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THE ROLE OF THE OXYTOCIN SYSTEM IN PATIENTS WITH HYPOTHALAMIC-PITUITARY DYSFUNCTION: A NARRATIVE REVIEW

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ABSTRACT

Oxytocin (OXT), a hypothalamic nonapeptide stored in the posterior pituitary, has emerged as a multifaceted regulator extending far beyond its classical roles in parturition and lactation. In this narrative review, we summarize current knowledge regarding the role of the OXT system in patients with hypothalamic-pituitary dysfunction (HPD). We explore evidence of OXT's clinical importance while highlighting specific symptoms of oxytocin deficiency (OXT-D), diagnostic limitations, and potential therapeutic strategies. A comprehensive literature search was performed in PubMed to identify relevant studies. Increasing evidence highlights OXT's significant involvement in the modulation of neuropsychiatric processes, including social behavior, emotional regulation, stress responsiveness, and psychological well-being. In parallel, this hormone plays an important role in metabolic homeostasis, as well as solely peripheral physiological functions, including bone remodeling and obstetric and reproductive functions. Its dual central and peripheral actions underscore its integrative role in maintaining systemic homeostasis. While OXT-D is increasingly recognized following HPD, its assessment is limited by a lack of reliable diagnostic testing. Furthermore, although initial small-scale studies on OXT therapy show promise, the current body of evidence remains insufficient to fully support its transition into routine clinical practice. In this review, we highlight the need for further large, well-designed studies to confirm these preliminary findings and establish their clinical relevance.

KEYWORDS

Oxytocin, Oxytocin Deficiency, Hypopituitarism, Hypothalamic–Pituitary Dysfunction, Hypothalamic Damage

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1. Introduction

Oxytocin (OXT), a nonapeptide hormone, is primarily synthesized by magnocellular neurons within the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus. The axons of these neurons project to the posterior pituitary gland, where oxytocin is triggered by exocytosis from neurosecretory vesicles in response to depolarization (Bhargava et al., 2019). The oxytocin receptor (OXTR) is widely expressed across numerous human tissues and organs. Its presence has been reported in the female reproductive system and male reproductive organs, as well as in the breast, adrenal glands, bone, myocardium, vascular endothelium, kidneys, thymus, gastrointestinal tract, skeletal muscle, adipose tissue, and multiple brain regions (Aulinas & Lawson, 2025; Gimpl & Fahrenholz, 2001; Leibnitz et al., 2026; Pierzynowska et al., 2023). OXT is classically recognized for its essential role in parturition and lactation. However, emerging evidence suggests that it has broad systemic effects, including the regulation of metabolism, bone homeostasis, and cardiovascular function (Aulinas et al., 2021; Gimpl & Fahrenholz, 2001; Leibnitz et al., 2026; Sun et al., 2016). Additionally, OXT functions as a key neuromodulator involved in the regulation of complex social, emotional, and behavioral processes (Bhargava et al., 2019; Froemke & Young, 2021; Leibnitz et al., 2026). It plays a fundamental role in the regulation of social attachment and parental behaviors, which are essential for offspring care and survival across species (Froemke & Young, 2021). Notably, the combination of OXT and social support appears to have a synergistic effect in alleviating the effects of stress (Aulinas & Lawson, 2025; Leibnitz et al., 2026). OXT is also involved in the regulation of sexual and reward-related behaviors (Aulinas & Lawson, 2025; Cera et al., 2021). Additionally, OXT appears to influence appetite regulation and food-related reward processing (Lawson, 2024; Liu et al., 2021; Plessow et al., 2018).

Hypopituitarism is a rare endocrine disorder characterized by partial or complete deficiency of anterior and/or posterior pituitary hormones (Rai et al., 2020). The condition may result from either primary pituitary pathology or secondary hypothalamic dysfunction. In children, craniopharyngiomas are the most frequent intracranial neoplasms leading to pituitary dysfunction (Kraljević et al., 2025). In contrast, in adults, the

predominant cause of hypopituitarism is nonfunctioning pituitary adenomas (NFPAs), which, together with their treatment (surgical resection and/or radiotherapy), account for the majority of cases, estimated at approximately 70% (Doknić et al., 2017; Kraljević et al., 2025). Additional etiologies include hypophysitis, traumatic brain injury, and subarachnoid hemorrhage, as well as less common disorders such as primary empty sella syndrome and Sheehan's syndrome (Kraljević et al., 2025).

