Does Intranasal Oxytocin Reduce Symptoms of Mental Disorders?

A Meta-Analysis of Clinical Trials

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ABSTRACT

Does Intranasal Oxytocin Reduce Symptoms of Mental Disorders?
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Intranasal administration of oxytocin has been shown to enhance social cognition and reduce stress reactivity in healthy individuals, indicating potential therapeutic benefits for mental disorders. However, clinical trials have produced mixed results. Following a systematic search, data were extracted from 42 double-blind, randomized controlled trials comparing symptoms following intranasal oxytocin versus placebo in autism spectrum disorder, schizophrenia spectrum disorders, substance use disorder, and other mental disorders. Random effects meta-analysis of the pooled sample (N = 2185) revealed a small, non-significant overall treatment effect with substantial between-trial heterogeneity (g = 0.17, 95% CI = –0.02 to 0.36, I^2 = 77.41%). The removal of two outlier studies with extremely large treatment effects in substance use disorder caused a significant moderation by mental disorder category to disappear. However, the removal of these outliers also revealed a significant moderation by biological sex whereby studies with more females showed greater treatment effects. No significant moderation by dose, number of administrations, or psychosocial interventions was detected. Despite promising findings in individual studies, intranasal oxytocin is not currently supported as an evidence-based treatment for mental disorders. Future clinical trials should systematically examine dose-response relations, optimize psychosocial intervention protocols, address the underrepresentation of females, and report individual participant data which will enable meta-analyses to investigate individual differences in treatment response.

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Dedication

This thesis is dedicated to my late grandmother, Emiline Hayden, who instilled in me a passion for the pursuit of knowledge from an early age. You may have been prevented from attending higher education yourself, but here you are in a master's thesis. I will never forget your unwavering support which continues to encourage me to learn and grow each day. Love, Justin.

Contribution of Authors

Stephanie Gumuchian, Justin Bonnieux, and Mark Ellenbogen designed the study. Stephanie Gumuchian and Justin Bonnieux conducted the systematic literature search. Justin Bonnieux, Stephanie Gumuchian, Florencia Trespalacios, Tiffany Resendes, Alexandra Harboun, Olivia Quintus-Bosz, Dave Garred, Lori Hazel, and Shiu Wong screened search results for reports to be included. Justin Bonnieux, Alexandra Harboun, Alexandra Haddad, Kellie-Anne Bélisle, Alison McLellan, Leo Chester-Trudel, Stephanie Gumuchian, Florencia Trespalacios, Lori Hazel, Shiu Wong, and Mark Ellenbogen extracted data from the included reports. Justin Bonnieux analyzed the data and wrote the manuscript. Mark Ellenbogen revised the manuscript.

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1. Introduction

Oxytocin is a hormone originally discovered in the early twentieth century for its role in stimulating uterine contractions during childbirth (Dale, 1909) and milk secretion during breastfeeding (Ott & Scott, 1910). Decades later, animal studies demonstrated its promotion of maternal behaviours (Pedersen & Prange, 1979), pair bonding (Williams et al., 1994), and other social functions (Young, 1999). The prosocial hypothesis was established following convergent evidence that oxytocin administered intranasally in humans promotes trust (Kosfeld et al., 2005), empathy (Hurlemann et al., 2010), emotion recognition (Guastella et al., 2010), theory of mind (Domes et al., 2007), and other prosocial functions. However, more nuanced accounts became necessary as evidence emerged of oxytocin's context-dependent social effects, including increased envy and gloating during competition (Shamay-Tsoory et al., 2009) and heightened defensiveness toward members of an "outgroup" (De Dreu et al., 2010). Additional complexity arises from individual differences in oxytocin responses, which have been linked to factors such as biological sex (Gao et al., 2016), attachment style (Bartz, et al., 2011a), and mental health symptomatology (Boyle et al., 2022). These contextual and individual response variations have informed updated theoretical frameworks. Most prominent among these is the social salience hypothesis, which posits that oxytocin enhances the salience of social cues rather than uniformly promoting social behaviours (Shamay-Tsoory & Abu-Akel, 2016). However, other theories may better account for oxytocin's non-social effects, such as improved stress regulation (Cardoso et al., 2014a) and reward processing (Takiguchi et al., 2023).

Despite mixed findings in healthy populations, interest in clinical applications has grown. Much of this work has focused on autism spectrum disorder (ASD), which is characterized by difficulties with social-emotional reciprocity, theory of mind, and other social functions associated

with oxytocin (Huang et al., 2021). Other trials have involved participants with schizophrenia, in whom positive symptoms like hallucinations are often effectively managed with antipsychotic medications but negative symptoms like asociality – whose severity correlates with endogenous oxytocin levels – lack established treatments (Sabe et al., 2021). Researchers have also shown considerable interest in substance use disorder (SUD) due to characteristic deficits in oxytocin-related processes like stress regulation and reward processing (King et al., 2020), as well as lower plasma oxytocin concentrations relative to healthy individuals (Mellentin et al., 2023). Surprisingly, anxiety and depressive disorders have received relatively little attention in intranasal oxytocin trials, despite their characteristic deficits in social functioning (American Psychiatric Association, 2022).

Intranasal oxytocin clinical trials have yielded mixed results. Although reductions in ASD symptoms have been reported (Yamasue et al., 2020; Yatawara et al., 2016), these are exceptions to the general observation that oxytocin lacks clinical efficacy in ASD (Zhang et al., 2025). Meta-analyses have also found no clear evidence that oxytocin reduces either positive or negative symptoms of schizophrenia (Martins et al., 2022; Sabe et al., 2021; Zheng et al., 2019). However, one meta-analysis of five trials found a small reduction in *general psychopathology* symptoms among individuals with schizophrenia (Martins et al., 2022). A recent systematic review of oxytocin trials in SUD highlighted promising reductions in withdrawal symptoms among opioid use disorder patients but cautioned against firm conclusions due to inconsistent findings and heterogeneous methods (Mellentin et al., 2023). Clinical outcomes in social anxiety disorder and major depressive disorder (MDD) are each represented by only one published report. While the former found null intranasal oxytocin effects (Guastella et al., 2009), the latter found that intranasal

oxytocin, in conjunction with psychotherapy, significantly reduced MDD symptoms post-treatment and at six-month follow-up (Ellenbogen et al., 2024).

Mixed findings across intranasal oxytocin trials may be linked to several methodological variables that warrant closer examination. For instance, dose–response relations in nonclinical studies tend to be nonlinear, with some evidence of greater effects from moderate (24 IU) doses compared to low (12 IU) or high (48 IU) doses (Cardoso et al., 2013, 2014b; Spengler et al., 2017). A similar nonlinear pattern has also been reported for social reciprocity enhancement in ASD (Yamasue et al., 2022). However, most intranasal oxytocin trials do not investigate multiple doses, and findings regarding dose-response relations remain inconclusive in clinical research. Importantly, differences in oxytocin formulation and delivery device likely influence how much of the hormone reaches the brain, making these critical factors to consider alongside dose (Insel, 2016; Quintana et al., 2017).

Administration frequency is another potentially crucial but understudied variable. A recent study in mice found that neurochemical responses differed following a single oxytocin injection versus 14 consecutive daily injections (Benner et al., 2021). Another trial in neurotypical men found that a single intranasal oxytocin dose reduced amygdala responses to facial emotions, but that this effect was attenuated following five consecutive daily doses – suggesting possible oxytocin receptor desensitization (Kou et al., 2022). Interestingly, the reduced amygdala responses were maintained following three alternate-day doses across the same five-day period, indicating that infrequent intranasal oxytocin dosing may prevent desensitization. Another study in men with ASD found reductions in resting-state amygdala activity and self-reported tension to be comparable following either a single intranasal oxytocin dose or 28 consecutive daily doses (Alaerts et al., 2022). However, brain scans were collected 45 minutes post-administration in the

single-dose condition but 24 hours later in the 28-dose condition, introducing a timing confound that limits comparability between conditions.

Additional methodological factors, independent of oxytocin administration, may also affect treatment outcomes and warrant further investigation. Some trials involve psychosocial interventions, such as psychotherapy, based on the premise that a supportive interpersonal context may enhance intranasal oxytocin's context-dependent prosocial effects (Bartz et al., 2011b). However, these combined interventions have not reliably improved outcomes, underscoring the need to better understand which interventions are most effective for which populations. It is also important to consider the timing of psychosocial interventions in relation to intranasal oxytocin administration, with neuroimaging evidence suggesting peak brain activation around 45 minutes following delivery (Paloyelis et al., 2016).

Biological sex is another key but understudied variable in the intranasal oxytocin literature (Quintana et al., 2021). Although oxytocin is known to interact with sex hormones, how these interactions influence treatment responses in mental disorders remains poorly understood. Advancement in this area has been greatly limited by the underrepresentation of females in oxytocin research. For example, a recent meta-analysis found that the proportion of male participants was positively associated with symptom reductions in schizophrenia; however, the pooled sample included approximately four times as many males as females (Martins et al., 2022).

In the present meta-analysis, we investigated whether intranasal oxytocin produces greater symptom reductions than placebo across various mental disorders. We also explored potential moderation by mental disorder, oxytocin dose, number of doses, psychosocial intervention use, and biological sex. By examining these factors, we aimed to identify the conditions under which intranasal oxytocin is most therapeutically effective and to highlight directions for future research.

2. Method

2.1 Inclusion Criteria

This PROSPERO pre-registered (Bonnieux et al., 2020) meta-analysis followed the JBI Manual for Evidence Synthesis (Aromataris et al., 2024) and PRISMA 2020 guidelines (Page et al., 2021). Original reports in English or French of double-blind, randomized controlled trials (RCTs) which met the following criteria were eligible for inclusion: (i) the *population* was individuals with a mental disorder diagnosed via structured clinical interview based on recent versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III to DSM-5-TR; American Psychiatric Association, 2022) or International Classification of Diseases (ICD-10 to ICD-11; World Health Organization, 2018), (ii) the *intervention* was intranasally administered oxytocin, (iii) the *comparator* was intranasally administered placebo, and (iv) the *outcome* was a psychometrically validated measure of disorder-specific symptom severity.

