



Title: The Role of Oxytocin in Psychiatric Disorders: A Review of Biological and Therapeutic Research Findings

Activity Date: This activity will be available as an online learning module starting August 30, 2013, and will be available for one year.

Activity Location: Online

Target Audience Statement: This CME activity is intended for psychiatrists.

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Learning Objectives: After completing this activity, the learner should be better able to:

- Identify the biological role of oxytocin in forming attachments.
- Evaluate the relationship between various neuropsychiatric disorders and oxytocin.
- Identify clinical implications of using oxytocin to treat various neuropsychiatric disorders.

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All faculty members in a position to control the content of this CME activity have disclosed that they and their spouse/life partners (if any) have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity.

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Method of Physician Participation in the Learning Process/Evaluation Method

Successful completion of this activity includes reading the entire article and successfully completing the post-quiz and an evaluation form.

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As you prepare to participate in this activity, please reflect on your practice and your patients and identify clinical challenges you hope to have addressed.

While participating in the training, identify ways you can use newly acquired knowledge, strategies, and skills to enhance patient outcomes and your own professional development.

Disclaimer

Clinicians should ensure that all diagnostic and therapeutic modalities are prescribed and used appropriately, based on accepted standards of care. Use of any drugs, devices, and imaging techniques should be guided by approved labeling/full prescribing information, best available evidence, and professional judgment.

Faculty have been instructed that their content should be fair balanced and based on best available evidence. The information presented in this activity is the responsibility of the faculty and does not reflect the opinions of the provider



The Role of Oxytocin in Psychiatric Disorders: A Review of Biological and Therapeutic Research Findings

David M. Cochran, MD, PhD, Daniel Fallon, MD, Michael Hill, BS, and Jean A. Frazier, MD

Learning Objectives: After participating in this educational activity, the physician should be better able to

1. Identify the biological role of oxytocin in forming attachments.
2. Evaluate the relationship between various neuropsychiatric disorders and oxytocin.
3. Identify clinical implications of using oxytocin to treat various neuropsychiatric disorders.

Oxytocin is a peptide hormone integral in parturition, milk letdown, 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, and 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 and thus pave the way for developing new therapeutic modalities. Articles were selected that involved human participants with various psychiatric disorders and that either compared oxytocin biology to healthy controls or examined the effects of exogenous oxytocin administration.

Keywords: anxiety, anxiety disorders, autism, humans, mood disorders, oxytocin, schizophrenia

Oxytocin is a peptide hormone that is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and is directly projected 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 bonding between mothers and infants and in mating pairs.³ Human studies have

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confirmed oxytocin's role as a social hormone that mediates many social behaviors involved in forming attachments.⁴ In healthy controls, oxytocin decreases both cortisol release and anxiety in response to social stress,⁵ reduces amygdala activity in response to fearful or threatening visual images⁶ 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 Ijzendorp and Bakermans-Kranenburg¹¹ 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. 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, a growing body of research has investigated the possible involvement of oxytocin in the pathophysiology of neuropsychiatric disorders that affect 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 birth²² and decreased

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) ²⁷ Green et al. (2001) ²⁸	59 males: 29 autism 30 healthy controls Age range = 6–11	Plasma levels of OT & 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 healthy controls (range = 0–2.72 pg/mL; mean = 1.16 ± 0.77 pg/mL; $p < .004$) Elevated OT levels were associated with lower VABS scores in autistic children Higher levels of OT precursor peptide in autistic disorder than in healthy controls
Jansen et al. (2006) ²⁹	24 subjects: 10 ASD (9M, 1F; mean age = 21.8 ± 2.0) 14 healthy controls (13M, 1F; mean age = 21.0 ± 3.4)	Plasma levels of OT before & after psychosocial stressor (public speaking)	No difference in OT response to stress Increased basal OT levels in adults with ASD ($F = 6.70$; $p < .05$) OT levels were not correlated with impairments in social interaction or communication, or with stereotyped behavior
Genetic studies			
Wu et al. (2005) ³⁰	195 Chinese Han autism proband-parent trios	FBAT of 4 SNPs within <i>OXTR</i> ; haplotype-specific FBAT	Significant association between autism & 2 SNPs: rs2254298 A ($Z = 2.287$; $p = .022$) & rs53576 A ($Z = 2.573$; $p = .01$) Number of haplotypes (in particular, involving rs53576) were significantly associated with autism
Jacob et al. (2007) ³¹	57 Caucasian autism proband-parent trios	FBAT of 4 SNPs within <i>OXTR</i> ; haplotype-specific FBAT	Significant association between autism & 1 SNP, rs2254298 G ($\chi^2 = 4.80$; $p = .03$) No haplotypes were significantly associated with autism
Lerer et al. (2008) ³²	152 Israeli ASD probands & their families	FBAT of 18 SNPs within <i>OXTR</i> ; haplotype-specific FBAT	Significant association between the following: ASD & 2 SNPs: rs2268494 ($p = .01$) & rs1042778 ($p = .01$) IQ & 2 SNPs: rs4686301 ($p = .003$) & rs1042778 ($p = .01$) VABS total score & 2 SNPs: rs4686301 ($p = .05$) & rs6770632 ($p = .03$) VABS subdomain scores & 8 SNPs: communication (rs2254298 [$p = .02$], rs4686301 [$p = .04$], rs2268490 [$p = .02$], rs237887 [$p = .04$] & rs6770362 [$p = .002$]); daily living skills (rs4564970 [$p = .04$], rs13316193 [$p = .02$], rs2254298 [$p = .03$], rs237888 [$p = .05$], rs237887 [$p = .02$] & rs6770632 [$p = .02$]); socialization (rs6770362 [$p = .02$]) Multiple haplotypes were significantly associated with ASD diagnosis

