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"The role of oxytocin in psychiatric disorders: A review of biological and therapeutic research findings"

David Cochran, MD, PhD[1], **Daniel Fallon, MD**[2], **Michael Hill, BS**[1], and **Jean A. Frazier, MD**[1]

[1]Division of Child and Adolescent Psychiatry, Department of Psychiatry, University of Massachusetts Medical School

[2]Department of Psychiatry, University of South Florida

Abstract

Oxytocin is a peptide hormone integral in parturition, milk let-down, and maternal behaviors that has been demonstrated in animal studies to be important in the formation of pair bonds and in social behaviors. This hormone is increasingly recognized as an important regulator of human social behaviors, including social decision making, evaluating and responding to social stimuli, mediating social interactions, and forming social memories. In addition, oxytocin is intricately involved in a broad array of neuropsychiatric functions, and may be a common factor important in multiple psychiatric disorders such as autism, schizophrenia, mood and anxiety disorders. This review article examines the extant literature on the evidence for oxytocin dysfunction in a variety of psychiatric disorders and highlights the need for further research to understand the complex role of the oxytocin system in psychiatric disease to pave the way for developing new therapeutic modalities. Articles were selected that involved human participants with various psychiatric disorders, either comparing oxytocin biology to healthy controls or examining the effects of exogenous oxytocin administration.

Keywords

oxytocin; autism; schizophrenia; mood disorders; anxiety disorders; humans; review

Introduction

Oxytocin is a peptide hormone synthesized in the supraoptic and paraventricular nuclei of the hypothalamus with direct projections into other brain areas where it acts as a neurotransmitter. It is also released into the bloodstream via the posterior pituitary gland to peripheral targets[1,2]. Animal studies highlight the importance of oxytocin in parturition, milk letdown, protective aggression, social behaviors and pair bonding between mothers and infants and in mating pairs[3]. Human studies have confirmed oxytocin's role as a social hormone, mediating many social behaviors involved in forming attachments[4]. In healthy controls (HC), oxytocin decreases cortisol release and anxiety in response to social stress[5],

Corresponding author: David Cochran, MD, PhD, Division of Child and Adolescent Psychiatry, Department of Psychiatry, 55 Lake Ave N, Worcester, MA 01655; david.cochran@umassmemorial.org.

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reduces amygdala activity to fearful or threatening visual images[6] or emotional faces[7], increases trust behavior in a money-transferring game[8], increases the ability to interpret mental states[9], and increases the amount of time spent gazing at the eyes when viewing faces.[10] Van Ijzendorn and Bakermans-Kranenburg provide a meta-analysis supporting the notion that intranasal oxytocin in healthy individuals enhances the recognition of emotion and elevates the level of trust in established relationships.[11] In addition to its prosocial effects, it has also been shown to be involved in jealousy, gloating, and out-group discrimination.[12–15] Given the effect of oxytocin on these basic interpersonal interactions, there has been a growing body of research on the possible involvement of oxytocin in the pathophysiology of neuropsychiatric disorders that impact social functioning, such as autism, schizophrenia, and depression.

Many studies have examined the relationship between oxytocin and parent-child interactions[16–20]. For a detailed review, see Galbally et al[21]. For example, studies have demonstrated decreased urinary oxytocin levels in children placed in orphanages shortly after birth[22] and decreased CSF oxytocin levels in adult women exposed to childhood maltreatment[23]. Men with a history of early parental separation had altered cortisol response to exogenous oxytocin[24], and oxytocin had differential effects on memories of maternal care and closeness depending on the participant's baseline level of anxious attachment[25]. Also, in males classified as having "insecure" attachments, oxytocin increased the level of attachment security in the majority of participants[26]. Clearly, there is a complex inter-relationship between oxytocin and an individual's experience of early childhood attachment, and it remains unclear to what extent this connection influences the role of oxytocin in the pathophysiology of psychiatric disorders.

Methods

This review provides a detailed summary of the evidence of oxytocin dysfunction and the therapeutic potential of oxytocin in psychiatric disorders, limited to human studies of various neuropsychiatric disorders (see Table 1). Studies were found using a PubMed search using Boolean combinations of the search terms 'oxytocin' and 'psychiatry', 'autism', 'schizophrenia', 'mood disorders', 'anxiety disorders', and 'personality disorders'. Searches were limited to human studies. Abstracts were reviewed and all relevant articles were reviewed in detail, including a review of the references in each publication to identify additional sources. Only primary sources were reviewed, the date range was restricted to 1970-present, and only English-language articles were reviewed.

Due to space considerations, specific information about single nucleotide polymorphisms (SNPs) and allelic variations in the various genetics studies are only included in the text as they pertain to the discussion of similarities and differences between the various studies. All of this detailed information can be found in Table 1, which provides a comprehensive sense of what is known regarding oxytocin genetics in psychiatric disorders. Inconsistencies in reporting of this information in the table is due to inconsistencies in the level of detail reported in the reviewed studies. Also, due to space considerations, specific methodological limitations of individual studies will not be presented in detail. Instead, the author's

synthesis of broader limitations to the currently available data that extend across studies will be presented in the concluding section.

This manuscript discusses published research studies of oxytocin in psychiatric disorders. This product is not approved by the FDA for use in any of the disorders discussed.

Oxytocin and Autism

Mouse models have demonstrated oxytocin's role in social recognition, attachment, and stereotyped behaviors.[111–113] Given that these correlate with core deficits in autism spectrum disorders (ASD), oxytocin has been investigated for its role in the pathophysiology of ASD as well as a potential therapeutic target for these disorders.

Plasma Levels

Modahl et al.[27] found lower mean oxytocin plasma levels in children with autism, compared with age-matched HC. Elevated oxytocin levels were associated with higher scores on the Vineland Adaptive Behavior Scale (VABS) for the typically developing children, but with lower scores for the children with autism. A follow-up study of individuals with autism demonstrated that decreased plasma oxytocin was associated with increased extended peptide inactive forms of oxytocin derived from the same prohormone, indicating a defect in peptide processing of oxytocin[28].

In sharp contrast, Jansen et al.[29] compared adults with an ASD with HC, and found that adults with ASD showed increased basal oxytocin plasma levels. Differences in oxytocin levels between these studies may be related to developmental differences (adults vs children), diagnostic subgroup differences, or differences in intellectual development. In the adult study, oxytocin levels did not correlate with impairments in social interaction, communication, or stereotyped behavior as measured by the Autism Diagnostic Interview-Revised (ADI-R)[114].

These studies suggest that there may be a dysfunction in oxytocin processing associated with ASD, and that there may be developmental changes associated with the oxytocin system over the lifespan of individuals with ASD. Further longitudinal studies or larger studies of broader age range are necessary to confirm this finding, along with adequate control for intellectual development across age groups.

Genetic Studies

Several studies have investigated the association of genetic variants in genes encoding oxytocin and the oxytocin receptor with autism. Wu et al.[30] reported a family-based association test (FBAT) of four single nucleotide polymorphisms (SNPs) within the oxytocin receptor gene (OXTR) of Chinese Han autism proband-parent trios. An association between autism and two of the SNPs was found (see Table 1). Haplotype-specific FBAT demonstrated a number of haplotypes (combinations of alleles in adjacent locations on the chromosome that are likely transmitted together) that were associated with autism. Jacob et al.[31] attempted to replicate this finding in caucasian autism parent-proband trios. They were able to detect an association at rs2254298 with overtransmission of the G allele, which

contrasts with the previous finding of overtransmission of the A allele[30]. The authors postulated that this may signify an undiscovered genetic variant associated with autism that may be transmitted along with rs2254298, but associated with different alleles in different populations.

Lerer et al.[32] performed FBAT on all 18 identified SNPs within the OXTR region in Israeli participants with ASD and their parents and unaffected siblings. They also evaluated associations between OXTR variants and intelligence quotient (IQ) and VABS scores. SNP analysis revealed 2 SNPs in association with ASD, 2 SNPs associated with IQ, and 2 SNPs associated with total VABS scores, as well as 8 SNPs associated with individual VABS subdomains (communication, daily living skills, and socialization). Several haplotypes were also associatedwith ASD, IQ, and VABS scores.

Yrigollen et al.[33] examined associations of both the oxytocin gene (OXT; 2 SNPs) and OXTR (3 SNPs) with autism in primarily caucasian ASD probands. Association with diagnosis was found with one SNP within OXTR, and association with stereotyped behaviors was found with one SNP within OXT. In a Japanese population[34], no association was found in FBAT of 11 SNPs within OXTR; however, in a population-based case-control analysis, differences were observed in allelic frequencies of four SNPs. Tansey et al.[35] examined three independent autism samples from Ireland, Portugal, and the United Kingdom for association of 18 SNPs in OXTR, and found no association with autism in any of the samples. However, the SNP most often implicated in previous studies (rs2254298) was not examined.

Wermter et al.[36] performed single marker and haplotype FBAT of 22 SNPs in the OXTR region in patients with high-functioning ASD. They found nominal associations of one SNP and one haplotype with autism, which did not withstand corrections for multiple comparisons. Patients carrying the implicated haplotype showed impairments in social interaction and communication as assessed with the ADI-R compared to noncarriers. Of note, the SNP with strongest evidence for association in other studies (rs2254298) was not associated with autism. In the largest study to date, Campbell et al.[37] performed FBAT on 25 SNPs in OXTR in over 1,000 families. They report association of three SNPs previously implicated in prior studies and these markers were associated with various measures of social communication dysfunction as assessed by the ADI-R, Autism Diagnostic Observation Schedule[115], and Social Responsiveness Scale[116].

Table 1 demonstrates the lack of consistency amongst studies in terms of specific alleles or variants associated with ASD. As with many candidate gene approaches to studying complex neuropsychiatric phenotypes, replicable findings are lacking. However, given the heterogeneous nature of ASD, the fact that associations with oxytocin and OXTR genes are found across multiple studies indicate that this hormone system may indeed play some role in the pathophysiology of ASD.