Emerging research suggests that patients with hypopituitarism are at increased risk of cardiovascular disease, impaired bone health, increased psychological burden, social isolation, reduced quality of life (QoL), and increased morbidity and mortality (Asla, Garrido, Urgell, Terzan, Santos, Varghese, et al., 2025; Aulinas et al., 2021; Aulinas & Lawson, 2025; Bhargava et al., 2019; Ebrahimi & Christ, 2023; Lynch et al., 1994; Sterkenburg et al., 2015). Oxytocin deficiency (OXT-D) has been proposed as a potential but underrecognized complication in patients with hypothalamic and pituitary dysfunction (HPD). However, no standardized diagnostic criteria or validated testing methods have yet been established (Asla, Garrido, Urgell, Terzan, Santos, Fernández, et al., 2025; Aulinas & Lawson, 2025; Sailer et al., 2021). OXT-D frequently co-occurs with arginine vasopressin deficiency (AVP-D), formerly known as central diabetes insipidus, which results from damage to the hypothalamic-posterior pituitary axis and causes hypotonic polyuria, polydipsia, and dehydration risk (Christ-Crain, 2025). Because the neurons producing OXT and AVP are located in proximity within the hypothalamus, a single lesion can impair both systems (Bhargava et al., 2019; Leibnitz et al., 2026).

This review summarizes the current understanding of the OXT system and the impact of OXT-D in patients with HPD, addressing obstetric, reproductive, and musculoskeletal consequences, as well as obesity, metabolic dysregulation, and neuropsychological dysfunctions. Furthermore, we evaluate emerging evidence of oxytocin's clinical importance while highlighting diagnostic limitations and potential therapeutic strategies.

2. Methodology

A comprehensive literature search was conducted using the PubMed database up to April 20, 2026. The search strategy included the following terms and combinations: "oxytocin," "oxytocin deficiency," "hypopituitarism," "pituitary disease," "oxytocin receptor," "peripheral effects of oxytocin," "central effects of oxytocin," "hypothalamic damage," and "oxytocin treatment." Furthermore, references cited in the initially retrieved articles were reviewed for additional relevant studies. Only articles published in English were considered for inclusion. To ensure a comprehensive overview, no restrictions were applied regarding article type.

3. Results

3.1. Oxytocin Deficiency in Patients with Hypothalamic–Pituitary Dysfunction

Genetic knockout murine models lacking either the OXT gene or the OXTR gene, which serve as experimental models of OXT-D, have substantially contributed to understanding the physiological role of the oxytocinergic system (J. Amico et al., 2008; J. A. Amico et al., 2004; Aulinas & Lawson, 2025). OXT-D mice exhibit a broad spectrum of abnormalities, including sexual dysfunction, increased social anxiety, impaired social behaviors, late-onset obesity, defective thermoregulation, metabolic dysregulation, sarcopenia, and osteoporosis (J. A. Amico et al., 2004; Aulinas & Lawson, 2025; Kasahara et al., 2007; Nishimori et al., 2008; Sclafani et al., 2007; Sun et al., 2016; Takayanagi et al., 2008). These findings highlight the pleiotropic role of OXT in the regulation of reproductive, metabolic, musculoskeletal, and socioemotional functions.

HPD frequently leads to multiple pituitary hormone deficiencies and is associated with numerous long-term complications, including sexual dysfunction, neuropsychological disturbances such as an increased prevalence of anxiety, depression, and impaired social functioning, as well as altered eating behaviors, obesity, metabolic disorders, and osteoporosis (Aulinas & Lawson, 2025; Kim & Choi, 2013; Lynch et al., 1994; Sterkenburg et al., 2015; Zada et al., 2013). Notably, many of these comorbidities overlap with the phenotype observed in animal models of OXT-D. These observations have provided the rationale for human studies investigating whether a comparable OXT-D phenotype may also be identified in patients with HPD (Aulinas & Lawson, 2025).

Several studies have reported evidence of reduced peripheral OXT secretion in patients with HPD. The study by Daubenbüchel et al. (2016) demonstrated that patients with craniopharyngiomas and postoperative lesions confined to the anterior hypothalamus, where SON and PVN are located, had lower fasting salivary OXT levels than patients without hypothalamic involvement and those with combined anterior and posterior hypothalamic damage (because craniopharyngiomas typically expand from anterior inferior to an upwards posterior direction, the PVN and SON are frequently bypassed, which allows for the continued production of

oxytocin, even in the presence of significant tumor mass) (Aulinas & Lawson, 2025; Daubenbüchel et al., 2016). In another report, salivary OXT levels were assessed at baseline and following an exercise stimulus in 26 adult patients with craniopharyngioma and 26 age- and sex-matched healthy controls. Despite the lack of significant differences in basal OXT concentrations between the groups, lower levels of OXT were observed only in patients with craniopharyngioma and hypothalamic damage. Interestingly, higher baseline OXT concentrations were associated with greater trait anxiety, whereas a decreased OXT response was linked to increased state anxiety. Although reduced basal OXT levels were observed only in patients with craniopharyngioma and hypothalamic injury, impaired exercise-induced OXT secretion was present across the entire craniopharyngioma group, suggesting functional OXT-D even in the absence of overt structural hypothalamic damage (Bhargava et al., 2019; Gebert et al., 2018).

3.2 Reproductive and Obstetric Manifestations

OXT has traditionally been associated with the regulation of parturition and lactation. During pregnancy, uterine sensitivity to OXT increases markedly, largely due to a substantial upregulation of OXTR expression, thereby facilitating effective uterine contractions (Leibnitz et al., 2026). OXT also promotes cervical ripening and dilation, enhances uterine contractility, and contributes to hemostasis in the postpartum period (Bhargava et al., 2019).