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Table 1			
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Authors	Subjects	Method of study	Main findings
Autism spectrum disorders			
Genetic studies			
Yrigollen et al. (2008) ³³	177 (93% Caucasian) ASD probands & their families	FBAT of 2 SNPs within <i>OXT</i> & 3 SNPs within <i>OXTR</i>	Significant association between the following: ASD & 1 SNP within <i>OXTR</i> , rs2268493 (p = 0.008) Stereotyped behaviors & 1 SNP within <i>OXT</i> , rs2740204 (p = .016) No associations remained significant after correction for multiple testing
Liu et al. (2010) ³⁴	Japanese subjects: 223 ASD probands & their families (FBAT) 65 unrelated ASD patients 440 unrelated healthy controls	FBAT of 11 SNPs within <i>OXTR</i> 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 = .023), rs2268491 T (p = .004), rs2254298 A (p = .001) & rs2268495 G (p = .032)
Tansey et al. (2010) ³⁵	436 Caucasian ASD probands & their families (Irish, Portuguese & UK samples)	FBAT of 18 SNPs within <i>OXTR</i>	Nominal association of 3 SNPs with ASD diagnosis in 1 sample that did not withstand correction for multiple comparisons: rs11720238 G (p = .03), rs7632287 G (p = .008) & rs4564970 C (p = .009)
Wermter et al. (2010) ³⁶	100 German ASD probands & their families	FBAT of 22 SNPs within <i>OXTR</i> ; haplotype-specific FBAT	Nominally significant association of 1 SNP & 1 haplotype with ASD that did not withstand correction for multiple comparisons: rs2270465 G (p = .02), rs237851-rs6791619-rs53576-rs237884 T-G-T-T (p = .007) Patients carrying this haplotype showed nominally significant impairments in social interaction & communication compared to noncarriers
Campbell et al. (2011) ³⁷	2333 (95% Caucasian) ASD probands & their families	FBAT of 25 SNPs within <i>OXTR</i>	Significant association between ASD & 3 SNPs that were also associated with measures of social-communication dysfunction (p values for ASD diagnosis on Autism Diagnostic Observation Schedule): rs2268493 T (p = .04), rs1042778 G (p = .04) & rs7632287 G (p = .007)

