REVIEW ARTICLE
https://doi.org/10.30773/pi.2024.0320
eISSN 1976-3026
OPEN ACCESS

Effects of Intranasal Oxytocin Across Various Depressive Disorders

Miao Wang[1], Shuaibiao Hou[1], Chaoyang Tian[1], Zhiyi Fu[2], and Jing Jie[1] ✉

[1]State Key Laboratory of Digital Medical Engineering, Key Laboratory of Biomedical Engineering of Hainan Province, School of Biomedical Engineering, Hainan University, Sanya, China
[2]Hainan Jingang Biotechnology Co., Ltd, Haikou, China

Objective Depression is a prevalent psychiatric disorder posing significant global public health challenges. Although traditional antidepressants are widely used, their full therapeutic effects typically require prolonged administration, which may compromise patient outcomes. To enhance treatment efficacy and patient well-being, identifying rapidly acting and safe therapeutic agents is critical. Oxytocin, an endocrine polypeptide hormone, has shown therapeutic potential in depression by modulating physiological, cognitive, and social behaviors via central and peripheral mechanisms.

Methods This review was conducted using the PubMed and Web of Science databases without time restrictions. It provides the first systematic synthesis of empirical evidence on the oxytocin's therapeutic efficacy across depressive disorders, comprehensively describes its potential neurobiological targets, and rigorously evaluates its therapeutic mechanisms. Data from randomized controlled trials were analyzed to assess the clinical feasibility and scientific validity of oxytocin.

Results Evidence from included studies suggested that oxytocin enhanced maternal perception of infants in females with postpartum depression, although its impact on maternal mood was inconsistent. Oxytocin demonstrated efficacy as an adjunctive therapy to psychotherapy or pharmacotherapy in major depressive disorder and treatment-resistant depression. Additionally, studies identified sex differences in oxytocin's antidepressant effects.

Conclusion The present study provides a comprehensive summary of oxytocin's antidepressant effects, offers new insights into its use for treating diverse subtypes of depression, and presents useful guidance for developing evidence-based depression treatment protocols.

Psychiatry Investig 2025;22(9):964-978

Keywords Oxytocin; Postpartum depression; Major depressive disorder; Persistent depressive disorder; Treatment resistant depression.

INTRODUCTION

Rapid societal change is increasing mental pressure among individuals, and leading to an increase in the prevalence of depression worldwide.[1,2] The condition has a complex nature and causes considerable suffering.[3] Data from the Global Health Data Exchange has shown that approximately 322 million individuals are affected by this condition worldwide. Prevalence rates reach 5.02% and 5.71% in adults over 20 and 60 years old, respectively.[4] Notably, the emergence of the novel coronavirus pandemic in 2019 triggered a significant increase in depression rates worldwide, posing a serious risk to public health and resulting in significant economic consequences.[5] This phenomenon may be attributed to the age of onset of depression, which is typically between the ages of 20 and 60. As the working population is largely made up of people in this age group, the reduced ability to work greatly increases the financial burden and leads to depression.[2]

Effective treatments aimed at shortening the duration of depressive episodes (or preventing their onset) can significantly reduce the overall burden of depression. Pharmacotherapy and psychosocial interventions are the mainstays of treatment for depression.[6] However, the significant individual variability in pharmacotherapy increases therapeutic complexity, delays the onset of action, and prolongs treatment duration.[7] In addition, psychosocial interventions require sustained specialist involvement and impose substantial financial burdens on patients. Given these challenges, new therapies are being actively explored.

Several basic and clinical studies have shown that oxytocin

Received: October 22, 2024 **Revised:** April 9, 2025
Accepted: July 3, 2025

✉ **Correspondence:** Jing Jie, PhD
State Key Laboratory of Digital Medical Engineering, Key Laboratory of Biomedical Engineering of Hainan Province, School of Biomedical Engineering, Hainan University, Sanya 572025, China
Tel: +86-13698954826, **E-mail:** jiejing@hainanu.edu.cn

exerts potential antidepressant effects.[8,9] Oxytocin is a cyclic peptide composed of nine amino acids. It is synthesized in the paraventricular nucleus, supraoptic nucleus, and accessory magnocellular nuclei of the hypothalamus. The majority of oxytocin is secreted into the bloodstream through axonal release from the posterior pituitary.[10] Oxytocin acts as a neuromodulator that affects multiple brain regions,[11] including those involved in memory activity,[12] social cognition,[13,14] and anxiety responses.[15] Furthermore, oxytocin has been demonstrated to promote prosocial behaviors,[16] improve the ability to accept empathy[17] and recognize emotions,[18] reciprocate trust among group members,[17] and increase the desire to share personal secrets.[19] It also enhances social bonding,[20] such as that between parents and infants[21] and within marital relationships.[22] Oxytocin therapy may therefore potentially alleviate depressive symptoms by positively influencing social interaction behaviors (such as promoting intimacy and enhancing empathy) and regulating responses to stressors. Its effect on depressive symptoms is currently being studied, and several clinical and basic research studies have demonstrated its antidepressant effects.[8,9] In this context, low peripheral oxytocin levels have been associated with depression,[23] and studies in mice[24] and rats[25] have demonstrated the antidepressant effects of oxytocin. Other studies have shown that it can significantly reduce negative thoughts in affected patients[26] and offer benefits in those with low mood.[27]

In recent years, a large number of randomized trials are investigating the potential antidepressant effect of oxytocin. However, the types of depression targeted by oxytocin, specific strategies used, neural circuits involved, and overall effectiveness of these interventions have not been comprehensively reviewed. To address this gap, we systematically analyzed data from randomized trials and thoroughly reviewed studies that used oxytocin to treat depression. Unlike prior reviews that focused solely on a single depressive subtype, this study dissects the differential effects of oxytocin across subtypes and proposes subtype-specific treatment strategies. Additionally, we comprehensively analyze the mechanisms underlying oxytocin's antidepressant effects, elucidating neurobiological pathways and offering insights into symptom alleviation. This study also explores potential causes of subtype-specific variability in efficacy. Lastly, based on sex differences in oxytocin's effects on healthy individuals and its differential impacts on emotion recognition in depressed patients, we hypothesize that there are sex differences in oxytocin's therapeutic efficacy.

METHODS

Literature search

The literature search was conducted by two authors in March 2024. A total of 273 articles were initially retrieved. Titles and abstracts were read and 36 articles were read in full after removing duplicate references. After further deleting literature that does not meet the requirements, 15 articles pertaining to oxytocin therapy in patients with depression were included in the final systematic review.

The PubMed and Web of Science were searched without year limitation for articles related to the use of oxytocin for depression. The search was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search was conducted in the databases using Medical Subject Headings (MeSH) terms, entry terms, and their combinations. Take "PubMed" as an example; the retrieval formula is: (Oxytocin or Ocytocin or Syntocinon or Pitocin) AND (Depression or Depressive Symptoms or Depressive Symptom or Symptom, Depressive or Emotional Depression or Depression, Emotional). More retrieval formulas were shown in Table 1.

The references of the included studies were also searched to further identify relevant references. This ensured the identification of articles missed during the initial search. The PRISMA flowchart of the selection process is shown in Figure 1.

Eligibility criteria

Studies were included if they met the following criteria: 1) patients were diagnosed with depression according to internationally recognized diagnostic criteria; 2) the study was of a randomized controlled design (case studies, though non-

Table 1. Search strategy

Database	Search strategy	Records
PubMed	((((Oxytocin[MeSH Terms]) OR (Ocytocin[MeSH Terms])) OR (Syntocinon[MeSH Terms])) OR (Pitocin[MeSH Terms])) AND ((((((Depression[MeSH Terms]) OR (Depressive Symptoms[MeSH Terms])) OR (Depressive Symptom[MeSH Terms])) OR (Symptom, Depressive[MeSH Terms])) OR (Emotional Depression[MeSH Terms])) OR (Depression, Emotional[MeSH Terms]))	55
Web of science	(TS=(Oxytocin) OR AB=(Oxytocin OR Ocytocin OR Syntocinon OR Pitocin)) AND (TS=(Depression) OR AB=(Depression or Depressive Symptoms or Depressive Symptom or Symptom, Depressive or Emotional Depression or Depression, Emotional)) AND (TS=(Randomized Controlled Trial) OR AB=(Randomized or Random or Randomise))	219

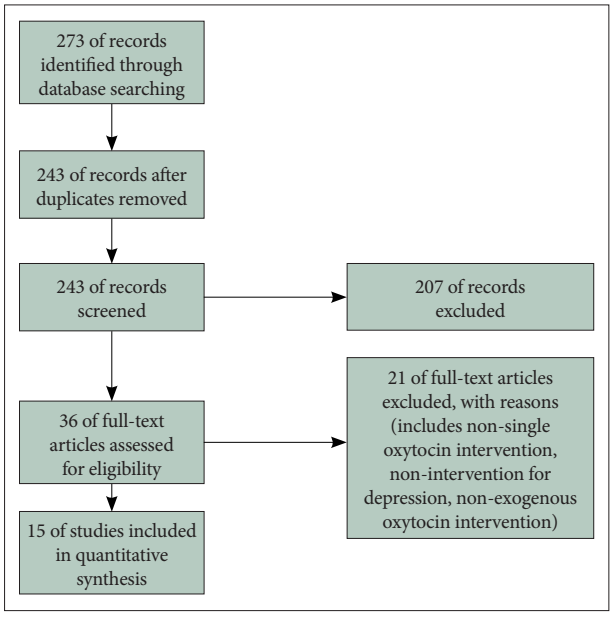

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart of the selection process.

randomized, were included due to the significance of their findings); 3) there were no restrictions on patient age, sex, race, etc; 4) the intervention involved exogenous oxytocin or placebo and; 5) outcome data from oxytocin interventions were available.

Studies were excluded if they met the following criteria: 1) studies of non-depressed patients; 2) studies that did not report sufficient outcome data; 3) non-exogenous oxytocin administration; 4) studies focusing on endogenous oxytocin levels without exogenous administration; and 5) letters, conference papers, newspaper articles were not included.