Epigenetics

Gregory et al.[38] studied an autism proband containing an inherited deletion in chromosome region 3p25.3 including the oxytocin receptor gene. Interestingly, the proband had a brother

with autism who did not inherit the deletion; however, bisulfite sequencing (BSS) analysis demonstrated that a critical region previously shown to regulate expression of OXTR[117] was heavily methylated in the affected sibling. The authors further performed BSS analysis of peripheral blood cells from typically developing controls and individuals with autism. Three of the sites identified as hypermethylated in the proband's sibling also displayed greater methylation in individuals with autism compared to controls. The authors then evaluated methylation of OXTR in post-mortem temporal cortex from individuals with autism and age- and sex-matched controls. Again, hypermethylation was seen in the autism cases compared to HC. Thus, even when there is no direct genetic evidence of alterations in oxytocin-related genes, the expression of these genes may be affected by epigenetic modification and provide a different mechanism for oxytocin's role in the clinical phenotype of ASD.

Response to Exogenous Oxytocin

Several studies have investigated the response of individuals with ASD to the administration of exogenous oxytocin peripherally or intranasally. Hollander et al.[39,40] enrolled adults with ASD in a randomized, double-blind, within-individual placebo-controlled study. Each participant received a continuous intravenous infusion of synthetic oxytocin (10–15 IU) or placebo over 4 hours in random order on two separate testing days. In the first experiment[39], severity of six repetitive behaviors was assessed at baseline and at several points during the infusion. There was a greater reduction in repetitive behaviors over time during oxytocin infusion compared to placebo.

In the second experiment[40], the participants were presented with four sentences of neutral content with one of four emotional intonations (happy, indifferent, angry, sad) and were asked to identify the emotional mood of the speaker. The task was repeated at baseline and several times over the course of the infusion. The authors report a Time×Treatment×Order effect for a comprehension of affective speech score. During the first trial, participants improved from baseline to endpoint regardless of whether they received placebo or oxytocin. Those who received oxytocin first retained their high performance at baseline during the second trial, and their performance did not change from baseline to endpoint during the second trial. Those who received placebo first showed a drop in score at baseline during the second trial, which then improved again after the course of oxytocin infusion. The authors interpret this result as oxytocin increasing retention of social cognition.

Guastella et al.[41] performed an emotion recognition experiment with a more difficult and more sensitive task. Their study involved adolescent males with ASD. In a double-blind, placebo-controlled crossover design, they administered oxytocin nasal spray (18–24 IU) or placebo to participants, who then completed the Reading the Mind in the Eyes Task (RMET), involving identifying emotion based on viewing of eyes. Oxytocin improved performance on the RMET for 60% of the participants. The effect of oxytocin was primarily for the easier items, with no difference between oxytocin and placebo for the harder items. In a similar experiment performed in HC adult males[9], intranasal oxytocin (24 IU) improved scores on RMET difficult items more than the easy items, and showed a ceiling effect in the HC. Bartz et al.[42] measured baseline social competency in HC adult males with the Autism

Spectrum Quotient (AQ), then measured empathic accuracy by having the participants rate the emotions of individuals in a video after receiving intranasal oxytocin (24 IU) or placebo. Participants with low AQ scores performed well on the task in placebo condition and maintained this performance in the oxytocin condition. However, those with high AQ scores indicating lower social-cognitive performance performed poorly in the placebo condition but better in the oxytocin condition. In the oxytocin condition, there was no difference in scores on the task between the low AQ and high AQ participants.

Andari et al.[43] performed a series of elegant experiments with adults with ASD and HC. The participants played a computerized ball-toss game with computerized players (A,B,C) in which the participant could choose to throw the ball to one of the three players. Player A was programmed to eventually throw the ball 70% of the time back to the participant, player B, 30% of the time, and player C, 10% of the time. Participants received an intranasal dose of 24IU oxytocin or placebo prior to playing the game. In HC participants, more balls were thrown to player A than the other two players. Under placebo treatment, the participants with ASD did not discriminate between the three players; however, when they received oxytocin they engaged more often with Player A compared to player C. Trust and preference ratings expressed toward the three players did not differ in participants with ASD receiving placebo, but were more similar to HC ratings after receiving oxytocin. Interestingly, participants with ASD classified as seeking social contact but in a socially inappropriate or one-sided manner tended to respond to oxytocin, while those classified as actively rejecting social contact tended to show little response to oxytocin. In a second experiment[43], eye gaze when viewing faces was analyzed. Intranasal oxytocin (24 IU) increased total gaze time spent on face regions in participants with ASD, largely accounted for by increased fixation time on the eye region. Oxytocin effects on social game performance were only weakly correlated with effects on face perception tasks, indicating that a different cohort of individuals tended to respond to oxytocin in the respective tasks. Therefore, oxytocin effects appear to be individualized and may have beneficial effects on different aspects of social functioning in different individuals.

There have been very few reports of long-term daily administration of oxytocin in individuals with ASD. Kosaka et al.[44] first reported a case report of a 16yo female with ASD receiving 8 IU of intranasal oxytocoin daily for two months. Subjective assessment of her social interactions and social communication demonstrated improvement from a Clinical Global Impression-Severity score of 6 (“severely ill”) to 3 (“mildly ill”), and improvements were seen in irritability and hyperactivity on the Aberrant Behavior Checklist. The first randomized controlled trial of intranasal oxytocin in ASD was reported by Anagnostou et al.[45] Nineteen adults with ASD (16 males; 33.20 ± 13.29 years) received intranasal oxytocin (24 IU twice daily; N = 10) or placebo (N = 9) for 6 weeks. Oxytocin participants had a significant improvement in RMET scores, a measurement of social cognition, compared to the placebo group, but no improvement in the Diagnostic Analysis of Nonverbal Accuracy, another measure of social perception. There was also no significant improvement in overall clinical global impression of social functioning, or Social Responsiveness Scale scores. There was a trend toward improvement in stereotyped and self-injurious repetitive behaviors, and a significant improvement in the emotional/social subscales of the World Health Organization Quality of Life Questionnaire.

These preliminary trials of oxytocin delivered to human participants with ASD provide some hope that it may be a useful treatment agent for improving some aspects of social cognition and for reducing repetitive behaviors. With the exception of one very small randomized controlled trial, most of the experimental studies have been of single-dose administration to date. The one longer-term study shows some promise that there may be some positive clinical effect, but the study was not appropriately powered to detect small to medium effect sizes of treatment. At this point, it can only be said that oxytocin is a promising agent that should be explored in larger, placebo-controlled trials designed to detect changes in well-validated measures of social cognition, social perception, and repetitive behaviors.

Oxytocin and Schizophrenia

Oxytocin has long been studied as having a potential role in the pathophysiology of schizophrenia, given its effects on cognition, memory, and social functioning. Preclinical mouse models have demonstrated that oxytocin has potential antipsychotic effect through inhibitory regulation of mesolimbic dopamine and that the oxytocin system is affected in mouse models of psychosis.[118]

Plasma/CSF Levels

Earlier human studies measured the levels of human neurophysin (NP) II (hNPII), rather than oxytocin. hNPII is a protein carrier of oxytocin that is more easily measured because it is more stable than oxytocin and is released simultaneously at the synaptic level with the active peptide in proportional amounts[119,120]. Linkowski et al.[46] found greater CSF levels of hNPII in individuals with schizophrenia than in age-matched nondepressed neurological controls. Beckmann et al.[47] reported similar findings of increased CSF oxytocin levels in adult males with paranoid schizophrenia compared to controls with nonspecific neurological symptoms. Likewise, Legros et al.[48] found increased basal levels of serum hNPII in male patients with schizophrenia compared to healthy male volunteers. Also, there was no change in hNPII levels in patients after an apomorphine (dopamine agonist) challenge, compared to a two-fold increase in hNPII in healthy volunteers. Importantly, basal hNPII was higher in the paranoid subgroup than in the nonparanoid subgroup. In contrast to the above findings, several studies reported no differences in CSF[49, 53] or plasma[50] oxytocin concentrations between patients with schizophreniaand HC.

Several studies have measured associations of plasma oxytocin levels with clinical measures in schizophrenia. Keri et al.[51] measured plasma oxytocin levels in patients and controls after neutral and trust-related interpersonal interactions. There was no difference in oxytocin levels between groups after neutral interactions; oxytocin levels increased in controls but not in patients after trust-related interactions. Low oxytocin levels after trust-related interactions were correlated with negative symptoms of schizophrenia as measured by Positive and Negative Syndrome Scale (PANSS) scores[121]. Sasayama et al.[53] also found that oxytocin plasma levels were negatively correlated with both second generation antipsychotic dose and negative symptom subscores on the PANSS.

Rubin et al.[52] measured oxytocin plasma levels and PANSS scores in patients with schizophrenia and in HC. There was no difference in oxytocin levels between any of the groups, or across phases of menstrual cycle in female patients or controls. In female patients only, higher oxytocin levels were associated with lower scores (less symptoms) on the PANSS total symptom, positive symptom, and general psychopathology subscores, and a trend toward association with lower negative symptom scores. In all patients, higher oxytocin levels were associated with better prosocial scores on PANSS.

In general, these studies present conflicting data about whether or not there are differences in oxytocin levels associated with schizophrenia. Some studies suggest higher levels of oxytocin in the CSF, but others indicate no difference. While it is unclear whether plasma levels correlate with brain levels of oxytocin because of the blood-brain barrier, interestingly some studies have indicated that lower plasma oxytocin levels correlate with more psychotic symptoms as indicated by the PANSS. Further study is needed to determine if differences in various studies may be explained by phenotypic differences in patient populations.

Genetic Studies

Few studies have examined the genetic association of oxytocin and OXTR genes with schizophrenia. Souza et al.[54] found one variant of OXT in a family-based association study and two variants of OXT in a case-control study that were associated with schizophrenia, but none remained significant after correction for multiple testing. They also identified one haplotype block within OXT that was nominally associated with schizophrenia in the case-control sample. Montag et al.[57] also performed a case-control analysis of individuals with schizophrenia and HC and found two different OXTR SNPs that were associated with schizophrenia.