Men and women with hypopituitarism demonstrate increased rates of infertility and frequently require assisted reproductive techniques (Aulinas et al., 2022; Aulinas & Lawson, 2025; Vila et al., 2015; Vila & Fleseriu, 2020). The elevated prevalence of infertility in patients with HPD is multifactorial and may result from deficiencies of anterior and/or posterior pituitary hormones, as well as from hyperprolactinemia.

AVP-D, prolactin deficiency, and/or OXT-D may contribute to impaired lactation and difficulties with breastfeeding. Furthermore, evidence shows that pregnant women with pre-existing hypopituitarism may require oxytocin administration or a cesarean delivery and might be at an increased risk for postpartum hemorrhage (Aulinas et al., 2022; Aulinas & Lawson, 2025; Kübler et al., 2009).

3.3 Musculoskeletal Consequences

OXTR expression has been identified in osteoblasts and osteoclasts, supporting a role for OXT in skeletal regulation. OXT exerts anabolic effects on bone, promoting bone formation and inhibiting resorption. Clinically, lower OXT levels have been associated with reduced bone mineral density and adverse bone geometry (Colaianni et al., 2014; Kerem & Lawson, 2021; Leibnitz et al., 2026).

Hypopituitarism is associated with unfavorable alterations in body composition and impaired bone quality, including osteopenia and osteoporosis, which contribute to increased skeletal fragility and fracture risk (Aulinas et al., 2021; Aulinas & Lawson, 2025). Considering the established role of OXT in maintaining musculoskeletal health and reducing adiposity, OXT-D may represent an additional contributing factor (Aulinas & Lawson, 2025). A cross-sectional study by Aulinas et al. (2021) evaluated the association between OXT-D and skeletal health in 37 men with hypopituitarism, including 17 patients with AVP-D and 20 with anterior pituitary deficiency (APD). Lower circulating OXT concentrations were associated with reduced bone mineral density (BMD) Z-scores at the lumbar spine, femoral neck, total hip, and subtotal body, as well as with unfavorable hip geometry and decreased estimated strength at the intertrochanteric region in men with AVP-D (Aulinas et al., 2021; Aulinas & Lawson, 2025; Lawson, 2024). These associations remained significant after adjustment for age, body mass index (BMI), and testosterone levels (Aulinas et al., 2021).

3.4 Neuropsychological Dysfunction

Patients with HPD frequently experience social and emotional dysfunction, which may contribute to interpersonal difficulties and social isolation. The underlying mechanisms are not fully understood but are likely multifactorial, involving hypothalamic damage, hypopituitarism, and obesity (Aulinas & Lawson, 2025; Wolfgang et al., 2025). Impaired OXT signaling may contribute to these manifestations, given its established role in supporting mental well-being, regulating impulse control, promoting prosocial behaviors, and reducing food intake (Aulinas & Lawson, 2025; Plessow et al., 2018, 2021). Alterations in OXT signaling have been implicated in several neuropsychiatric conditions, including depression, schizophrenia, autism spectrum disorder, posttraumatic stress disorder (PTSD), and personality disorders, including borderline and antisocial personality disorders (Bradley & Woolley, 2017; Florea et al., 2022; John & Jaeggi, 2021; Neumann & Slattery, 2016; Scantamburlo et al., 2007). A diminished salivary OXT response to physical stress induction has been associated with increased anxiety, elevated autistic traits, and reduced hedonic experience during social interactions in patients with HPD (Aulinas & Lawson, 2025; Brandi et al., 2020). In the cross-sectional study of 62 men (20 with AVP-D, 20 with APD, and 22 healthy controls), integrated assessment of basal and pulsatile OXT secretion was performed using pooled blood samples collected at 5-minute intervals over one hour

(Aulinas et al., 2019; Aulinas & Lawson, 2025). Although basal OXT concentrations were comparable across study groups, men with AVP-D exhibited approximately 20% lower pooled OXT concentrations than both age- and BMI-matched healthy controls and patients with APD without AVP-D. Notably, only the AVP-D subgroup demonstrated significantly higher levels of anxiety, depressive symptoms, and alexithymia, together with poorer mental health–related quality of life (HRQoL) (Aulinas et al., 2019; Aulinas & Lawson, 2025; Leibnitz et al., 2026). However, Daughters et al. (2017) reported reduced basal OXT levels in patients with hypopituitarism irrespective of AVP-D. Lower OXT concentrations were associated with impaired recognition of facial expressions, suggesting a link between OXT-D and social cognitive dysfunction (Aulinas & Lawson, 2025; Bhargava et al., 2019; Daughters et al., 2017; Leibnitz et al., 2026). Further evidence of impaired OXT release was demonstrated in a randomized, double-blind, placebo-controlled study using 3,4-methylenedioxymethamphetamine (MDMA) as a pharmacological stimulus. In healthy adults, a single 100 mg dose induced an almost tenfold increase in plasma OXT concentrations and was accompanied by the expected prosocial, empathogenic, and anxiolytic subjective effects. In contrast, patients with AVP-D showed no significant OXT response and reported only minimal subjective changes, suggesting impaired OXT release and dysfunction of central pathways involved in socioemotional processing (Atila et al., 2023).