2.2 Systematic Search

A comprehensive search strategy was developed in collaboration with librarians at Concordia University and executed in February 2024 across five electronic databases: PubMed (National Library of Medicine), APA PsycINFO (APA PsycNet), Web of Science Core Collection (Clarivate), Scopus (Elsevier), and EMBASE (Elsevier). Core search concepts included clinical trials, mental disorders, and oxytocin. Subject headings and keywords were used alongside Boolean and database-specific operators to enhance search sensitivity. Detailed search strategies are presented in Appendix 1, Tables 2-6.

2.3 Study Selection

Identified database records were imported into DistillerSR (2023) systematic review software, where duplicates were automatically detected and manually removed. Two authors independently reviewed each remaining record based on its title and abstract, with a third author resolving disagreements. The same two-step procedure was then used to identify full-texts meeting inclusion criteria.

2.4 Data Extraction

A data extraction form was developed to retrieve the following information from each included report: (i) general information including article title and authors; (ii) methodological information including oxytocin dose, number of administrations, and psychosocial interventions; (iii) sample characteristics including diagnosed mental disorders and biological sex; (iv) baseline and post-intervention outcome scores; and (v) adverse events. All data were extracted according to the intention-to-treat principle, whereby all participants randomized to an intervention were included regardless of whether or not they received it (McCoy, 2017). Cochrane's Risk of Bias 2 tool (Sterne et al., 2019) was incorporated into the data extraction form to streamline risk of bias assessment. Once data extraction and risk of bias assessment were completed by two authors independently, inconsistencies were discussed until consensus was reached. Where trials reported multiple clinically relevant outcomes, two authors independently identified a primary one – as specified by the trial authors or, when unspecified, based on their clinical and research judgment – and then met to resolve any disagreements. Where crucial data were only published in figures, the PlotDigitizer (n.d.) web application was used to obtain numerical values. Where crucial data were not published, they were requested from authors via email. Where authors withheld data or did not respond to three email requests, reports were excluded.

2.5 Data Analysis

The analysis script and corresponding dataset are publicly accessible in Zenodo (Bonnieux, 2025). Analyses were conducted using R version 4.4.1 (R Core Team, 2024) in R Studio version 2024.12.1 (Posit Team, 2024). The primary statistical package was metafor (Viechtbauer, 2010), with dplyr (Wickham et al., 2023) and ggplot2 (Wickham, 2016) providing important data manipulation and visualization functions, respectively. Because baseline-adjusted post-intervention means and standard errors produce more accurate effect estimates than traditional pre-post change scores (Morris, 2008), articles that did not report these values had them approximated via multiple linear regression. These adjusted scores were then used to calculate Hedges' *g* and its associated variance for each oxytocin-placebo comparison.

A random effects meta-analysis was then conducted using restricted maximum likelihood (REML) estimation along with a power-analysis to determine the smallest detectable effect size. Between-study heterogeneity was quantified with tau-squared (τ^2) and I-squared (I^2) and tested for statistical significance with Cochran's Q (Higgins et al., 2003). Leave-one-out diagnostics identified influential studies based on their impact on model estimates, standard errors, and heterogeneity (Viechtbauer & Cheung, 2010). Studies were flagged as outliers if they had absolute standardized residuals >2 or confidence intervals not overlapping those of the pooled effect size. Sensitivity analyses assessed the robustness of all findings to outlier removal. Publication bias was examined by creating a funnel plot, applying Egger's regression test for funnel plot asymmetry, and using the trim and fill method to identify potentially unpublished findings.

Subgroup analyses and meta-regressions were conducted to investigate potential effect size moderation by the following a priori-defined variables: (i) mental disorder category, (ii) oxytocin dose – including a comparison of linear and quadratic dose-response models, (iii) number of doses,

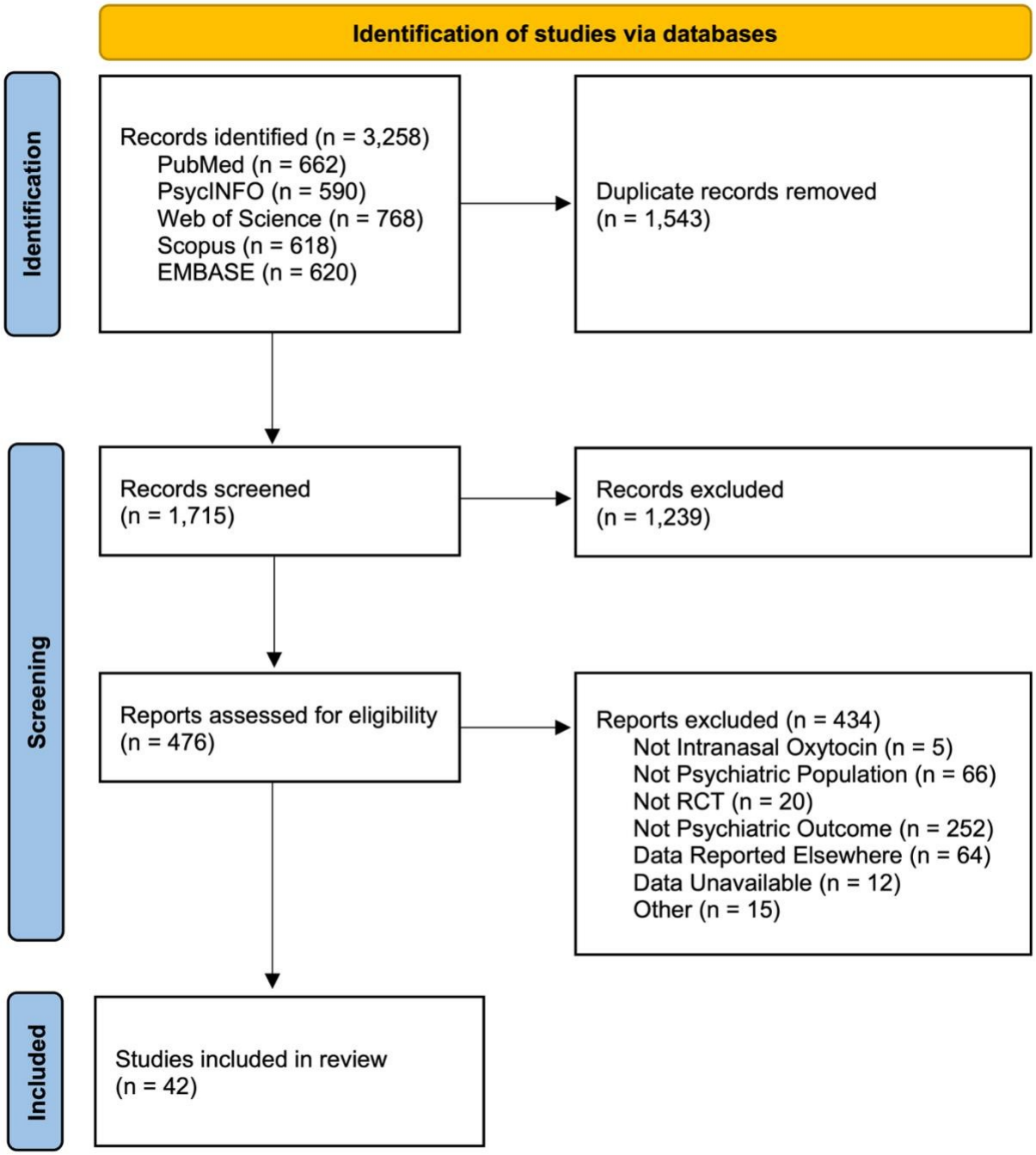
(iv) the presence of psychosocial interventions, and (v) the proportion of male participants. REML estimation was used for all meta-regression models except when linear and quadratic dose-response models were compared using maximum likelihood (ML) estimation.

3. Results

3.1 Search Results

A systematic search yielded 3258 records, of which 1543 were removed as duplicates. The remaining 1715 records were screened, 476 assessed for eligibility, and 54 deemed eligible. Necessary but unpublished data for five reports were obtained by emailing authors, including one who provided an unpublished manuscript (Pedersen et al., 2017). Data could not be retrieved from 12 reports following three or more email requests, leaving 42 studies to be included in the review. Figure 1 summarizes the article identification and screening process in a PRISMA 2020 (Page et al., 2021) flow diagram. References for the reports that were included or excluded due to unretrieved data are presented in Appendices 2 and 3, respectively.

Figure 1. *PRISMA 2020 flow diagram.*



Note: PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses (Page et al., 2021)

3.2 Study Characteristics

Among the 42 reports published between 2009 and 2024, two investigated multiple oxytocin doses (Kosaka et al., 2016; Yamasue et al., 2022), resulting in 46 oxytocin-placebo comparisons which are summarized in Table 1. These included 19 comparisons in ASD, 11 in schizophrenia spectrum disorders, nine in SUD, two in anxiety disorders, one in anorexia nervosa, one in MDD, one in posttraumatic stress disorder (PTSD), one in disruptive disorders, and one in mixed diagnoses.

The most common intranasal oxytocin dose was 24 IU ($k = 16$), with others ranging from 8 to 40 IU per administration – excluding 3 IU doses of a formulation with 3.6 times the bioavailability of *Syntocinon* nasal spray (Yamasue et al., 2022). Across the 42 comparisons which used standardized doses, the bioavailability-adjusted mean was equivalent to 26.75 IU *Syntocinon.* The remaining four comparisons used bodyweight-adjusted (Dadds et al., 2014; Hwang et al., 2024), age-adjusted (Guastella et al., 2015), or individually adjusted doses (Sikich et al., 2021).

The most common number of administrations was 84, observed in eight comparisons – of which six used twice-daily doses over six weeks and two used once-daily doses over twelve weeks. Across the 44 comparisons which standardized the number of doses, the mean was 65.66, ranging from a single dose (in three comparisons) to 336 doses. The remaining two comparisons either combined data from two trials of different duration (Russell et al., 2018) or used a flexible number of doses (Sikich et al., 2021). Only 15 comparisons involved psychosocial interventions, which varied widely in scope – from a single one-hour session to comprehensive inpatient programs and outpatient psychotherapy spanning 24 weeks.

Of the 46 oxytocin-placebo treatment comparisons, 15 included exclusively male participants, 26 were predominantly male, four were predominantly female, and only one was sex-balanced, yielding a pooled sample that was 82.7% male.