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Authors	Subjects	Method of study	Main findings
Autism spectrum disorders			
Epigenetic studies			
Gregory et al. (2009) ³⁸	Single male proband and brother, both with autism but only former with deletion in 3p25.3 containing <i>OXTR</i>	BSS of <i>OXTR</i> in peripheral blood cells to determine methylation status	Autistic brother of patient with <i>OXTR</i> deletion had hypermethylation of <i>OXTR</i>
	20 patients with autism (10M, 10F) 20 healthy controls (10M, 10F)	BSS of <i>OXTR</i> in peripheral blood cells to determine methylation status	Significant hypermethylation of <i>OXTR</i> regions in individuals with autism compared to controls
	Postmortem tissue from 8 autism patients & 8 healthy controls	BSS of <i>OXTR</i> in temporal cortex tissue to determine methylation status	Significant hypermethylation of <i>OXTR</i> regions in autism cases compared to controls
Response to exogenous OT			
Hollander et al. (2003) ³⁹ Hollander et al. (2007) ⁴⁰	15 subjects: 6 autism 9 Asperger's syndrome 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 OT (10–15 IU) or placebo over 4 hours	Significantly greater reduction in repetitive behaviors over time following OT (drug × time interaction: $F = 3.487$; $p = .027$) Increased retention of ability between trials to accurately identify effect of speech in auditory comprehension task if OT was received first compared to placebo being received first (time × treatment × order interaction: $Z = -2.134$; $p = .033$)
Guastella et al. (2010) ⁴¹	16 males with autistic disorder or Asperger's syndrome Mean age = 14.9 ± 2.4 (range = 12–19)	Randomized, double-blind, placebo-controlled, crossover challenge of intranasal OT (18 IU for ages 12–15, 24 IU for ages 16–19) or placebo	OT improved performance on RMET for 60% of participants ($t(14) = 2.43$; $p = .03$) Highly significant difference on easier items in the RMET ($t(14) = 4.39$; $p = .001$); no significant difference for harder items
Bartz et al. (2010) ⁴²	27 male healthy controls Mean age = 26.8 ± 7.0	Randomized, double-blind, placebo-controlled, crossover challenge of intranasal OT (24 IU) or placebo	OT increased accuracy of empathic rating of others' emotions only in those with high AQ scores (drug condition × AQ interaction: $b = 0.11$; $t(232) = 2.01$; $p < .05$)
Andari et al. (2010) ⁴³	26 subjects: 10 Asperger's syndrome 3 high-functioning autism 11M, 2F Mean age = 26 (range = 17–39) Mean IQ = 99 ± 23.5 13 healthy controls (age- & sex-matched)	Randomized, double-blind, placebo-controlled, crossover challenge of intranasal OT (24 IU) or placebo	OT increased participants' interactions with a cooperative player in a computerized ball-throwing game compared to noncooperative players ($Z = 2.04$; $p < .04$) OT significantly increased time spent gazing at the face in eye-tracking experiment, with significantly increased fixation time on the eye region ($Z = 2.12$; $p < .04$)

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Authors	Subjects	Method of study	Main findings
Autism spectrum disorders			
Response to exogenous OT			
Kosaka et al. (2012) ⁴⁴	1 16-year-old female with autistic disorder	Case report of administration of intranasal OT (8 IU once daily for 2 months)	Improvement in social behaviors noted: Aberrant Behavior Checklist score dropped from 69 to 15, with marked decreases in irritability & hyperactivity subscores CGI-Severity score improved from 6 ("severely ill") to 3 ("mildly ill") CGI-Improvement = 1 ("very much improved")
Anagnostou et al. (2012) ⁴⁵	19 adults with high-functioning autism or Asperger's syndrome 16 M, 3 F Mean age = 33.2 ± 13.3 Mean IQ = 107 ± 24	Randomized, double-blind, placebo-controlled trial of intranasal OT (24 IU twice daily for 6 weeks; n = 10) or placebo (n = 9)	OT group: Significant improvement in ability to identify emotions compared to placebo (p = .002) Significant improvement in World Health Organization Quality of Life Questionnaire emotional/social subscale (p = .031) Trend toward improvement on Repetitive Behavior Scale (p = .065) Nonsignificant improvement in Diagnostic Analysis of Nonverbal Accuracy, Social Responsiveness Scale, Yale-Brown Obsessive-Compulsive Scale & CGI
Schizophrenia			
Plasma/CSF levels			
Linkowski et al. (1984) ⁴⁶	24 subjects: 12 schizophrenia (9M, 3F) 12 age-matched neurological controls (8 hydrocephalus, 1 acoustic neuroma, 3 cerebral atrophy; 8M, 4F) Age range = 29–65	CSF hNP11 levels	hNP11 was higher in patients with schizophrenia (4.5 ± 1.2 ng/mL) than in controls (3.05 ± 1.4 ng/mL; t = 2.82; p < .01)
Beckmann et al. (1985) ⁴⁷	43 subjects: 28 males with schizophrenia, paranoid type (mean age = 30.6 ± 8.0) 15 healthy controls (13M, 2F; mean age = 35.0 ± 15.7)	CSF OT levels	OT was higher in patients with schizophrenia after haloperidol treatment (13.46 ± 5.96 pg/mL; p < .01) & in patients without neuroleptic treatment (10.03 ± 4.03 pg/mL; p < .05) than in healthy controls (7.11 ± 4.03 pg/mL)

