

ABSTRACT

Interest in the therapeutic potential of oxytocin for the treatment of mental health disorders, especially those involving social dysfunction, has increased considerably in recent years. To date, most studies have only evaluated oxytocin as monotherapy, with highly inconsistent results. A new line of research is exploring the effects of combining oxytocin with psychotherapy. The aim of the present review was to evaluate the therapeutic effects of intranasal oxytocin combined with psychotherapy in individuals with psychiatric disorders. Only randomized clinical trial design was eligible for inclusion. A search of relevant databases yielded 2480 articles published through April 30, 2024. Of these, 13 trials (518 participants) were included in this review and 4 of them in a meta-analysis. The trials evaluated a range of different psychotherapeutic interventions, oxytocin doses, and mental disorders. Overall, the trials suggested that combined treatment reduced negative mental representations, decreased stress, and increased therapeutic alliance. Meta-analysis showed that combined treatment significantly reduced depressive symptoms ($d = -1.58$, 95% CI: -3.15 to -0.01). However, the treatment with oxytocin had no significant effects on psychiatric symptoms ($d = 0.00$, 95% CI: -0.56 to 0.57) or social functioning ($d = 0.21$, 95% CI: -0.07 to 0.49). Limitations included the heterogeneity and limited sample sizes of the trials. The findings suggest that the combination of intranasal oxytocin and psychotherapy may be an effective therapeutic approach to reduce depressive symptoms in individuals with mental disorders and may improve retention and therapeutic alliance.

Keyword: Oxytocin, psychotherapy, systematic review, meta-analysis, mental disorders.

1. INTRODUCTION

Oxytocin is a neuropeptide that plays a significant role in physiological and psychological processes, including reproductive functions such as sexual behavior, pregnancy, childbirth, and maternal behavior. In recent years, oxytocin has emerged as a key determinant of human social cognition and behavior (Barraza et al., 2021; Leppanen et al., 2017). Oxytocin serves as a biological substrate underlying attachment and adaptation to the social environment, which is why it has been described as a “social hormone” (Andari et al., 2021; Cochran et al., 2013; Ditzen et al., 2023). Several studies have shown that this hormone acts on the central nervous system to regulate emotional and cognitive processes (Hwang et al., 2024; Ishak et al., 2011).

Interest in oxytocin has increased in recent years due to the growing body of evidence pointing to a possible therapeutic role in several mental health disorders, particularly those characterized by deficits in social functioning (Ferreira & Osorio, 2022; Kosfeld et al., 2005; Parker et al., 2017; Peled-Avron et al., 2020). Oxytocin system dysfunction may contribute to various neuropsychiatric conditions, including stress-related disorders, anxiety, and social fear (Neumann & Slattery, 2016), autism spectrum disorders (ASD) (Audunsdottir, et al., 2024; Ooi et al., 2017), psychosis (Hernández-Díaz et al., 2021; Korann et al., 2022), mood disorders (Domes et al., 2016), post-traumatic stress disorder (PTSD) (Sippel et al., 2024; Szafoni & Piegza, 2022), addictive behaviors (Lee & Weerts, 2016; Sundar et al., 2021), eating disorders (Leppanen et al., 2017), and personality disorders such as borderline personality disorder (BPD) (Carrasco et al., 2020; Peled-Avron et al., 2020; Servan et al., 2018).

Social dysfunction is the core feature of ASD, and some studies suggest that oxytocin plays a key role in this dysfunction. Treatment with intranasal oxytocin has shown promising results in facilitating social development and in reducing social

disability in ASD (Anagnostou, 2012; Daniels et al., 2023; Griffiths, et al., 2022; Ooi et al., 2017; Preti et al., 2014; Wilczyński et al., 2019; Yamasue et al., 2020). However, due to heterogeneous results reported to date, it is difficult to draw any definitive conclusions with regard to the effectiveness of oxytocin in ASD. Similarly, while some studies suggest that the social regulatory effects of oxytocin may ameliorate negative symptoms in schizophrenia, the available data supporting these beneficial effects are based on studies with modest sample sizes and thus caution is warranted (Peled-Avron et al. 2020). Several studies suggest that oxytocin may also improve social functioning in schizophrenia (Goh et al., 2024; Wigton et al., 2021), especially when administered in combination with psychotherapy (Ettinger et al., 2018; İmamoğlu et al., 2024; Martins et al., 2022). However, when oxytocin is administered as monotherapy in this setting, the results are highly heterogeneous (Peled-Avron et al., 2020).

Affective disorders are commonly associated with poor interpersonal functioning, including cognitive processing bias towards negative stimuli (Jiang et al., 2023; Peled-Avron et al., 2020). Several studies in individuals with depressive disorders have shown that oxytocin positively influences mood symptoms and social skills, although the results appear to be inconsistent (Baron-Cohen et al., 2022; MacDonald et al. 2013; Peled-Avron et al., 2020). In anxiety disorders, most clinical studies have failed to confirm the efficacy of oxytocin with heterogeneous and/or unfavorable results (Cochran et al., 2013).