Table 1. *Included study characteristics.*

Study	Design	Disorder Category	Specifier	Outcome	Participants	Dose	Total Doses	Trial Duration[a]
Acheson et al. (2015)	Parallel	Anxiety	Arachnophobia	SPQ	N = 23 OT = 10 PL = 13	24 IU	1	7 days
Anagnostou et al. (2012)	Parallel	ASD	-	SRS	N = 19 OT = 10 PL = 9	24 IU	84	42 days
Azadbakht et al. (2022)	Parallel	SUD	Methamphetamine	CCQ-Br	N = 42 OT = 21 PL = 21	20 IU	56	28 days
Barnaerts et al. (2020)	Parallel	ASD	-	SRS	N = 40 OT = 22 PL = 18	24 IU	28	28 days
Buchanan et al. (2017)	Parallel	Schizophrenia Spectrum	Schizophrenia or Schizoaffective Disorder	SANS	N = 34 OT = 15 PL = 19	24 IU	84	42 days
Buchanan et al. (2021)	Parallel	Schizophrenia Spectrum	Schizophrenia or Schizoaffective Disorder	SANS	N = 62 OT = 31 PL = 31	36 IU	336	168 days
Caccioti-Saija et al. (2015)	Parallel	Schizophrenia Spectrum	Schizophrenia, Schizophreniform, or Schizoaffective Disorder	SANS	N = 52 OT = 27 PL = 25	24 IU	96	42 days
Dadds et al. (2014)	Parallel	ASD	-	SRS	N = 38 OT = 19 PL = 19	12 or 24 IU	4	4 days
Dagani et al. (2016)	Crossover	Schizophrenia Spectrum	Schizophrenia	PANSS Negative	N = 64 OT = 32 PL = 32	40 IU	122	122 days

Study	Design	Disorder Category	Specifier	Outcome	Participants	Dose	Total Doses	Trial Duration[a]
Daniels et al. (2023)	Parallel	ASD	-	SRS	N = 77 OT = 38 PL = 39	12 IU	56	28 days
Davis et al. (2014)	Parallel	Schizophrenia Spectrum	Schizophrenia	CAINS	N = 27 OT = 13 PL = 14	40 IU	12	49 days
Ellenbogen et al. (2024)	Parallel	MDD	-	IDS-C	N = 23 OT = 12 PL = 11	24 IU	16	112 days
Fastman et al. (2021)	Parallel	ASD	Phelan McDermid Syndrome	ABC-SW	N = 16 OT = 7 PL = 9	24 IU	168	84 days
Feifel et al. (2010)	Crossover	Schizophrenia Spectrum	Schizophrenia	PANSS Negative	N = 30 OT = 15 PL = 15	40 IU	42	21 days
Flanagan et al. (2018)	Parallel	PTSD	-	CAPS-5	N = 17 OT = 8 PL = 9	40 IU	8	56 days
Gibson et al. (2014)	Parallel	Schizophrenia Spectrum	Schizophrenia	PANSS Negative	N = 14 OT = 8 PL = 6	24 IU	84	42 days
Grossman-Giron et al. (2023)	Parallel	Transdiagnostic	Severe mental illness	HAM-D	N = 87 OT = 44 PL = 43	16 IU	56	28 days

Study	Design	Disorder Category	Specifier	Outcome	Participants	Dose	Total Doses	Trial Duration[a]
Guastella et al. (2009)	Parallel	Anxiety	Social Anxiety Disorder	SPAI	N = 25 OT = 12 PL = 13	24 IU	4	21 days
Guastella et al. (2015)	Parallel	ASD	-	SRS	N = 50 OT = 26 PL = 24	18 or 24 IU	112	56 days
Guastella et al. (2023)	Parallel	ASD	-	SRS	N = 87 OT = 45 PL = 42	16 IU	168	84 days
Hwang et al. (2024)	Parallel	Disruptive Disorders	ADHD, ODD, CD, and/or DMDD	ARI	N = 52 OT = 25 PL = 27	12 or 24 IU	21	21 days
Jarksog et al. (2017)	Parallel	Schizophrenia Spectrum	Schizophrenia or Schizoaffective Disorder	PANSS Negative	N = 67 OT = 35 PL = 32	24 IU	168	84 days
Kosaka et al. (2016a)	Parallel	ASD	-	CGI-S	N = 30 OT = 20 PL = 10[b]	16 IU	84	84 days
Kosaka et al. (2016b)	Parallel	ASD	-	CGI-S	N = 30 OT = 20 PL = 10[b]	32 IU	84	84 days
Le et al. (2022)	Crossover	ASD	-	ADOS	N = 82 OT = 41 PL = 41	24 IU	21	42 days
Lee et al. (2013)	Parallel	Schizophrenia Spectrum	Schizophrenia or Schizoaffective Disorder	SANS	N = 28 OT = 13 PL = 15	20 IU	42	21 days
McRae-Clark et al. (2013)	Parallel	SUD	Marijuana	MCQ	N = 16 OT = 8 PL = 8	40 IU	1	<1 day

Study	Design	Disorder Category	Specifier	Outcome	Participants	Dose	Total Doses	Trial Duration[a]
Melby et al. (2019)	Parallel	SUD	Alcohol	CIWA-Ar	N = 40 OT = 20 PL = 20	24 IU	6	3 days
Modabbernia et al. (2013)	Parallel	Schizophrenia Spectrum	Schizophrenia	PANSS Negative	N = 40 OT = 20 PL = 20	40 IU	112	56 days
Moeini et al. (2019)	Parallel	SUD	Heroin	COWS	N = 51 OT = 27 PL = 24	40 IU	1	<1 day
Munesue et al. (2016)	Crossover	ASD	With comorbid Intellectual Disability	CARS	N = 58 OT = 29 PL = 29	8 IU	112	56 days
Pedersen et al. (2011)	Parallel	Schizophrenia Spectrum	Schizophrenia	PANSS Negative	N = 20 OT = 11 PL = 9	24 IU	28	14 days
Pedersen et al. (2013)	Parallel	SUD	Alcohol	CIWA-Ar	N = 11 OT = 7 PL = 4	24 IU	6	3 days
Pedersen et al. (2017)	Parallel	SUD	Alcohol	TLFB	N = 22 OT = 12 PL = 10	40 IU	168	84 days
Russell et al. (2018)	Parallel	Anorexia Nervosa	-	EDE	N = 33 OT = 16 PL = 17	18 IU	55 or 83	28 or 42 days
Sherman et al. (2017)	Parallel	SUD	Cannabis	TLFB	N = 15 OT = 8 PL = 7	40 IU	2	21 days
Sikich et al. (2021)	Parallel	ASD	-	ABC-SW	N = 277 OT = 139 PL = 138	8-40 IU	168-336	168 days

Study	Design	Disorder Category	Specifier	Outcome	Participants	Dose	Total Doses	Trial Duration[a]
Stauffer et al. (2020)	Parallel	SUD	Methamphetamine	MCQ-Br	N = 47 OT = 24 PL = 23	40 IU	6	35 days
Stauffer et al. (2022)	Parallel	SUD	Methamphetamine and/or Cocaine	STCQ-Br	N = 40 OT = 18 PL = 22	40 IU	84	42 days
Watanabe et al. (2015)	Crossover	ASD	-	ADOS Reciprocity	N = 36 OT = 18 PL = 18	24 IU	84	42 days
Yamasue et al. (2020)	Parallel	ASD	-	ADOS Reciprocity	N = 104 OT = 51 PL = 53	24 IU	84	42 days
Yamasue et al. (2022a)	Crossover	ASD	-	ADOS Reciprocity	N = 48 OT = 25 PL = 23	3[c] IU	28	28 days
Yamasue et al. (2022b)	Crossover	ASD	-	ADOS Reciprocity	N = 49 OT = 25 PL = 24	3[c] IU	56	28 days
Yamasue et al. (2022c)	Crossover	ASD	-	ADOS Reciprocity	N = 53 OT = 26 PL = 27	10[c] IU	28	28 days
Yamasue et al. (2022d)	Crossover	ASD	-	ADOS Reciprocity	N = 47 OT = 24 PL = 23	10[c] IU	56	28 days
Yatawara et al. (2016)	Crossover	ASD	-	ADOS	N = 62 OT = 31 PL = 31	12 IU	70	35 days

Note: OT = oxytocin, PL = placebo, IU = international units, ADHD = Attention-Deficit/Hyperactivity Disorder, ASD = CD = Conduct Disorder, DMDD = Disruptive Mood Dysregulation Disorder, MDD = Major Depressive Disorder, ODD Disorder, PTSD = Posttraumatic Stress Disorder, SUD = Substance Use Disorder, ABC-SW = Aberrant Behavior Check subscale, ADOS = Autism Diagnostic Observation Schedule, ADOS Reciprocity = Autism Diagnostic Observation Sch ARI = Affective Reactivity Index, CAINS = Clinical Assessment Interview for Negative Symptoms, CAPS-5 = Clinicia for DSM-5, CARS = Childhood Autism Rating Scale, CCQ-Br = Cocaine Craving Questionnaire – Brief, CGI-S = Clini Severity, CIWA-Ar = Clinical Institute Withdrawal Assessment of Alcohol revised scale, COWS = Clinical Opioid Witl Disorders Examination, HAM-D = Hamilton Rating Scale for Depression, IDS-C = Inventory of Depressive Symptomat = Marijuana Craving Questionnaire, MCQ-Br = Methamphetamine Craving Questionnaire – Brief, PANSS Nega Syndrome Scale – Negative subscale, SANS = Scale for the Assessment of Negative Symptoms, SPAI = Social Phobia A Spider Phobia Questionnaire, SRS = Social Responsiveness Scale, STCQ-Br = Stimulant Craving Questionnaire – Brief Back.

[a]Trial duration represents the number of days from the first treatment dose to the first outcome measure occurring after t

[b]One placebo group with 20 participants served as a comparison for two oxytocin groups; therefore, its sample was even comparisons.

[c]Dose prior to adjustment for enhanced bioavailability of TTA-121 formulation compared to Syntocinon.