3.5 Hypothalamic Obesity and Metabolic Dysregulation

Studies demonstrate that oxytocin reduces caloric intake and modulates activity in brain regions associated with reward, including the ventral tegmental area, as well as the hypothalamus, which is responsible for homeostatic control of feeding (Lawson, 2024; Liu et al., 2021; Plessow et al., 2018). The presence of panhypopituitarism may indicate underlying hypothalamic injury and the subsequent development of hypothalamic obesity (HO), primarily due to the close anatomical and functional relationship between the pituitary gland and hypothalamic structures. In this context, panhypopituitarism should be regarded as a clinical marker of hypothalamic damage rather than a direct cause of obesity (Shoemaker & Tamaroff, 2023). More than half of patients undergoing conventional treatment for sellar tumors involving the hypothalamic–pituitary region develop hyperphagic obesity (Aulinas & Lawson, 2025; Sterkenburg et al., 2015). The pathogenesis of HO is multifactorial and is mainly attributed to damage of hypothalamic nuclei involved in the regulation of energy homeostasis, particularly the PVN. Disruption of these regulatory pathways may lead to hyperphagia and reduced energy expenditure (Aulinas & Lawson, 2025). In a cross-sectional study by Daubenbüchel et al. (2016), salivary oxytocin concentrations before and after a standardized breakfast were analyzed in 34 long-term childhood-onset craniopharyngioma survivors and 73 healthy controls. Changes in salivary OXT concentrations before and after breakfast have been negatively associated with BMI and maladaptive eating behaviors in patients with craniopharyngioma (Daubenbüchel et al., 2016).

3.6 Oxytocin Measurement

Oxytocin is a pleiotropic neuropeptide involved in many important physiologic and psychological mechanisms. Given its broad biological relevance, accurate assessment of endogenous OXT is of considerable clinical and research importance. In this context, MDMA has emerged as a promising pharmacological stimulus for OXT release. While MDMA is reported to significantly elevate plasma OXT levels in healthy controls, this effect is not significant in patients with AVP-D, which may serve as a useful tool to differentiate the cohort with an OXT release pathway lesion from healthy individuals (Atila et al., 2023). In addition to increasing peripheral OXT concentrations, MDMA enhances central OXT-mediated behavioral responses, reflected by its characteristic prosocial, empathogenic, and anxiolytic effects, likely mediated through limbic structures such as the amygdala (Kirkpatrick et al., 2014; Leibnitz et al., 2026). However, its broader clinical use is limited by cardiovascular risks and regulatory restrictions. Its incorporation into routine clinical practice remains challenging (Leibnitz et al., 2026; Sze Jing Yong et al., 2025). Although short-term limited-dose administration in PTSD trials has not been associated with tolerance or major safety concerns, robust long-term safety data remain insufficient (Leibnitz et al., 2026; Mitchell et al., 2021; Wolfgang et al., 2025).

Several randomized controlled trials investigated alternative provocative tests for diagnosing OXT-D in patients with HPD.

Corticotropin-releasing hormone (CRH) was initially hypothesized to be a candidate because CRH receptors are present on oxytocinergic neurons, and intravenous CRH has been shown to increase plasma OXT concentrations (Aulinas & Lawson, 2025; Dabrowska et al., 2011). However, a randomized, crossover, placebo-controlled study using CRH at 1 μg/kg demonstrated no significant difference in OXT responses between patients with HPD and healthy controls (Asla, Garrido, Urgell, Terzan, Santos, Fernández, et al., 2025). Glucagon (1 mg) also failed to significantly stimulate plasma OXT concentrations in both patients with AVP-D and healthy individuals (Atila et al., 2024).

Melatonin also emerged as a potential candidate for identifying OXT-D. As a neurohormone acting through hypothalamic receptors, melatonin may influence oxytocinergic pathways (Aulinas & Lawson, 2025). In a recent study, oral administration of low-dose melatonin (1.95 mg) significantly increased plasma OXT levels in healthy controls, whereas this response was attenuated in patients with HPD (Asla, Garrido, Urgell, Terzan, Santos, Varghese, et al., 2025). The patients with HPD also demonstrated more severe depressive symptoms, higher alexithymia scores, impaired sexual function, and reduced quality of life (Asla, Garrido, Urgell, Terzan, Santos, Varghese, et al., 2025).

Kisspeptin, a hypothalamic neuropeptide involved in neuroendocrine regulation, has also been proposed as a candidate because its receptors are expressed on oxytocinergic neurons. Furthermore, animal studies showed increased plasma OXT levels following kisspeptin administration (Seymour et al., 2017). Moreover, in 12 healthy adults, intravenous kisspeptin increased plasma OXT concentrations, with a more pronounced effect in men than in women, suggesting possible sex-specific diagnostic utility (Galbiati et al., 2025).