PTSD often has a bidirectional relationship with interpersonal relationships. Anger, avoidance, and social withdrawal—all of which negatively impact relationship quality and social behavioural skills—are common in PTSD (Sippel et al., 2024). Most of the studies that have evaluated oxytocin in PTSD (Giovanna et al., 2020; Peled-Avron et al. 2020; Sippel et al. 2024) have found improvements in relationship satisfaction and interpersonal dysfunction. However, most of those studies only had modest sample sizes.

As a result, studies with larger sample sizes are needed to confirm those findings. Oxytocin has also been used to treat alcohol relapse in PTSD, and the limited data reported to date support its therapeutic potential in that clinical setting (Becker et al., 2023).

In eating disorders, one study found that intranasal oxytocin might enhance nutritional rehabilitation in anorexia nervosa by reducing eating concerns and cognitive rigidity (Russell et al., 2018). Another study found that oxytocin may moderate automated information processing biases and reduce neurobiological stress (Leppanen et al., 2017). Oxytocin may also have a role to play in the treatment of obesity, with some studies suggesting that oxytocin monotherapy could reduce food intake by reducing stress (Burmester et al., 2019; Hong et al., 2021). A similar mechanism (i.e., oxytocin-related stress reduction) has been proposed to explain the potential of oxytocin to reduce craving in addictive behaviors (Houghton et al., 2021; King et al., 2020; Köhne et al., 2024). For example, Van Hedger et al. (2020) found that oxytocin decreases cigarette craving and use. However, other studies have not found any impact on stress-induced cravings for cigarettes or methadone (Woolley et al., 2016). A few studies have examined the effects of oxytocin on social dysfunction in BPD (Bertsch, & Herpertz, 2018; Peled-Avron et al., 2020), but those studies were small and reported heterogeneous results. As a result, the therapeutic potential of oxytocin in this clinical population remains highly uncertain.

The available evidence suggests that the effects of oxytocin are complex and appear to be context-dependent. Although oxytocin has been proven beneficial in many settings, in some contexts it may decrease cooperation and increase envy and even aggression (Bartz et al., 2011; Peled-Avron et al., 2020). The current evidence shows that oxytocin administered as monotherapy can have highly heterogeneous effects, both positive and negative. However, those data are based on a limited number of studies with

modest sample sizes and heterogeneous methods, doses, and sociodemographic factors. Not surprisingly, the results of those studies are highly inconsistent.

In recent years, a growing number of studies have been conducted to explore the potential therapeutic effect of intranasal oxytocin combined with psychotherapy. Some studies suggest that there may be synergistic effects between oxytocin and psychotherapeutic interventions, which could potentially enhance social functioning and quality of life (De Jong & Neumann, 2018; Patin et al. 2018). The data from these studies are highly promising, suggesting that oxytocin combined with several different psychotherapeutic modalities may be effective. However, there is a notable lack of data comparing combination therapy to oxytocin alone, which is needed to better define the real contribution of oxytocin to clinical response. Combined treatment could help to personalize treatment in some clinical populations (Jawad et al., 2021). By harnessing the synergistic effect of combined therapy, clinicians could potentially unlock novel ways to enhance social cognition, improve treatment adherence, and ultimately improve outcomes for individuals with mental health disorders.

Although some preliminary research has been performed, only a few studies have evaluated the combination of oxytocin and psychotherapy in the treatment of psychiatric disorders such as PTSD, affective disorder, and schizophrenia. Therefore, more studies are needed to fill this knowledge gap. In this context, the aim of the present systematic review and meta-analysis was to examine the available evidence for the effectiveness of psychotherapeutic interventions combined with intranasal oxytocin in individuals diagnosed with mental health disorders.

2. METHOD

2.1. Search Strategy

This study was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The search strategy used the Boolean operator “AND” combined with the terms “Intranasal Oxytocin and Therapy”, “Borderline Personality Disorder and Oxytocin”, “Mood Disorders and Oxytocin”, “Schizophrenia and Oxytocin”, “Autism Spectrum Disorder and Oxytocin”, “Eating Disorders and Oxytocin”, “Posttraumatic Stress Disorder and Oxytocin”, “Anxiety and Oxytocin”, “Addiction and Oxytocin” across multiple databases, including PubMed, APA PsycArticles, APA PsycInfo, Prospero, Psycodoc, Psyke and PsyArXiv. The search was conducted in English, with no limitations on year of publication. No additional filters were used.

2.2. Eligibility Criteria

The terminology used to search articles was possible under the use of criteria currently validated by the American Psychiatric Association (APA) and the DSM-5-TR for Mental Health disorders. Inclusion criteria for this systematic review and meta-analysis were as follows: 1) clinical trial design (only randomized clinical trials [RCT] to ensure methodological standard); 2) treatment arm consisting of a psychotherapeutic intervention (group and/or individual format) combined with intranasal oxytocin for individuals diagnosed with any mental disorder. There were no restrictions with regard to study sample size, patient age, sex, level of functionality, or oxytocin dosage.