3.3 Study Effects

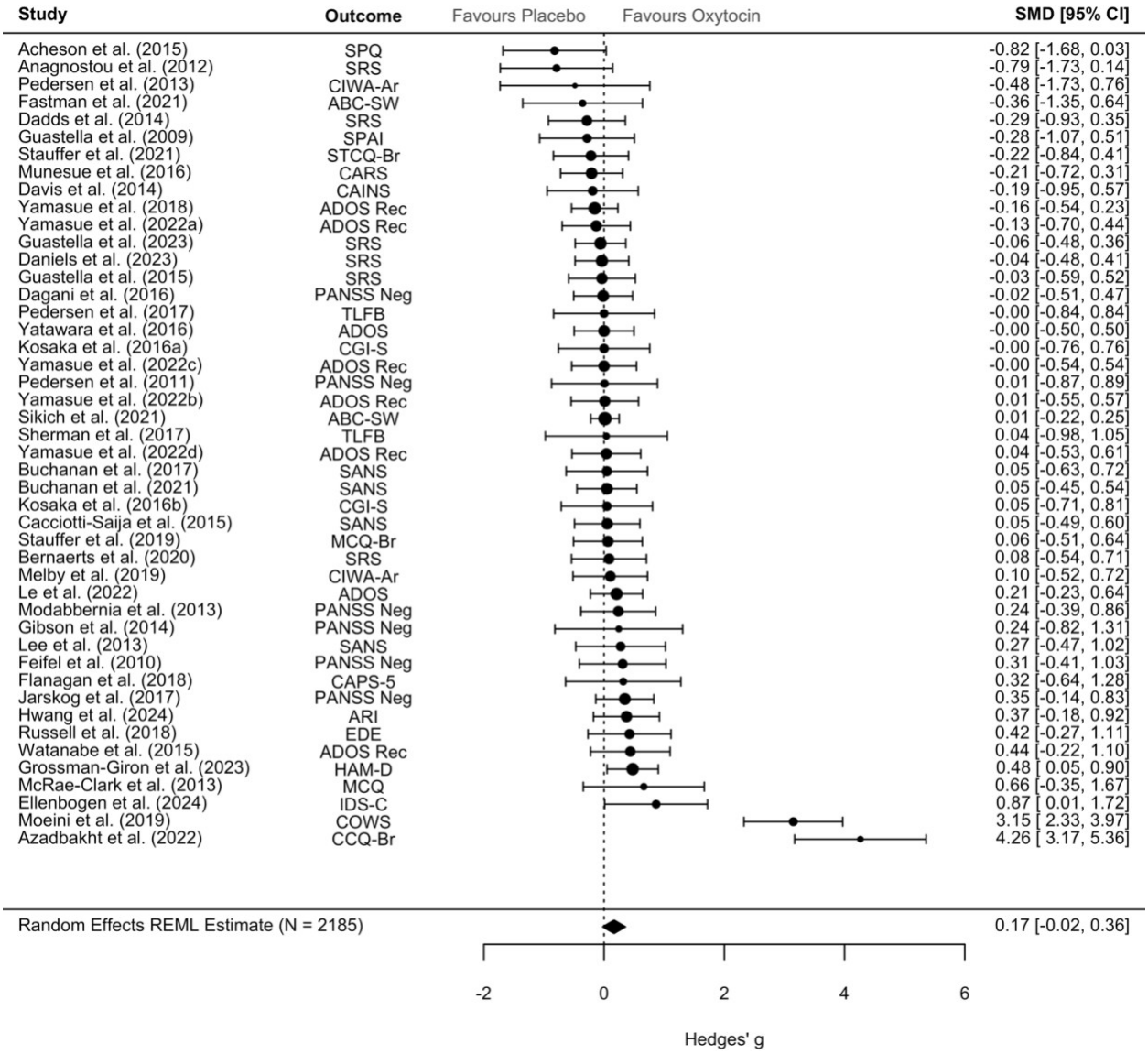
Standardized mean differences from the 46 oxytocin–placebo comparisons ranged from a large but non-significant effect favouring placebo in arachnophobia (g = –0.82, 95% CI = –1.68 to 0.03; Acheson et al., 2015) to two outliers with extremely large and statistically significant effects favouring oxytocin in SUD (g = 3.15, 95% CI = 2.33 to 3.97; g = 4.26, 95% CI = 3.17 to 5.35), both from the same research team (Azadbakht et al., 2022; Moeini et al., 2019). One outlier found substantially lower cocaine craving in 21 outpatients who received twice-daily 20 IU oxytocin alongside 22 psychoeducational group treatment sessions over a four-week period, compared to 21 participants undergoing the same protocol with placebo (Azadbakht et al., 2022). The other outlier found substantially lower opioid withdrawal symptoms in 27 addiction rehabilitation centre inpatients who received a single 40 IU dose of oxytocin with no psychosocial intervention, compared to 24 participants undergoing the same protocol with placebo (Moeini et al., 2019).

3.4 Random Effects Meta-Analysis

As shown in Figure 2, the overall random-effects REML estimate indicated a small but non-significant effect favouring oxytocin (g = 0.17, 95% CI = –0.02 to 0.36, p = .08) with substantial heterogeneity (τ^2 = 0.31, I^2 = 77.41%) that was statistically significant (Q = 140.41, p < .0001). Post-hoc power analysis revealed the minimum detectable effect size to be g = 0.27 given α = .05 and a power of 80%. The 95% prediction interval estimating the range of effects that might be expected in future studies was calculated at –0.93 to 1.27, demonstrating considerable uncertainty in both the direction and magnitude of oxytocin's overall treatment efficacy across mental disorders. Leave-one-out influence diagnostics did not identify either outlier study as influential on its own. Excluding both from the random effects model reduced its estimated effect size (g =

0.05, 95% CI = –0.04 to 0.13, $p = .28$) and heterogeneity ($\tau^2 = 0.00$, $I^2 = 0.00\%$). This did not change the conclusion that there was no overall treatment effect. However, it revealed that the remaining studies had substantial within-study variability, making it difficult for the random-effects model to distinguish true differences in effect sizes from those attributable to sampling error.

Figure 2. *Forest plot of standardized mean differences from 46 treatment comparisons.*

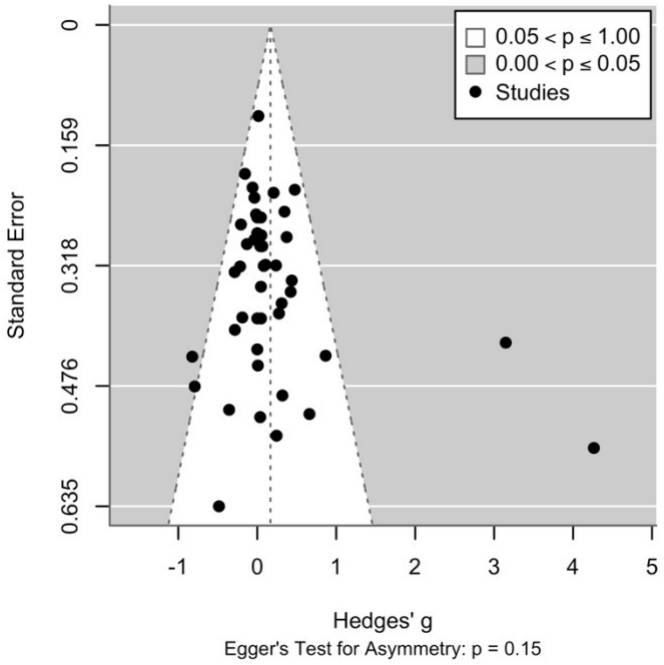


Note. REML = Restricted Maximum Likelihood, ABC-SW = Aberrant Behavior Checklist – Social Withdrawal subscale, ADOS = Autism Diagnostic Observation Schedule, ADOS Rec = Autism Diagnostic Observation Schedule – Reciprocity subscale, ARI = Affective Reactivity Index, CAINS = Clinical Assessment Interview for Negative Symptoms, CAPS-5 = Clinician-Administered PTSD Scale for DSM-5, CARS = Childhood Autism Rating Scale, CCQ-Br = Cocaine Craving Questionnaire - Brief, CGI-S = Clinical Global Impression – Severity, CIWA-Ar = Clinical Institute Withdrawal Assessment of Alcohol revised scale, COWS = Clinical Opioid Withdrawal Scale, EDE = Eating Disorders Examination, HAM-D = Hamilton Rating Scale for Depression, IDS-C = Inventory of Depressive Symptomatology – Clinician rated, MCQ = Marijuana Craving Questionnaire, MCQ-Br = Methamphetamine Craving Questionnaire – Brief, PANSS Neg = Positive and Negative Syndrome Scale – Negative subscale, SANS = Scale for the Assessment of Negative Symptoms, SPAI = Social Phobia Anxiety Inventory, SPQ = Spider Phobia Questionnaire, SRS = Social Responsiveness Scale, STCQ-Br = Stimulant Craving Questionnaire – Brief, TLFB = Timeline Follow-Back.

3.5 Publication Bias

As shown in Figure 3, Egger's regression test for funnel plot asymmetry was not statistically significant (p = .15), suggesting no evidence of publication bias. Additionally, the trim-and-fill method did not suggest any missing studies, further supporting an absence of selective reporting.

Figure 3. *Funnel plot of included studies' effect sizes and standard errors.*



3.6 Moderation Analyses

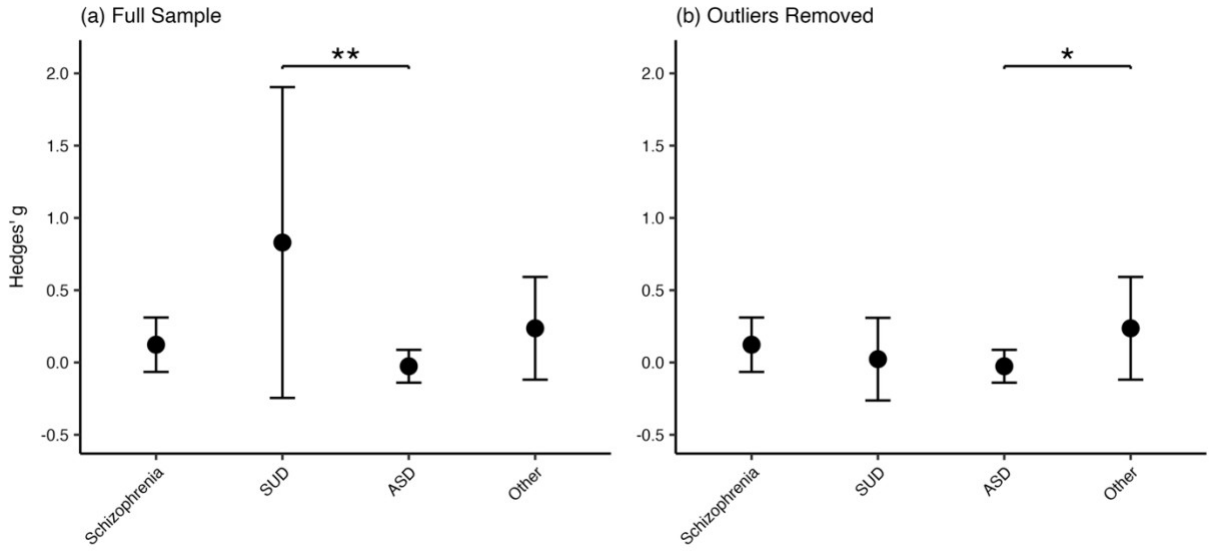
3.6.1 Moderation by Mental Disorder

Effect sizes were compared across subgroups of mental disorders represented by at least three oxytocin–placebo comparisons (19 in ASD, 11 in schizophrenia spectrum disorders, 9 in SUD) and an additional subgroup for the remaining 7 comparisons. A large but non-significant oxytocin treatment effect was observed in SUD (g = 0.83, 95% CI = –0.25 to 1.90, p = .13), whereas no treatment effects were observed in ASD (g = –0.03, 95% CI = –0.14 to 0.09, p = .65), schizophrenia

spectrum disorders (g = 0.12, 95% CI = –0.07 to 0.31, p = .20), or "other" disorders (g = 0.24, 95% CI = –0.12 to 0.59, p = .19).