Quality assessment

The tool recommended by the Cochrane Collaboration was used to assess the risk of bias in the included studies. The tool includes the judgments and the basis for each entry in the risk of bias table. The following sources of bias were evaluated: 1) random sequence generation (selection bias), 2) allocation concealment (selection bias), 3) blinding of participants and personnel (performance bias), 4) blinding of outcome assessment (detection bias), 5) incomplete outcome data (attrition bias), 6) selective reporting (reporting bias), and 7) other bias. Each entry included an assessment of the risk of bias (low/high/unclear). In this context, an unclear risk of bias indicates a lack of information or uncertainty regarding potential bias. The results of quality assessment of the included literature are presented in Figure 2.

Data extraction

Fourteen studies that met the criteria were included in the

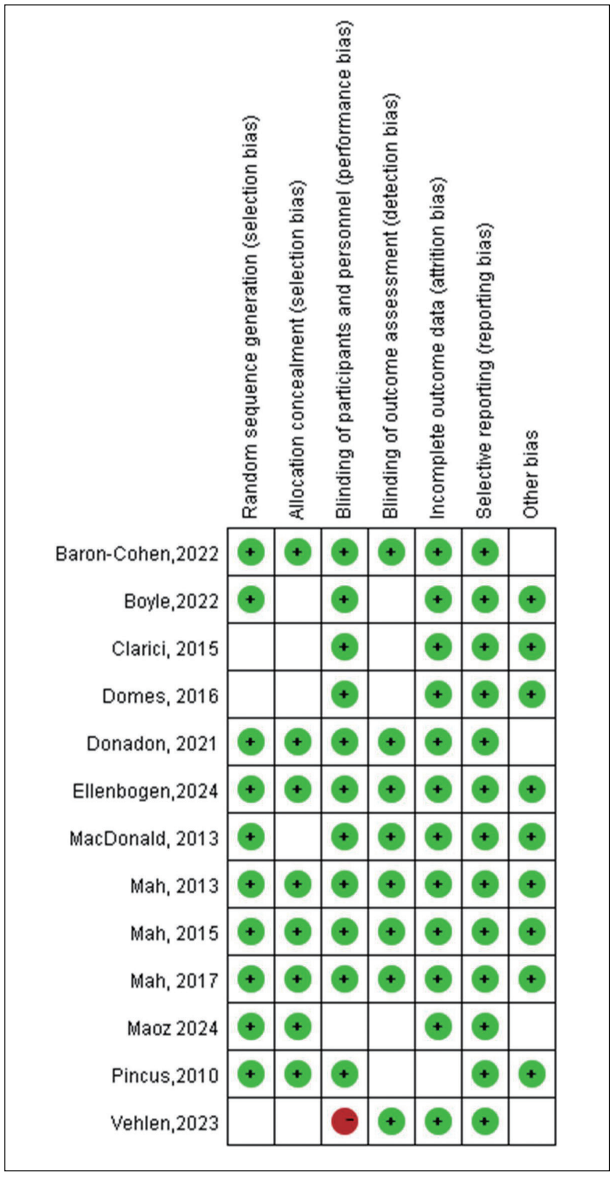

Figure 2. Risk of bias assessment in the included studies.

analysis, examining the impact of oxytocin on individuals with depression. These studies covered various types of depression, including postpartum depression (PPD), major depressive disorder (MDD), persistent depressive disorder (PDD), and treatment resistant depression (TRD). Information from the studies was collected in a standardized manner and organized in an Excel spreadsheet, detailing study and sample characteristics, interventions, controls, outcomes, and key results.

RESULTS

Research selection

In this systematic review, a total of 424 participants were included, with 6 studies involving 195 PPD patients. Among

them, 4 studies diagnosed patients based on the Edinburgh Postnatal Depression Scale (EPDS),[26-29] while the other two studies diagnosed patients based on Beck's criteria scale and the Diagnostic and Statistical Manual of Mental Disorders (DSM).[28,30] The primary attributes of the PPD patients included in the study are detailed in Table 2.

The identification of MDD in the participants of the research was determined using a combination of diagnostic tools, including the DSM-IV Axis I Disorders, Antidepressant Treatment History Form[31]; Mini International Neuropsychiatric Interview (MINI), validation from the patients' healthcare providers[32]; Beck Depression Inventory[33]; Structured Clinical Interview for DSM-IV-TR (SCID), Inventory of Depressive Symptomatology-Clinician Rated (IDS-C),[34] and Hamilton Depression Rating Scale (HDRS).[34,35] The essential attributes of the individuals diagnosed with MDD are outlined in Table 3.

Two studies on patients with PDD were diagnosed based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision[36] and DSM-V[37] criteria and the main characteristics of the included PDD patients are shown in Table 4.

A study on TRD utilized diagnostic criteria from the DSM-IV, MINI, and the 17-item HDRS (HDRS-17).[38] Table 5 presents the key characteristics of the patients with TRD included in the study.

Different types of depression treated with oxytocin intervention

Oxytocin intervention for PPD

PPD is a multifaceted and multifactorial disorder that not only affects postpartum females but also has significant implications for the entire family and society at large. PPD is frequently overlooked in the general population,[39] with its occurrence rising each decade.[40] The worldwide prevalence of PPD in new mothers stands at 17.7%.[41] Additionally, mothers experiencing PPD may impact their children's emotional and executive capabilities from infancy through later childhood.[42,43] Previous studies have indicated that oxytocin has a beneficial influence on parental behavior.[44] The characteristics of the oxytocin intervention trials are shown in Table 2. Females suffering from PPD exhibit reduced sensitivity to infant cues,[45] an increased risk of neglecting their babies, and (in severe cases) may adopt aggressive parenting styles.[46] Research suggests that oxytocin can enhance protective behaviors toward offspring in females with PPD. Mah et al.[47] conducted research explored whether intranasal oxytocin administration would increase the protective behaviors of PPD mothers towards their children. The results showed that under the influence of oxytocin, mothers exhibited enhanced protective responses towards infants when in the company of strangers (p=0.036). Mah et al.[28] also found that PPD patients receiving oxytocin treatment perceived infant crying as a more urgent event (p=0.04) and were likely to adopt stricter parenting practices (p=0.03). This suggests that oxytocin has a significant impact on the urgency

Table 2. Characteristics of randomized controlled trials evaluating the effect of intranasal oxytocin in patients with PPD

Study	Study design	Randomized		Age (mean±SD, yr)	Dose (IU)	Intervention (min)	Outcome measures
		Oxytocin	Con				
Mah et al.[29]	Crossover	13	12	28.24±5.93	24	4 post-treatment	SAM, COWAT, FMSS,
Mah et al.[47]	Crossover	Roughly half of 16	Roughly half of 16	26.50±4.71	24	55 post-treatment	ESP
Clarici et al.[30]	Parallel	5	11	36.5±5.6	16 for 3 mon+ psychological psychodynamic	End of treatment	EPDS, HDRS, ANPS, SWAP
Mah et al.[28]	Crossover	Roughly half of 25	Roughly half of 25	28.24±5.93	24	30–50 post-treatment	Maternal sensitivity cry paradigm
Donadon et al.[26]	Crossover	20	35	PPD: 27.4±6.4, Con: 28.1±6.4	24	30 post-treatment	FER, PNTQ
Lindley Baron-Cohen et al.[27]	Crossover	26	32	33.62±4.48	24	35–45 post-treatment	PANAS, EPDS

PPD, postpartum depression; Con, controls; SD, standard deviation; SAM, Self-Assessment Manikin; COWAT, Controlled Oral Word Association Test; FMSS, Five Minute Speech Sample; ESP, Enthusiastic Stranger Paradigm; PANAS, Positive and Negative Affective Scales; EPDS, Edinburgh Postnatal Depression Scale; HDRS, Hamilton Depression Rating Scale; ANPS, Affective Neuroscience Personality Scales; SWAP, Shedler-Westen Assessment Procedure; FER, facial emotion recognition; PNTQ, Postnatal Negative Thoughts Questionnaire.

Table 3. Characteristics of randomized controlled trials evaluating the effect of intranasal oxytocin in patients with major disorder

Study	Study design	Randomized oxytocin, control	Age (yr)	Dose	Intervention	Outcome measures
Pincus et al.[31]	Crossover	17	35.50±10.62	40 IU	10 min post-treatment	fMRI, speed of reaction time
Scantamburlo et al.[35]	Single-group	1	38	16 IU+20 mg escitalopram after 1 wk 36 IU+20 mg escitalopram	End of treatment	Ham-D, STAI-A, Q-LES-Q
MacDonald et al.[32]	Crossover	17	43.65±12.20	40 IU	50 min post-treatment	Vital signs, salivary cortisol, PANAS, STAI, RMET
Boyle et al.[33]	Crossover	19	24.44±4.27	24 IU	30 min post-treatment	Eye tracking
Ellenbogen et al.[34]	Crossover	23	27.2±5.4	24 IU	30 min post-treatment	IDS-C
Maoz et al.[55]	Randomized controlled	28, 28	44.74±17.36	32 IU+treated	4 wk	HAM-D, STAI, OQ-45, HSCL-11, SAI

STAI-A, Spielberger State-Anxiety Inventory; RMET, Reading the Mind in the Eyes Test; STAI, State-Trait Anxiety Inventory; PANAS, Positive and Negative Affective Scales; IDS-C, Inventory of Depressive Symptomatology-Clinician Rated; HAM-D, Hamilton Rating Scale for Depression; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; OQ-45, The Outcome Questionnaire-45; HSCL-11, The Hopkins Symptom Checklist-short form scale; SAI, The Session Alliance Inventory.