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Authors	Subjects	Method of study	Main findings
Schizophrenia			
Plasma/CSF levels			
Legros et al. (1992) ⁴⁸	23 subjects: 9 male patients with schizophrenia 14 healthy controls	Serum hNP11 levels before & after apomorphine challenge	Basal levels of hNP11 were higher in schizophrenia (3.34 ± 0.04 ng/mL) than in healthy controls (0.92 ± 0.21 ng/mL; $p = .001$) No significant change in schizophrenia after apomorphine challenge compared to 2-fold increase in healthy controls Basal levels were higher in paranoid subgroup (5.15 ± 0.99 ng/mL; $n = 4$) than in nonparanoid subgroup (1.92 ± 0.61 ng/mL; $n = 4$; $p < .03$)
Glovinsky et al. (1994) ⁴⁹	66 subjects: 20 neuroleptic-treated patients 31 neuroleptic-withdrawn patients 15 healthy controls	CSF OT levels	No significant differences between groups ($p = .11$)
Goldman et al. (2008) ⁵⁰	22 subjects: 6 polydipsic, hyponatremic patients 4 polydipsic, normonatremic patients 5 nonpolydipsic, normonatremic patients 7 healthy controls	Plasma OT levels before & after stress induction	OT was 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, respectively; $p = .07$) OT levels were inversely correlated with anterior hippocampal volumes in structural MRI OT levels were correlated with patients' ability to correctly identify facial emotions ($r = 0.62$; $p = .02$)
Keri et al. (2009) ⁵¹	100 subjects: 50 with schizophrenia 50 healthy controls	Plasma OT levels	No significant differences in OT levels after neutral interactions with examiner OT levels increased significantly in healthy controls after trust-related interactions ($p < .001$) but not in patients with schizophrenia ($p > .5$) Significantly lower OT levels in patients after trust-related interactions ($p < .0001$) Low OT levels after trust-related interactions significantly correlated with negative symptoms as measured by PANSS score ($F(1,48) = 35.03$, $p < .0001$; $\beta = -0.65$; $R^2 = 0.42$)

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Authors	Subjects	Method of study	Main findings
Schizophrenia			
Plasma/CSF levels			
Rubin et al. (2010) ⁵²	108 subjects: 50 patients with schizophrenia (27M, 23F) 58 healthy controls (27M, 31F)	Plasma OT levels	No significant difference between patients & controls, or across phases of menstrual cycle in females Female patients: higher OT levels associated with lower PANSS total symptom, positive symptom & general psychopathology subscores ($p < .01$ for all); trend toward association with lower negative symptom subscore ($p = .06$) All patients: higher OT levels associated with better prosocial scores on PANSS ($p < .01$ for females; $p < .05$ for males)
Sasayama et al. (2012) ⁵³	48 subjects: 27 patients with schizophrenia 21 healthy controls	CSF OT levels	CSF levels did not differ significantly between patients & controls OT levels were significantly negatively correlated with second generation antipsychotic dose ($r = -0.49$; $p = .010$) & negative symptom PANSS subscore ($r = -0.47$; $p = .016$)
Genetic studies			
Souza et al. (2010) ⁵⁴	358 subjects (case-control): 179 patients with schizophrenia 179 healthy controls FBAT: 49 probands & their healthy parents	Case-control comparison of 7 SNPs within <i>OXT</i> & 13 SNPs in <i>OXTR</i> ; FBAT of same SNPs	FBAT analysis: <i>OXT</i> , rs2740204 T ($p = .027$) Case-control study: <i>OXTR</i> rs4813625 C ($p = .036$) & rs3761248 C ($p = .030$) None remained significant after correction for multiple testing
Souza et al. (2010) ⁵⁵	140 patients with schizophrenia treated with clozapine	Association of <i>OXT</i> & <i>OXTR</i> variants with symptom severity & response to clozapine	<i>OXT</i> rs2740204 G: significantly associated with treatment response ($p = .042$ after correction for multiple testing); nominally significant association with negative symptoms ($p = .01$ prior to correction) <i>OXTR</i> rs237885 T & rs237887 A: nominally significant association with severity of overall symptoms ($p = .014$ & $.033$, respectively, prior to correction) <i>OXTR</i> rs11706648 A, rs4686301 C & rs237899 G: nominally significant association with improvement of positive symptoms on clozapine ($p = .0002$, $.0002$ & $.039$, respectively, prior to correction)