2.3. Information Sources

We searched the following databases for relevant articles published up to April 30, 2024: 1) PubMed (United States National Library of Medicine), 2) American Psychological Association (APA) PsycArticles and PsycInfo; 3) Prospero (University of

York, United Kingdom), 4) Psicodoc (Official College of Psychology; Madrid, Spain); 5) Psyke (Psychology Library of the Complutense University of Madrid), and 6) PsyArXiv (Society for the Improvement of Psychological Science).

2.4. Selection Process and Data Collection

The first author screened the titles of all articles retrieved from these databases to initially determine their possible eligibility for study inclusion. During the first screening, the researcher read all of the titles and included or excluded the article based on whether it met the inclusion criteria.

A second round of screening was carried out jointly with an external researcher. Both researchers read the article abstracts and jointly decided whether the contents of the abstract article met the inclusion criteria. Finally, all of the articles that passed the initial screening process (title and abstract) were read in full. No automation tools were used during the screening and selection process.

Table 1 shows the data extracted from the selected studies, including the authors, study design, year conducted, country, participant characteristics, diagnosis, type of intervention and duration, outcome measures, and a summary of findings.

2.5. Risk of Bias Assessment

Risk of bias was assessed with “Quality Assessment Tool of Controlled Intervention Studies” (for RCT). The tool was developed by the National Heart, Lung and Blood Institute (NHLBI) (2021) and contains 14 items designed to assess the quality of research. Each question has three possible responses: “yes”, “no” or “other”. The first five items refer to the assigned procedure, the next five refer to comparability between groups, and the last four refer to the analyses. The tool provides a final rating for the overall quality of the study (good, fair, or poor) (NHLBI, 2021).

2.6. Effect measures and synthesis method for the meta-analysis

The standardized mean difference (SMD) was used to measure the effects. The SMD is calculated by determining the difference between pre-post mean scores divided by an estimate of the within-group standard deviation (preintervention data). The SMD was calculated for the outcomes obtained in all treatment arms in the RCTs included in this meta-analysis. To make this estimation, it was necessary to find common patterns in the instruments. All of the RCTs assessed social functioning, psychiatric symptoms, and depressive symptoms. Consequently, we used these measures to compare the RCTs. Given that none of the trials provided the intraindividual correlations between pre-post measures, we assumed that the correlation coefficient (r) was 0.5. Since one article did not provide standard deviation values, the standard deviation of the difference (σD) was calculated using the combined total mean difference and a provided z value. The σD value obtained was 1.26.

To conduct the meta-analysis, we used the random-effect meta-analysis method with the DerSimonian-Laird estimator to estimate heterogeneity. We prepared a forest plot for each outcome variable to graphically represent the results. Estimates of total heterogeneity were obtained using the Tau^2 index and the I^2 index. The funnel plot for each outcome was used to evaluate reporting bias and Egger's regression test was used to evaluate asymmetry. The trim and fill algorithm was used to estimate the effect of missing studies on the global estimate. The metafor package from the R statistical program (v. 4.3.3) was used to conduct the statistical analyses.

3. RESULTS

3.1. Study selection

The database search identified 2480 articles from the following databases: PubMed (n = 2308), PsycInfo (n = 88), PsyArXiv (n = 43), Prospero (n = 30), PsycArticles (n = 8), Psyke (n = 2), and Psycodoc (n = 1). A total of 222 duplicates were detected and removed before further screening. The titles of the remaining 2258 articles were screened to determine eligibility for inclusion; of these, 2112 were excluded, leaving 146 articles. The abstracts of these articles were screened and 101 were eliminated, thus leaving 45 studies for full-text review. Of these, 31 were subsequently excluded because psychotherapy was not part of the treatment protocol, and 1 was removed because it was a pre-post clinical trial. Therefore, a total of 13 studies met all eligibility criteria and were included in the systematic review (see PRISMA flowchart, Figure 1).

3.2. Study characteristics

Table 1 shows the characteristics of the 13 studies (518 participants) included in the systematic review. The publication dates ranged from 2009 to 2024. The trials were carried out in the following countries: Australia, the United States, Italy, Canada, Israel, and Germany. In most cases, psychotherapy was delivered in a group setting. Although several different therapeutic approaches were used, the most common approach was cognitive behavioural therapy (CBT). The trials evaluated a wide range of clinical conditions, including schizophrenia (n = 6 trials), depression (n = 3), PTSD (n = 1), addictive behaviour (n = 1), anxiety (n = 1) and one study mixed anxiety, depressive disorders and others disorders (n = 1) (Grossman-Giron et al., 2023). The oxytocin doses ranged from 16 to 40 international units. In most of the trials, oxytocin was administered ≤ 45 minutes prior to the start of the psychotherapy session. The questionnaires used in these trials all had apparent predictive validity and reliability.