Table 4. Characteristics of randomized controlled trials evaluating the effect of intranasal oxytocin in patients with chronic depression disorders

Study	Study design	Randomized OT, control	Age (mean±SD, yr)	Dose (IU)	Intervention (min)	Outcome measures
Domes et al.[36]	Parallel	22, 21	OT: 46.7±11.1, Pla: 47.2±9.0	24	60 post-treatment	Reaction time, attentional bias
Vehlen et al.[37]	Crossover	20, 19	PDD_{OT}: 45.6±11.8, PDD_{Pla}: 47.9±9.7	24	45 post-treatment	FER

OT, oxytocin; Pla, placebo; PDD_{OT}, persistent depressed patients in the oxytocin group; PDD_{Pla}, persistent depressed patients in the placebo group; FER, facial emotion recognition.

Table 5. Characteristics of randomized controlled trials evaluating the effect of intranasal oxytocin in patients with treatment-resistant depression

Study	Study design	Randomized oxytocin, control	Age (mean±SD, yr)	Dose	Intervention	Outcome measures
Scantamburlo et al.[38]	Single-group	14	Females: 48.5±13.9, males: 44.75±9.1	16 IU+40 mg of escitalopram	4 wk	HDRS-17, STAI-A, CGI-S, Q-LES-Q

HDRS-17, 17-item Hamilton Depression Rating Scale; STAI-A, Spielberger State-Anxiety Inventory; CGI-S, Clinical Global Impressions Severity of Illness scale; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire.

perception and caregiving strategies of mothers with PPD.

Negative thoughts are considered a hallmark of depression. Research has found that oxytocin can reduce negative thoughts in mothers with PPD. Donadon et al.[26] conducted a randomized double-blind crossover trial evaluated the effects of oxytocin on facial emotion recognition (FER) and negative thoughts in mothers with PPD. Participants received 24 IU of oxytocin or a placebo. The results indicated that mothers with PPD had more negative thoughts compared to healthy mothers, but there were no significant differences in FER. Compared to the placebo group, the oxytocin group showed a significant reduction in the frequency of negative thoughts (factor baby-related and motherhood negative thoughts: PNTQ-BRM-NT; oxytocin: 5.33±4.43; placebo: 2.13±6.13; p=0.02). This suggests that oxytocin may have a positive impact on maternal affiliative behavior, maternal care, and mother-infant interactions, potentially reducing the negative effects of PPD on infant development.

Additionally, the effects of oxytocin on mood in PPD patients are contradictory. Mah et al.[29] conducted a randomized double-blind within-subject clinical trial to investigate the

impact of intranasal oxytocin administration on emotional expressions related to sensitive parenting. The study involved 25 PPD participants randomly assigned to receive either 24 IU of oxytocin or a placebo. The findings indicated that participants exhibited heightened sadness following oxytocin intervention (p=0.01) and reported more frequent initial difficulties in engaging with their infants (p=0.038). Nevertheless, the nature of their bond with the infants was more favorable (p=0.036), and it did influence their perception of the relationship with their babies. Similarly, Lindley Baron-Cohen et al.[27] conducted a randomized double-blind within-subject crossover trial investigated the impact of oxytocin on negative mood in mothers with PPD. Participants received 24 IU of oxytocin or a placebo, and their mood was assessed using the Positive and Negative Affect Scale at baseline and post-intervention. The results showed that negative mood was significantly higher in PPD patients compared to the control group (p<0.002). Although oxytocin did not significantly affect the mood of PPD patients, it significantly reduced negative mood in the control group (baseline: 11.64±1.81, placebo: 11.28±2.04, oxytocin: 10.69±1.40). Notably, oxytocin significantly alleviated negative mood in PPD patients with moderate EPDS scores, implying therapeutic potential for moderate sub-clinical levels of PPD.

Beyond core mood disorders, PPD may involve narcissistic affective dysregulation, while oxytocin intervention can modulate this type of affective disturbance. Clarici et al.[30] conducted a randomized double-blind study evaluated the potential therapeutic effects of oxytocin on PPD. Sixteen patients received either 16 IU of oxytocin (n=5) or a placebo (n=11) daily and short-term psychodynamic psychotherapy for 12 weeks. The results indicated no significant differences in depressive symptoms between the oxytocin and placebo groups (change in EPDS scores before and after administration: oxytocin group=3.4, placebo group=3.93). However, patients treated with oxytocin showed a significant reduction in narcissistic traits (p=0.006), suggesting that oxytocin may help ameliorate narcissistic affective imbalance in patients with PPD. The abovementioned studies indicate that oxytocin may improve PPD patients' perception of infants and ameliorate egocentric-narcissistic affective imbalances, rather than directly alleviating depressive symptoms.

However, contradictions persist regarding its efficacy in mood management among females with PPD. Future studies should consider oxytocin as an adjunctive therapy for PPD. To establish robust clinical evidence, research should employ larger, multi-center cohorts. The study protocol should include standardized dose-response evaluations, encompassing various oxytocin concentrations and administration regimens. Additionally, comprehensive assessment protocols should be implemented, incorporating validated psychometric scales and biochemical markers. The multimodal integration of advanced neuroimaging techniques, e.g., functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), could elucidate the neurobiological mechanisms underlying oxytocin's potential therapeutic effects in PPD pathophysiology.

Oxytocin intervention for MDD

The core symptoms of MDD include persistent depressive mood, anhedonia, fatigue, and difficulty concentrating.[48] Additionally, depression leads to impaired mentalization,[49] characterized by abnormal neural activity in ventral limbic and paralimbic regions, which are critically involved in the development of socio-cognitive abilities.[50] Although existing therapies are effective for some patients in the short term,[51] approximately 40%−50% of patients discontinue treatment prematurely due to poor efficacy or adverse effects or experience incomplete symptom remission in the later stages of treatment.[52] Furthermore, the relapse rate for patients with MDD is high within 1 to 2 years of treatment,[53] and even after symptom remission, impairments in psychosocial functioning may persist.[54] Oxytocin could be a potential treatment modality for MDD. The characteristics of the oxytocin intervention trials are shown in Table 3.

Oxytocin, whether used as psychotherapy or as an adjunct to antidepressant medication, can alleviate the severity of depression in MDD patients without borderline personality disorder (BPD).

MacDonald et al.[32] randomized double-blind crossover trial aimed to evaluate whether oxytocin enhances the efficacy of psychotherapy. The study included 17 adult patients with MDD who received 40 IU of intranasal oxytocin or placebo before psychotherapy, followed by the Reading the Mind in the Eyes Test (RMET) after the treatment sessions. The results indicated that the oxytocin group had a significantly higher number of correct interpretations on the RMET compared to the placebo group (oxytocin group: 29.29±3, placebo group: 26.76±5; p=0.046), with the percentage of correct responses increasing from 74.3% in the placebo group to 81.4% in the oxytocin group.

To investigate the role of oxytocin in modulating neural activity in MDD patients and its association with mental attribution of others' psychological states, Pincus et al.[31] conducted a randomized double-blind crossover trial comparing 8 MDD patients and 9 healthy controls. Participants received 40 IU intranasal oxytocin or placebo before undergoing the RMET. The results indicated that oxytocin slowed reaction time in the healthy control group (pre-oxytocin: 4,198.5±1,728.6 ms; post-oxytocin: 4,222.8±1,293 ms), while it accelerated reaction time in the depressed group (pre-oxytocin: 4,201.6±1,169.3 ms; post-oxytocin: 4,119.8±1,297.2 ms). Furthermore, oxytocin increased the accuracy of responses in the

depressive group (pre-oxytocin: 67%; post-oxytocin: 70.6%), consistent with findings from other studies.[32]

Ellenbogen et al.[34] randomized double-blind placebo-controlled trial aimed to evaluate whether oxytocin enhancement could improve the efficacy of psychotherapy for MDD. In the study, 23 patients with MDD were divided into two groups: 12 patients received interpersonal psychotherapy (IPT) combined with 24 IU of oxytocin. In comparison, 11 patients received IPT combined with 24 IU of placebo. The efficacy of the interventions was assessed using the IDS-C. The results indicated that oxytocin significantly reduced the severity of depression in patients with MDD (pre-oxytocin: 32.8±11.5, post-oxytocin: 7.2±6.6).

Maoz et al.[55] conducted a randomized controlled trial to compare the efficacy of intranasal oxytocin between MDD patients with and without BPD. The study enrolled 58 participants (BPD: n=35; non-BPD: n=23). Patients were randomly assigned and underwent double-blind treatment ($N_{oxytocin}$: BPD [n=17], non-BPD [n=12]; $N_{placebo}$: BPD [n=18], non-BPD [n=11]) to receive either 32 IU of oxytocin per day or a placebo, which was used to adjunct the hospital's in-ward treatment 2−3 times per week (pharmacotherapy, group therapy and individual psychotherapy) for 4 weeks. The results demonstrated that MDD patients without BPD exhibited significantly greater improvement following oxytocin treatment (p=0.001), whereas those with BPD showed no statistically significant improvement (p=0.76). Consistent findings were observed on the Hopkins Symptom Checklist: non-BPD patients displayed marked improvement compared to the placebo group (p=0.0009), while BPD patients showed no significant improvement (p=0.55).

Scantamburlo et al.[35] pioneered the use of oxytocin as an adjunctive therapy for MDD. Their case report documented a male patient with a 15-year MDD history who received 16 IU intranasal oxytocin combined with 20 mg escitalopram. Within 1 week, clinical assessments revealed that his HDRS score decreased from 17 to 11, and his Spielberger State-Anxiety Inventory (STAI-A) score decreased from 57 to 49. Upon discontinuation of intranasal oxytocin for one week, the patient's condition deteriorated. Subsequently, he was treated with 36 IU of intranasal oxytocin daily alongside 20 mg of escitalopram. After 1 week, his HDRS score further decreased to 5, and his STAI-A score decreased to 48. This suggests that oxytocin may be an adjunct to antidepressant medication for the improvement of mood and anxiety symptoms in patients with MDD.