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Table 1			
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Authors	Subjects	Method of study	Main findings
Schizophrenia			
Genetic studies			
Teltsh et al. (2011) ⁵⁶	Clan of 56 Arab-Israeli individuals 52 Arab-Israeli nuclear families (n = 276) Jewish case-control sample (n = 545)	Identified gene variants in <i>OXT</i> in individuals in clan with schizophrenia; then sought association with schizophrenia in this pedigree and in 2 larger population samples	Two variants of <i>OXT</i> were significantly associated with schizophrenia in initial clan studied: rs4813626 G (p = .002) & rs2740204 A (p = .00059) Opposite allele of one variant (rs4813626 A) was significantly associated with schizophrenia in nuclear family sample (p = .0055) & in men only in the Jewish case-control sample (p = .0006)
Montag et al. (2012) ⁵⁷	812 subjects: 406 patients with schizophrenia 406 healthy controls	Case-control comparison of 2 SNPs within <i>OXT</i> & 4 SNPs within <i>OXR</i>	Significant association of 2 <i>OXR</i> variants with diagnosis of schizophrenia: rs53576 A (p = .008) & rs237885 T (p = .025) (post hoc analysis revealed association with General Psychopathology PANSS subscores)
Montag et al. (2012) ⁵⁸	290 subjects: 145 patients with schizophrenia 145 healthy controls	Case-control comparison of 2 SNPs within <i>OXR</i>	No significant association of rs2254298 or rs53576 with diagnosis Within schizophrenia group, rs2254298 A was associated with higher levels of empathic concern in the Interpersonal Reactivity Index
Watanabe et al. (2012) ⁵⁹	1218 subjects: 544 patients with schizophrenia 674 healthy controls FBAT: 105 trios of patients with schizophrenia & their parents	Case-control comparison of 14 SNPs within <i>OXR</i> ; FBAT of same SNPs	No significant associations between any of 14 SNPs examined & the diagnosis
Response to exogenous OT			
Bakharev et al. (1986) ⁶⁰	45 male subjects with schizophrenia	Placebo-controlled study of OT for 2 nonconsecutive weeks (5 IU bid; 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) ⁶¹	19 patients with schizophrenia	Randomized, double-blind, crossover study; 3 weeks of OT (titrated to 40 IU bid) or placebo as adjunctive treatment to stable antipsychotic regimen	Significant reduction in PANSS & CGI-Improvement at 3-week endpoint compared to placebo (p < .001) Significant reduction in positive symptom subscore (p = .006) & negative symptom subscore (p = .023) at week 3

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Table 1			
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Authors	Subjects	Method of study	Main findings
Schizophrenia			
Response to exogenous OT			
Goldman et al. (2011) ⁶²	24 subjects: 5 polydipsic patients with schizophrenia 8 nonpolydipsic patients with schizophrenia 11 healthy controls	Randomized, double-blind order of administration of single intranasal dose of 10 IU OT, 20 IU OT, or placebo	Low dose OT: emotion recognition was significantly decreased in both patient groups ($p < .02$) High dose OT: emotion recognition was significantly improved in polydipsic patients only ($p < .01$)
Pedersen et al. (2011) ⁶³	20 patients with schizophrenia	Randomized, placebo-controlled, double-blind trial; intranasal OT for 2 weeks (24 IU bid; $n = 11$) or placebo ($n = 9$)	Significant reduction in PANSS total score ($p = .047$) compared to placebo; also significant reduction in multiple subscores Theory of Mind Picture Stories task: significant improvements in identification of second-order false beliefs ($p < .01$) & trend toward improvement in recognition of deception ($p = .08$)
Averbeck et al. (2012) ⁶⁴	Experiment 1, with 59 subjects: 30 with schizophrenia 29 healthy controls Experiment 2, with 21 patients with schizophrenia	Experiment 1: emotion-recognition task Experiment 2: double-blind, placebo-controlled, crossover study of effects of intranasal OT (single dose; 24 IU) on emotion-recognition task	Experiment 1: patients had significant deficit relative to controls in recognition of emotions ($p < .001$) Experiment 2: OT improved ability to recognize emotions ($p = .006$), but absolute effect was modest (58% correct vs. 54% correct); no significant difference on any individual emotion recognition
Feifel et al. (2012) ⁶⁵	15 patients with schizophrenia	Randomized, double-blind, crossover study; 3 weeks of OT (titrated to 40 IU bid) or placebo as adjunctive treatment to stable antipsychotic regimen	After 3 weeks of OT treatment, patients had significantly better performance on number of subtests of California Verbal Learning Test: total recall trials 1–5 ($p = .027$); short-delayed free recall ($p = .032$); total recall discrimination ($p = .020$)
Modabbernia et al. (2013) ⁶⁶	40 patients with schizophrenia	Randomized, double-blind, crossover study; 8 weeks of OT (titrated to 40 IU bid) or placebo as adjunctive treatment to stable risperidone treatment	OT group had significantly greater improvement on the PANSS: total score ($p < .001$; Cohen's $d = 1.9$); positive subscale ($p < .001$; Cohen's $d = 1.2$); negative subscale ($p < .001$; Cohen's $d = 1.4$); general psychopathology subscale ($p = .021$; Cohen's $d = 0.8$) No significant difference in side effects between the two groups
Mood disorders			
Plasma/CSF levels			
Legros et al. (1983) ⁶⁷	28 patients: 15 MDD 13 BD, currently depressed	CSF hNP11 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; $p < .001$)