With outliers included, meta-regression revealed significant moderation by mental disorder category, $QM(3) = 9.78$, p = .021. The moderation explained 18.40% of between-study variance (R^2) with substantial residual heterogeneity (τ^2 = 0.25, I^2 = 73.41%). As shown in Figure 4a, oxytocin effects were substantially more positive in SUD than in ASD (b = 0.80, SE = 0.26, p = .002), while other pairwise comparisons were non-significant. With outliers excluded, moderation by mental disorder was non-significant, $QM(3) = 5.87$, p = .12, and explained no between-study variance (R^2). However, as shown in Figure 4b, studies in "other" mental disorders yielded significantly more positive oxytocin effects than those in ASD (b = 0.31, SE = 0.14, p = .02), while other contrasts were non-significant.

Figure 4. *Oxytocin treatment effect by mental disorder subgroup*



Note: ASD = autism spectrum disorder, SUD = substance use disorder. Effect size estimates and 95% confidence intervals are from separate meta-analyses within each mental disorder subgroup. Asterisks represent statistically significant subgroup differences identified in an overall meta-regression model with mental disorder as a moderator (*p < .05 **p < .01).

3.6.2 Moderation by Dose

Meta-regression was used to investigate intranasal oxytocin's dose-response relation. Four studies that reported variable dosing were excluded from this analysis (Dadds et al., 2014; Guastella et al., 2015; Hwang et al., 2024; Sikich et al., 2021), and one study had its doses multiplied by 3.6 to account for the formulation's enhanced bioavailability relative to *Syntocinon* nasal spray (Yamasue et al., 2022). Linear regression revealed no significant dose-response relation whether outliers were included, $QM(1) = 0.47$, $p = .49$, or excluded, $QM(1) = 0.10$, $p = .75$. Adding a quadratic term did not improve model fit, as indicated by higher AIC values compared to the linear model both with outliers (105.61 vs. 103.61) and without (22.17 vs. 20.63). Controlling for the number of doses administered did not meaningfully change these findings.

3.6.3 Moderation by Number of Doses

A separate linear regression model investigated potential moderation by the number of doses. Two studies in which the number of doses varied between participants were excluded from this analysis (Russell et al., 2018; Sikich et al., 2021). Linear regression revealed no significant moderation whether outliers were included, $QM(1) = 0.73$, $p = .39$, or excluded, $QM(1) = 0.05$, $p = .82$.

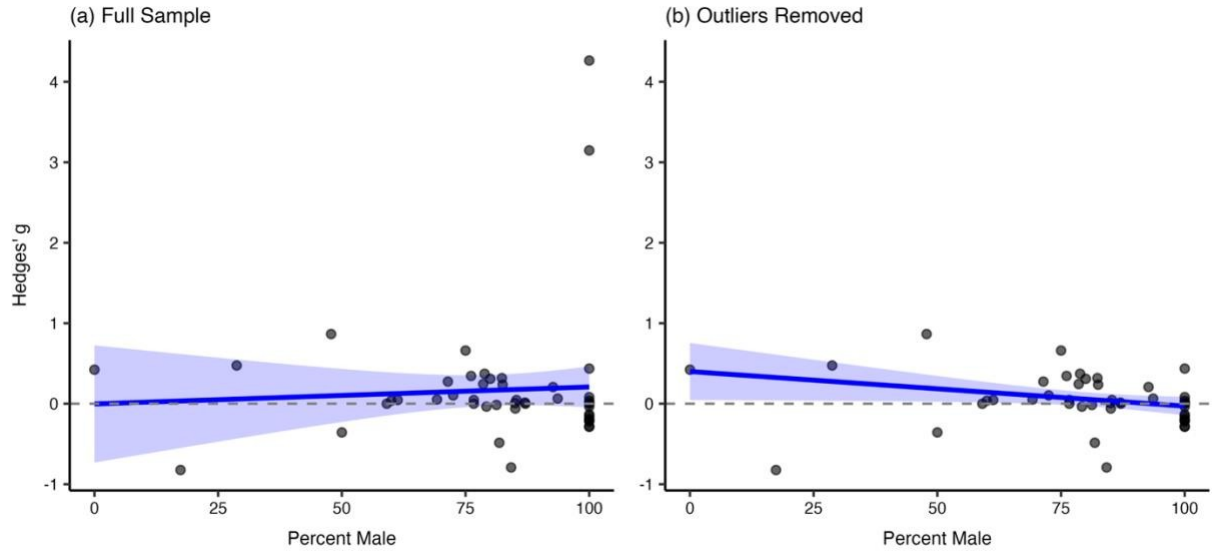
3.6.4 Moderation by Psychosocial Interventions

Despite substantial heterogeneity among psychosocial interventions, this variable was investigated in a binary fashion – comparing effect sizes from the 15 comparisons that involved a psychosocial intervention to those from the 31 comparisons that did not. Linear regression revealed no significant moderation by the presence of psychosocial interventions whether outliers were included, $QM(1) = 0.38$, $p = .54$, or excluded, $QM(1) = 0.48$, $p = .49$.

3.6.5 Moderation by Biological Sex

To examine biological sex as a potential moderator, effect sizes were regressed on the percentage of male participants in each treatment comparison. As shown in Figure 5a, there was no evidence of moderation in the full sample, $QM(1) = 0.23$, $p = .64$. However, Figure 5b shows that removing outliers revealed a pattern of larger effects in trials with a higher proportion of female participants, $QM(1) = 4.03$, $p = .04$. The estimated slope was -0.0043 (95% CI = -0.0085 to -0.0001), meaning that for every 1% increase in the proportion of male participants, there was a 0.0043 decrease in Hedges' *g*.

Figure 5. *Oxytocin treatment effect moderation by percent male participants.*



Note. Shaded regions represent 95% confidence intervals around linear regression estimates. (a) no moderation in the full sample. (b) significant moderation after outlier removal, $p = .04$.

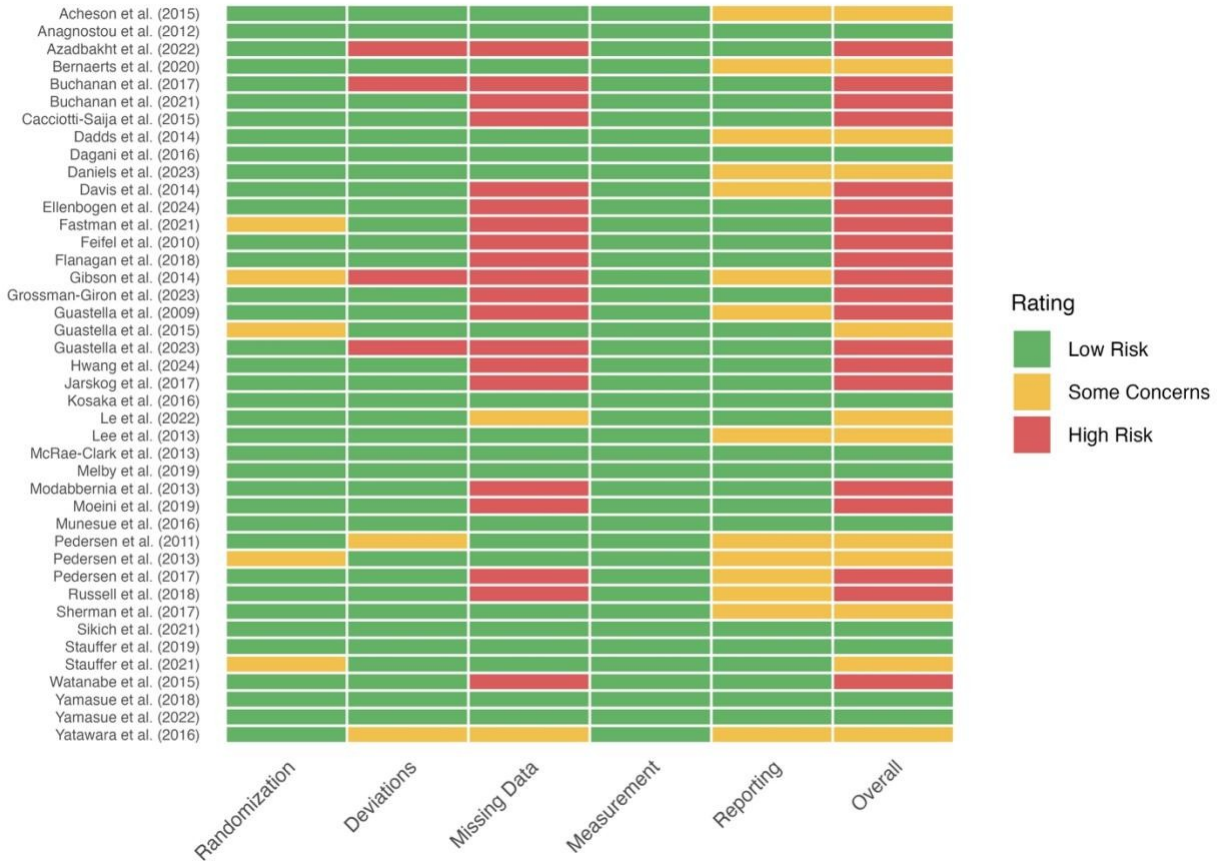
3.7 Adverse Events

Explicit statements about serious adverse events were reported in 25 out of 42 studies. Among these, such events were rare in both the placebo (1.36%) and oxytocin (1.81%) groups, with no significant between-group difference, $\chi^2(1) = 0.49$, $p = .48$.