Overall, the studies found that oxytocin reduced negative self-representations and improved empathy. They also showed changes in depressive presentation and a reduction

in negative symptoms. Most of the studies found that oxytocin increased adherence and therapeutic alliance. In general, the results suggest that oxytocin had a positive impact, mainly a decrease in discomfort and symptoms.

3.3. Quality of studies

The results of the methodological quality assessment of the RCTs are shown in Figure 2. Seven studies provided adequate descriptions of the study design (question [Q1: Was the study described as randomized?]). The randomization procedure was appropriate in all of the trials (Q2). Two studies did not provide information on allocation concealment (Q3). Most of the studies (12/13) adequately blinded participants and providers (Q4), although this could not be determined in one study. Statistician blinding (Q5) could not be determined in eight of the 13 trials. In all of the trials, the baseline characteristics of the experimental and control groups were comparable (Q6). The overall drop-out rate was $> 20\%$ in three studies (Q7 and Q8); however, the differential drop-out rate between treatment groups was $\leq 15\%$ in all of the RCTs. Protocol adherence (Q9) was high in all 13 trials and all avoided other interventions (Q10) and used precise and reliable outcome measures (Q11). In all of the trials, the sample size was too small to detect a difference between groups in the main outcome measure with at least 80% power (Q12). All of the trials reported the results in a prespecified manner (Q13). Only five studies performed an intention-to-treat analysis (Q14). Based on the assessment questionnaire, the quality of the trials was classified as good (28.6%), fair (50%), and poor (21.4%).

3.4. Meta-analysis

Figure 3 shows the results of the meta-analysis with forest plots showing the effect sizes for the combined treatment for each study. It also shows the summary effect for the

three outcome variables: psychiatric symptoms, social functioning, and depressive symptoms. To ensure the comparability of the effects, we only included in the meta-analysis these outcomes because standardized measures with the same instrument were needed. To measure depression, the studies by Clarici et al. (2015) and Grossman-Girón (2023) used the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960). This scale measures depressive symptoms from the perspective of the clinician. The investigations used the original scale, which is composed of 17 items related to the symptoms of depression experienced during the last week by the patient. Otherwise, the Brief Psychiatric Rating Scale (BPRS) created by Overall & Gorham (1962) was used to measure Psychiatric Symptoms in the researches carried out by Davis et al. (2014) and Buchanan et al. (2021). BPRS is a key tool in clinical trials, which is generally used to evaluate the response to treatment in psychotic patients, being especially useful in cases of psychosis and allows the classification of the predominant symptoms. Finally, to assess Social Functioning, the Birchwood Social Functioning Scale (BSFS) created by Birchwood et al. (1990) was used in the trials of Cacciotti-Saija et al. (2015) and Buchanan et al. (2021). This scale is designed to assess social function across six domains of social function: 1) social engagement/withdrawal; 2) interpersonal communication; 3) independence-performance; 4) independence-competence; 5) recreation; and 6) prosocial activities. The scale allows obtaining a total score of social functioning and scores corresponding to the 6 specific areas, facilitating a profile of social functioning. The studies by Davis et al. (2014), Cacciotti-Saija et al. (2015), Buchanan et al. (2021) and Grossman-Girón (2023), all included both a placebo and oxytocin arm. Consequently, those two interventions were included in the quantitative analysis for the study variables.

The effect sizes for psychiatric symptoms with the SMD was 0.00 (95% CI: -0.56, 0.57), indicating that the effect was not statistically significant. Heterogeneity was

substantial ($I^2 = 64.5\%$), and Cochran's Q test for psychiatric symptoms was significant ($p < 0.04$), suggesting variability in the effect sizes across the studies, which could be due to differences in study populations or treatment protocols. Egger's test detected asymmetry ($p < 0.03$), indicating potential publication bias. The trim and fill method estimated one missing study on the left side ($SE = 1.5779$), suggesting that the results should be interpreted with caution.

The SMD for social functioning across the four arms was 0.21 (95% CI: -0.07, 0.49), indicating that the effect was not statistically significant. Heterogeneity was low ($I^2 = 0\%$) and Cochran's Q test was not significant ($p = 0.58$), indicating consistency between studies, probably because all the studies included corresponded to schizophrenic spectrum populations (Buchanan et al., 2021; Cacciotti-Saija et al., 2015). Additionally, the Egger's test ($p = 0.41$) indicated that no asymmetries were present. Nevertheless, the effect size did not reach statistical significance, implying that oxytocin did not have a notable impact on social functioning within the observed parameters.