Based on rat studies demonstrating that clozapine enhances oxytocin release from neurons, the same research group[55] evaluated OXT and OXTR variants for association with symptom severity and response to clozapine in individuals with schizophrenia treated for a minimum of 6 months. One variant within OXT was associated with treatment response and nominally associated with negative symptoms. Variants in OXTR were nominally associated with severity of overall symptoms as well as improvement of positive symptoms on clozapine. The OXT variant had also been previously associated with stereotyped behaviors in autism[33].

Finally, Teltsh et al.[56] examined the association of OXT variants with schizophrenia in a large clan of Arab-Israeli individuals. They further sought to confirm results in a group of nuclear families of Arab-Israeli origin and a Jewish case-control sample. In the extended pedigree, one variant in the 5’-promoter region of OXT and a previously reported variant in the 3’-promoter region were associated with schizophrenia after correction for multiple testing. One haplotype of the seven gene variants studied was also found to be associated with schizophrenia after multiple corrections, and affected individuals with this haplotype demonstrated prominent negative symptoms.

The genetic evidence for association of oxytocin and OXTR gene variants with schizophrenia is weaker than that for ASD, and two more recent reports have not found an

association between genetic variants and diagnosis.[58,59] Most of the variants that have been nominally associated have not been replicated, and have not withstood statistical corrections for multiple comparisons (see Table 1). Taking the combination of equivocal studies of plasma or CSF levels of oxytocin and the inconsistent findings in genetic studies, there is less evidence for a clear dysfunction in the oxytocin system in patients with schizophrenia than there is for ASD.

Response to Exogenous Oxytocin

Despite the equivocal evidence for a clear dysfunction in the oxytocin system in schizophrenia, there is a line of evidence supporting the possible therapeutic use of oxytocin in these disorders. Nearly four decades ago, Bujanow reported[122,123] that after giving patients daily injections of IV or intramuscular oxytocin (10–25 IU), there were “favorable” and “rapid therapeutic effects”, and prevention of hospitalization. A decade later, Bakharev et al.[60] reported the first controlled study of oxytocin, with men with the “simple form of schizophrenia” receiving IV or intranasal oxytocin (5 IU twice daily), or placebo, during two nonconsecutive weeks. They reported positive effects, particularly in negative symptoms and depressed mood, in patients receiving oxytocin.

More recently, interest has revived in the use of oxytocin as a therapeutic agent in schizophrenia. Averbeck et al.[64] administered intranasal oxytocin (24 IU) or placebo in a randomized, double-blind crossover study to individuals with schizophrenia and HC in two sessions separated by approximately one week. Following administration, participants carried out an emotion discrimination task in which they were asked to identify various facial emotions. At baseline, compared to control participants, individuals with schizophrenia had deficits in recognizing fear, happiness, and surprise. The overall performance was improved on oxytocin, but the absolute effect was modest and none of the individual emotion recognitions showed an improvement.

Goldman et al.[62] performed a detailed study in which they administered two different doses of intranasal oxytocin (10 IU, 20 IU) or placebo to three groups: HC, polydipsic, and nonpolydipsic patients with schizophrenia. Following administration, individuals were asked to rate the presence and intensity of various facial emotions. Emotion recognition decreased in both patient groups on the lower dose of oxytocin, due to the increased propensity to identify all emotions whether or not they were present (nonspecific positive bias). In the polydipsic patients but not the nonpolydipsic patients, emotion recognition improved following the higher dose of oxytocin, primarily because of a decreased propensity to identify fear in nonfearful faces. Despite limitations in interpretation given the small sample sizes, it appears that the effects of oxytocin on emotion recognition are dose-, emotion-, and patient characteristic-dependent.

Feifel et al.[61] performed a randomized, double-blind crossover study of patients with residual symptoms. Patients were given 3 weeks of daily intranasal oxytocin (40 IU twice daily) or placebo as adjunctive treatment to their stable psychotropic regimen. Oxytocin reduced scores on the PANSS Total Score, Positive Symptoms subscale, and Negative Symptoms subscale (effect sizes ranging from 0.40–0.50) and Clinical Global Impressions-Improvement scale (CGI-I; effect size 0.74) compared with placebo at endpoint. Feifel et

al.[65] also reported that patients receiving the same course of oxytocin had improvement on several verbal memory learning tasks compared to placebo, indicating that oxytocin has the potential to improve cognition in schizophrenia. Trials with higher doses, longer treatments or in groups not on stable antipsychotic regimens may result in more substantial effects.

Pedersen et al.[63] conducted a randomized, placebo-controlled 2-week treatment trial in patients with schizophrenia receiving intranasal oxytocin (24 IU twice daily) or placebo. PANSS scores declined in the oxytocin group but not the placebo group, including improvements in the suspiciousness/persecutory, anxiety, and paranoia subscales. In addition, on the Brune Theory of Mind Picture Stories Task, a social cognition measure, the oxytocin group demonstrated improvements in accurate identification of second-order false beliefs and trends toward improvement in accurate recognition of deception.

Finally, Modabbernia et al.[66] reported an 8-week double-blind, placebo-controlled study in 40 patients with schizophrenia who had partial remission of symptoms on a stable dose of risperidone (5 or 6 mg/day). Patients were randomized to receive intranasal oxytocin (N = 20; 20 IU twice daily for 1 week, followed by 40 IU twice daily for 7 weeks) or placebo (N = 20). The group receiving oxytocin had a greater response on the PANSS total score ($p < 0.001$), positive subscale ($p < 0.001$), negative subscale ($p < 0.001$) and psychopathology score ($p = 0.021$). Effect sizes ranged from 0.8 to 1.9, indicating medium to large effects.

Overall, oxytocin shows great promise in small, preliminary studies as being a possible effective adjunctive treatment for residual positive and negative symptoms of schizophrenia. Larger studies are needed to determine the generalizability of the findings to broader populations, and to use validated measures of overall functioning and quality of life to determine the magnitude of the clinical effect of oxytocin.

Oxytocin and Mood Disorders

Oxytocin inhibits stress-induced activity in the hypothalamic-pituitary axis in rats[124], and plays an important role in the response to stress through its close association with corticitrophin-releasing factor.[125] Therefore, it has been studied extensively for its connection to mood and anxiety disorders. Many studies have examined oxytocin levels in both major depressive disorder (MDD) and bipolar disorder (BD), with sometimes conflicting results. The aggregate of studies summarized here indicate a complex relationship between oxytocin levels and mood disorders, with multiple factors contributing to the observed pathophysiological state in any given patient.

Plasma/CSF levels

Legros et al.[67] measured CSF hNPII levels in patients with MDD and patients with BD, currently depressed. Levels in those with MDD were no different from neurologic controls, while the bipolar depressed group had higher levels (replicated in Linkowski et al.[46]). Several studies demonstrate consistently that patients with MDD do not differ from HC in CSF hNPII levels[46], plasma hNPII levels[74], CSF oxytocin levels[69], or plasma oxytocin levels[53,70]. There was also no correlation between plasma oxytocin levels and measures of motor activity[71] or neuropsychological testing results[72].

In contrast to these findings, Frasch et al.[68,126] compared nocturnal plasma oxytocin levels in patients with MDD and HC. Eighty-three percent showed a reduction of plasma oxytocin compared with age-matched controls. Differences were more pronounced in older patients, who tended to have lower plasma oxytocin levels than younger patients. Supporting the finding of lower plasma oxytocin levels in patients with MDD, Anderberg and Uvnas-Moberg[73] reported lower plasma oxytocin levels in female patients with both MDD and fibromyalgia than in patients with fibromyalgia without MDD or HC. Low levels of oxytocin were also seen in patients who self-reported high daily levels of pain, stress and depression. A negative correlation was found between oxytocin levels and the scores for depression and anxiety, and a positive correlation was found between oxytocin levels and the scores for happiness.

Ozsoy et al.[78] also reported decreased serum oxytocin levels in inpatients with MDD or BD, currently depressed, compared with HC. Levels were decreased both pre- and post-treatment with antidepressants or ECT and were unaffected by either treatment. The difference in oxytocin was also gender-specific, with female patients having lower levels than female controls while no difference was seen between the male groups. In this study, there was no difference between patients with MDD and those with BD, currently depressed. A single study[79] of small sample size (11 MDD, 19 HC) reported an increase in nocturnal plasma oxytocin levels in patients with MDD compared to HC, with the difference most apparent during the nocturnal peak of oxytocin levels.

Recent studies have begun to elucidate patient characteristics that may contribute to the differing results across studies. Scantamburlo et al.[76] found a negative correlation in patients with MDD between oxytocin plasma levels and Hamilton Depression Rating Scales scores (HAM-D), in line with some of the above reports. However, they also found that oxytocin levels were negatively correlated with anxiety scores on the State-Trait Anxiety Inventory, indicating that comorbid anxiety may be a moderating factor of the effects in depression. In a nuanced study of correlations with personality dimensions using the Temperament and Character Inventory in outpatients with MDD, Bell et al.[75] demonstrated a positive correlation of oxytocin plasma levels with the temperament dimensions of reward dependence and novelty seeking, indicating a relationship between temperamental factors and oxytocin levels that may confound results in studies that fail to control for this relationship. Finally, Cyranowski et al.[77] demonstrated using plasma levels that a group of women with MDD had greater variability in pulsatile oxytocin release during two 1-hour experimental task sessions than a HC group, and greater oxytocin concentrations during a guided imagery task focused on attachment-related images. During this task, oxytocin concentrations were also positively correlated with both clinician-observed and self-reported depressive symptoms, as well as self-reported anxiety symptoms. This demonstrates that MDD may be associated with a dysregulation of oxytocin release that may be task-dependent, so that any measurement of oxytocin levels at a particular point in time may lead to conflicting results.

Response of Oxytocin Levels to Electroconvulsive Therapy

Multiple reports of the effect of electroconvulsive therapy (ECT) for unipolar and bipolar depression on oxytocin levels have led to investigations of the possible importance of oxytocin in the therapeutic response to ECT. Early reports identified an increase of approximately 50–70% in hNPII plasma levels within the first minute following seizure during ECT with a return to baseline within 60 minutes[127,128]. Scott et al.[80,81] reported that peak plasma hNPII response to ECT was greater in patients who recovered from depression than in those who did not, and that increase in hNPII concentration correlated with improvement in HAM-D and MADRS scores. This effect was replicated in a later study by the same group[129], which further demonstrated that it was the release of hNPII after the first ECT treatment that correlated with improvement over the course of ECT. In this study, neither basal levels nor the peak response of hNPII changed between the first and last treatment.