Moreover, patients with MDD exhibit impairments in certain domains of social cognition, such as emotion recognition. These deficits may contribute to interpersonal difficulties.[56] Oxytocin administration improves emotional recognition capacity in individuals with MDD, consequently ameliorating social cognitive functioning. Boyle et al.[33] randomized double-blind placebo-controlled trial aimed to examine the effects of intranasal oxytocin on selective attention to emotional facial expressions and facial features, as well as to determine whether depressive symptoms are associated with heightened sensitivity to oxytocin, relative to placebo. In this study, 19 patients with MDD received either 24 IU of intranasal oxytocin or placebo, followed by two eye-tracking tasks. The results indicated that male patients with depression were more sensitive to oxytocin, showing a significant increase in attention to the mouth regions of surprised and happy facial expressions and a decrease in overall attention to angry expressions, whereas female patients exhibited an increase in overall attention to angry expressions following oxytocin administration.

Emerging evidence positions oxytocin as a promising neuromodulator, with these collective findings providing an empirical foundation for novel therapeutic development in MDD. Future research should adopt a multidimensional approach to investigate oxytocin's therapeutic potential in MDD. Treatment protocols should be tailored according to critical clinical variables, such as disease duration, medication history, psychosocial stress levels, and sex differences. A comprehensive research framework should integrate advanced neuroimaging techniques (e.g., fMRI) with standardized behavioral assessments to elucidate the neural mechanisms underlying oxytocin's antidepressant effects. This multimodal approach will allow researchers to establish dose-response relationships, identify optimal treatment windows, and develop personalized therapeutic strategies for MDD patients.

Oxytocin intervention for PDD

PDD refers to a mental disorder characterized by depressive symptoms persisting for more than two years, with symptom-free periods lasting no longer than two months.[57] Compared to episodic depression, PDD exhibits more severe psychopathological features,[37] including higher rates of psychiatric and somatic comorbidity, more profound impairments in social-cognitive functioning,[58] and an increased frequency of suicide attempts.[59] Simultaneously, studies have shown that intranasal administration of oxytocin can enhance social-cognitive functioning in patients with depression.[32] The characteristics of the oxytocin intervention trials are shown in Table 4.

Oxytocin has shown positive effects in modulating attentional allocation in patients with PDD. Domes et al.[36] conducted a randomized, double-blind, placebo-controlled trial to investigate whether oxytocin modulates attentional biases toward threatening social cues (angry faces) and prosocial cues (happy faces) in patients with PDD. The study included 22 patients who received intranasal oxytocin at a dose of 24

IU and 21 patients who received an equivalent dose of placebo, followed by a dot-probe task. The results indicated that patients receiving oxytocin treatment exhibited increased attentional bias toward the eye region of positive facial expressions, reduced allocation of attention toward aversive social cues (p=0.046), and an increased and longer duration of adherence to positive social cues (p=0.046), revealing the potential role of oxytocin in social perception and positive social interactions.

Beyond attentional modulation, oxytocin may directly influence social perception. In a randomized placebo-controlled trial by Vehlen et al.,[37] researchers evaluated the effects of a single oxytocin dose on gaze preferences using remote eye-tracking during a FER task in patients with PDD. The study included 39 patients and 19 healthy controls. Twenty patients received 24 IU of oxytocin, and 19 received an equivalent placebo dose. The healthy control group did not receive any treatment. The FER was conducted 45 minutes post-administration. The results showed that patients with PDD retained basic FER and that oxytocin treatment had no effect on emotion recognition (p=0.736). However, oxytocin significantly reduced the avoidance of eye gaze during happy facial expressions (p=0.042). This compensatory effect suggests that oxytocin may act as a modulator of social perception by enhancing attention to positive social cues, thereby facilitating social interactions.

Collectively, these studies demonstrate that oxytocin has shown positive effects in modulating social perception, attentional allocation, and emotion recognition in patients with PDD. However, future research should investigate the effects of varying oxytocin doses and long-term administration effects of oxytocin in PDD, as well as incorporate broader outcome measures (e.g., neural correlates or long-term behavioral changes) to fully elucidate its therapeutic potential.

Oxytocin intervention for TRD

TRD is defined as a lack of response to two different classes of major antidepressants at their maximum recommended doses, with symptoms persisting for at least two years. Scantamburlo et al.[38] conducted an open-label study to investigate oxytocin as an adjunctive treatment for antidepressant therapy. The characteristics of the oxytocin intervention trials are shown in Table 5.

The study included 14 patients with an HDRS-17 score of at least 17, who did not respond to 40 mg of escitalopram over 8 weeks. These patients subsequently received a daily dose of 16 IU intranasal oxytocin for 4 consecutive weeks. Outcome measures included the HDRS-17, STAI-A, Clinical Global Impressions Severity of Illness scale (CGI-S), and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). The results demonstrated significant differences in the scores of these scales between day 1 and day 28 of treatment (HDRS, p<0.01; STAI-A, p=0.04; CGI-S, p<0.01; Q-LES-Q, p=0.014), with the CGI-S score decreasing from 4.3 (standard deviation [SD]=0.95) to 2 (SD=1.5), indicating that oxytocin can serve as an adjunctive treatment for antidepressant therapy in TRD.

As mentioned above, future research should further explore these directions through large-sample randomized controlled trials to validate the efficacy of exogenous oxytocin as an adjunct to neuromodulation techniques, particularly its synergistic effects with repetitive transcranial magnetic stimulation (rTMS). Building upon prior findings that rTMS alleviates TRD,[60] the integration of oxytocin as an adjunct therapy warrants further exploration through controlled trials. Additionally, rigorous control of variables such as sex, baseline oxytocin concentrations, depression severity, and oxytocin dosage is essential. Subgroup analyses should be utilized to identify predictors of treatment response and optimize personalized protocols.

Intervention mechanism

The antidepressant effects of oxytocin may involve the hypothalamic-pituitary-adrenal (HPA) axis, raphe nuclei-nucleus accumbens septi pathway, amygdala-hippocampal network, anti-inflammatory and antioxidative pathways, and genetic polymorphisms. The antidepressant mechanisms of these pathways and factors are described in detail below.

HPA

The hypothalamic-pituitary system represents one of the targets in the treatment of depression. In this context, abnormal activation of the hypothalamus and its downstream neuroendocrine pathways is widely recognized as the ultimate common mechanism in the pathogenesis of depression.[61] In particular, hyperactivation of the HPA axis is a risk factor for the development of depression.[62] The hormones released by the hypothalamus, pituitary, and adrenal glands include corticotropin-releasing factor, adrenocorticotropic hormone, and cortisol, respectively. The elevation of hormone levels in the plasma or body fluids represents one of the most common neurobiological manifestations in patients with depression.[63] Oxytocin may regulate the emotional function of the hypothalamus,[64] and may also regulate the stress response by reducing HPA axis activity.[65] In this context, the inhibition of oxytocin signaling in the hypothalamic paraventricular and dorsal raphe nuclei leads to an increase in symptoms of PPD.[66] This suggests that decreased levels of oxytocin may lead to dysregulation of the HPA system and that oxytocin may regulate depressive symptoms by influencing HPA axis function.

Raphe nuclei-nucleus accumbens septi pathway

The raphe nuclei-nucleus accumbens septi pathway repre-

sents another target in the treatment of depression. The monoamine transmitter hypothesis suggests that depressive symptoms are caused by an imbalance of monoamine transmitters in the brain.[67] The nucleus accumbens septi contains several monoamine neurotransmitters including serotonin (5-HT) and dopamine, which play important roles in emotion and motor regulation. Previous studies have shown that the neural mechanisms of social reward require co-regulation of oxytocin and 5-HT in the nucleus accumbens septi.[68] As anhedonia or lack of desire for reward, is a hallmark of individuals with depression, the nucleus accumbens septi in these cases is likely to demonstrate an imbalance between oxytocin and 5-HT. In this context, oxytocin can modulate 5-HT release by directly activating oxytocin receptors (OXTR) on 5-HTergic neurons in the nucleus accumbens septi.[69]

As this nucleus receives projections from 5-HTergic fibers of the midbrain raphe nucleus,[70] the raphe nuclei nucleus accumbens septi pathway is likely to be one of the brain networks that are targeted by oxytocin during alleviation of depressive symptoms.

Amygdala-hippocampal network

The amygdala-hippocampal network is yet another target for the treatment of depression, as it is linked to negative emotional memory bias which is observed in depression.[71] Interventions that weaken negative memories and strengthen positive ones are therefore likely to be beneficial in the treatment of depression. Notably, studies have found that the volumes of the amygdala and hippocampus correlate negatively with depressive symptoms[72,73] and that chemogenetic-specific activation of neural circuits that extend from the posterior part of the basolateral amygdala to the CA1 area of the ventral hippocampus significantly attenuate depressive-like behaviors induced by chronic unpredictable mild stress.[74] This suggests that structural and functional changes in these two brain regions are related to the occurrence of depression. Oxytocin, however, specifically regulates human emotion-processing networks in brain regions centered on the amygdala[75] and directly affects neuroplasticity in hippocampal brain regions, thereby ameliorating depressive symptoms.[76] The amygdala-hippocampal emotional memory network may therefore represent one of the target brain networks via which oxytocin exerts antidepressant effects.

Anti-inflammatory and antioxidant effects of oxytocin

Neuroinflammation is an intrinsic immune response of the central nervous system. It is characterized by microglial activation and is accompanied by astrocyte activation and increased levels of inflammatory mediators.[77] Research indicates the presence of prominent signs of neuroinflammation in patients with depression; this is mediated via microglial activation in relevant brain regions.[78] Notably, studies have shown levels of inflammatory markers to be higher in untreated patients with depression, and antidepressant treatment may exert its effects by increasing levels of anti-inflammatory cytokines.[79] Pretreatment with oxytocin significantly inhibits lipopolysaccharide-induced microglial activation and reduces levels of pro-inflammatory mediators. The effect may be attributed to the blocking of microglial extracellular signal-regulated kinase and p38 phosphorylation by oxytocin.[80]

Findings from studies suggest that depression is often associated with oxidative damage and an impairment in antioxidant systems.[81] Oxidative stress is believed to result from an imbalance between the oxidative and antioxidant systems.[82] In this context, mitochondria are a major target of stress, and abnormal mitochondrial function triggers the onset of immune-inflammatory responses in the brain.[83] Studies have shown that neonatal maternal separation can lead to abnormal mitochondrial function in the hippocampus and trigger an inflammatory response. Adult male mice have also been found to demonstrate obvious depressive behavior after maternal separation. Notably, the administration of intranasal oxytocin has been found to improve mitochondrial function and reduce hippocampal expression of immunoinflammatory genes, which reduce depressive-like behavior during forced swim, open field, and sucrose preference tests.