The SMD for depressive symptoms was -1.58 (95% CI: -3.15, -0.01), showing that oxytocin led to greater decrease in these symptoms than placebo. Heterogeneity was large ($I^2 = 97.6\%$), and Cochran's Q test was highly significant ($p < 0.001$), indicating substantial variability among the study results, perhaps because the studies incorporated for this analysis included populations with affective, anxious, and personality disorders (Clarici et al., 2015; Grossman-Giron et al., 2023). Egger's test for depressive symptoms showed no significant asymmetry ($p = 0.16$), suggesting no publication bias.

4. DISCUSSION

The present study is the first systematic review performed to evaluate the effects of intranasal oxytocin combined with psychotherapy in clinical samples with mental health disorders. Most of the studies performed to date have evaluated the role of oxytocin alone in treating psychiatric disorders. By contrast, only 14 clinical trials have evaluated the combination of oxytocin and psychotherapy in this setting. Overall, our systematic review suggest that this treatment combination could provide better outcomes than psychotherapy alone. The meta-analysis only found a significant effect of oxytocin on depressive symptoms. The findings of this systematic review should be interpreted cautiously given the limited number of studies included in this review, most of which had only modest sample sizes.

In individuals with social anxiety, oxytocin plus psychotherapy improved evaluations of appearance and speech performance, and also reduced negative self-representations (enhancement of positive social cues and cognitive dysfunction associated with social threat) (Guastella et al., 2009). Although these benefits did not persist after treatment, they suggest that oxytocin may facilitate a more accurate and adaptive self-appraisal in individuals facing social challenges (Hoge et al., 2008).

Davis et al. (2014) showed that social cognitive skills training plus oxytocin improved empathic accuracy in patients with schizophrenia at treatment completion, and that this improvement was maintained during follow-up. The combined treatment had small effects on both positive and negative symptoms, but especially on negative symptoms (Cacciotti-Saija et al., 2015). However, other studies found that adding oxytocin to social skills training did not yield any additional benefits or further improve social cognition (Buchanan et al., 2021; Strauss et al., 2019). By contrast, Browne et al. (2022) found that oxytocin combined with CBSST increased positive affect, reduced negative affect, and increased warmth and competence in interpersonal relationships in a

group context. Several studies have found that oxytocin alone has a therapeutic effect on social cognition (Brambilla et al., 2016; Uhrig et al., 2016), general psychopathology, and positive symptoms (Wynn et al., 2019; Zheng et al., 2019). The heterogeneous treatment outcomes in these studies underscore the importance of considering the type of psychotherapy and characteristics of the disorder when deciding whether to offer combined therapy. Similarly, the differences in treatment outcomes among these studies highlight the urgent need for more studies to better understand the effect of this combined intervention in schizophrenia. More research is required to fully understand the effects of oxytocin, including its pharmacodynamics and individual differences in response to treatment. More specifically, large, adequately powered trials are needed to detect the effects on social cognition (Moher et al., 2001; Schulz & Grimes, 2002).

The trials conducted in people with depressive disorder suggest that oxytocin plus psychotherapy could improve therapeutic alliance and reduce overall distress and depressive symptoms in individuals without comorbid BPD (Clarici et al., 2015; Maoz et al., 2024). In postpartum depression, combined therapy has been shown to reduce depressive symptoms and improve the interpersonal relationship between mother and child (Clarici et al., 2015). More recently, Ellenbongen et al. (2024) found that combined therapy improved outcomes in patients with major depressive disorder and that these positive results were maintained at six months. Moreover, the combined treatment also improved therapeutic alliance and goal agreement.

In a study involving patients with methamphetamine addiction, oxytocin improved attendance at the therapy sessions and decreased negative relationships within the group (Stauffer et al., 2020). Studies involving patients with PTSD have shown that oxytocin plus psychotherapy improves therapeutic retention and satisfaction while also reducing PTSD-related symptoms (Flanagan et al., 2018; Sippel et al., 2024). Another

study evaluated brief couple therapy for PTSD, showing that the combined approach improved interpersonal relationships and satisfaction in the couple (Sippel et al., 2024). Research into the role of oxytocin in other mental health disorders, such as eating disorders and BPD, is still in the early stages, with only a few small studies performed to date (Giel et al., 2018; Maguire et al., 2024; Russell & Hunt, 2023). Although the available data support a potential therapeutic role for oxytocin in BPD (Díaz-Marsá et al., 2024; Schneider et al., 2020; Servan et al., 2018) and ASD (Yamasue et al., 2020), oxytocin combined with psychotherapy has not yet been evaluated in these clinical populations.

The findings of the present review underscore the need for more studies to better elucidate the true therapeutic potential of intranasal oxytocin combined with psychotherapy. This treatment approach has the potential to broaden the spectrum of treatment possibilities for numerous psychiatric disorders, which generally require a multidimensional approach consisting of pharmaceuticals such as oxytocin and psychotherapy. Oxytocin could be useful to maximize the effects of psychosocial interventions by facilitating the action of psychotherapy, without the need to focus so much on reducing clinical symptoms (Pedersen, 2014). More interdisciplinary research is needed to determine its potential to improve therapeutic alliance and reduce dropout rates (Bartholomeusz et al., 2015).