3.8 Risk of Bias

Included reports were categorized as having high risk of bias ($k = 20$), some concerns ($k = 12$), or low risk of bias ($k = 10$). Figure 6 shows ratings in each of the five risk of bias sub-domains pertaining to the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result (Sterne et al., 2019). Conflicts of interest were reported in 13 trials. Disclosures included receiving funding from pharmaceutical companies and researchers having financial interests or serving as consultants for companies that could benefit from positive findings. Of the remaining 31 reports, 26 indicated having no conflicts of interest while three made no explicit statement.

Figure 6. *Risk of bias assessment heat map.*



Note: Risk of bias assessments were conducted using Cochrane's Risk of Bias 2 tool (Sterne et al., 2019). Overall assessments as well as ratings for each of the five subdomains are shown.

4. Discussion

The present meta-analysis pooled data from 42 clinical trials in various mental disorders to investigate whether individuals experienced greater symptom reductions following intranasal oxytocin compared to placebo. Effect size moderation by mental disorder, oxytocin dose, number of doses, psychosocial intervention use, and biological sex were also examined. We found that intranasal oxytocin was not associated with greater overall symptom reductions relative to placebo. While we identified mental disorder and biological sex as moderators, both were influenced by two outlier studies. No significant moderation was found for oxytocin dose, number of doses, or psychosocial intervention use.

The main finding of the present meta-analysis is that intranasal oxytocin, compared to placebo, provided no overall therapeutic benefit across 42 clinical trials in various mental disorders. This is broadly consistent with previous meta-analyses focusing on clinical outcomes in ASD (Martins et al., 2022; Zhang et al., 2025) and schizophrenia (Sabe et al., 2021; Zheng et al., 2019). One notable exception is a meta-analysis of five trials reporting a small reduction in *general psychopathology* symptoms among individuals with schizophrenia (Martins et al., 2022). However, this symptom domain was not investigated in the current study, as it is specific to the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and is therefore less commonly reported than positive and negative symptoms – the latter being our focus due to stronger theoretical support for targeting by oxytocin (Sabe et al., 2021). Another meta-analysis of 19 trials found a small, positive effect of intranasal oxytocin in various mental disorders (Bakermans-Kranenburg & van IJzendoorn, 2013). However, this study aggregated nonclinical measures (e.g., emotion recognition tasks, neuroimaging) with clinical measures (i.e., psychiatric symptoms) and therefore did not directly assess therapeutic benefit. It should be noted that the effect sizes for

studies in the present meta-analysis were often smaller than those reported in the original articles. This is because we conducted an intent-to-treat analysis that included all participants randomized to an intervention (McCoy, 2017) and adjusted for baseline scores (Morris, 2008), both of which reduce bias in effect size estimates.

The present meta-analysis indicates that oxytocin's effects on mental disorder symptoms are substantially smaller than its well-documented effects on social cognition, neural activity, and endocrine responses. For example, intranasal oxytocin has been shown to improve facial emotion recognition (g = 0.18 to 0.29; Leppanen et al., 2017; Shahrestani et al., 2013; van IJzendoorn & Bakermans-Kranenburg, 2012) and attenuate the cortisol response to stress (g = 0.15), with larger effects under conditions that strongly activate the hypothalamic-pituitary-adrenal axis (g = 0.43; (Cardoso et al., 2014a). Medium to large effect sizes have also been observed for oxytocin's impact on cooperative behaviour (Yang et al., 2021) and brain activation (Wigton et al., 2015). Thus, the null overall finding of the present study suggests that oxytocin's effects on specific functions like emotion recognition and prosocial behaviour have not translated to clinical benefits. Given the multifactorial nature of mental disorders, it should not be surprising that boosting a single neuropeptide system does not produce consistent therapeutic benefits. However, substantial heterogeneity among the included studies suggests that there may be conditions under which therapeutic benefits occur.

Another key finding of the present study was that intranasal oxytocin's therapeutic benefit differed across mental disorders. Trials in SUD produced substantially larger effect sizes than those in ASD (b = 0.80), although this moderation disappeared after removing two outliers that reported extremely positive effects in SUD (Azadbakht et al., 2022; Moeini et al., 2019). This is the first meta-analytic evidence that individuals with SUD may be more responsive to oxytocin

treatment than other clinical populations. While this finding should be interpreted with caution due to its sensitivity to outlier removal, it emphasizes SUD as a promising area for future research.

Another key finding involved the moderating role of biological sex. Analysis of the full sample showed no significant effect of the proportion of male participants on symptom changes. However, removing the two outliers revealed a significant moderation effect, with every 1% increase in the proportion of males associated with a 0.0043 decrease in Hedges' *g*. Although this difference appears small on a per-unit basis, it implies that moving from an all-female to an all-male sample would yield an estimated treatment effect approximately 0.43 lower – a difference that could have clinical implications. This result contrasts with a schizophrenia meta-analysis that found greater symptom reductions in trials with a higher proportion of males (Martins et al., 2022). A similarly inconsistent pattern of sex differences in oxytocin's effects has emerged in nonclinical research. Some studies have shown that intranasal oxytocin enhances attention to emotional facial expressions and empathic accuracy more strongly in males than females (Bartz et al., 2019; Boyle et al., 2022), while others have found greater enhancements in sharing behaviours among female participants (Ma et al., 2018). In sum, there is currently insufficient evidence to draw robust conclusions about sex differences in oxytocin's clinical efficacy.

We found no significant moderation by dose – whether modeled linearly or quadratically – nor by number of doses. This contrasts the quadratic dose-response relation reported in some non-clinical studies (Cardoso et al., 2014b; Quintana et al., 2017; Spengler et al., 2017). However, this null finding is unsurprising given the substantial variability in dosing protocols across the included trials and the limited number of studies that directly compared different doses. It is therefore possible that some non-significant findings reflect suboptimal dosing rather than a true lack of oxytocin efficacy. Future research should systematically investigate the dose-response

relation – while also accounting for other important factors such as number of doses, frequency of administration, oxytocin formulation, and intranasal delivery device.

We also found no significant moderation by psychosocial intervention use. This is unsurprising given that only 15 studies involving psychosocial interventions were included in our analyses, and these showed considerable methodological variability. Given the hypothesis that oxytocin's effects might be context-dependent, future clinical trials should incorporate psychosocial interventions tailored to the mental disorder being studied. This could involve supportive psychotherapy in MDD, cognitive-behavioural social skills training in schizophrenia, or intensive outpatient treatment involving group psychotherapy in SUD. Although more research is needed to determine the optimal timing of these interventions following oxytocin administration, neuroimaging studies have reported effects from approximately 25 to 80 minutes, with peak response around 45 minutes (Paloyelis et al., 2016). This has informed 30-minute waiting periods in some trials (Ellenbogen et al., 2024), likely contributing to larger effect sizes compared to protocols where psychosocial interventions were delivered outside this timeframe (Le et al., 2022).

Consistent with the consensus that oxytocin is safe and well-tolerated (Cai et al., 2018), serious adverse events were equally rare in the placebo and oxytocin conditions. However, inadequate safety reporting was a problem in many studies. Risk of bias was another area of concern, with studies rated as "high risk" more often than "some concerns" or "low risk." Importantly, "high risk" ratings were often a result of missing outcome data from a small number of participants, which is common in psychiatric research – especially for longer trials (Fernandez et al., 2015). Furthermore, because overall risk of bias ratings reflect the highest rating in any of the five subdomains (Sterne et al., 2019), they do not capture the fact that many "high risk" studies were rated as "low risk" in the four other subdomains.

We acknowledge several limitations of the current study. Our inclusion of trials with notable methodological differences means that the intranasal oxytocin effect sizes we estimated may reflect a combination of heterogeneous effects that would ideally be examined separately – highlighting the "apples and oranges" problem commonly encountered in meta-analytic research (Sharpe, 1997). A further limitation is the small number of trials per mental disorder and their generally modest sample sizes, which constrained statistical power in our moderator analyses and precluded multivariable moderator analyses altogether. Another limitation is our reliance on trial-level data which provide low-resolution information about individual participant variables like biological sex. Future studies should consider following individual participant data meta-analysis (IPD-MA) methodologies, which have successfully differentiated treatment responders from non-responders in other fields (Gülpen et al., 2025).

Research into intranasal oxytocin as a treatment for mental disorders has yet to produce findings that can be translated into treatment recommendations. Some promising results have emerged, but their replicability and generalizability remain to be established. Future RCTs should systematically examine dose-response relations, optimize psychosocial intervention protocols, and address the underrepresentation of females. Moreover, individual participant data should be reported wherever possible to help future meta-analyses distinguish between treatment responders and non-responders, thus promoting a personalized medicine approach.