Studies of oxytocin plasma levels show an initial peak oxytocin level after the first ECT approximately 9-fold higher than baseline[83,84], greater than the previously reported response of hNPII. In a study within the same group of patients, the initial increase in oxytocin level was approximately four-fold greater than the increase in hNPII[82]. Also, unlike the response of hNPII, the increase of oxytocin was attenuated by the third treatment to an approximately 5-fold increase over baseline[84]. Riddle et al.[130] demonstrated that the mean plasma oxytocin level shortly after ECT was greater after suprathreshold stimulation than after threshold stimulation. Similar to hNPII, there was no change in baseline oxytocin plasma levels following a course of ECT[78,85], indicating that any relationship to clinical response is not due to an underlying change in peptide concentrations. In contrast to hNPII, the peak oxytocin response to ECT is not as sensitive a predictor of clinical response. In a study of patients with MDD[84], there was no association between baseline or peak responses of plasma oxytocin levels and clinical outcome. In a larger study of patients with MDD[85], plasma oxytocin peak responses after the second treatment were not correlated with clinical response; however, there was a trend-level association between higher peak oxytocin response after the ninth ECT treatment and clinical response. These studies collectively suggest that the therapeutic effect of ECT may at least in part be modulated through its effects on the release of oxytocin and its related carrier protein (hNPII).

Neuropathological Correlations

Two studies[86,87] have reported on neuropathological differences in oxytocin-related functioning in patients with mood disorders compared to HC. Purba et al. evaluated post-mortem brain tissue of patients and age-matched controls, staining for oxytocin in the paraventricular nucleus of the hypothalamus. The number of oxytocin-producing neurons in patients was increased by 23%, with no differences found between subgroups of patients with MDD, BD, and Depressive Disorder Not Otherwise Specified (NOS). Correspondingly, Meynen et al. performed quantitative oxytocin mRNA in-situ hybridization in the paraventricular nucleus of post-mortem samples of patients with MDD and controls. They found an increase of oxytocin mRNA in melancholic depressive patients compared to non-melancholic depressive patients, and a trend toward higher oxytocin mRNA levels in the melancholic patients compared with controls. Therefore, these neuropathologic studies

confirm the impression that patient characteristics and endophenotypic differences influence the overall functioning of the oxytocin system in mood disorder patients.

Genetic Studies

Two published studies have examined genetic associations between the oxytocin receptor and mood disorders. Costa et al.[88] studied OXTR in a cohort of adult patients with MDD, BD I, or BD II, and age-matched controls. There were differences between MDD patients and HC in 2 SNPs, found previously to be associated with ASD. There was no difference in the BD group compared with the controls.

Thompson et al.[89] focused on the rs2254298 polymorphism, because being an 'AG' carrier had been previously shown to be associated with loneliness in adolescents[131]. They studied the interaction of early adverse parental environment and the polymorphism in predicting poor psychosocial outcomes by interviewing girls (ages 9–14 years) and their mothers. They measured depressive and anxiety symptoms in the girls, and performed genotyping. Heterozygous ('AG') girls with maternal history of recurrent MDD reported higher symptoms of depression, physical anxiety, and social anxiety than did girls without maternal history of MDD and/or with homozygous ('GG') genotype. The difference between this study and the previous one[88], which showed an association between the 'GG' genotype and MDD, may be due to developmental differences between adolescents and adults. Supporting this difference are previous findings[131] of different patterns of association between the rs2254298 genotypes and loneliness in adolescents than in adults.

Response to Exogenous Oxytocin

Given the evidence of oxytocinergic dysfunction in depression and the response of oxytocin to ECT, it might be expected that administration of oxytocin may have an effect on individuals experiencing depressive symptoms. Pincus et al.[90] enrolled adults with MDD and matched HC in a crossover, double-blind placebo-controlled trial with a wrap-around fMRI study. Each participant performed the RMET emotion recognition task in the fMRI scanner. The experiment was repeated before and after administration of 40 IU intranasal oxytocin or placebo. HC showed decreased reaction time to the task after oxytocin administration while patients with MDD had increased reaction time. There was no difference in accuracy of response between groups or after administration of oxytocin. Oxytocin differentially activated the brain in the two groups during the RMET task. In controls, oxytocin enhanced activation of the inferior frontal gyrus, amygdala, parahippocampal gyrus, left caudate, and superior temporal gyrus. In individuals with MDD, oxytocin enhanced activation in the bilateral superior temporal gyri, and cingulate gyri, left anterior cingulum and supramarginal gyrus, right precentral gyrus, inferior frontal gyrus, insula and superior frontal gyri and middle frontal gyri. In this brief experiment, there was no effect of oxytocin on general mood state or depressive scores.

There have been no randomized, placebo-controlled long-term studies of the effects of oxytocin on MDD. There is one case report[91] of a 38yo man with MDD with multiple failed antidepressant trials, who had a decrease in depressive and anxiety-related symptoms during a 3-week trial of adjunctive intranasal oxytocin (8 IU twice daily), while on escitalopram 20

mg daily, as measured by a reduction in HAM-D and Spielberger State-Anxiety Inventory scores.

Given the suggestive preclinical evidence that oxytocin plays a role in the stress response, and the evidence for a complex interrelationship of the oxytocin system and mood, there is ample need for larger clinical studies of oxytocin in mood disorder patients. Currently, the lack of available data prevents any supposition about its potential role in the treatment of mood disorders.

Oxytocin and Other Disorders

While human studies of oxytocin in clinical populations have largely taken place in ASD, schizophrenia, and mood disorders, its roles in the stress response, repetitive behaviors, and temperamental differences have also led to preliminary investigations into anxiety disorders, obsessive-compulsive disorder, and personality disorders.

Anxiety Disorders

Hoge et al.[92] measured plasma levels of oxytocin in patients with Generalized Social Anxiety Disorder (GSAD) and HC. There was no difference in oxytocin level between patients and controls. However, within the GSAD sample, higher social anxiety symptom severity adjusted for age and gender was associated with higher oxytocin levels. In another study[93], patients with GSAD had similar plasma oxytocin levels to a HC group at baseline, but lower oxytocin levels after completing a trust game with a partner.

Pitman et al.[94] measured heart rate, skin conductance, and electromyographic responses in Vietnam veterans with PTSD during personal combat imagery exercises. The patients were randomized to receive a single dose of intranasal vasopressin (20 IU), intranasal oxytocin (20 IU), or placebo one hour before the exercises. There was a trend toward lower physiological response to personal combat-related imagery in the oxytocin group, but without any subjective response reported by the patients.

Two studies examined the effect of a single dose of intranasal oxytocin (24 IU) compared to placebo in a group of male patients with GSAD and a group of male HC, specifically examining fMRI activation patterns when viewing emotional faces[96,97]. Relative to the control group, patients with GSAD displayed hyperactivity of the bilateral amygdala when viewing fearful faces[96] and hyperactivity of the medial prefrontal cortex (mPFC) extending into the anterior cingulate cortex (ACC) when viewing sad faces[97]. There were no differences between groups in the response to angry or happy faces. Oxytocin had no effect in either study on the control group; however, in the GSAD patients the heightened activity in response to fearful and sad faces was attenuated and “normalized” such that the hyperactivity relative to controls was reduced or eliminated. There was no subjective change in mood or anxiety reported by patients or controls following administration of oxytocin.

Guastella et al.[95] randomized male patients with GSAD to receive intranasal oxytocin (24 IU) or placebo at the start of the second through fifth therapy sessions of a 5-session weekly group exposure therapy. Following each administration, the participants gave a speech in

front of group members about increasingly difficult topics. In general, there was a reduction in self-reported symptoms on measures of anxiety between pre- and post-treatment that was maintained at one month follow-up, with no differences between those receiving oxytocin or placebo. There was no main effect of drug or interaction between treatment session and drug for self-reported anxiety during the speech task across the treatment sessions. Participants who received oxytocin rated their appearance and performance as improved as sessions progressed. In a similar study with HC, administration of oxytocin prior to an impromptu speech presentation decreased the negative self-appraisal in individuals with high trait anxiety[132]. The authors posit that future studies are warranted to determine if oxytocin's benefit on negative self-appraisal can be enhanced by more frequent administrations or administration in a broader array of contexts, potentially having an additive effect that more robustly alters overall symptoms and functioning.

Obsessive-Compulsive Disorder

Swedo et al.[98] found that CSF oxytocin concentration was positively correlated with depressive symptoms in children with severe obsessive-compulsive disorder (OCD). Comorbid anxiety disorder was also associated with increased CSF oxytocin levels. There was no correlation between oxytocin concentrations and OCD symptoms. Leckman et al.[99] compared patients with OCD, patients with Tourette's Disorder (TS), and HC. They found increased CSF oxytocin levels in the patients with OCD compared to the other two groups, but the elevation was only significant in a subgroup of patients without a personal or family history of tic disorder. They found that the oxytocin level correlated with the current severity of OCD symptoms in the non-tic related OCD group only. In this study, there were no correlations between ratings of depression or anxiety and oxytocin levels. Altemus et al.[100] also measured CSF oxytocin levels in patients with OCD and HC, and found no differences between the groups. Differences in these studies may have been due to small sample sizes, inherent differences in participants between the studies, or different collection times of CSF.