Genetic polymorphisms in oxytocin

Research indicates that the A allele of the OXTR rs53576 is associated with higher levels of suicide attempts.[84] Kushner et al.[85] reported that a single nucleotide polymorphism (rs53576) in the OXTR gene mitigated the severity of depression. Similarly, Thompson et al.[86] demonstrated a significant association between depressive symptom levels and OXTR genotypes in adolescent females with depression. Adolescents carrying at least one A allele of the OXTR rs53576 polymorphism and a history of early maternal separation exhibited more severe depressive symptoms during adolescence. The OXTR rs53576 polymorphism also correlates with variations in maternal sensitivity and depressive symptoms.[87] Epigenetic studies have further revealed that methylation levels of OXTR exon 1 are linked to depression, with decreased methylation leading to altered or reduced OXTR expression.[88] These findings suggest that depression may downregulate OXTR levels, thereby inhibiting the oxytocin signaling pathway.

The potential targets involved in oxytocin's antidepressant effects are illustrated in Figure 3. The identification of these targets provides new perspectives for biological interventions in depression.

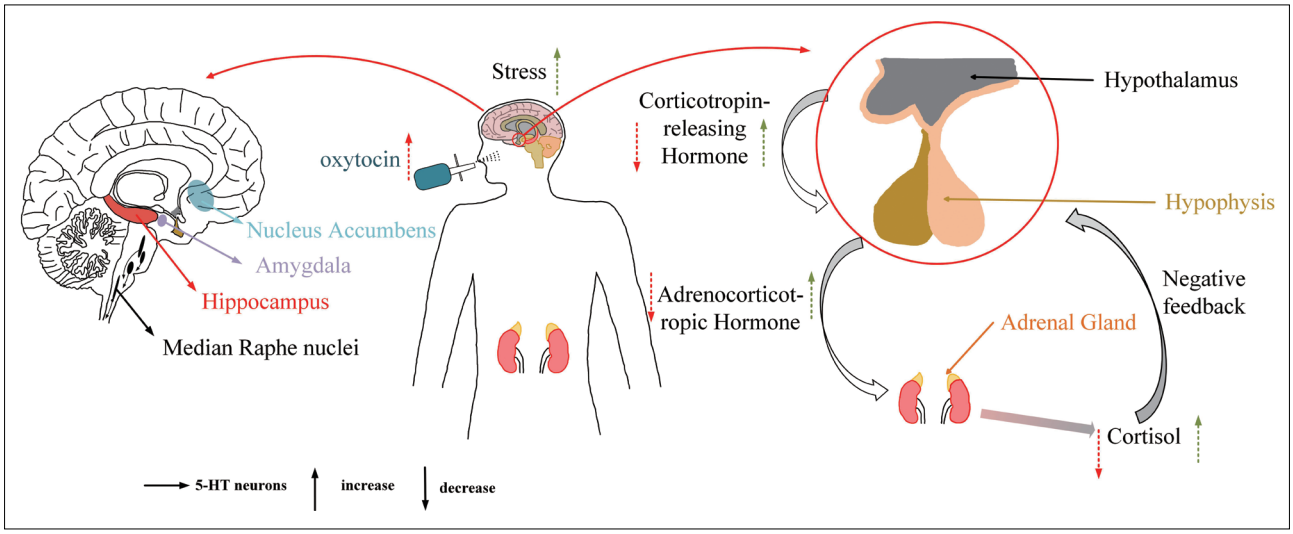

Figure 3. The relevant targets of oxytocin's antidepressant effects. The colours of the brain regions in the figure remain consistent. The process of activation of the hypothalamic-pituitary-adrenal (HPA) axis is indicated by the green dashed arrow. When the brain is stimulated by stress, the hypothalamus begins to secrete corticotropin-releasing hormone (CRF), which in turn stimulates the pituitary gland, which releases adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. ACTH then stimulates the adrenal cortex, which in turn releases cortisol. Stress causes hyperactivation of the HPA axis. The red dashed arrow illustrates the process by which oxytocin attenuates HPA axis activity and thereby regulates the stress response. Oxytocin acts as an antidepressant by down-regulating the CRF, which reduces stimulation of the pituitary gland, leading to a decrease in ACTH and cortisol secretion.

DISCUSSION

The detrimental impact of depression on human well-being is undeniable. People suffering from depression are in urgent need of appropriate therapeutic interventions to alleviate their suffering. This review provides novel clinical insights into the treatment modalities for depression. The review included a total of 15 studies: 6 on PPD, 6 on MDD, 2 on PDD, and 1 on TRD. Despite 2 studies lacking randomized controlled designs,[35,38] their findings were still considered valuable and thus included in this systematic review.

A growing body of evidence suggests that oxytocin is associated with PPD. Females with lower levels of oxytocin are more susceptible to developing PPD.[89] In PPD research, four studies have indicated that oxytocin can modulate the emotions of PPD patients, but the results are inconsistent. Two studies showed that oxytocin could reduce negative thoughts in patients,[26,27] while one study suggested that oxytocin might worsen mood in PPD patients.[29] Three studies suggested that oxytocin improved the relationship between PPD females and their infants,[28,29,47] but research also indicated that oxytocin did not affect FER[26] and sensitivity to infant interactions.[28] The results of the study demonstrated that oxytocin improved maternal perception of their infants and enhanced paternal stimulating parenting.[44] The hypothesis that the combined use of oxytocin by parents may be more beneficial to the healthy development of their offspring than oxytocin use by mothers alone was also put forward. This hypothesis could be investigated further in future research.

In intervention studies on MDD, oxytocin primarily serves as an adjunctive treatment and demonstrates significant efficacy. This is evident in the significantly increased accuracy of emotional recognition,[32] enhanced attention to positive expressions,[33] and reduced severity of depression.[34] Oxytocin notably improves depressive mood and anxiety in MDD patients.[35] It is noteworthy that the effectiveness of oxytocin intervention in MDD shows sex differences, with males being more responsive to oxytocin.

Previous studies have demonstrated sex differences in the response to oxytocin among healthy populations. For instance, intranasal oxytocin administration was found to enhance trust in males but reduce trust in females during a trust game.[90] In a one-shot ultimatum game, oxytocin was found to reduce aggression in males, whereas no such effect was observed in females.[91] Compared to placebo, oxytocin consistently attenuated brain activity in response to negative emotions in males, whereas it enhanced such activity in females.[92] The present study revealed sex differences in the modulation of mood recognition by oxytocin in depressed patients. Specifically, compared to females, males with depressive symptoms showed increased attention to happy faces and decreased attention to negative facial expressions following intranasal oxytocin administration, suggesting greater oxytocin sensitivity in males.[33] This aligns with previous evidence.[93] However, previous studies have not systematically investigated the precise sex differences in the antidepressant effects of oxytocin in depressed patients. In particular, one study reported sex differences in the efficacy of oxytocin as an adjunctive treatment for

severe mental illness, with females showing a significant reduction in depressive symptoms, whereas males showed no improvement.[94] Currently, research investigating sex differences in response to intranasal oxytocin administration in depressed patients is relatively limited. Given the variability in responses to oxytocin administration during mood recognition tasks between healthy individuals and patients with depression, future studies should prioritize balanced sex representation in sample sizes and integrate multidisciplinary approaches, including neuroimaging and molecular biology, to further elucidate the antidepressant effects of oxytocin and the underlying mechanisms of sex differences.

Patients diagnosed with depression who demonstrate sex disparities in emotion recognition subsequent to oxytocin administration may be attributable to alterations in amygdala activation levels following intranasal oxytocin administration. Several studies indicate that in males, oxytocin reduces amygdala activity in response to negative social cues and enhances amygdala activity as well as functional connectivity between the amygdala and other regions of the social salience network in response to positive social cues.[95] In studies involving exogenous oxytocin among females, results are varied: some studies indicate no reduction in amygdala activity in response to negative social cues,[96] others show increased amygdala activation to threatening social cues,[97] and some demonstrate decreased functional connectivity between the amygdala and other regions of the social salience network following negative social interactions.[98] Therefore, the hypothesis posits that oxytocin enhances the reward value or salience of positive social interactions and reduces the stress response to negative interactions in males while diminishing the reward value or salience of positive social interactions in females.[99] The sex differences in these neural responses may explain why there are variations in the therapeutic effects of oxytocin between male and female participants.

PDD is primarily characterized by impaired social cognitive functioning, and oxytocin therapy may have a protective effect against relapse by redirecting attention from negative to positive social cues.[100] This indicates that oxytocin may play a crucial role in modulating social cognition and promoting positive social cognitive tendencies in patients. However, to advance this field, future research should systematically investigate specific dimensions of social cognition in PDD patients, such as emotion recognition, theory of mind, and social reward processing, to elucidate the mechanisms underlying oxytocin's therapeutic effects.

The combination of oxytocin and escitalopram has been shown to significantly alleviate depressive symptoms in patients with MDD.[35] Similar effects have also been observed in TRD patients, with a concomitant reduction in their anxiety scores.[38] It is recommended that future studies investigate the potential of oxytocin as an adjunctive therapy in combination with antidepressants. To further validate and extend these findings, future studies should prioritize large-scale, long-term trials in such patient populations. These trials should investigate the efficacy of different oxytocin doses based on depression severity and administration times. This will enable confirmation of oxytocin's efficacy as an adjunctive therapy and establishment of optimal treatment regimens.