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Appendix 1. Database Searches

Table 2. *Search Strategy in PubMed database.*

#	Searches	Results
1	trial[Title/Abstract] OR “double blind”[Title/Abstract] OR “single blind”[Title/Abstract] OR random*[Title/Abstract] OR assign*[Title/Abstract] OR allocat*[Title/Abstract] OR placebo[Title/Abstract] OR factorial*[Title/Abstract] OR crossover*[Title/Abstract] OR “cross over*”[Title/Abstract] OR “follow-up study”[Title/Abstract] OR “prospective study”[Title/Abstract] OR “comparative study”[Title/Abstract] OR “drug therap*”[Title/Abstract] OR “therapeutic use”[Title/Abstract] OR "double-blind method"[MeSH] OR “single-blind method”[MeSH] OR "random allocation"[MeSH] OR "placebos"[MeSH] OR "clinical trials as topic"[MeSH] OR "drug therapy"[MeSH] OR "therapeutic use"[MeSH Subheading] OR "prospective Studies"[MeSH] OR "clinical trial"[Publication Type] OR "comparative Study"[Publication Type]	8,964,116
2	animals[mh] NOT humans[mh]	5,190,590
3	1 NOT 2	7,698,345
4	“oxytocin”[MeSH] OR oxytocin OR ocytocin OR oxt OR syntocinon OR Pitocin	31,519
5	“administration, intranasal”[MeSH] OR intranasal* OR “intra nasal” OR internasal OR nasal	274,197
6	4 AND 5	1,390
7	“mental disorders”[MeSH] OR “mental disorder*” OR “mental health” OR “mental illness*” OR “mental disease*” OR “psychiatric illness*” OR “psychiatric disorder”	1,753,540
8	anxiety OR anxious OR mutism OR phobia OR panic OR agoraphobia OR bipolar OR cyclothymic OR “disruptive mood dysregulation” OR depress* OR dysthymia OR “premenstrual dysphoric disorder” OR “oppositional defiant” OR “intermittent explosive” OR “conduct disorder” OR pyromania OR kleptomania OR “dissociative identity” OR dissoc* OR “dissociative amnesia” OR depersonalization OR derealization OR enuresis OR encopresis OR “elimination disorder” OR eating disorder OR pica OR “rumination disorder” OR avoidant/restrictive OR anorexia OR bulimia OR binge-eating OR binge eating OR “gender dysphoria” OR “neurocognitive disorder” OR delirium OR “intellectual disability” OR “developmental delay” OR “language disorder” OR “speech sound disorder” OR “childhood-onset fluency disorder” OR “communication disorder” OR autism OR autistic OR	6,230,505

	attention-deficit/hyperactivity disorder OR ADHD OR ADD OR “learning disorder” OR “developmental coordination disorder” OR “stereotypic movement disorder” OR tic OR obsessive-compulsive OR obsessive compulsive OR OCD OR “body dysmorphic” OR hoarding OR trichotillomania OR hair-pulling OR excoriation OR skin-picking OR “sexual masochism disorder” OR “sexual sadism disorder” OR “pedophilic disorder” OR “fetishistic disorder” OR “transvestic disorder” OR “personality disorder” OR paranoid OR schizoid OR schizotypal OR antisocial OR borderline OR histrionic OR narcissistic OR avoidant OR dependent OR delusion* OR psychotic OR psychosis OR schizophrenia OR hallucination OR schizoaffective OR catatonia OR “sexual dysfunction” OR “delayed ejaculation” OR “erectile disorder” OR “female orgasmic disorder” OR “female sexual interest/arousal disorder” OR “genito-pelvic pain/penetration disorder” OR “hypoactive sexual desire disorder” OR “premature ejaculation” OR “early ejaculation” OR “sleep wake” OR “sleep-wake” OR insomnia OR hypersomnolence OR narcolepsy OR “obstructive sleep apnea hypopnea” OR “central sleep apnea” OR “sleep-related hypoventilation” OR “sleep arousal disorder” OR “nightmare disorder” OR “restless legs syndrome” OR “somatic symptom disorder” OR “illness anxiety disorder” OR “conversion disorder” OR “factitious disorder” OR substance-related OR substance use OR substance-induced OR “alcohol use disorder” OR “cannabis-related disorder” OR “opioid-related disorder” OR “sedative-related disorder” OR trauma OR “stressor-related disorder” OR “reactive attachment disorder” OR “disinhibited social engagement disorder” OR “posttraumatic stress disorder” OR PTSD OR “acute stress disorder” OR “adjustment disorder”	
9	7 OR 8	6,804,767
10	3 AND 6 AND 9	662

Note. Database accessed on February 2, 2024 via the National Library of Medicine platform with all default settings.

Table 3. *Search Strategy in APA PsycINFO database.*

#	Searches	Results
1	**Index Terms** (randomized clinical trial OR randomized controlled trials OR clinical trials OR drug therapy OR placebo OR random sampling)	168,838
2	**Title** OR **Abstract** (trial* OR "double blind*" OR "single blind*" OR random* OR assign* OR allocat* OR placebo* OR factorial* OR crossover* or “cross over*” OR "follow-up stud*" OR "prospective stud*" OR "comparative stud*" OR "drug therap*" OR "therapeutic use”)	551,175
3	1 OR 2	655,301
4	**Index Terms** (oxytocin)	4,131
5	**Title** OR **Abstract** ((o?ytocin OR syntocinon OR OXT OR pitocin) AND (intranasal OR “intra nasal” OR internasal OR nasal))	807
6	4 OR 5	4,164
7	**Index Terms** (mental disorders)	109,241
8	**Title** OR **Abstract** (“mental disorder*” OR “mental health” OR “mental illness*” OR “mental disease*” OR “psychiatric illness*” OR “psychiatric disorder” OR anxiety OR anxious OR mutism OR phobia OR panic OR agoraphobia OR bipolar OR cyclothymic OR “disruptive mood dysregulation” OR depress* OR dysthymia OR “premenstrual dysphoric disorder” OR “oppositional defiant” OR “intermittent explosive” OR “conduct disorder” OR pyromania OR kleptomania OR “dissociative identity” OR dissoc* OR “dissociative amnesia” OR depersonalization OR derealization OR enuresis OR encopresis OR “elimination disorder” OR eating disorder OR pica OR “rumination disorder” OR avoidant/restrictive OR anorexia OR bulimia OR binge-eating OR binge eating OR “gender dysphoria” OR “neurocognitive disorder” OR delirium OR “intellectual disability” OR “developmental delay” OR “language disorder” OR “speech sound disorder” OR “childhood-onset fluency disorder” OR “communication disorder” OR autism OR autistic OR attention-deficit/hyperactivity disorder OR ADHD OR ADD OR “learning disorder” OR “developmental coordination disorder” OR “stereotypic movement disorder” OR tic OR obsessive-compulsive OR obsessive compulsive OR OCD OR “body dysmorphic” OR hoarding OR trichotillomania OR hair-pulling OR excoriation OR skin-picking OR “sexual masochism disorder” OR “sexual sadism disorder” OR “pedophilic disorder” OR “fetishistic disorder” OR “transvestic disorder” OR “personality disorder” OR paranoid OR schizoid OR schizotypal OR antisocial OR borderline OR histrionic OR narcissistic OR avoidant OR dependent OR delusion* OR psychotic OR psychosis OR schizophrenia OR hallucination OR schizoaffective OR catatonia OR “sexual	1,352,708

	dysfunction" OR "delayed ejaculation" OR "erectile disorder" OR "female orgasmic disorder" OR "female sexual interest/arousal disorder" OR "genito-pelvic pain/penetration disorder" OR "hypoactive sexual desire disorder" OR "premature ejaculation" OR "early ejaculation" OR "sleep wake" OR "sleep-wake" OR insomnia OR hypersomnolence OR narcolepsy OR "obstructive sleep apnea hypopnea" OR "central sleep apnea" OR "sleep-related hypoventilation" OR "sleep arousal disorder" OR "nightmare disorder" OR "restless legs syndrome" OR "somatic symptom disorder" OR "illness anxiety disorder" OR "conversion disorder" OR "factitious disorder" OR substance-related OR substance use OR substance-induced OR "alcohol use disorder" OR "cannabis-related disorder" OR "opioid-related disorder" OR "sedative-related disorder" OR trauma OR "stressor-related disorder" OR "reactive attachment disorder" OR "disinhibited social engagement disorder" OR "posttraumatic stress disorder" OR PTSD OR "acute stress disorder" OR "adjustment disorder")	
9	7 OR 8	1,373,467
10	3 AND 6 AND 9	590

Note. Database accessed on February 2, 2024 via the APA PsycNet platform with all default settings.

Table 4. *Search Strategy in Web of Science Core Collection database (all editions).*

#	Searches	Results
1	TS=(trial* OR "double blind*" OR "single blind*" OR random* OR assign* OR allocat* OR placebo* OR factorial* OR crossover* or “cross over*” OR "follow-up stud*" OR "prospective stud*" OR "comparative stud*" OR "drug therap*" OR "therapeutic use”)	5,179,139
2	TS=((o?ytocin OR syntocinon OR OXT OR pitocin) AND (intranasal OR “intra nasal” OR internasal OR nasal))	2,081
3	TS=(“mental disorder*” OR “mental health” OR “mental illness*” OR “mental disease*” OR “psychiatric illness*” OR “psychiatric disorder” OR anxiety OR anxious OR mutism OR phobia OR panic OR agoraphobia OR bipolar OR cyclothymic OR “disruptive mood dysregulation” OR depress* OR dysthymia OR “premenstrual dysphoric disorder” OR “oppositional defiant” OR “intermittent explosive” OR “conduct disorder” OR pyromania OR kleptomania OR “dissociative identity” OR dissoc* OR “dissociative amnesia” OR depersonalization OR derealization OR enuresis OR encopresis OR “elimination disorder” OR eating disorder OR pica OR “rumination disorder” OR avoidant/restrictive OR anorexia OR bulimia OR binge-eating OR binge eating OR “gender dysphoria” OR “neurocognitive disorder” OR delirium OR “intellectual disability” OR “developmental delay” OR “language disorder” OR “speech sound disorder” OR “childhood-onset fluency disorder” OR “communication disorder” OR autism OR autistic OR attention-deficit/hyperactivity disorder OR ADHD OR ADD OR “learning disorder” OR “developmental coordination disorder” OR “stereotypic movement disorder” OR tic OR obsessive-compulsive OR obsessive compulsive OR OCD OR “body dysmorphic” OR hoarding OR trichotillomania OR hair-pulling OR excoriation OR skin-picking OR “sexual masochism disorder” OR “sexual sadism disorder” OR “pedophilic disorder” OR “fetishistic disorder” OR “transvestic disorder” OR “personality disorder” OR paranoid OR schizoid OR schizotypal OR antisocial OR borderline OR histrionic OR narcissistic OR avoidant OR dependent OR delusion* OR psychotic OR psychosis OR schizophrenia OR hallucination OR schizoaffective OR catatonia OR “sexual dysfunction” OR “delayed ejaculation” OR “erectile disorder” OR “female orgasmic disorder” OR “female sexual interest/arousal disorder” OR “genito-pelvic pain/penetration disorder” OR “hypoactive sexual desire disorder” OR “premature ejaculation” OR “early ejaculation” OR “sleep wake” OR “sleep-wake” OR insomnia OR hypersomnolence OR narcolepsy OR “obstructive sleep apnea hypopnea” OR “central sleep apnea” OR “sleep-related hypoventilation” OR “sleep arousal disorder” OR “nightmare disorder” OR “restless legs syndrome” OR “somatic symptom disorder” OR “illness anxiety disorder” OR “conversion disorder” OR “factitious disorder” OR substance-related OR substance use OR substance-induced OR “alcohol use disorder” OR “cannabis-related disorder” OR “opioid-related disorder” OR “sedative-related disorder” OR trauma OR	6,348,014

	"stressor-related disorder" OR "reactive attachment disorder" OR "disinhibited social engagement disorder" OR "posttraumatic stress disorder" OR PTSD OR "acute stress disorder" OR "adjustment disorder")	
4	1 and 2 and 3	768

Note. Database accessed on February 2, 2024 via the Clarivate platform with all default settings.