Established pituitary stimulation tests, hypertonic saline and arginine infusion known to stimulate copeptin, and oral macimorelin used for growth hormone stimulation, were evaluated for their potential to provoke OXT release. Hypertonic saline infusion induced only a modest increase in OXT concentrations, accompanied by substantial interindividual variability, whereas arginine infusion showed no significant effect, and oral macimorelin tended to reduce OXT levels (Sailer et al., 2021).

Neurophysin I (NP-I), the carrier protein of OXT, represents a particularly promising surrogate biomarker. OXT and NP-I are derived from the same precursor peptide and released in equimolar amounts after enzymatic cleavage during axonal transport. In contrast to OXT, NP-I has a longer half-life, circulates at substantially higher concentrations, and, owing to its larger molecular size, can be measured using sandwich immunoassays rather than competitive assays. This provides superior analytical sensitivity and specificity and allows reliable quantification in complex biological matrices such as plasma and urine without extensive extraction procedures (MacLean et al., 2024). Experimental studies strongly support NP-I as a valid marker of endogenous OXT secretion. In a secondary analysis of MDMA administration, healthy participants showed an 8-fold increase in OXT and a 20-fold increase in NP-I, whereas patients with hypothalamic–posterior pituitary dysfunction demonstrated only minimal changes in both biomarkers (Atila et al., 2025). NP-I increases are strongly correlated with OXT elevations and with subjective effects such as increased trust, reduced fear, "good effect," "liking effect," and "feeling high" (Atila et al., 2025). Similarly, when OXT was measured after solid-phase extraction, plasma NP-I and OXT concentrations showed a strong positive correlation, confirming that NP-I reliably reflects endogenous OXT secretion under appropriate analytical conditions (MacLean et al., 2024). In contrast, OXT measured in unextracted plasma showed a weak, negative, and non-significant correlation with NP-I, further highlighting the analytical unreliability of non-extracted OXT assays (MacLean et al., 2024). NP-I also offers important practical advantages, including the absence of complex extraction procedures, substantially shorter assay time (<2 hours compared with 16–24 hours for OXT), and reliable detectability even when OXT concentrations approach or fall below standard assay detection limits (MacLean et al., 2024). A major methodological controversy concerns sample extraction, which removes interfering substances and concentrates peptide levels. A study by (Szeto et al., 2011) demonstrated that human plasma oxytocin concentrations measured by enzyme immunoassay (EIA) were more than 100-fold higher in unextracted samples than in extracted samples, and no significant correlation was observed between extracted and unextracted measurements. In contrast, the radioimmunoassay (RIA) exhibited insufficient sensitivity, with most plasma samples showing oxytocin concentrations below the detection threshold regardless of extraction status (Szeto et al., 2011). An additional methodological challenge is the pulsatile nature of OXT secretion, which makes single-point measurements unreliable and supports the need for repeated or dynamic sampling. Evidence for this was demonstrated in a study of five healthy young men who underwent intensive overnight blood sampling under standardized resting conditions. Serum OXT concentrations were measured every 5 minutes from 10 p.m. to 8 a.m. to account for the short half-life of OXT and to enable precise deconvolution analysis. Participants remained fasting in a quiet, dark environment and were isolated from social and environmental stimuli to minimize external influences on OXT release. The results confirmed that OXT is secreted in a clearly pulsatile and biologically non-random manner. Importantly, OXT pulse characteristics were significantly associated with psychosocial measures. Lower pulse height and pulse mass correlated with higher avoidant attachment scores, whereas greater OXT exposure and stronger pulsatility were associated with higher perceived social support and lower alexithymia scores, suggesting better emotional awareness and interpersonal functioning (Baskaran et al., 2017).