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Table 1			
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Authors	Subjects	Method of study	Main findings
Mood disorders			
Plasma/CSF levels			
Linkowski et al. (1984) ⁴⁶	28 subjects: 8 patients with MDD 8 patients with BD, currently depressed 12 age-matched controls	CSF hNP11 levels	No difference between patients with MDD & controls BD patients had significantly higher levels ($p < .005$)
Frasch et al. (1995) ⁶⁸	24 subjects: 12 patients with MDD 12 healthy controls	Nocturnal plasma OT levels	OT levels were significantly lower in patients with MDD compared to healthy controls ($p < .05$)
Pitts et al. (1995) ⁶⁹	36 subjects: 19 inpatients with MDD 17 healthy controls	CSF OT levels	No significant difference between MDD & healthy controls
Van Londen et al. (1997) ⁷⁰	89 subjects: 52 patients with MDD 37 healthy controls	Plasma OT levels	No significant difference between MDD & healthy controls
Van Londen et al. (1998) ⁷¹	78 subjects: 48 patients with MDD 30 healthy controls	Plasma OT levels & motor activity during sleep	Plasma OT levels were not related to measures of motor activity in patients with MDD
Van Londen et al. (1998) ⁷²	49 patients: 8 BD, currently depressed 5 MDD with psychosis 36 MDD	Plasma OT levels & neuropsychological testing	No association between neuropsychological performance & OT levels
Anderberg & Uvnas-Moberg (2000) ⁷³	69 subjects: 14 patients with MDD & fibromyalgia 25 patients with fibromyalgia but no MDD 30 healthy controls	Plasma OT levels & measures of pain, stress & depression	Patients with MDD & fibromyalgia had significantly lower OT levels than patients without MDD ($p = .01$) or healthy controls ($p = .05$) Lower levels of OT in patients with self-reported high daily levels of pain, stress & depression Negative correlation between OT levels & scores for depression ($r = -0.41$; $p = .008$) & anxiety ($r = -0.46$; $p = .003$) Positive correlation between OT levels & scores for happiness ($r = 0.35$; $p = .03$)
Scantamburlo et al. (2005) ⁷⁴	50 subjects: 25 patients with MDD 25 healthy controls	Plasma hNP11 levels	No significant difference between MDD & healthy controls at baseline or in response to clonidine or apomorphine
Bell et al. (2006) ⁷⁵	60 patients with MDD	Plasma OT levels	Positive correlation between OT levels & temperament dimensions of reward dependence ($r = 0.425$; $p = .001$) & novelty seeking ($r = 0.264$; $p = .041$)

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Table 1			
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Authors	Subjects	Method of study	Main findings
Mood disorders			
Plasma/CSF levels			
Scantamburlo et al. (2007) ⁷⁶	25 patients with MDD	Plasma OT levels	Negative correlation between OT levels & HAM-D scores Negative correlation between OT levels & anxiety scores on State-Trait Anxiety Inventory
Cyranowski et al. (2008) ⁷⁷	34 subjects: 17 females with MDD 17 healthy controls	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 were correlated with depressive symptoms & anxiety symptoms
Ozsoy et al. (2009) ⁷⁸	72 subjects: 29 inpatients with MDD 11 inpatients with BD, currently depressed 32 healthy controls	Plasma OT levels	Significantly lower plasma OT levels in both MDD & BD, depressed ($p = .004$); difference was significant only in female patients No significant difference between MDD & BD, currently depressed Levels were not significantly affected by treatment with antidepressants or ECT
Parker et al. (2010) ⁷⁹	30 subjects: 11 patients with MDD 19 healthy controls	Nocturnal plasma OT levels	Significantly higher OT levels in patients with MDD, most apparent during nocturnal OT peak
Sasayama et al. (2012) ⁵³	38 subjects: 17 patients with MDD 21 healthy controls	CSF OT levels	CSF levels did not differ significantly between patients & controls No significant correlation of OT level with antidepressant dose or HAM-D score
Response to electroconvulsive therapy			
Scott et al. (1986) ⁸⁰ Scott et al. (1989) ⁸¹ Scott et al. (1991) ⁸²	25 patients (24 MDD; 1 schizoaffective disorder, currently depressed) 19 patients with MDD 17 patients with MDD	Plasma hNP11 levels	hNP11 levels increased after ECT & returned to baseline within 1 hour Peak response to ECT was greater in patients who recovered ($n = 16$) than those who did not Increase in hNP11 after first ECT treatment correlated with improvement in depression rating scales
Smith et al. (1990) ⁸³ Smith et al. (1994) ⁸⁴	20 patients with MDD	Plasma OT levels	Substantial & immediate increase in OT seen after the first treatment; significantly attenuated responses after third & fifth treatments No association between baseline levels or peak responses & clinical outcome