Numerous factors must be also considered to evaluate the additional benefits to adding oxytocin to psychotherapy, including large variability in diagnoses, sample size, oxytocin doses (which that may depend on the specific psychiatric disorder), specific therapy used, and individual characteristics such as the gender (Ferreira & Osorio, 2022; Szafoni & Piezga, 2022). For example, the studies that evaluated the role of oxytocin in schizophrenia and PTSD were performed mainly in men (Davis et al., 2014; Cacciotti-

Saija et al., 2015; Buchanan et al., 2021; Browne et al., 2022). Given that gender differences may have important implications for the clinical presentation, treatment, and outcomes of mental disorders, it is important to include clinical samples with both men and women and to ensure that interventions in both clinical research and practice are sensitive to the specific needs of each gender.

The most common therapeutic approach used in these trials was CBT, which was primarily delivered in group format. Studies have shown that improving therapeutic alliance augments the positive effects of psychotherapy and, in this regard, oxytocin could complement and potentiate the effects of psychotherapy (Berceanu et al., 2024; Kagizman & Hocaoglu, 2023). Oxytocin is a prosocial hormone that plays a crucial role in promoting positive social behaviour and strengthening interpersonal bonds. It can also promote trust, empathy, and cooperation between individuals, all of which are essential for healthy social interaction (Kosfeld et al., 2005). In the context of psychotherapy, a safe and welcoming therapeutic environment enhances affinity and connection between the therapist and the patient (Bell et al., 2006). The synergistic effects of oxytocin and psychotherapy may amplify the effectiveness of therapeutic interventions, thereby promoting emotional well-being and resilience (MacDonald & MacDonald, 2010). Several studies have shown that oxytocin not only increases positive affect during social interactions but can also improve therapeutic outcomes by encouraging greater openness and emotional communication, which, in turn, facilitate the healing process and personal growth (Berceanu et al., 2024; Zink & Meyer-Lindenberg, 2012).

The meta-analysis findings revealed mixed results with regards to the effectiveness of intranasal oxytocin. Although some of the individual studies found that oxytocin improved some outcomes (Buchanan et al., 2021), overall the results of this meta-analysis show that oxytocin had no significant impact on social functioning

(Buchanan et al., 2021; Cacciotti-Saija et al., 2015), which suggests that oxytocin may not have a substantial impact on social aspects in different contexts. By contrast, oxytocin did significantly reduce depressive symptoms, a finding that supports the therapeutic potential of oxytocin to treat this symptom. That said, the trials reported considerable variability in this regard, possibly due to differences in the psychotherapeutic techniques and patient characteristics. Given the promising results overall in terms of the reduction of depressive symptoms, more research is warranted.

The studies included in this review share similar methodological limitations, most notably limited sample sizes, as noted by several authors who recognized the need for larger samples to improve the statistical power of their findings (Buchanan et al., 2021; Clarici et al., 2015; Davis et al., 2014). This limitation is compounded by the lack of homogeneity in terms of the age, sex, and other psychopharmacological treatments of the participants in some samples (Ellenbogen et al., 2024; Maoz et al., 2024), which makes it difficult to generalize our findings to broader populations. An important limitation reported in many studies was failure to use blinding for the data analysis. Although this practice is not uncommon, it represents an important limitation in terms of potential bias, which is why the results should be interpreted with caution (Karanicolas et al., 2010). Another limitation of this review is that we only included a relatively limited number of trials ($n = 14$), mainly due to the relative scarcity of clinical trials performed to assess the combination of oxytocin and psychotherapy in mental disorders. In addition, as the highly heterogeneous results of those trials show (in terms of the effects of combination therapy on psychiatric symptoms and social functioning), the effectiveness of these interventions was highly variable. The heterogeneity of these studies indicates substantial differences in the methodological approaches and/or patient populations. The effect estimate was not

significant, and the wide confidence interval suggests that more research is needed to draw more definitive conclusions.

5. CONCLUSIONS

The findings of this systematic review and meta-analysis show that intranasal oxytocin combined with psychotherapy is a promising approach for the treatment of various psychiatric disorders, especially in the reduction of depressive symptoms where significant improvement was observed despite high heterogeneity between studies. This variability suggests that treatment response might depend on differences in the populations studied. However, effects on social functioning were modest and often non-significant, indicating variable efficacy depending on the type of disorder and individual patient characteristics.

Although some studies reported improvements in the therapeutic alliance, the results are not conclusive. Despite the therapeutic potential of oxytocin, these results underline the need for more rigorous and better designed research. Specifically, RCTs with larger and diverse samples are required to effectively evaluate the combination of intranasal OT and psychotherapy. These studies should include assessments of therapeutic and prosocial behavior, with longitudinal follow-up to determine whether the treatment effects persist over time.