3.7 Oxytocin Treatment

Only a limited number of OXT-based therapies are currently available for routine clinical use. Parenteral administration, including intravenous (IV) and intramuscular (IM) routes, is primarily utilized in obstetric practice, particularly for labor induction and the prevention of postpartum hemorrhage. For outpatient settings, intranasal (IN) delivery represents a more practical approach and is the most commonly employed route in clinical research (Aulinas & Lawson, 2025). The reported studies have evaluated the effects of IN OXT in patients with HPD. In a pilot cross-sectional study involving 10 patients with childhood-onset CP, a single 24 IU dose of intranasal OXT increased both salivary and urinary OXT concentrations. Patients with postsurgical lesions confined to the anterior hypothalamic region demonstrated improved emotional recognition, particularly of negative emotional expressions, compared with those with combined anterior and posterior hypothalamic lesions (Hoffmann et al., 2017). Another reported case described a 13-year-old boy with hypothalamic obesity following resection of a CP. The patient received OXT at a dose of 6 IU/day for 10 weeks, followed by combination therapy with naltrexone (100 mg/day) for an additional 38 weeks. This treatment was associated with reductions in BMI and hyperphagia (Hsu et al., 2018). IN OXT administration has generally been shown to be safe and well-tolerated, with no serious adverse events and no significant differences in overall side-effect profiles compared with placebo (McCormack et al., 2023; Rung et al., 2021). The most frequently reported adverse effects included epistaxis, nasal mucosal irritation, headache, and nausea (McCormack et al., 2023). Although preclinical data have suggested a potential for OXT to prolong the QT interval, available human data are limited and have not demonstrated any clinically relevant effects of IN OXT on QT interval duration or arrhythmia risk (Aulinas & Lawson, 2025; McCormack et al., 2023; Plessow et al., 2024). In the context of HPD, supraphysiological doses of IN OXT may theoretically exhibit cross-reactivity with arginine vasopressin receptors (AVPRs) (Song & Albers, 2018). However, a small pilot study evaluating chronic IN OXT administration over eight weeks in patients with hypothalamic obesity and AVP-D showed no significant differences in hyponatremia incidence or desmopressin (DDAVP) dose adjustments between treatment and placebo groups (McCormack et al., 2023). Although IN administration is considered a viable route for delivering OXT into the systemic circulation, there remains a need for more practical, stable, and efficient delivery methods. Oral formulations have recently emerged as a potential alternative. In a randomized, double-blind, placebo-controlled study, women exhibited lower endogenous OXT concentrations compared with men. However, oral OXT administration increased OXT concentrations to a similar extent in both sexes. Furthermore, oral OXT has been demonstrated to modulate neural responses to emotional stimuli in a sex-dependent manner (Lan et al., 2024).

In addition, a rapidly dissolving sublingual (SL) OXT tablet was evaluated by Zhu et al. (2018) for its pharmacokinetic profile in Yucatan miniature swine. The study reported that plasma concentrations increased proportionally with larger SL doses. Nevertheless, plasma OXT levels were lower with SL administration than via the IM route in anesthetized pigs (Zhu et al., 2018).

Furthermore, another study in men demonstrated that OXT delivered via medicated lollipops (24 IU) increased plasma OXT concentrations and improved social attention and anxiety-related behaviors, with effects comparable to IN and SL administration (Xu et al., 2022). Moreover, a heat-stable inhaled formulation of OXT emerged as a potential therapeutic option for labor induction and the prevention of postpartum hemorrhage. Phase I randomized studies demonstrated a safety profile comparable to that of IM OXT in both healthy volunteers and women in the third stage of labor (Fernando et al., 2017; Gajewska-Knapik et al., 2023). Carbetocin, a long-acting OXTR agonist administered IV or IM, exhibits lower potency than endogenous oxytocin but has a prolonged plasma half-life of approximately 40 minutes and greater selectivity for OXTR, with minimal affinity for vasopressin receptors. An intranasal formulation of carbetocin was shown to be well tolerated, and a 3.2 mg dose, more than a 9.6 mg dose, was associated with clinically meaningful improvements in hyperphagia as well as anxiety- and distress-related behaviors in individuals with Prader–Willi syndrome (a rare genetic neurodevelopmental disorder associated with hypothalamic dysfunction) (Aulinas & Lawson, 2025; Roof et al., 2023).

3.8 Basal vs. Pulsatile Oxytocin Secretion

Basal OXT concentrations and pulsatile OXT secretion may exert distinct physiological effects. For instance, pulse characteristics of OXT were found to be strongly correlated with measures of socioemotional functioning in a small cohort of healthy men. Participants exhibiting lower OXT pulse height and pulse mass demonstrated a more avoidant attachment style, reported lower perceived social support, and showed greater difficulty in identifying and describing their emotions (Baskaran et al., 2017). In contrast, among men with AVP-D, single-time-point circulating OXT measurements likely reflecting basal secretion were associated with bone health, whereas one-hour pooled samples, representing approximately two oxytocin pulses per hour, showed no such relationship (Aulinas et al., 2021).