Interest in oxytocin as a potential treatment for OCD heightened after a case report of a hospitalized patient with severe OCD symptoms, who had a dramatic reduction in OCD symptoms after 4 weeks of daily intranasal oxytocin therapy (14.4 IU)[101]. However, this patient developed psychotic symptoms in the context of developing hyponatremia and possibly developed delirium due to the electrolyte imbalance, which may have masked his OCD symptoms. Several attempts to replicate the findings have been unsuccessful. The effects of oxytocin in patients with OCD have been reported in 2 case reports (10 IU intramuscular daily)[102], a double-blind placebo-controlled study (4.5–13.5 IU intranasal four times daily)[103], a single dose study (8 IU intranasal)[104], a placebo-controlled crossover study in patients with trichotillomania (40 IU intranasal four times daily)[105], and a placebo-controlled crossover study in patients with comorbid OCD and MDD (40–80 IU intranasal four times daily)[106]. There was no effect in any of the studies on OCD symptoms, and only a small decrease in Beck Depression Inventory scores in the comorbid depression study. In short, there is no evidence for the effectiveness of oxytocin in the treatment of OCD, although the total number of patients studied is small (N = 29).

Personality Disorders

On the basis of animal experiments demonstrating a connection between social aggressive behavior and oxytocin, Lee et al.[107] postulated a connection between oxytocin levels and socially aggressive behavior in humans. In a study of individuals with a DSM-IV diagnosis of a personality disorder (See Table 1 for specific diagnoses) and HC, CSF oxytocin level was inversely correlated with Lifetime History of Aggression (LHA) scores. Exploratory analysis indicated that the only subscale that was an independent predictor of CSF oxytocin level was the history of a suicide attempt, with attempters having lower oxytocin levels than non-attempters. This relationship was independent of personality disorder diagnosis. Bertsch et al.[108] demonstrated lower plasma oxytocin levels in females with borderline personality disorder (BPD) that correlated negatively with experiences of childhood emotional neglect and abuse.

To date, studies evaluating oxytocin for the treatment of BPD have shown some possible benefit but also some risk. In a pilot study of BPD patients and HC[110] participants received intranasal oxytocin (40 IU) or placebo in double-blind randomized order followed by a social stress test involving public speaking and a mental arithmetic task in front of an audience. Subjective dysphoria and plasma cortisol levels were followed. There was greater attenuation of stress-induced dysphoria in the BPD group relative to controls after oxytocin administration. There was also a trend toward greater attenuation of cortisol in the BPD group after oxytocin administration. In the combined sample, the difference between stress-induced dysphoria after oxytocin vs placebo was predicted by the presence of childhood trauma, whereas the difference in stress-induced cortisol surge after oxytocin vs placebo was predicted by a measure of insecure attachment.

Bartz et al.[109] demonstrated that oxytocin may have very different, even opposite, effects in BPD patients than in HC. It had been shown previously that in HC, oxytocin administration increased trusting behavior in a social dilemma game[8] and increased the perceived trustworthiness of faces[133]. In healthy adults and adults with BPD, Bartz et al. administered intranasal oxytocin (40 IU) or placebo in a double-blind randomized study. Following administration, the participants played an Assurance Game in which the individual is playing a game with a “partner”. BPD participants had decreased expectation of their partner’s cooperativeness following oxytocin administration (decreased “trust”), and they were more likely to defect in response to partner hypothetical cooperation despite the fact that their payoff would be less for defection. HC, by contrast, demonstrated increased “trust” and more cooperation in response to partner hypothetical cooperation following oxytocin administration, although neither of these comparisons reached statistical significance. Thus, whereas oxytocin in HC leads to a more trusting, collaborative strategy in which both partners “win”, BPD patients respond to oxytocin by becoming less trusting and developing a more competitive strategy.

CLINICAL IMPLICATIONS AND LIMITATIONS

The implications of the growing evidence for the role of oxytocin in neuropsychiatric disorders are far-reaching. First, the evidence suggests a role of oxytocin in the pathophysiology of some psychiatric disorders, particularly those characterized by

impairments in social functioning. However, the preliminary nature of the currently available data precludes a clear understanding of the exact nature of this role. Perhaps it is not surprising that a hormone that so directly impacts interpersonal and social functioning has implications in diagnostic groups ranging from ASD to schizophrenia spectrum disorders to mood disorders, all of which demonstrate significant interpersonal and social dysfunction as core features of the disorder. There also seems to be similarity in terms of the genetic risk associated with variations in OXTR across disorders, with several polymorphisms identified as risk variants in multiple disorders. Second, the complex and sometimes contradictory aspects of oxytocin dysfunction within these disorders point to the role of individual variation in the presentation of oxytocin dysfunction and the need for more research into the core underlying dysfunctions. For example, the finding that low-functioning children with ASD have lower plasma oxytocin levels, while high-functioning adults with ASD have higher baseline levels, indicates that there may be developmental and individual patient factors that are poorly understood that contribute to the underlying pathophysiology of the disorders.

The effects of oxytocin seem to be determined by individual factors that may be related to clinical presentation. For example, the effects of oxytocin on trust behaviors in patients with BPD are opposite those in HC. Likewise, oxytocin caused those with more anxious attachment styles to remember their mothers as less caring, while those with less anxious attachments remembered their mothers as more caring. Indeed, the evidence suggests that rather than being a truly “prosocial” hormone, oxytocin may reinforce and enhance the saliency of attachment representations that already exist. Therefore, those patients with BPD who may be predisposed to view interpersonal interactions negatively are more prone to negatively respond to oxytocin administration. This idea cannot be broadly assumed to be true, given the positive social response of oxytocin in individuals with ASD who may be expected to be predisposed to have limited attachment capability. However, even in ASD, there is evidence that those actively avoiding social contact were less responsive to oxytocin than those who sought out social contact but in a socially inappropriate manner[43].

The accumulation of evidence that there may be some therapeutic benefit to the administration of oxytocin is heartening. Particularly in individuals with ASD and schizophrenia, there is some evidence that oxytocin may affect the core deficits in the disorders, improving social cognition in autism and decreasing positive and negative symptoms in schizophrenia. There is also more limited evidence that there may be some therapeutic benefit in MDD and in social anxiety disorder. Overall, the effect sizes are small. However, an important caveat to all treatment studies to date is the inherent limitation of the currently available delivery methods for oxytocin. Currently, given that intravenous dosing is not a practical clinical alternative, the only available delivery method that allows for frequent dosing and a chance of crossing the blood-brain barrier is the intranasal delivery method. While many of these studies have assumed that intranasal delivery of peptides can achieve transport across the blood-brain barrier[134], there is still debate about this point and whether intranasally administered oxytocin reaches the pertinent receptors in the brain to influence neural activity.[135] Also, there is evidence that oxytocin acts in a positive feed-forward mechanism in which small doses of oxytocin might have sustained effects beyond the short half-life of the peptide (~20 minutes), i.e., elevated salivary levels of oxytocin were

measured for greater than 2 hours after administration of a relatively small dose (16IU) of intranasal oxytocin.[136] This feed-forward mechanism may have contributed to the finding in one reviewed study of greater effect on emotion recognition in schizophrenia at lower doses.[62] Thus, even with multiple daily dosing, it is not clear whether this results in pulsatile or sustained levels of oxytocin in the central nervous system. There still remain a number of critical research questions regarding the pharmacokinetics and pharmacodynamics of intranasal oxytocin that can only be answered by larger, randomized controlled trials before appropriate dosing strategies for these various disorders can be developed.

It is unknown whether other therapeutic strategies for targeting the oxytocin system, which have been demonstrated in animal models, would have more efficacy in human studies. For example, oxytocin receptor agonists have been developed that can be delivered orally and stimulate the oxytocin receptor[137,138], and there is evidence that melanocortin 4 receptor agonists stimulate the central release of oxytocin in rats[139]. Given the evidence presented here of the potentially broad and diverse impact of oxytocin across a range of neuropsychiatric disorders, drug development along these lines would presumably be advantageous for a wide number of patients. Importantly, the studies to date have been primarily experimental or preclinical in nature, and proper clinical trials are only recently being undertaken, so that we can have a proper understanding of the extent and limitations of the clinical effects of externally delivered oxytocin.

Overall, the search for genetic contributions of the oxytocin and oxytocin receptor genes to the disorders reviewed here is plagued by the limitations of the candidate gene approach to studying complex psychiatric phenotypes that are likely multifactorial in origin. On the one hand, the multiple studies indicating a possible link between polymorphisms and these disorders suggests that there is indeed a role for this peptide and receptor system in the pathophysiology of the various disorders. However, the inconsistency of the individual findings and identified SNPs across studies indicates that no single finding is likely to have more than a small additive role in the complex genetics and gene-environment interactions that underlie the various psychiatric disorders discussed here. While these findings contribute to the body of knowledge about the involvement of the oxytocin system in these disorders, pursuit of this candidate gene approach has been disappointing in terms of major breakthroughs in our understanding of these disorders.

In summary, the evidence for the role of oxytocin in a broad range of neuropsychiatric disorders is accumulating, and further research is needed to determine the exact nature of its role and to translate these findings into a better understanding of the underlying pathophysiology of the disorders and effective treatment strategies targeting the oxytocinergic system.