Conflicts of interest: The authors declare that they have no competing financial interests or personal relationships that may have influenced the work reported in this study.

Availability of data and materials: Data are available upon reasonable request.

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María Arqueros: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing Original Draft, Writing Review and Editing.

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LEGENDS

Figure 1. Prisma flowchart

Figure 2. Risk of bias in the included trials

Figure 3. Forest plot with effect sizes for the meta-analysis of oxytocin effects on psychiatric symptoms, social functioning and depressive symptoms.

The author, year, and intervention group (placebo or oxytocin) are given on the left.

Effect sizes are represented by diamonds. The thin lines show 95% confidence intervals (CI). The filled diamond represents the summary estimate of Cohen's d with 95% CIs.

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Table 1. Characteristics of the 13 studies included in the systematic review

N°	Author	Year	Country	Participants	Diagnosis	Type of therapy and total duration/week	Measures	Outcomes
1	Guastella et al.	2009	Australia	25 men (12 OT vs. 13 placebo) (24 IU) - (Taken at begin of session).	SAD	- Group Exposure Therapy - 5 sessions once a week	- SPAI. - LSAS. - BFNE. - LIS. - CEQ. - APS. - SPQ.	Oxytocin reduced exaggerated negative mental representations
2	Davis et al.	2014	United States	27 males (13 OT vs. 14 placebo) (40 IU) - (OT taken 30 min before session).	Schizophrenia	- Social Cognitive Skills Training (Group Therapy) - 12 Sessions once a week	- FAR. - BPRS. - PONS. - TEAT. - MSCEIT. - TASIT.	Significantly greater improvement in empathic accuracy
3	Clarici et al.	2015	United States & Italy	16 mothers (5 OT vs. 11 to placebo) (16 IU) – (OT taken in the morning).	Postnatal depression	- Psychodynamic Therapy (Individual) - 12 weekly sessions	- SWAP. - HAM-D. - EPDS. - ANPS.	Changes in the presentation of depression (narcissistic attitude)
4	Cacciotti-Saija et al.	2015	Australia	52 (27 to OT vs. 25 to placebo) (24 IU/ twice daily) – (OT taken additionally at begin of session).	Schizophrenia (early psychosis)	- Social Cognition Training (Group Therapy). - 6 weekly sessions (2 hours)	- BSFS - RMET. - SAPS - SANS. - FEEST - AIHQ. - DASS-21. - K-10. - CGI-S. - SSPA. - ICQ. - SDS.	Reductions in negative symptoms in the OT condition only
5	Flanagan et al.	2018	United States	13 participants (6 OT vs. 7 to placebo) (40 I.U) - (OT taken 45 min before session).	PTSD	- Prolonged Exposure Therapy (Individual). - 10 sessions once a week	- MINI. - CAP-5. - PCL-5. - BDI-II. - CSQ.	Reduced symptoms of PTSD, depression and increased therapeutic alliance

6	Strauss et al.	2019	United States	62 patients (31 OT vs. 31 to placebo) (36 IU) – (OT taken 45 min before session and each day morning/night).	Schizophrenia	- Cognitive-Behavioral Social Skills Training (Group Therapy). - 48 sessions, two a week	- RMET. - EAT. - TG. - FERT.	The addition of oxytocin prior to each group session had no additional benefits
7	Stauffer et al.	2020	United States	39 patients (20 OT vs. 19 to placebo) (40 IU.) - (OT taken 30 min before session).	Methamphetamine use disorder	- Motivational interviewing group therapy (MIGT). - 6 sessions, once a week	- ACEQ. - STAI. - GQ. - ECR. - RCQ - MCQ-Br.	Increased adherence and group cohesion
8	Buchanan et al.	2021	United States	62 outpatients (31 OT vs. 31 placebo) (36 IU) - (OT taken 45 min before session and each day morning/night).	Schizophrenia	- Cognitive Behavioral Social Skills Training (Group Therapy) - 48 sessions, twice weekly	- BSFS. - DPAS. - ABS. - BPRS. - CGI. - CDS.	Addition of intranasal oxytocin to CBSST did not significantly enhance social function
9	Browne et al.	2022	United States	62 outpatients (31 OT vs. 31 placebo) (36 IU twice daily).	Schizophrenia	- Cognitive Behavioral Social Skills Training (Group Therapy) - 48 sessions, two a week	- EMA. - BSFS. - DPAS. - ABS. - BPRS. - CGI - CDS.	Positive and negative affect and defeatist interaction appraisals improved with treatment
10	Grossman-Giron et al.	2023	Israel	86 patients (43 OT vs 43 Placebo) (32 IU) (16 I.U/twice daily) – (OT taken at 08:00 a.m. and 5:00 p.m.).	Affective Disorders Anxiety Disorders Personality Disorders	- Psychodynamic Therapy. - Individual psychotherapy. - 4 sessions, two a week.	- HAM-D. - STAI. - OQ-45. - HSCL-11. - SAI.	Decrease in symptomatic distress.
11	Maoz et al.	2024	Israel	58 patients (35 with comorbid BDP vs. 23 without comorbid BDP) (32 IU) (16 IU/twice daily) (OT taken at 08:00 a.m. and 5:00 p.m.).	MDD with and without BPD	- Relationship-focused Psychotherapy - Group therapy and individual psychotherapy carried out 2–3 times a week	- HAM-D. - STAI. - OQ-45. - HSCL-11. - SAI.	Improvement in overall distress and symptom severity in patients without BPD
12	Zierhut et al.	2024	Germany	41 participants (22 to OT vs. 19 to placebo) (24 IU)	Schizophrenia	- Mindfulness-Based-Group Therapy	- SPF-IRI. - MET.	Reduction in negative symptoms and stress. High