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Table 1			
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Authors	Subjects	Method of study	Main findings
Mood disorders			
Response to electroconvulsive therapy			
Devanand et al. (1998) ⁸⁵	55 patients with MDD	Plasma OT levels	Peak response after second treatment did not correlate with clinical response Peak response after ninth treatment had trend-level association with clinical response ($p < .07$)
Neuropathological studies			
Purba et al. (1996) ⁸⁶	16 subjects: 3 patients with MDD 3 patients with BD, currently depressed 2 depressive disorder NOS 8 healthy controls	Immunostaining of postmortem paraventricular nucleus for OT	Number of OT neurons in PVN of patients increased by 23%; no difference between MDD, BD & depressive disorder NOS
Meynen et al. (2007) ⁸⁷	18 subjects: 9 patients with MDD 9 healthy controls	Postmortem OT mRNA in-situ hybridization in paraventricular nucleus	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) ⁸⁸	377 subjects: 185 patients with MDD, BD-I, or BD-II 192 healthy controls	Genotyping for 2 SNPs within <i>OXTR</i>	MDD patients had a reduced number of A allele carriers at both SNPs: rs53576 (OR [A-carrier vs. GG] = 0.56; $p = .02$) & rs2254298 (OR [A-carrier vs. GG] = 0.55; $p = .04$) BD groups: no significant difference
Thompson et al. (2011) ⁸⁹	92 adolescent females Age range = 9–14	Genotyping of rs2254298 SNP of <i>OXTR</i>	Heterozygous (AG) females with maternal history of recurrent MDD reported significantly higher symptoms of depression, physical anxiety & social anxiety than homozygous females or females without maternal MDD history ($p < .05$)
Response to exogenous OT			
Pincus et al. (2010) ⁹⁰	17 subjects: 8 patients with MDD 9 healthy controls	Double-blind, placebo-controlled, crossover trial; single dose of intranasal OT (40 IU) vs. placebo	During an emotion-identification task, healthy controls showed decreased reaction times to task after OT administration, whereas patients with MDD had increased reaction times 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)

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Table 1			
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Authors	Subjects	Method of study	Main findings
Mood disorders			
Response to exogenous OT			
Scantamburlo et al. (2011) ⁹¹	Case report: 38-year-old male	Intranasal OT (8 IU 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; and after 1 more week, to 2 and 37, respectively Symptoms returned after stopping OT & resolved again on reintroduction of OT treatment
Anxiety disorders			
Plasma levels			
Hoge et al. (2008) ⁹²	46 subjects: 24 patients with GSAD 22 healthy controls	Plasma OT levels	No significant difference between patients & controls ($p = .8$) Higher social anxiety symptom severity was associated with higher OT levels ($R^2 = 0.21$; $p = .04$)
Hoge et al. (2012) ⁹³	67 subjects: 39 patients with GSAD 28 healthy controls	Plasma OT levels before & after a trust game	No significant difference between patients & controls at baseline ($p = .06$) Patients had significantly lower plasma OT levels at the endpoint after playing a trust game with a partner ($p = .025$)
Response to exogenous OT			
Pitman et al. (1993) ⁹⁴	43 Vietnam veterans with PTSD	Randomized, placebo-controlled trial of single dose of intranasal vasopressin (20 IU; $n = 13$), intranasal OT (20 IU; $n = 15$), or placebo ($n = 15$)	Nonsignificant tendency toward lower physiological response to personal combat-related imagery in OT group
Guastella et al. (2009) ⁹⁵	25 male patients with GSAD	Randomized, placebo-controlled trial of four doses of intranasal OT (24 IU; $n = 12$) 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 ($p = .008$) & performance ($p = .07$) as more improved than placebo group as sessions progressed
Labuschagne et al. (2010) ⁹⁶ Labuschagne et al. (2011) ⁹⁷	36 subjects: 18 male patients with GSAD 18 healthy controls	Randomized, placebo-controlled, crossover trial of single dose of intranasal OT (24 IU) or placebo	fMRI: GSAD patients had heightened amygdala activity when viewing fearful faces & heightened mPFC/ACC activity when viewing sad faces, which were both attenuated after receiving OT