Our study revealed that oxytocin exerts distinct effects across various diagnostic subtypes of depression. The divergent mechanisms underlying these effects may stem from multiple factors. First, depression is a complex condition that includes a range of signs and symptoms that vary in severity and course from patient to patient, with no single factor fully accounting for its etiology.[101] Both familial factors and social stressors are implicated in the pathogenesis of depression.[102] Notably, the oxytocin system is transgenerational and can be passed on to children through parental care patterns. Mothers with lower oxytocin levels show reduced sensitivity in parenting, and their offspring have lower oxytocin levels[103]; this can lead to depression and anxiety later in life. In addition to the impact of PPD on offspring, the heritability of MDD is estimated to be as high as 30%−50%.[104] In addition to genetic influences, exposure to traumatic or adverse life events can result in varying levels and types of depressive symptoms, characterized by differences in symptom duration and heterogeneous degrees of brain impairment. These factors may contribute to the observed variability in the therapeutic effects of oxytocin.

Second, individual variability in endogenous oxytocin levels significantly modulates the therapeutic efficacy of exogenous oxytocin for depression. Emerging evidence suggests that lower endogenous oxytocin levels are associated with increased susceptibility to depression. For example, patients with PPD have reduced oxytocin levels compared to healthy controls.[89,105] Notably, sex differences further complicate this dynamic, with females generally having higher endogenous oxytocin levels than males.[106] Taken together, these findings highlight how baseline oxytocin levels influence response to exogenous oxytocin therapy in depression.

Finally, the heterogeneity of neural circuits across depression subtypes may explain divergent responses to oxytocin therapy. For instance, PDD is characterized by dysregulation in the amygdala,[107] striatum,[108] and prefrontal cortex neural circuits.[109] In contrast, MDD is primarily driven by HPA axis dysregulation and elevated glucocorticoid.[110] TRD, in turn, is associated with inflammation-induced dysregulation of the dopaminergic system[110] and HPA axis dysfunction.[111] Collectively, the distinct neurobiological mechanisms of these subtypes are likely to alter oxytocin system responsiveness, lead-

ing to variable therapeutic effects.

To address these inconsistencies, future research should focus on several key areas. Firstly, longitudinal studies are required to track oxytocin levels over time in individuals with depression, to clarify whether oxytocin dysregulation is a cause or consequence of depressive symptoms. Secondly, researchers should investigate potential mediating variables, such as genetic polymorphisms, early life stress, and social support, which may influence the relationship between oxytocin and depression. Thirdly, the role of moderating variables, including sex, age, comorbid conditions, and dose of oxytocin should be systematically examined to identify subgroups that may benefit most from oxytocin interventions.

The present study has certain limitations. First, the scope of the results is limited by the paucity of relevant randomized controlled trials. In addition, multiple studies were from the same laboratory; this may have led to bias during interpretation. Second, the study included a small sample size; the conclusions, therefore, need to be interpreted with caution. Finally, the studies included in this review mostly used single-dose oxytocin treatment protocols. It remains unclear whether such interventions may immediately and consistently improve core symptoms of depression. Therefore, in future research, expanding the sample size and conducting randomized controlled trials across diverse depression subtypes are crucial to validate the current findings and enhance the generalizability of the results. Additionally, longitudinal studies should be implemented to evaluate the efficacy of long-term oxytocin regimens, to determine whether sustained dosing can produce enduring therapeutic benefits and inform optimal treatment protocols.

Conclusions

This systematic review evaluated randomized controlled trials assessing the effects of intranasal oxytocin on various types of depression. The results indicated that oxytocin significantly improved the relationship between PPD patients and their infants. As an adjunct to psychotherapy or antidepressant medication, oxytocin notably alleviated depressive symptoms in patients with MDD and PDD. Conclusions regarding the efficacy of oxytocin should be interpreted with caution due to the limited number of randomized controlled trials and small sample sizes. Future research should account for patients' baseline oxytocin levels, sex, and depression severity, while exploring optimal oxytocin dosage, administration timing, and long-term efficacy as an adjunctive treatment. This study comprehensively summarizes the antidepressant effects of oxytocin, advances understanding of its application in treating diverse depressive disorders, and contributes to the development of evidence-based treatment protocols.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Jing Jie. Data curation: Miao Wang. Formal analysis: Miao Wang, Shuaibiao Hou. Investigation: Miao Wang. Methodology: Jing Jie. Software: Miao Wang, Shuaibiao Hou. Validation: Zhiyi Fu, Chaoyang Tian. Writing—original draft: Miao Wang. Writing—review & editing: Jing Jie.

ORCID iDs

Miao Wang	https://orcid.org/0009-0006-8538-6943
Shuaibiao Hou	https://orcid.org/0009-0001-4606-7222
Chaoyang Tian	https://orcid.org/0000-0002-7985-1793
Zhiyi Fu	https://orcid.org/0009-0004-5887-543X
Jing Jie	https://orcid.org/0000-0002-7437-0069

Funding Statement

This research was supported by the National Natural Science Foundation of China (Grant Nos. 32200892 and 32460207), and the Ministry of Education in China Project of Humanities and Social Sciences (23YJC190026).

Acknowledgments

We also thank all the authors of the main studies who provided additional information and data for the systematic reviews.

REFERENCES

1. Zhang X, Wang Y, Xue S, Gong L, Yan J, Zheng Y, et al. Chronic stress in adulthood results in microvascular dysfunction and subsequent depressive-like behavior. Sci Rep 2024;14:24022.
2. Zadow AJ, Dollard MF, Dormann C, Landsbergis P. Predicting new major depression symptoms from long working hours, psychosocial safety climate and work engagement: a population-based cohort study. BMJ Open 2021;11:e044133.
3. Ren LN, Pang JS, Jiang QN, Zhang XF, Li LL, Wang J, et al. Self-compassion, automatic thoughts, and mental pain in depression: mediating effects and clinical implications. World J Psychiatry 2025;15:101105.
4. Global Health Data Exchange. Data request process [Internet]. Available at: https://vizhub.healthdata.org/gbd-results/. Accessed June 2, 2024.
5. Greenberg PE, Fournier AA, Sisitsky T, Simes M, Berman R, Koenigsberg SH, et al. The economic burden of adults with major depressive disorder in the United States (2010 and 2018). Pharmacoeconomics 2021;39:653-665.
6. Simon GE, Moise N, Mohr DC. Management of depression in adults: a review. JAMA 2024;332:141-152.
7. Maslej MM, Furukawa TA, Cipriani A, Andrews PW, Mulsant BH. Individual differences in response to antidepressants: a meta-analysis of placebo-controlled randomized clinical trials. JAMA Psychiatry 2020;77:607-617.
8. Ji H, Su W, Zhou R, Feng J, Lin Y, Zhang Y, et al. Intranasal oxytocin administration improves depression-like behaviors in adult rats that experienced neonatal maternal deprivation. Behav Pharmacol 2016;27:689-696.
9. Corwin EJ, Pajer K. The psychoneuroimmunology of postpartum depression. J Womens Health (Larchmt) 2008;17:1529-1534.
10. Froemke RC, Young LJ. Oxytocin, neural plasticity, and social behavior. Annu Rev Neurosci 2021;44:359-381.
11. Carter CS, Kenkel WM, MacLean EL, Wilson SR, Perkeybile AM, Yee JR, et al. Is oxytocin "nature's medicine"? Pharmacol Rev 2020;72:

829-861.
12. Thirtamara Rajamani K, Barbier M, Lefevre A, Niblo K, Cordero N, Netser S, et al. Oxytocin activity in the paraventricular and supramammillary nuclei of the hypothalamus is essential for social recognition memory in rats. Mol Psychiatry 2024;29:412-424.
13. Erdozain AM, Peñagarikano O. Oxytocin as treatment for social cognition, not there yet. Front Psychiatry 2020;10:930.
14. Long P, Scholl JL, Wang X, Kallsen NA, Ehli EA, Freeman H. Intranasal oxytocin and pain reduction: testing a social cognitive mediation model. Brain Sci 2023;13:1689.
15. Flechsenhar A, Levine SM, Müller LE, Herpertz SC, Bertsch K. Oxytocin and social learning in socially anxious men and women. Neuropharmacology 2024;251:109930.
16. Marsh N, Marsh AA, Lee MR, Hurlemann R. Oxytocin and the neurobiology of prosocial behavior. Neuroscientist 2020;27:604-619.
17. Le J, Kou J, Zhao W, Fu M, Zhang Y, Becker B, et al. Oxytocin facilitation of emotional empathy is associated with increased eye gaze toward the faces of individuals in emotional contexts. Front Neurosci 2020; 14:803.
18. Daughters K, Manstead ASR, van der Schalk J. Oxytocin and emotion recognition: investigating the possible roles of facial synchrony and eye gaze. Curr Res Ecol Soc Psychol 2021;2:100019.
19. Mikolajczak M, Pinon N, Lane A, de Timary P, Luminet O. Oxytocin not only increases trust when money is at stake, but also when confidential information is in the balance. Biol Psychol 2010;85:182-184.
20. Itskovich E, Bowling DL, Garner JP, Parker KJ. Oxytocin and the social facilitation of placebo effects. Mol Psychiatry 2022;27:2640-2649.
21. Rigney N, de Vries GJ, Petrulis A, Young LJ. Oxytocin, vasopressin, and social behavior: from neural circuits to clinical opportunities. Endocrinology 2022;163:bqac111.
22. Acevedo BP, Poulin MJ, Collins NL, Brown LL. After the honeymoon: neural and genetic correlates of romantic love in newlywed marriages. Front Psychol 2020;11:634.
23. Chen Q, Zhuang J, Zuo R, Zheng H, Dang J, Wang Z. Exploring associations between postpartum depression and oxytocin levels in cerebrospinal fluid, plasma and saliva. J Affect Disord 2022;315:198-205.
24. Azari AE, Peeri M, Masrour FF. The role of the oxytocinergic system in the antidepressant-like effect of swimming training in male mice. Behav Brain Res 2023;449:114474.
25. Liu R, Sun D, Xing X, Chen Q, Lu B, Meng B, et al. Intranasal oxytocin alleviates comorbid depressive symptoms in neuropathic pain via elevating hippocampal BDNF production in both female and male mice. Neuropharmacology 2024;242:109769.
26. Donadon MF, Martin-Santos R, L Osório F. Oxytocin effects on the cognition of women with postpartum depression: a randomized, placebo-controlled clinical trial. Prog Neuropsychopharmacol Biol Psychiatry 2021;111:110098.
27. Lindley Baron-Cohen K, Feldman R, Fearon P, Fonagy P. Intranasal oxytocin administration improves mood in new mothers with moderate low mood but not in mothers with elevated symptoms of postnatal depression: a randomised controlled trial. J Affect Disord 2022; 300:358-365.
28. Mah BL, Van Ijzendoorn MH, Out D, Smith R, Bakermans-Kranenburg MJ. The effects of intranasal oxytocin administration on sensitive caregiving in mothers with postnatal depression. Child Psychiatry Hum Dev 2017;48:308-315.
29. Mah BL, Van Ijzendoorn MH, Smith R, Bakermans-Kranenburg MJ. Oxytocin in postnatally depressed mothers: its influence on mood and expressed emotion. Prog Neuropsychopharmacol Biol Psychiatry 2013;40:267-272.
30. Clarici A, Pellizzoni S, Guaschino S, Alberico S, Bembich S, Giuliani R, et al. Intranasal adminsitration of oxytocin in postnatal depression: implications for psychodynamic psychotherapy from a randomized double-blind pilot study. Front Psychol 2015;6:426.
31. Pincus D, Kose S, Arana A, Johnson K, Morgan PS, Borckardt J, et al. Inverse effects of oxytocin on attributing mental activity to others in depressed and healthy subjects: a double-blind placebo controlled fMRI study. Front Psychiatry 2010;1:134.
32. MacDonald K, MacDonald TM, Brüne M, Lamb K, Wilson MP, Golshan S, et al. Oxytocin and psychotherapy: a pilot study of its physiological, behavioral and subjective effects in males with depression. Psychoneuroendocrinology 2013;38:2831-2843.
33. Boyle A, Johnson A, Ellenbogen M. Intranasal oxytocin alters attention to emotional facial expressions, particularly for males and those with depressive symptoms. Psychoneuroendocrinology 2022;142:105796.
34. Ellenbogen MA, Cardoso C, Serravalle L, Vadaga K, Joober R. The effects of intranasal oxytocin on the efficacy of psychotherapy for major depressive disorder: a pilot randomized controlled trial. Psychol Med 2024;54:2122-2132.
35. Scantamburlo G, Ansseau M, Geenen V, Legros JJ. Intranasal oxytocin as an adjunct to escitalopram in major depression. J Neuropsychiatry Clin Neurosci 2011;23:E5.
36. Domes G, Normann C, Heinrichs M. The effect of oxytocin on attention to angry and happy faces in chronic depression. BMC Psychiatry 2016;16:92.
37. Vehlen A, Kellner A, Normann C, Heinrichs M, Domes G. Reduced eye gaze during facial emotion recognition in chronic depression: effects of intranasal oxytocin. J Psychiatr Res 2023;159:50-56.
38. Scantamburlo G, Hansenne M, Geenen V, Legros JJ, Ansseau M. Additional intranasal oxytocin to escitalopram improves depressive symptoms in resistant depression: an open trial. Eur Psychiatry 2015; 30:65-68.
39. Suryawanshi IV O, Pajai S. A comprehensive review on postpartum depression. Cureus 2022;14:e32745.
40. Granat A, Gadassi R, Gilboa-Schechtman E, Feldman R. Maternal depression and anxiety, social synchrony, and infant regulation of negative and positive emotions. Emotion 2017;17:11-27.
41. Hahn-Holbrook J, Cornwell-Hinrichs T, Anaya I. Economic and health predictors of national postpartum depression prevalence: a systematic review, meta-analysis, and meta-regression of 291 studies from 56 countries. Front Psychiatry 2018;8:248.
42. Van Niel MS, Payne JL. Perinatal depression: a review. Cleve Clin J Med 2020;87:273-277.
43. Priel A, Zeev-Wolf M, Djalovski A, Feldman R. Maternal depression impairs child emotion understanding and executive functions: the role of dysregulated maternal care across the first decade of life. Emotion 2020;20:1042-1058.
44. Shorey S, Asurlekar AR, Chua JS, Lim LHK. Influence of oxytocin on parenting behaviors and parent-child bonding: a systematic review. Dev Psychobiol 2023;65:e22359.
45. Ramsauer B, Mühlhan C, Lotzin A, Achtergarde S, Mueller J, Krink S, et al. Randomized controlled trial of the Circle of Security-Intensive intervention for mothers with postpartum depression: maternal unresolved attachment moderates changes in sensitivity. Attach Hum Dev 2019;22:705-726.
46. Agrawal I, Mehendale AM, Malhotra R. Risk factors of postpartum depression. Cureus 2022;14:e30898.
47. Mah BL, Bakermans-Kranenburg MJ, Van IJzendoorn MH, Smith R. Oxytocin promotes protective behavior in depressed mothers: a pilot study with the enthusiastic stranger paradigm. Depress Anxiety 2015; 32:76-81.
48. Marx W, Penninx BWJH, Solmi M, Furukawa TA, Firth J, Carvalho AF, et al. Major depressive disorder. Nat Rev Dis Primers 2023;9:44.
49. Uekermann J, Channon S, Lehmkämper C, Abdel-Hamid M, Vollmoeller W, Daum I. Executive function, mentalizing and humor in major depression. J Int Neuropsychol Soc 2008;14:55-62.
50. Guo W, Liu B, Wei X, Ju Y, Wang M, Dong Q, et al. The longitudinal change pattern of cognitive subtypes in medication-free patients with major depressive disorder: a cluster analysis. Psychiatry Res 2023;327: 115413.