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Table 1

Human Studies of Oxytocin in Psychiatric Disorders

Authors	Subjects	Method of Study	Main Findings
Autism Spectrum Disorders			
Plasma Levels			
Modahl et al. (1998)[22]; Green et al. (2001)[23]	59 Males 29 Autism 30 HC Ages 6–11	Plasma levels of OT and unprocessed precursor to OT	Significantly lower OT levels in autistic disorder (Range: 0 – 2.48 pg/mL; Mean: 0.64 ± 0.58 pg/mL) than in HC (Range: 0 – 2.72 pg/mL; Mean: 1.16 ± 0.77 pg/mL; $p < 0.004$); Elevated OT levels associated with lower VABS scores in autistic children; Higher levels of OT precursor peptide in autistic disorder than in HC
Jansen et al. (2006)[24]	24 Subjects 10 ASD (9M, 1F) Mean Age: 21.8 ± 2.0 14 HC (13M, 1F) Mean Age: 21.0 ± 3.4	Plasma Levels of oxytocin before and after psychosocial stressor (public speaking)	No difference in OT response to stress, increased basal OT levels in adults with ASD ($F = 6.70$, $p < 0.05$); OT levels not correlated with impairments in social interaction, communication, or stereotyped behavior
Genetic Studies			
Wu et al. (2005)[25]	195 Chinese Han autism proband-parent trios	FBAT of 4 SNPs within OXTR gene; Haplotype-specific FBAT	Significant association - autism and 2 SNPs rs2254298 A ($Z = 2.287$, $p = 0.022$) rs53576 A ($Z = 2.573$, $p = 0.01$) Number of haplotypes significantly associated with autism, particularly involving rs53576
Jacob et al. (2007)[26]	57 Caucasian autism proband-parent trios	FBAT of 4 SNPs within OXTR gene; Haplotype-specific FBAT	Significant association - autism and 1 SNP rs2254298 G ($\chi^2 = 4.80$, $p = 0.03$) No haplotypes were significantly associated with autism
Lerer et al. (2008)[27]	152 Israeli ASD probands and their families	FBAT of 18 SNPs within OXTR gene; Haplotype-specific FBAT	Significant association - ASD and 2 SNPs rs2268494 ($p = 0.01$), rs1042778 ($p = 0.01$) Significant association - IQ and 2 SNPs rs4686301 ($p = 0.003$), rs1042778 ($p = 0.01$) Significant association - VABS total score and 2 SNPs rs4686301 ($p = 0.05$), rs6770632 ($p = 0.03$) Significant association - VABS subdomain scores and 8 SNPs Communication: rs2254298 ($p = 0.02$), rs4686301 ($p = 0.04$), rs2268490 ($p = 0.02$), rs237887 ($p = 0.04$), rs6770362 ($p = 0.002$) Daily Living Skills: rs4564970 ($p = 0.04$), rs13316193 ($p = 0.02$), rs2254298 ($p = 0.03$), rs237888 ($p = 0.05$), rs237887 ($p = 0.02$), rs6770632 ($p = 0.02$) Socialization: rs6770362 ($p = 0.02$) Multiple haplotypes significantly associated with ASD diagnosis
Yrigollen et al. (2008)[28]	177 (93% Caucasian) ASD probands and their families	FBAT of 2 SNPs within OXT gene and 3 SNPs within OXTR gene	Significant association - ASD and 1 SNP within OXTR rs2268493 ($p = 0.008$) Significant association - Stereotyped behaviors and 1 SNP within OXT gene rs2740204 ($p = 0.016$) No associations remained significant after correction for multiple testing
Liu et al. (2010)[29]	223 Japanese ASD probands and their families (FBAT) 65 unrelated Japanese ASD patients 440 unrelated Japanese HC (case-control analysis)	FBAT of 11 SNPs within OXTR gene; Population-based case-control comparison	No association found in FBAT analysis Significant differences in allelic frequencies of 4 SNPs in case-control analysis rs237887 G ($p = 0.023$) rs2268491 T ($p = 0.004$) rs2254298 A ($p = 0.001$) rs2268495 G ($p = 0.032$)

Authors	Subjects	Method of Study	Main Findings
Tansey et al. (2010)[30]	436 Caucasian ASD probands and their families (Irish, Portugal, and UK samples)	FBAT of 18 SNPs within OXTR gene	Nominal association of 3 SNPs with ASD diagnosis in 1 sample that did not withstand correction for multiple comparisons rs11720238 G (p = 0.03) rs7632287 G (p = 0.008) rs4564970 C (p = 0.009)
Wermter et al. (2010)[32]	100 German ASD probands and their families	FBAT of 22 SNPs within OXTR region; Haplotype-specific FBAT	Nominally significant association of 1 SNP and 1 haplotype with ASD; did not withstand correction for multiple comparisons rs2270465 G (p = 0.02) rs237851-rs6791619-rs53576-rs237884 T-G-T-T (p = 0.007) Patients carrying this haplotype showed nominally significant impairments in social interaction and communication compared to noncarriers
Campbell et al. (2011)[33]	2333 (95% Caucasian) ASD probands and their families	FBAT of 25 SNPs within OXTR	Significant association - ASD and 3 SNPs, also associated with measures of social communication dysfunction (p-values for ASD diagnosis on Autism Diagnostic Observation Schedule) rs2268493 T (p = 0.04) rs1042778 G (p = 0.04) rs7632287 G (p = 0.007)
Epigenetic Studies			
Gregory et al. (2009)[34]	Single male proband with autism containing deletion in 3p25.3 containing OXTR gene and his brother with autism without deletion 20 patients with autism (10M, 10F) and 20 HC (10M, 10F) Post-mortem tissue from 8 autism patients and 8 HC	Bisulfite sequencing (BSS) of OXTR region in peripheral blood cells to determine methylation status BSS of OXTR region in peripheral blood cells to determine methylation status BSS of OXTR region in temporal cortex tissue to determine methylation status	Autistic brother of patient with OXTR deletion had hypermethylation of OXTR gene Significant hypermethylation of OXTR gene regions in individuals with autism compared to controls Significant hypermethylation of OXTR gene regions in autism cases compared to controls
Response to Exogenous OT			
Hollander et al. (2003)[35]; Hollander et al. (2007)[36]	15 Subjects with autism (n = 6) or Asperger's disorder (n = 9) 14 M, 1 F Mean Age 32.9 (Range 19.4 – 55.6) Mean IQ 90.3 ± 9.9 (Range 74 – 110)	Randomized, double-blind, placebo-controlled, crossover challenge of continuous intravenous infusion of oxytocin (10–15 IU) or placebo over 4 hours	Significantly greater reduction in repetitive behaviors over time following oxytocin (drug × time interaction: F = 3.487, df = 4, 52, p = 0.027) Increased retention of ability between trials to accurately identify affect of speech in auditory comprehension task if oxytocin was received first compared to placebo being received first (Time × Treatment × Order interaction: Z = −2.134, p = 0.033)
Guastella et al. (2010)[37]	16 Male subjects with Autistic Disorder or Aspergers Disorder Mean Age 14.9 ± 2.4 (Range 12–19)	Randomized, double-blind, placebo-controlled, crossover challenge of intranasal oxytocin (18IU for age 12–15, 24IU for age 16–19) or placebo	OT improved performance on Reading the Mind in the Eyes Test for 60% of participants (t(14) = 2.43, p = 0.03); Highly significant difference on easier items (t(14) = 4.39, p = 0.001); no significant difference for harder items
Bartz et al. (2010)[38]	27 Male HC Mean Age 26.8 ± 7.0	Randomized, double-blind, placebo-controlled, crossover challenge of intranasal oxytocin (24 IU) or placebo	OT increased accuracy of empathic rating of others' emotions only in those with high Autism Spectrum Quotient (AQ) scores (Drug Condition × AQ interaction: b = 0.11, t(232) = 2.01, p < 0.05)
Andari et al. (2010)[39]	13 subjects with Aspergers Disorder (n = 10) or high-functioning autism (n = 3) 11M, 2F	Randomized, double-blind, placebo-controlled, crossover challenge of intranasal oxytocin (24 IU) or placebo	OT increased participants' interactions with a cooperative player in a computerized ball-throwing game compared to noncooperative players (Z = 2.04, p < 0.04) OT significantly increased time spent gazing at the face in eye tracking experiment, with

Authors	Subjects	Method of Study	Main Findings
	Mean Age = 26, Range = 17 – 39 Mean IQ 99 ± 23.5 13 HC (age- and sex-matched)		significantly increased fixation time on the eye region (Z = 2.12, p < 0.04)
Schizophrenia			
Plasma/CSF Levels			
Linkowski et al. (1984)[40]	12 subjects with schizophrenia, 12 age-matched neurological controls (8 hydrocephalus, 1 acoustic neuroma, 3 cerebral atroph) S: 9M, 3F; HC: 8M, 4F Age Range 29–65	CSF hNPII levels	hNPII higher in patients with schizophrenia (4.5 ± 1.2 ng/mL) than in controls (3.05 ± 1.4 ng/mL; t = 2.82, p < 0.01)
Beckmann et al. (1985)[41]	28 males with schizophrenia (mean age 30.6 ± 8.0), paranoid type 15 HC (13M, 2F; mean age 35.0 ± 15.7)	CSF OT levels	OT higher in patients with schizophrenia after haldol treatment (13.46 ± 5.96 pg/mL, p < 0.01) and in patients without neuroleptic treatment (10.03 ± 4.03 pg/mL, p < 0.05) than in HC (7.11 ± 4.03 pg/mL)
Legros et al. (1992)[42]	9 male patients with schizophrenia 14 HC	Serum hNPII levels before and after apomorphine challenge	Basal levels of hNPII higher in schizophrenia (3.34 ± 0.04 ng/mL) than in HC (0.92 ± 0.21 ng/mL, p = 0.001) No significant change in schizophrenia after apomorphine challenge, compared to two-fold increase in HC Basal levels higher in paranoid subroup (5.15 ± 0.99 ng/mL, n = 4) than in nonparanoid subgroup (1.92 ± 0.61 ng/mL, n = 4, p < 0.03)
Glovinsky et al. (1994)[43]	66 Subjects 20 neuroleptic-treated patients 31 neuroeptic withdrawn patients 15 HC	CSF OT levels	No significant differences between groups (p = 0.11)
Goldman et al. (2008)[44]	22 subjects 6 polydipsic hyponatremic patients 4 polydipsic normonatremic patients 5 nonpolydipsic normatremic patients 7 HC	Plasma OT levels before and after stress induction	OT nonsignificantly lower in hyponatremic patients (100 ± 35 pg/mL) than in other three groups (266 ± 309 pg/mL, 301 ± 338 pg/mL, 240 ± 224 pg/mL, p = 0.07) OT levels inversely correlated with anterior hippocampal volumes in structural MRI OT levels correlated with patients' ability to correctly identify facial emotions (r = 0.62, p = 0.02)
Keri et al. (2009)[45]	100 Subjects 50 with schizophrenia 50 HC	Plasma OT levels	No significant differences in OT levels after neutral interactions with examiner OT levels increased significantly in HC after trust-related interactions (p < 0.001) but not in patients with schizophrenia (p > 0.5) Significantly lower OT levels in patients after trust-related interactions (p < 0.0001) Low OT levels after trust-related interactions were significantly correlated with negative symptoms as measured by PANSS score ($F(1,48) = 35.03$, $p < 0.0001$, $\beta = -0.65$, $R^2 = 0.42$)
Rubin et al. (2010)[46]	108 Subjects 50 patients with schizophrenia (27M, 23F) 58 HC (27M, 31F)	Plasma OT levels	No significant difference between patients and controls, or across phases of menstrual cycle in females Female patients - higher OT levels associated with lower PANSS total symptom, positive symptom, and general psychopathology subscores (p < 0.01 for all), and trend toward