4. Discussion:

4.1 Oxytocin Deficiency and Clinical Implications in Patients with Hypothalamic–Pituitary Dysfunction

Overall, preclinical and clinical observations suggest that impaired OXT signaling may represent an underrecognized contributor to the complex phenotype of hypopituitarism, particularly in patients with hypothalamic involvement. Findings from the limited available studies suggest that impaired endogenous OXT secretion in pregnant women with pre-existing hypopituitarism may contribute to inadequate uterine contractility during labor and the postpartum period (Aulinas et al., 2022; Kübler et al., 2009). A cross-sectional study demonstrated that OXT may act as an important anabolic regulator of skeletal metabolism and that OXT-D in patients with hypopituitarism may contribute to impaired bone integrity. However, further research is warranted to determine whether OXT-based therapies could be a strategy for optimizing bone health in this patient population (Aulinas et al., 2021). Dysregulation of OXT signaling has been implicated in the pathophysiology of several neuropsychiatric disorders (Bradley & Woolley, 2017; Florea et al., 2022; John & Jaeggi, 2021; Scantamburlo et al., 2007). The available evidence suggests that dysfunction of the oxytocinergic system may represent a critical neurobiological mechanism underlying the social, emotional, and behavioral disturbances observed in patients with HPD. Although the pathophysiology of these impairments is likely multifactorial, the reviewed studies consistently indicate that disrupted OXT signaling may contribute substantially to altered socioemotional functioning in this population. In particular, men with AVP-D demonstrated lower pooled OXT concentrations despite comparable baseline levels, accompanied by significantly greater psychological burden, including anxiety, depressive symptoms, alexithymia, and poorer mental health–related quality of life (Aulinas et al., 2019). These findings propose that static measurements of circulating OXT may inadequately reflect biologically relevant dysfunction and that dynamic secretory responses may better characterize oxytocinergic impairment. Nevertheless, due to the rarity of AVP-D, the study cohort was relatively small (62 men), thereby limiting the statistical power to identify significant associations between OXT levels and clinical outcomes (Aulinas et al., 2019). The absence of a significant OXT response following both MDMA and melatonin administration in patients with HPD suggests a profound impairment of stimulus-induced oxytocinergic activation, potentially reflecting dysfunction of hypothalamic pathways involved in socioemotional regulation, stress responsiveness, and quality-of-life–related behavioral processes (Asla, Garrido, Urgell, Terzan, Santos, Varghese, et al., 2025; Atila et al., 2023). Taken together, these studies support a clinically meaningful association between impaired OXT secretion and adverse neuropsychological outcomes in HPD. The reviewed studies suggest that OXT may modulate reward-related eating behavior through effects on the hypothalamic–pituitary–adrenal (HPA) axis (Daubenbüchel et al., 2016; Hsu et al., 2018). The interpretation of these findings is limited by methodological constraints, including small study populations, challenges in accurately quantifying OXT concentrations (Daubenbüchel et al., 2016), and the inability to obtain objective measurements of caloric intake due to uncontrolled hedonic eating behaviors in patient (Hsu et al., 2018). Although evidence remains preliminary, OXT-based interventions may represent a promising therapeutic strategy for selected patients with HO, particularly when hyperphagia is a dominant clinical feature.

4.2 Oxytocin Measurement

Direct quantification of circulating OXT remains methodologically challenging and continues to generate substantial analytical controversy. There is a growing need for more stable and analytically reliable surrogate biomarkers that more accurately reflect endogenous OXT secretion. Interestingly, findings from Atila et al. (2023) suggest that MDMA has emerged as a promising candidate for pharmacologically induced endogenous OXT release. Therefore, further research should focus on the development of safer and more accessible alternative approaches, including the possibility of replicating the oxytocinergic effects of MDMA using agents that are already approved for clinical use (Leibnitz et al., 2026). Additionally, recent evidence highlights melatonin as a promising candidate for further investigation as a diagnostic stimulus in OXT-D (Asla, Garrido, Urgell, Terzan, Santos, Varghese, et al., 2025). However, this discovery should also be interpreted cautiously due to the lack of a placebo group, which does not allow to determine with certainty that melatonin was the only factor increasing OXT secretion. Furthermore, a recent study identified kisspeptin as a potential candidate for a provocative test aimed at detecting OXT-D in males (Galbiati et al., 2025). Nevertheless, larger studies are required before clinical application can be considered. The findings from clinical trials support NP-I as a robust and clinically useful biomarker of OXT system activity, analogous to copeptin as a surrogate marker of arginine vasopressin. NP-I may therefore represent a valuable tool for investigating OXT-D and monitoring responses to OXT-based therapies in hypopituitarism and

neuropsychiatric disorders (Atila et al., 2025; MacLean et al., 2024). Despite these promising findings, additional studies involving larger populations and a wider range of psychosocially impaired conditions are needed to confirm these observations.

In contrast, a recent study suggests that none of the currently established pituitary stimulation tests, including hypertonic saline infusion, arginine infusion, and oral macimorelin, can be recommended for the diagnosis of OXT-D, since a diagnostically useful provocation test requires a consistent and predictable increase in OXT secretion (Sailer et al., 2021). Similarly, CRH and glucagon appear to have limited diagnostic utility (Asla, Garrido, Urgell, Terzan, Santos, Fernández, et al., 2025; Atila et al., 2024).

An important limitation in research on endogenous OXT is the lack of standardized measurement techniques. Importantly, findings from Szeto et al. (2011) suggest that sample extraction is essential for obtaining valid and reliable assay results. Variations in OXT degradation products may partially account for the previously reported changes in circulating OXT concentrations observed in response to behavioral and social stimuli. These findings underscore the critical need for standardized, validated, and reproducible methodologies for the accurate measurement of OXT in biological specimens. In addition, the reported study provides important evidence that resting-state OXT secretion is inherently pulsatile in healthy men, highlighting the limitations of single-sample assessment and the importance of dynamic measurement approaches (Baskaran et al., 2017). Nevertheless, the authors emphasized that further studies involving larger cohorts of both male and female participants are warranted to provide greater insight into the secretory patterns of OXT.

