interventions by facilitating stress regulation, emotional appraisal, and coping strategies. This facilitation may occur

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through oxytocin-mediated modulation of affective brain regions and downregulation of negative emotions that exacerbate pain perception, thereby improving overall pain management outcomes.

Paradigm Shift: From Analgesic to Biopsychosocial Adjuvant

Taken together, we argue that the identified gaps point toward a necessary paradigm shift. Rather than conceptualizing oxytocin as a straightforward analgesic, future research should evaluate it as a biopsychosocial adjuvant: a modulator of stress, coping, and affective dimensions of pain. Clinical findings already hint at this broader role. For example, an 8-week mindfulness-based pain management program was found to increase oxytocin levels in chronic pain patients, while simultaneously dampening inflammatory markers and showing a trend toward reduced stress markers [69]. Such results suggest that oxytocin may amplify the benefits of psychosocial interventions, supporting resilience and stress regulation rather than directly blocking nociceptive input. By stratifying patients according to endogenous oxytocin profiles, developmental stage, sex, and psychosocial context, and by embedding oxytocin within integrative treatment frameworks, research can move toward precision medicine approaches. This shift may not only clarify oxytocin's therapeutic potential but also illuminate fundamental mechanisms linking neuropeptide signaling, stress, and chronic pain [70].

Conclusions

Oxytocin is a promising yet underutilized candidate for chronic pain management. Its combined (neuro)physiological, anti-inflammatory, and psychosocial effects align with contemporary biopsychosocial models of chronic pain [24]. Although preclinical evidence is compelling, clinical studies remain inconclusive due to methodological limitations. This opinion paper emphasizes the urgent need for hypothesis-driven, stratified, and translationally oriented research. By advancing our understanding of oxytocin's mechanisms and clinical applications, we may uncover novel pathways to improve chronic pain treatment and patient well-being.

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