Authors	Subjects	Method of Study	Main Findings
			association with lower negative symptom subscore (p = 0.06) All patients - higher OT levels associated with better prosocial scores on PANSS (p < 0.01 for females, p < 0.05 for males)
Sasayama et al. (2012)[47]	27 patients with schizophrenia 21 HC	CSF OT levels	CSF levels did not differ significantly between patients and controls OT levels were significantly negatively correlated with second generation antipsychotic dose (r = −0.49, p = 0.010) and negative symptom PANSS subscore (r = −0.47, p = 0.016)
Genetic Studies			
Souza et al. (2010)[49]	358 subjects (case-control) 179 patients with schizophrenia 179 HC 49 probands and their healthy parents (FBAT)	Case-control comparison of 7 SNPs within OXT gene and 13 SNPs in OXTR gene; FBAT of same SNPs	FBAT Analysis OXT gene: rs2740204 T (p = 0.027) Case-control Study OXT gene: rs4813625 C (p = 0.036); rs3761248 C (p = 0.030) None remained significant after correction for multiple testing
Souza et al. (2010)[50]	140 patients with schizophrenia treated with clozapine	Association of OXT and OXTR variants with symptom severity and response to clozapine	OXT gene rs2740204 G - Significantly associated with treatment response (p = 0.042 after correction for multiple testing) and nominally significant association with negative symptoms (p = 0.01 prior to correction) OXTR gene rs237885 T, rs237887 A - nominally significant association with severity of overall symptoms (p = 0.014, 0.033 prior to correction) rs11706648 A, rs4686301 C, rs237899 G - nominally significant association with improvement of positive symptoms on clozapine (p = 0.0002, 0.0002, 0.039 prior to correction)
Teltsh et al. (2011)[51]	Clan of 56 Arab-Israeli individuals 52 Arab-Israeli nuclear families (n = 276) Jewish case-control sample (n = 545)	Identified gene variants in OXT gene in individuals in clan with schizophrenia, then sought association with schizophrenia in this pedigree as well as two larger population samples	Two variants of oxytocin gene significantly associated with schizophrenia in initial clan studied - rs4813626 G (p = 0.002) and rs2740204 A (p=0.00059) Opposite allele of one variant (rs4813626 A) significantly associated with schizophrenia in nuclear family sample (p = 0.0055) and in men only in the Jewish case-control sample (p = 0.0006)
Montag et al. (2012)[52]	406 patients with schizophrenia 406 HC	Case-control comparison of 2 SNPs within OXT gene and 4 SNPS within OXTR gene	Significant association of 2 OXTR gene variants with diagnosis of schizophrenia rs53576 A (p = 0.008); post-hoc analysis revealed association with General Pscyhopathology PANSS subscores rs237885 T (p = 0.025)
Response to Exogeneous OT			
Bakharev et al. (1986)[53]	45 male subjects with schizophrenia	Placebo-controlled study of OT (5 IU bid) daily for 2 nonconsecutive weeks (n = 27) vs placebo (n = 18)	No complications or side effects; Positive results but methodological limitations - “best results achieved in persons whose predominant symptoms were anergy, asthenia, and apathy combined with depressed mood.”
Feifel et al. (2010)[54]	19 patients with schizophrenia	Randomized, double-blind crossover study; 3 weeks of daily OT, titrated to 40 IU bid, or placebo as adjunctive treatment to stable antipsychotic regimen	Significant reduction in PANSS and CGI-I at 3-week endpoint compared with placebo (p < 0.001); Significant reduction in Positive Symptom subscore (p = 0.006) and Negative Symptom subscore (p = 0.023) at week 3

Authors	Subjects	Method of Study	Main Findings
Goldman et al. (2011)[55]	24 subjects 5 polysipsic patients with schizophrenia 8 nonpolydipsic patients with schizophrenia 11 HC	Randomized double-blind order of administration of single intranasal dose of 10 IU OT, 20 IU OT, or placebo	Low dose oxytocin - Emotion recognition significantly decreased in both patient groups ($p < 0.02$) High dose oxytocin - Emotion recognition significantly improved in polydipsic patients only ($p < 0.01$)
Pedersen et al. (2011)[56]	20 patients with schizophrenia	Randomized, placebo-controlled double-blind trial – 24 IU bid intranasal OT for 2 weeks (n = 11) or placebo (n = 9)	Significant reduction in PANSS total score ($p = 0.047$) compared to placebo, as well as significant reduction in multiple subscores Theory of Mind Picture Stories task Significant improvements in identification of second-order false beliefs ($p< 0.01$) and trend toward improvement in recognition of deception ($p = 0.08$)
Averbeck et al. (2012)[57]	Exp 1: 59 subjects 30 with schizophrenia 29 HC Exp 2: 21 patients with schizophrenia	Exp 1: Emotion recognition task Exp 2: Double-blind placebo-controlled crossover study of effects of intranasal OT (single dose of 24 IU) on emotion recognition task	Exp 1: Patients had significant deficit relative to controls in recognition of emotions ($p < 0.001$) Exp 2: OT improved ability to recognize emotions ($p = 0.006$), but absolute effect was modest (58% correct vs 54% correct); no significant difference on any individual emotion recognition
Feifel et al. (2012)[58]	15 patients with schizophrenia	Randomized, double-blind crossover study; 3 weeks of daily OT, titrated to 40 IU bid, or placebo as adjunctive treatment to stable antipsychotic regimen	After 3 weeks of oxytocin treatment, patients had significantly better performance on number of subtests of California Verbal Learning Test Total Recall trials 1–5: $p = 0.027$ Short delayed free recall: $p = 0.032$ Total recall discrimination: $p = 0.020$
Mood Disorders			
Plasma/CSF Levels			
Legros et al. (1983)[59]	15 patients with MDD 13 patients with BD, currently depressed	CSF hNPII levels	Bipolar depressed patients had significantly higher levels than unipolar depressed patients (7.25 ± 1.54 ng/mL vs 3.31 ± 0.83 ng/mL; $p < 0.001$)
Linkowski et al. (1984)[40]	8 patients with MDD 8 patients with BD, currently depressed 12 age-matched controls	CSF hNPII levels	No difference between patients with MDD and controls; BD patients had significantly higher levels ($p < 0.005$)
Frasch et al. (1995)[60]	12 patients with MDD 12 HC	Nocturnal plasma OT levels	OT levels significantly lower in patients with MDD compared with HC ($p < 0.05$)
Pitts et al. (1995)[61]	19 inpatients with MDD 17 HC	CSF OT levels	No significant difference between MDD and HC
Van Londen et al. (1997)[62]	52 patients with MDD 37 HC	Plasma OT levels	No significant difference between MDD and HC
Van Londen et al. (1998)[63]	48 patients with MDD 30 HC	Plasma OT levels and motor activity during sleep	Plasma OT levels not related to measures of motor activity in patients with MDD
Van Londen et al. (1998)[64]	8 patients with BD, currently depressed 5 patients with MDD with psychosis 36 patients with MDD	Plasma OT levels and neurpsychological testing	No association between neuropsychological performance and OT levels
Anderberg and Uvnas-Moberg (2000)[65]	14 patients with MDD and fibromyalgia 25 patients with fibromyalgia but no MDD 30 HC	Plasma OT levels and measures of pain, stress and depression	Patients with MDD and fibromyalgia had significantly lower OT levels than patients without MDD ($p = 0.01$) or HC ($p = 0.05$) Lower levels of OT in patients with self-reported high daily levels of pain, stress, and depression Negative correlation between OT levels and scores for depression ($r = -0.41$, $p = 0.008$) and anxiety ($r = -0.46$, $p = 0.003$)

Authors	Subjects	Method of Study	Main Findings
			Positive correlation between OT levels and scores for happiness (r = 0.35, p = 0.03)
Scantamburlo et al. (2005)[66]	25 patients with MDD 25 HC	Plasma hNPII levels	No significant difference between MDD and HC at baseline or in response to clonidine or apomorphine
Bell et al. (2006)[67]	60 patients with MDD	Plasma OT levels	Positive correlation between OT levels and temperament dimensions of reward dependence (r = 0.425, p = 0.001) and novelty seeking (r = 0.264, p = 0.041)
Scantamburlo et al. (2007)[68]	25 patients with MDD	Plasma OT levels	Negative correlation between OT levels and Hamilton Depression Rating Scales scores Negative correlation between OT levels and anxiety scores on State-Trait Anxiety Inventory
Cyranowski et al. (2008)[69]	17 women with MDD 17 HC	Plasma OT levels	Greater variability in pulsatile OT release in MDD patients Higher OT levels in MDD patients during a guided-imagery task focused on attachment-related images OT levels positively correlated with depressive symptoms and anxiety symptoms
Ozsoy et al. (2009)[70]	29 inpatients with MDD 11 inpatients with BD, currently depressed 32 HC	Plasma OT levels	Significantly lower plasma OT levels in both MDD and BD, depressed (p = 0.004); Difference was only significant in female patients; No significant difference between MDD and BD, currently depressed Levels were not significantly affected by treatment with antidepressants or ECT
Parker et al. (2010)[71]	11 patients with MDD 19 HC	Nocturnal plasma OT levels	Significantly higher OT levels in patients with MDD, most apparent during nocturnal OT peak
Sasayama et al. (2012)[47]	17 patients with MDD 21 HC	CSF OT levels	CSF levels did not differ significantly between patients and controls No signifant correlation of OT level with antidepressant dose or Hamilton Depression Scale score
Response to Electroconvulsive Therapy			
Scott et al. (1986)[73], Scott et al. (1989)[74], Scott et al. (1991)[75]	25 patients with MDD (n = 24) or schizoaffective disorder, currently depressed (n = 1) 19 patients with MDD 17 patients with MDD	Plasma hNPII levels	hNPII levels increased after ECT and returned to baseline within one hour; peak response to ECT was greater in patients who recovered (n = 16) than those who did not; Increase in hNPII after first ECT treatment correlated with improvement in depression rating scales
Smith et al. (1990)[76], Smith et al. (1994)[77]	20 patients with MDD	Plasma OT levels	Substantial and immediate increase in OT seen after the first treatment, significantly attenuated responses after third and fifth treatments; no association between baseline levels or peak responses and clinical outcome
Devanand et al. (1998)[78]	55 patients with MDD	Plasma OT levels	Peak response after second treatment were not correlated with clinical response; Peak response after ninth treatment had trend-level association with clinical response (p < 0.07)
Neuropathological Studies			
Purba et al. (1996)[79]	8 patients with MDD (n = 3), BD, currently depressed (n = 3), or Depressive Disorder NOS (n = 2) 8 HC	Immunostaining of postmortem paraventricular nucleus (PVN) for oxytocin	Number of OT neurons in PVN of patients increased by 23%; no difference between MDD, BD, and Depressive Disorder NOS