51. Liu B, Deng A, Dong C, Chen W, Zhang Q, Zhou L, et al. Enhanced mGluR5 availability marks the antidepressant efficacy in major depressive disorder: an [18F] FPEB PET study. Nat Mental Health 2025;3: 298-305.
52. Chebli H, Berrada H, Chtibi M, Belbachir S, Ouanass A. Quality of remission in the major depressive disorder. European Psychiatry 2023; 66:S832-S832.
53. Cui L, Li S, Wang S, Wu X, Liu Y, Yu W, et al. Major depressive disorder: hypothesis, mechanism, prevention and treatment. Signal Transduct Target Ther 2024;9:30.
54. Harkness KL, Theriault JE, Stewart JG, Bagby RM. Acute and chronic stress exposure predicts 1-year recurrence in adult outpatients with residual depression symptoms following response to treatment. Depress Anxiety 2014;31:1-8.
55. Maoz H, Grossman-Giron A, Sedoff O, Nitzan U, Kashua H, Yarmishin M, et al. Intranasal oxytocin as an adjunct treatment among patients with severe major depression with and without comorbid borderline personality disorder. J Affect Disord 2024;347:39-44.
56. Krause FC, Linardatos E, Fresco DM, Moore MT. Facial emotion recognition in major depressive disorder: a meta-analytic review. J Affect Disord 2021;293:320-328.
57. Klein DN. Chronic depression: diagnosis and classification. Curr Dir Psychol Sci 2010;19:96-100.
58. Domes G, Spenthof I, Radtke M, Isaksson A, Normann C, Heinrichs M. Autistic traits and empathy in chronic vs. episodic depression. J Affect Disord 2016;195:144-147.
59. Seemüller F, Kolter M, Musil R, Schennach R, Adli M, Bauer M, et al. Chronic vs non-chronic depression in psychiatric inpatient care - data from a large naturalistic multicenter trial. J Affect Disord 2022;299: 73-84.
60. Kojima R, Tateishi H, Kunitake H, Imamura Y, Kunitake Y, Murakawa T, et al. Negative association between basal oxytocin and oxytocin changes after repetitive transcranial magnetic stimulation in patients with treatment-resistant depression. Peptides 2024;177:171217.
61. Ding Y, Wei Z, Yan H, Guo W. Efficacy of treatments targeting hypothalamic-pituitary-adrenal systems for major depressive disorder: a meta-analysis. Front Pharmacol 2021;12:732157.
62. Mikulska J, Juszczyk G, Gawrońska-Grzywacz M, Herbet M. HPA axis in the pathomechanism of depression and schizophrenia: new therapeutic strategies based on its participation. Brain Sci 2021;11: 1298.
63. Sahu MK, Dubey RK, Chandrakar A, Kumar M, Kumar M. A systematic review and meta-analysis of serum and plasma cortisol levels in depressed patients versus control. Indian J Psychiatry 2022;64:440-448.
64. Yoon S, Kim YK. Possible oxytocin-related biomarkers in anxiety and mood disorders. Prog Neuropsychopharmacol Biol Psychiatry 2022; 116:110531.
65. Jiang J, Yang M, Tian M, Chen Z, Xiao L, Gong Y. Intertwined associations between oxytocin, immune system and major depressive disorder. Biomed Pharmacother 2023;163:114852.
66. Hedges VL, Heaton EC, Amaral C, Benedetto LE, Bodie CL, D'Antonio BI, et al. Estrogen withdrawal alters oxytocin signaling in the paraventricular hypothalamus and dorsal raphe nucleus to increase postpartum anxiety. BioRxiv 2020.06.16.154492 [Preprint]. June 17, 2020 Accessed January 5, 2024. Available at: https://doi.org/10.1101/2020.06.16.154492.
67. Fries GR, Saldana VA, Finnstein J, Rein T. Molecular pathways of major depressive disorder converge on the synapse. Mol Psychiatry 2023; 28:284-297.
68. Dölen G, Darvishzadeh A, Huang KW, Malenka RC. Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. Nature 2013;501:179-184.
69. Oubraim S, Shen RY, Haj-Dahmane S. Oxytocin excites dorsal raphe serotonin neurons and bidirectionally gates their glutamate synapses. iScience 2023;26:106707.
70. Yoshitake T, Kehr J, Todoroki K, Nohta H, Yamaguchi M. Derivatization chemistries for determination of serotonin, norepinephrine and dopamine in brain microdialysis samples by liquid chromatography with fluorescence detection. Biomed Chromatogr 2006;20:267-281.
71. Song J. Amygdala activity and amygdala-hippocampus connectivity: Metabolic diseases, dementia, and neuropsychiatric issues. Biomed Pharmacother 2023;162:114647.
72. Liu Y, Meng J, Wang K, Zhuang K, Chen Q, Yang W, et al. Morphometry of the hippocampus across the adult life-span in patients with depressive disorders: association with neuroticism. Brain Topogr 2021; 34:587-597.
73. Kim H, Han KM, Choi KW, Tae WS, Kang W, Kang Y, et al. Volumetric alterations in subregions of the amygdala in adults with major depressive disorder. J Affect Disord 2021;295:108-115.
74. Ma H, Li C, Wang J, Zhang X, Li M, Zhang R, et al. Amygdala-hippocampal innervation modulates stress-induced depressive-like behaviors through AMPA receptors. Proc Natl Acad Sci U S A 2021;118: e2019409118.
75. Kou J, Lan C, Zhang Y, Wang Q, Zhou F, Zhao Z, et al. In the nose or on the tongue? Contrasting motivational effects of oral and intranasal oxytocin on arousal and reward during social processing. Transl Psychiatry 2021;11:94.
76. Scatliffe N, Casavant S, Vittner D, Cong X. Oxytocin and early parent-infant interactions: a systematic review. Int J Nurs Sci 2019;6:445-453.
77. Wu A, Zhang J. Neuroinflammation, memory, and depression: new approaches to hippocampal neurogenesis. J Neuroinflammation 2023; 20:283.
78. Guo X, Rao Y, Mao R, Cui L, Fang Y. Common cellular and molecular mechanisms and interactions between microglial activation and aberrant neuroplasticity in depression. Neuropharmacology 2020;181: 108336.
79. Gay F, Romeo B, Martelli C, Benyamina A, Hamdani N. Cytokines changes associated with electroconvulsive therapy in patients with treatment-resistant depression: a meta-analysis. Psychiatry Res 2021; 297:113735.
80. Yuan L, Liu S, Bai X, Gao Y, Liu G, Wang X, et al. Oxytocin inhibits lipopolysaccharide-induced inflammation in microglial cells and attenuates microglial activation in lipopolysaccharide-treated mice. J Neuroinflammation 2016;13:77.
81. Riveros ME, Ávila A, Schruers K, Ezquer F. Antioxidant biomolecules and their potential for the treatment of difficult-to-treat depression and conventional treatment-resistant depression. Antioxidants (Basel) 2022;11:540.
82. Rani V, Deep G, Singh RK, Palle K, Yadav UCS. Oxidative stress and metabolic disorders: pathogenesis and therapeutic strategies. Life Sci 2016;148:183-193.
83. Wang L, Xu Y, Jiang M, Wang M, Ji M, Xie X, et al. Chronic stress induces depression-like behavior in rats through affecting brain mitochondrial function and inflammation. Psychoneuroendocrinology 2025;172:107261.
84. Parris MS, Grunebaum MF, Galfalvy HC, Andronikashvili A, Burke AK, Yin H, et al. Attempted suicide and oxytocin-related gene polymorphisms. J Affect Disord 2018;238:62-68.
85. Kushner SC, Herzhoff K, Vrshek-Schallhorn S, Tackett JL. Depression in early adolescence: contributions from relational aggression and variation in the oxytocin receptor gene. Aggress Behav 2018;44:60-68.
86. Thompson SM, Hammen C, Starr LR, Najman JM. Oxytocin receptor gene polymorphism (rs53576) moderates the intergenerational transmission of depression. Psychoneuroendocrinology 2014;43:11-19.
87. Asherin RM, Everhart KD, Stophaeros SL, Vogeli JM, Fowler J, Phiel CJ, et al. Associations between maternal depression and mother and infant oxytocin receptor gene (OXTR_rs53576) polymorphisms. Dev Psychobiol 2020;62:496-504.

88. Reiner I, Van IJzendoorn MH, Bakermans-Kranenburg MJ, Bleich S, Beutel M, Frieling H. Methylation of the oxytocin receptor gene in clinically depressed patients compared to controls: the role of OXTR rs53576 genotype. J Psychiatr Res 2015;65:9-15.
89. Leziak M, Niedobylski S, Żak K, Piwoński M, Krasowska D, Skórzyńska-Dziduszko K. Oxytocin and postpartum depression - a possible treatment for depressed mothers. J Edu Health Sport 2020; 10:161-172.
90. Schiller B, Brustkern J, Walker M, Hamm A, Heinrichs M. Oxytocin has sex-specific effects on trust and underlying neurophysiological processes. Psychoneuroendocrinology 2023;151:106076.
91. Zhu R, Liu C, Li T, Xu Z, Fung B, Feng C, et al. Intranasal oxytocin reduces reactive aggression in men but not in women: a computational approach. Psychoneuroendocrinology 2019;108:172-181.
92. Tully J, Gabay AS, Brown D, Murphy DGM, Blackwood N. The effect of intranasal oxytocin on neural response to facial emotions in healthy adults as measured by functional MRI: a systematic review. Psychiatry Res Neuroimaging 2018;272:17-29.
93. Carvalho Silva R, Pisanu C, Maffioletti E, Menesello V, Bortolomasi M, PROMPT consortium, et al. Biological markers of sex-based differences in major depressive disorder and in antidepressant response. Eur Neuropsychopharmacol 2023;76:89-107.
94. Maoz H, Grossman-Giron A, Baruch N, Sedoff O, Mama Y, Nitzan U, et al. Sex differences in response to intranasal oxytocin as an adjunctive therapy for patients with severe mental illness. Psychiatry Res 2024; 342:116269.
95. Feng C, Hackett PD, DeMarco AC, Chen X, Stair S, Haroon E, et al. Oxytocin and vasopressin effects on the neural response to social cooperation are modulated by sex in humans. Brain Imaging Behav 2015; 9:754-764.
96. Skvortsova A, Veldhuijzen DS, de Rover M, Pacheco-Lopez G, Bakermans-Kranenburg M, van IJzendoorn M, et al. Effects of oxytocin administration and conditioned oxytocin on brain activity: an fMRI study. PLoS One 2020;15:e0229692.
97. Lieberz J, Scheele D, Spengler FB, Matheisen T, Schneider L, Stoffel-Wagner B, et al. Kinetics of oxytocin effects on amygdala and striatal reactivity vary between women and men. Neuropsychopharmacology 2020;45:1134-1140.
98. Rilling JK, Chen X, Chen X, Haroon E. Intranasal oxytocin modulates neural functional connectivity during human social interaction. Am J Primatol 2018;80:e22740.
99. Chen X, Nishitani S, Haroon E, Smith AK, Rilling JK. OXTR methylation modulates exogenous oxytocin effects on human brain activity during social interaction. Genes Brain Behav 2020;19:e12555.
100. Woody ML, Owens M, Burkhouse KL, Gibb BE. Selective attention toward angry faces and risk for major depressive disorder in women: converging evidence from retrospective and prospective analyses. Clin Psychol Sci 2016;4:206-215.
101. Pan Y, Jie J, Yin M. Detection of event-related potentials as a biomarker in major depressive disorder using an XGBoost model. Biomed Signal Process Control 2025;108:107879.
102. Herrman H, Patel V, Kieling C, Berk M, Buchweitz C, Cuijpers P, et al. Time for united action on depression: a Lancet-World Psychiatric Association Commission. Lancet 2022;399:957-1022.
103. Servin-Barthet C, Martínez-García M, Pretus C, Paternina-Die M, Soler A, Khymenets O, et al. The transition to motherhood: linking hormones, brain and behaviour. Nat Rev Neurosci 2023;24:605-619.
104. Kendall KM, Van Assche E, Andlauer TFM, Choi KW, Luykx JJ, Schulte EC, et al. The genetic basis of major depression. Psychol Med 2021;51:2217-2230.
105. Monks DT, Palanisamy A. Oxytocin: at birth and beyond. A systematic review of the long-term effects of peripartum oxytocin. Anaesthesia 2021;76:1526-1537.
106. Marazziti D, Carter CS, Carmassi C, Della Vecchia A, Mucci F, Pagni G, et al. Sex matters: the impact of oxytocin on healthy conditions and psychiatric disorders. Compr Psychoneuroendocrinol 2022;13:100165.
107. Horáková A, Němcová H, Mohr P, Sebela A. Structural, functional, and metabolic signatures of postpartum depression: a systematic review. Front Psychiatry 2022;13:1044995.
108. Zhang K, He L, Li Z, Ding R, Han X, Chen B, et al. Bridging neurobiological insights and clinical biomarkers in postpartum depression: a narrative review. Int J Mol Sci 2024;25:8835.
109. Wellman CL, Bollinger JL, Moench KM. Chapter six-effects of stress on the structure and function of the medial prefrontal cortex: insights from animal models. Int Rev Neurobiol 2020;150:129-153.
110. Herbert J, Lucassen PJ. Depression as a risk factor for Alzheimer's disease: Genes, steroids, cytokines and neurogenesis - what do we need to know? Front Neuroendocrinol 2016;41:153-171.
111. Walsh CP, Bovbjerg DH, Marsland AL. Glucocorticoid resistance and β2-adrenergic receptor signaling pathways promote peripheral proinflammatory conditions associated with chronic psychological stress: a systematic review across species. Neurosci Biobehav Rev 2021;128: 117-135.