Table 5. *Search Strategy in Scopus database.*

#	Searches	Results
1	TITLE-ABS-KEY (trial* OR "double blind*" OR "single blind*" OR random* OR assign* OR allocat* OR placebo* OR factorial* OR crossover* or “cross over*” OR "follow-up stud*" OR "prospective stud*" OR "comparative stud*" OR "drug therap*" OR "therapeutic use”)	9,517,820
2	TITLE-ABS-KEY ((o?ytocin OR OXT OR pitocin OR syntocinon) AND (intranasal OR “intra nasal” OR internasal OR nasal))	1,500
3	TITLE-ABS-KEY (“mental disorder*” OR “mental health” OR “mental illness*” OR “mental disease*” OR “psychiatric illness*” OR “psychiatric disorder” OR anxiety OR anxious OR mutism OR phobia OR panic OR agoraphobia OR bipolar OR cyclothymic OR “disruptive mood dysregulation” OR depress* OR dysthymia OR “premenstrual dysphoric disorder” OR “oppositional defiant” OR “intermittent explosive” OR “conduct disorder” OR pyromania OR kleptomania OR “dissociative identity” OR dissoc* OR “dissociative amnesia” OR depersonalization OR derealization OR enuresis OR encopresis OR “elimination disorder” OR “eating disorder” OR pica OR “rumination disorder” OR “avoidant/restrictive” OR anorexia OR bulimia OR “binge eating” OR “gender dysphoria” OR “neurocognitive disorder” OR delirium OR “intellectual disability” OR “developmental delay” OR “language disorder” OR “speech sound disorder” OR “childhood-onset fluency disorder” OR “communication disorder” OR autism OR autistic OR “attention deficit hyperactivity disorder” OR ADHD OR ADD OR “learning disorder” OR “developmental coordination disorder” OR “stereotypic movement disorder” OR tic OR “obsessive compulsive” OR OCD OR “body dysmorphic” OR hoarding OR trichotillomania OR “hair pulling” OR excoriation OR “skin picking” OR “sexual masochism disorder” OR “sexual sadism disorder” OR “pedophilic disorder” OR “fetishistic disorder” OR “transvestic disorder” OR “personality disorder” OR paranoid OR schizoid OR schizotypal OR antisocial OR borderline OR histrionic OR narcissistic OR avoidant OR dependent OR delusion* OR psychotic OR psychosis OR schizophrenia OR hallucination OR schizoaffective OR catatonia OR “sexual dysfunction” OR “delayed ejaculation” OR “erectile disorder” OR “female orgasmic disorder” OR “female sexual interest/arousal disorder” OR “genito pelvic pain/penetration disorder” OR “hypoactive sexual desire disorder” OR “premature ejaculation” OR “early ejaculation” OR “sleep wake” OR insomnia OR hypersomnolence OR narcolepsy OR “obstructive sleep apnea hypopnea” OR “central sleep apnea” OR “sleep related hypoventilation” OR “sleep arousal disorder” OR “nightmare disorder” OR “restless legs syndrome” OR “somatic symptom disorder” OR “illness anxiety disorder” OR “conversion disorder” OR “factitious disorder” OR “substance related” OR “substance use” OR “substance induced” OR “alcohol use disorder” OR “cannabis related disorder” OR “opioid related disorder” OR “sedative related	7,347,663

	disorder" OR trauma OR "stressor related disorder" OR "reactive attachment disorder" OR "disinhibited social engagement disorder" OR "posttraumatic stress" OR "post traumatic stress" OR PTSD OR "acute stress disorder" OR "adjustment disorder")	
4	1 AND 2 AND 3	618

Note. Database accessed on February 2, 2024 via the Elsevier platform with all default settings.

Table 6. *Search Strategy in the EMBASE (1947-) database.*

#	Searches	Results
1	crossover-procedure/ OR double-blind procedure/ OR randomized controlled trial/ OR single-blind procedure/ OR (trial* OR (doubl* adj blind*) OR (singl* adj blind*) OR random* OR assign* OR allocat* OR placebo* OR factorial* OR crossover* OR "cross over*" OR "follow-up stud*" OR "prospective stud*" OR "comparative stud*" OR "drug therap*" OR "therapeutic use").tw.	4,315,753
2	((o?ytocin OR syntocinon OR OXT OR pitocin) AND (intranasal OR "intra nasal" OR internasal OR nasal)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	2,191
3	(mental disorder* or mental health or mental illness* or mental disease* or psychiatric illness* or psychiatric disorder*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	765,676
4	Anxiety/ or Anxiety disorder/	395,823
5	Depression/	508,556
6	Bipolar disorder/	71,705
7	Mood disorder/	55,002
8	Impulse control disorder/	4,461
9	Dissociative disorder/	4,441
10	Incontinence/	18,853
11	Eating disorder/	32,925
12	Gender dysphoria/	3,152
13	Autism/	92,120
14	"Disorders of higher cerebral function"/	3,625
15	Tic/	11,450

16	Obsessive compulsive disorder/	32,421
17	Paraphilic disorder/ or Psychosexual disorder/	3,084
18	Exp personality disorder/	75,559
19	Schizophrenia/	216,855
20	Psychosis/	123,620
21	Sexual dysfunction/	31,808
22	Exp sleep disorder/	256,357
23	Psychosomatic disorder/	17,823
24	Substance abuse/	59,227
25	Addiction/	59,695
26	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	1,515,985
27	3 or 26	1,972,632
28	1 and 2 and 27	620

Note. Database accessed on February 2, 2024 via the Ovid platform with all default settings.

Appendix 2. Included Reports

Acheson, D. T., Feifel, D., Kamenski, M., Mckinney, R., & Risbrough, V. B. (2015). Intranasal oxytocin administration prior to exposure therapy for arachnophobia impedes treatment response. *Depression and Anxiety*, *32*(6), 400–407. https://doi.org/10.1002/da.22362

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Bernaerts, S., Boets, B., Bosmans, G., Steyaert, J., & Alaerts, K. (2020). Behavioral effects of multiple-dose oxytocin treatment in autism: A randomized, placebo-controlled trial with long-term follow-up. *Molecular Autism*, *11*(1), 6. https://doi.org/10.1186/s13229-020-0313-1

Buchanan, R. W., Kelly, D. L., Strauss, G. P., Gold, J. M., Weiner, E., Zaranski, J., Chen, S., Blatt, F., Holden, J., & Granholm, E. (2021). Combined oxytocin and cognitive behavioral social skills training for social function in people with schizophrenia. *Journal of Clinical Psychopharmacology*, *41*(3), 236. https://doi.org/10.1097/JCP.0000000000001397

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Cacciotti-Saija, C., Langdon, R., Ward, P. B., Hickie, I. B., Scott, E. M., Naismith, S. L., Moore, L., Alvares, G. A., Redoblado Hodge, M. A., & Guastella, A. J. (2015). A double-blind randomized controlled trial of oxytocin nasal spray and social cognition training for young people with early psychosis. *Schizophrenia Bulletin*, *41*(2), 483–493. https://doi.org/10.1093/schbul/sbu094

Dadds, M. R., MacDonald, E., Cauchi, A., Williams, K., Levy, F., & Brennan, J. (2014). Nasal oxytocin for social deficits in childhood autism: A randomized controlled trial. *Journal of Autism and Developmental Disorders*, *44*(3), 521–531. https://doi.org/10.1007/s10803-013-1899-3

Dagani, J., Sisti, D., Abelli, M., Di Paolo, L., Pini, S., Raimondi, S., Rocchi, M. B., Saviotti, F. M., Scocco, P., Totaro, S., Balestrieri, M., & de Girolamo, G. (2016). Do we need oxytocin to treat schizophrenia? A randomized clinical trial. *Schizophrenia Research*, *172*(1), 158–164. https://doi.org/10.1016/j.schres.2016.02.011

Daniels, N., Moerkerke, M., Steyaert, J., Bamps, A., Debbaut, E., Prinsen, J., Tang, T., Van der Donck, S., Boets, B., & Alaerts, K. (2023). Effects of multiple-dose intranasal oxytocin administration on social responsiveness in children with autism: A randomized, placebo-controlled trial. *Molecular Autism*, *14*(1), 16. https://doi.org/10.1186/s13229-023-00546-5

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Guastella, A. J., Boulton, K. A., Whitehouse, A. J. O., Song, Y. J., Thapa, R., Gregory, S. G., Pokorski, I., Granich, J., DeMayo, M. M., Ambarchi, Z., Wray, J., Thomas, E. E., & Hickie, I. B. (2023). The effect of oxytocin nasal spray on social interaction in young children with autism: A randomized clinical trial. *Molecular Psychiatry*, *28*(2), 834–842. https://doi.org/10.1038/s41380-022-01845-8

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Moeini, M., Omidi, A., Sehat, M., & Banafshe, H. R. (2019). The effects of oxytocin on withdrawal, craving and stress response in heroin-dependent patients: A randomized, double-blind clinical trial. *European Addiction Research*, *25*(1), 41–47. https://doi.org/10.1159/000496194

Munesue, T., Nakamura, H., Kikuchi, M., Miura, Y., Takeuchi, N., Anme, T., Nanba, E., Adachi, K., Tsubouchi, K., Sai, Y., Miyamoto, K., Horike, S., Yokoyama, S., Nakatani, H., Niida, Y., Kosaka, H., Minabe, Y., & Higashida, H. (2016). Oxytocin for male subjects with autism spectrum disorder and comorbid intellectual disabilities: A randomized pilot study. *Frontiers in Psychiatry*, *7*, 2. https://doi.org/10.3389/fpsyt.2016.00002

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Appendix 3. Excluded Reports Due to Unretrieved Data

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