In summary, despite the growing clinical relevance of OXT, significant methodological limitations continue to hinder its reliable assessment. Future progress depends on the development of standardized analytical protocols, validated provocation tests, and robust surrogate biomarkers, which may substantially improve both research quality and clinical applicability. Accurate and reproducible OXT measurement remains essential for understanding OXT-D and for advancing the use of OXT-based therapeutic strategies in HPD.

4.3 Oxytocin Treatment Several important therapeutic challenges must be addressed before OXT can be considered a viable treatment option in patients with hypopituitarism. Key considerations include the identification of an optimal route of administration and the evaluation of the safety profile associated with long-term use. IN OXT represents one of the limited methods available for off-label OXT-D treatment. Interestingly, findings from Hoffmann et al. (2017) and Hsu et al. (2018) support the potential role of IN OXT replacement therapy in improving psychological well-being, social functioning, and overall QoL in selected patients with HPD and concomitant OXT-D. Nevertheless, further studies involving larger cohorts are warranted to validate these findings. Although clinical trials suggest that IN OXT administration is safe and well tolerated, with no observed effects on the QT interval or increased risk of hyponatremia, data from human studies remain limited (McCormack et al., 2023; Plessow et al., 2024; Rung et al., 2021). While IN administration remains the predominant route of OXT delivery, alternative administration strategies are increasingly being explored. Oral, SL, and inhaled routes of OXT administration have emerged as potentially promising therapeutic approaches (Fernando et al., 2017; Gajewska-Knapik et al., 2023; Lan et al., 2024; Xu et al., 2022; Zhu et al., 2018). However, additional clinical studies are needed to establish their safety profiles, optimal dosing regimens, therapeutic efficacy, and underlying mechanisms of action. Recent evidence from Roof et al. (2023) supports carbetocin as a potential treatment strategy. Interestingly, the study demonstrated unexpectedly greater efficacy of carbetocin at a dose of 3.2 mg compared with 9.6 mg. The authors suggest that this finding may be explained by increased off-target vasopressin receptor agonism at higher doses, which has been associated with emotional dysregulation. However, such effects may, in turn, attenuate or counteract the beneficial behavioral effects mediated by OXT receptor agonism. Findings from Aulinas et al. (2021) and Baskaran et al. (2017) suggest that different therapeutic strategies may be required depending on the target clinical outcome. Since basal and pulsatile OXT may exert distinct physiological effects, interventions producing repeated short-acting OXT bursts several times per hour may be more beneficial for improving socioemotional functioning, whereas lower-dose, long-acting OXT analogs aimed at increasing basal levels may be more appropriate for the management of osteopenia. Ideally, OXT replacement therapy should replicate normal physiological secretion patterns.

5. Conclusions

This review examined the potential role of the OXT system in patients with HPD. Growing evidence suggests that OXT-D may be present in patients with HPD and may contribute to reproductive and obstetric functions, neuropsychological disturbances, metabolic abnormalities, and reduced bone mineral density, thereby negatively impacting their overall QoL. Preliminary findings suggest that OXT replacement therapy could potentially improve clinical outcomes and provide a novel therapeutic approach for optimizing the management of these patients.

Despite the increasing clinical interest in OXT and its potential therapeutic implications, substantial methodological challenges continue to limit the reliable assessment of OXT status. Furthermore, the development and validation of standardized, reliable methods for assessing OXT concentrations in human biological samples, as well as the OXT stimulation tests, may constitute important steps toward the accurate diagnosis of OXT-D. The assessment of NP-I as a surrogate biomarker, together with encouraging findings from MDMA-, kisspeptin-, and melatonin-based stimulation testing, may contribute to the development of more accurate diagnostic methods.

Another important challenge is the currently limited availability of OXT-based therapeutic strategies for routine clinical practice. IN administration represents the most commonly utilized route in outpatient settings and clinical research. Although IN administration is considered a viable method for delivering OXT into the systemic circulation, there remains a need for more practical, stable, and efficient delivery systems. In this context, oral, SL, and heat-stable inhaled formulations have recently emerged as potential alternative approaches under investigation. Another potential therapeutic option under consideration is carbetocin. Although these therapeutic approaches appear promising, further clinical investigations are required to establish their safety profile, optimal dosing strategies, therapeutic efficacy, and underlying mechanisms of action.

In summary, OXT is increasingly recognized as a potentially important yet insufficiently recognized hormone in HPD, with accumulating evidence indicating possible diagnostic and therapeutic relevance that warrants further clinical validation.

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Declaration of the use of AI and AI-assisted technologies in the writing process: Artificial intelligence (AI) tools, including ChatGPT, were used during the preparation of this manuscript exclusively to support language editing, improvement of readability, text organization, and limited data-processing assistance. These tools were employed to enhance grammatical accuracy, stylistic consistency, and clarity of scientific communication in accordance with academic writing standards. After using this tool/service, the authors critically reviewed and revised the generated content as necessary and assumed full responsibility for the scientific accuracy and substantive content of the publication.

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