Authors	Subjects	Method of Study	Main Findings
Meynen et al. (2007)[80]	9 patients with MDD 9 HC	Postmortem OT mRNA in situ hybridization in the PVN	Significant increase of OT mRNA in patients with melancholic depression (n = 6) compared to patients with nonmelancholic depression (n = 3); Trend toward higher OT mRNA in patients with melancholic depression vs controls
Genetic Studies			
Costa et al. (2009)[81]	185 patients with MDD, BD-I, or BD-II 192 HC	Genotyping for 2 SNPs within the OXTR gene	MDD: Reduced number of 'A' allele carriers at both SNPs rs53576: Odds Ratio (OR) [A-carrier vs GG] = 0.56, p = 0.02 rs2254298: OR [A-carrier vs GG] = 0.55, p = 0.04 BD groups: no significant difference
Thompson et al. (2011)[82]	92 adolescent females (age range 9–14)	Genotyping of rs2254298 SNP of OXTR gene	Heterozygous ('AG') females with maternal history of recurrent MDD reported significantly higher symptoms of depression, physical anxiety, and social anxiety than homozygous females and/or without maternal MDD history ($p < 0.05$)
Response to Exogenous OT			
Pincus et al. (2010)[83]	8 patients with MDD 9 HC	Double-blind placebo-controlled crossover trial; single dose of 40 IU intranasal OT vs placebo	During an emotion identification task, HC showed decreased reaction time to task after OT administration while patients with MDD had increased reaction time after OT; reaction times of two groups converged after treatment fMRI: Differential enhancement of activation by OT in patients with MDD vs controls (see text for details)
Scantamburlo et al. (2011)[84]	Case report - 38 yo male	Intranasal OT 8IU bid added as adjunct treatment to escitalopram	After 1 week: HAM-D decreased from 17 to 11; STAI-A score decreased from 57 to 49; one week later, HAM-D 2, STAI-A 37; Symptoms returned after stopping OT and resolved again on reintroduction of OT treatment
Anxiety Disorders			
Plasma Levels			
Hoge et al. (2008)[85]	24 patients with GSAD 22 HC	Plasma OT levels	No significant difference between patients and controls ($p = 0.8$) Higher social anxiety symptom severity was associated with higher OT levels ($R^2 = 0.21$, $p = 0.04$)
Hoge et al. (2012)[86]	39 patients with GSAD 28 HC	Plasma OT levels before and after a trust game	No significant difference between patients and controls at baseline ($p = 0.06$) Patients had significantly lower plasma oxytocin levels at the endpoint after playing a trust game with a partner ($p = 0.025$)
Response to Exogenous OT			
Pitman et al. (1993)[87]	43 Vietnam veterans with PTSD	Randomized, placebo-controlled trial of single dose of 20IU intranasal vasopressin (N = 13), 20IU intranasal OT (N = 15), or placebo (N = 15)	Nonsignificant tendency toward lower physiological response to personal combat-related imagery in OT group
Guastella et al. (2009)[88]	25 male patients with GSAD	Randomized, placebo-controlled trial of four doses of 24 IU intranasal OT (N = 12) or placebo (N = 13) in conjunction with group exposure therapy	No significant difference in self-reported anxiety symptoms during public performances over the course of treatment between groups; OT group rated their appearance ($p = 0.008$) and performance ($p = 0.07$) as more improved than placebo group as sessions progressed

Authors	Subjects	Method of Study	Main Findings
Labuschagne et al. (2010)[89], Labuschagne et al. (2011)[90]	18 male patients with GSAD 18 HC	Randomized, placebo-controlled crossover trial of single dose of 24 IU intranasal OT or placebo	fMRI: GSAD patients had heightened amygdala activity when viewing fearful faces and heightened mPFC/ACC activity when viewing sad faces, which were both attenuated after receiving OT
Obsessive-Compulsive Disorder			
CSF Levels			
Swedo et al. (1992)[91]	43 children (mean age 13.9 ± 3.0) with severe OCD	CSF OT levels	OT levels positively correlated with depressive symptoms (r = 0.33 – 0.40, p = 0.007 – 0.03) Comorbid anxiety disorder also associated with increased OT levels (p = 0.02) No correlation between OT levels and OCD symptoms
Leckman et al. (1994)[92]	29 patients with OCD 23 patients with Tourette's Disorder 31 HC	CSF OT levels	Increased levels in OCD patients compared to other groups, but only statistically significant in subgroup without a personal or family history of tic disorder OT levels positively correlated with severity of OCD symptoms (r = 0.27, p = 0.02) in non-tic related OCD group
Altemus et al. (1999)[93]	14 patients with OCD 26 HC	CSF OT levels	No significant difference between patients and controls
Response to Exogenous OT			
Ansseau et al. (1987)[94]	Case report of hospitalized inpatient with OCD	4 weeks of 14.4 IU daily intranasal OT therapy	Dramatic reduction in OCD symptoms, in context of developing hyponatremia and psychosis
Charles et al. (1989)[95]	2 case reports of patients with OCD	10IU intramuscular OT daily for 2 years or 3 weeks	No symptomatic improvement in OCD symptoms
Den Boer and Westenberg (1992)[96]	14 patients with OCD	Randomized, placebo-controlled trial of intranasal OT, 4.5 IU qid (N = 6), or placebo (N = 6) for 6 weeks; open-label treatment with 13.5 IU qid for 6 weeks (N = 2)	No reduction in obsessions or compulsions in either group
Salzberg and Swedo (1992)[97]	3 patients with OCD	Two doses of 8 IU intranasal OT administered 90 minutes apart	No discernible changes in mood, memory, or OCD symptoms in 3 hours post-administration
Epperson et al. (1996)[98]	2 patients with trichotillomania	Randomized, crossover trial of 40 IU intranasal OT or placebo four times daily for 1 week each	No significant difference on any patient or clinician ratings of symptom severity
Epperson et al. (1996)[99]	7 patients with comorbid OCD and depression	Randomized, crossover trial of intranasal OT (40 IU or 80 IU) or placebo four times daily for 1 week each	No significant difference on any patient or clinician ratings of obsessive-compulsive symptoms, anxiety symptoms, or memory; small but significant decrease in Beck Depression Inventory scores in oxytocin group after acute administration, not sustained
Personality Disorders			
CSF Levels			
Lee et al. (2009)[100]	40 patients with personality disorder: 8 Paranoid, 3 Schizoid, 1 Schizotypal, 7 Borderline, 5 Antisocial, 3 Histrionic, 3 Narcissistic, 6 Obsessive-Compulsive, 2 Avoidant, 1 Dependent, 16 PD NOS	CSF OT levels	CSF OT levels were inversely correlated with Lifetime History of Aggression scores (p = 0.043); History of suicide attempt was independent predictor of significantly lower OT levels; Results were independent of specific diagnosis

Authors	Subjects	Method of Study	Main Findings
	(9 met criteria for more than one disorder) 14 HC		
Response to Exogenous OT			
Bartz et al. (2011)[101]	14 patients with borderline personality disorder 13 HC	Randomized, double-blind administration of single dose of 40 IU intranasal OT (N = 6 PD, 8 HC) or placebo (N = 8 PD, 5 HC)	PD patients, after OT administration, had significantly decreased trust of partner in cooperative game ($p < 0.05$) and were significantly more likely to defect in response to partner cooperation ($p < 0.05$); HC had opposite responses to OT
Simeon et al. (2011)[102]	14 patients with borderline personality disorder 13 HC	Randomized, double-blind crossover administration of 40 IU intranasal OT or placebo	Significantly greater attenuation of dysphoria after social stress task in PD group relative to controls after OT administration ($p = 0.04$); nonsignificant tendency toward greater attenuation of cortisol in PD group after OT administration ($p = 0.10$)

ACC, anterior cingulate cortex; ADHD, Attention-deficit/hyperactivity disorder; ASD, Autism Spectrum Disorder; BD, Bipolar Disorder; bid, twice daily; BSS, Bisulfite sequencing; CGI-I, Clinical Global Impression-Improvement score; CSF, Cerebrospinal fluid; ECT, Electroconvulsive Therapy; F, female; FBAT, Family-Based Association Test; fMRI, functional magnetic resonance imaging; GSAD, Generalized Social Anxiety Disorder; HAM-D, Hamilton Depression Rating Scale; HC, Healthy Controls; hNP, human neurophysin; IU, International Unit; M, male; MADRS, Montgomery and Asberg Depression Rating Scale; MDD, Major Depressive Disorder; mPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; NOS, Not Otherwise Specified; OCD, Obsessive-Compulsive Disorder; OT, oxytocin; OXT, oxytocin gene; OXTR, oxytocin receptor gene; PANSS, Positive and Negative Syndrome Scale; PD, Personality Disorderl; PTSD, Post-Traumatic Stress Disorder; PVN, paraventricular nucleus; qid, four times daily; SNP, Single nucleotide polymorphism; STAI-A, Spielberger State Anxiety Inventory-Anxiety scale; VABS, Vineland Adaptive Behavior Scale