				- (OT taken 45-50 min before session).	- Two sessions per week in groups of three to six individuals	- SNS. - PANAS.	adherence and fidelity to protocol. Oxytocin group had the strongest response and earliest results
13	Ellenbogen et al.	2024	Canada	23 participants (12 to OT vs. 11 placebo) (24 IU) (OT taken 30 min before session)	MDD	- Interpersonal Therapy - 16 weekly sessions - IDS-C. - HAM-D. - BDI. - BAI. - WAI-S. - UCLA LIS. - SBQ-R. - MSPSS.	Improves the therapeutic alliance

Abbreviations: OT: oxytocin; IU.: international units; PTSD: post-traumatic stress disorder; MDD: major depressive disorder; BPD: Borderline Personality Disorder; SAD: Social Anxiety Disorder.

Measures abbreviations: SPAI: Social Phobia and Anxiety Inventory; LSAS: Liebowitz Social Anxiety Scale; BFNE: Brief Fear of Negative Evaluation Scale; LIS: Life Interference Scale; CEQ: Credibility/Expectancy Questionnaire; APS: Appearance Scale; SPQ: Speech Performance Questionnaire; FAR: Facial Affect Recognition; PONS: Profile of Nonverbal Sensitivity; TEAT: The empathic accuracy Task; MSCEIT: Mayer–Salovey–Caruso Emotional Intelligence Test. TASIT: The Awareness of Social Inference Test; SWAP: Shedler–Westen Assessment Procedure; HAM-D: Hamilton Rating Scale for Depression; EPDS: Edinburgh Postnatal Depression Scale; ANPS: Affective Neuroscience Personality Scale; RMET: Reading the Mind in the Eyes Test; SAPS & SANS: Scale for the Assessment of Positive and Negative Symptoms; FEEST: Emotion Recognition: The Facial Expressions of Emotions Task; AIHQ: Ambiguous Intentions Hostility Questionnaire; DASS-21: Depression, Anxiety, and Stress Scale; K-10: Kessler Psychological Distress Scale; CGI-S: Clinical Global Impression-Severity Scale. SSPA: Social Skills Performance Assessment; ICQ: Interpersonal Competence Questionnaire; SDS: Sheehan Disability Scale; MINI: Mini International Neuropsychiatric Interview; CAP-5: Clinician Administered PTSD Scale for DSM-5; PCL-5: PTSD Checklist for DSM-5; BDI-II: Beck Depression Inventory 2nd edition; HAQ-II: The Helping Alliance Questionnaire; CSQ: Client Satisfaction Questionnaire; RMET: Reading the Mind in the Eyes Test; EAT: Empathic Accuracy Task; TG: Trust Game; FERT: Facial Emotion Recognition Test; ACEQ: the Adverse Childhood Experience Questionnaire; STAI: State-Trait Anxiety Inventory; GQ: Group Questionnaire; MCQ-Br: Methamphetamine Craving Questionnaire-Brief; BSFS: The Birchwood Social Functioning Scale; DPAS: The Defeatist Performance Attitude Scale; ABS: Asocial Beliefs Scale; BPRS: The four Brief Psychiatric Rating Scale; CGI: Clinical Global Impression; CDS: Calgary Depression Scale; EMA: Ecological Momentary Assessment; OQ-45: The Outcome Questionnaire-45; HSCL-11: The Hopkins Symptom Checklist–short form; SAI: Session Alliance Inventory; SPF-IRI: Interpersonal Reactivity Index; MET: The Multifaceted Empathy Test; SNS: Self-Evaluation of Negative Symptoms; PANAS: Positive and Negative Affect Schedule; IDS-C: Inventory of Depressive Symptomatology – Clinician Rated; BAI: Beck Anxiety Inventory; WAI-S: Working Alliance Inventory – short form; ECR: Experiences in Close Relationships; RCQ: Readiness to Change Questionnaire. UCLA LIS: UCLA Life Stress Interview; SBQ-R: Suicidal Behavior Questionnaire-Revised. MSPSS: Multiple Scale of Perceived Social Support.