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Table 1			
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Authors	Subjects	Method of study	Main findings
Obsessive-compulsive disorder			
CSF levels			
Swedo et al. (1992) ⁹⁸	43 children with severe OCD Mean age = 13.9 ± 3.0	CSF OT levels	OT levels were positively correlated with depressive symptoms (r = 0.33–0.40; p = .007–.03) Comorbid anxiety disorder was also associated with increased OT levels (p = .02) No correlation between OT levels & OCD symptoms
Leckman et al. (1994) ⁹⁹	83 subjects: 29 patients with OCD 23 patients with Tourette's syndrome 31 healthy controls	CSF OT levels	Increased levels in OCD patients compared to other groups, but statistically significant only in subgroup without a personal or family history of tic disorder OT levels were positively correlated with severity of OCD symptoms (r = 0.27; p = .02) in non-tic-related OCD group
Altemus et al. (1999) ¹⁰⁰	40 subjects: 14 patients with OCD 26 healthy controls	CSF OT levels	No significant difference between patients & controls
Response to exogenous OT			
Anseau et al. (1987) ¹⁰¹	Case report of hospitalized inpatient with OCD	4 weeks intranasal OT therapy (14.4 IU daily)	Dramatic reduction in OCD symptoms, though in context of developing hyponatremia & psychosis
Charles et al. (1989) ¹⁰²	2 case reports of patients with OCD	Intramuscular OT (10 IU daily) for 3 weeks or 2 years	No symptomatic improvement in OCD symptoms
Den Boer & Westenberg (1992) ¹⁰³	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 (13.5 IU qid for 6 weeks; n = 2)	No reduction in obsessions or compulsions in either group
Salzberg & Swedo (1992) ¹⁰⁴	3 patients with OCD	Two doses intranasal OT (8 IU) administered 90 minutes apart	No discernible changes in mood, memory, or OCD symptoms in 3 hours post-administration
Epperson et al. (1996) ¹⁰⁵	2 patients with trichotillomania	Randomized, crossover trial of intranasal OT (40 IU qid) or placebo for 1 week each	No significant difference on any patient or clinician ratings of symptom severity
Epperson et al. (1996) ¹⁰⁶	7 patients with comorbid OCD & depression	Randomized, crossover trial of intranasal OT (40 IU or 80 IU qid) or placebo qid 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 OT group after acute administration, but not sustained

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Table 1			
Continued			
Authors	Subjects	Method of study	Main findings
Personality disorders			
Plasma/CSF levels			
Lee et al. (2009) ¹⁰⁷	54 subjects: 40 patients with personality disorders (8 paranoid; 7 BPD; 6 obsessive-compulsive; 5 antisocial; 3 histrionic; 3 narcissistic; 3 schizoid; 2 avoidant; 1 dependent; 16 PD NOS (9 met criteria for more than one disorder)) 14 healthy controls	CSF OT levels	CSF OT levels were inversely correlated with Lifetime History of Aggression scores ($p = .043$) History of suicide attempt was independent predictor of significantly lower OT levels Results were independent of specific diagnosis
Bertsch et al. (2012) ¹⁰⁸	74 subjects: 34 female patients with BPD 40 female healthy controls Mean age = 24.4 ± 4.7	Plasma OT levels in follicular phase of menstrual cycle	Plasma OT levels were significantly lower in BPD group ($p < .001$) Significant negative correlation between OT levels & self-report experiences of childhood trauma ($r = -0.44$; $p < .001$); strongest association for emotional neglect & emotional abuse
Response to exogenous OT			
Bartz et al. (2011) ¹⁰⁹	27 subjects: 14 patients with BPD 13 healthy controls	Randomized, double-blind administration of single dose of intranasal OT (40 IU; $n = 6$ BPD, 8 healthy controls) or placebo ($n = 8$ BPD, 5 healthy controls)	BPD patients, after OT administration, had significantly decreased trust of partner in cooperative game ($p < .05$) & were significantly more likely to defect in response to partner cooperation ($p < .05$); healthy controls had opposite responses to OT
Simeon et al. (2011) ¹¹⁰	27 subjects: 14 patients with BPD 13 healthy controls	Randomized, double-blind, crossover administration of intranasal OT (40 IU) or placebo	Significantly greater attenuation of dysphoria after social-stress task in BPD group relative to controls after OT administration ($p = .04$) Nonsignificant tendency toward greater attenuation of cortisol in BPD group after OT administration ($p = .10$)

ACC, anterior cingulate cortex; AQ, autism spectrum quotient; ASD, autism spectrum disorder; BD, bipolar disorder; bid, twice daily; BPD, borderline personality disorder; BSS, bisulfite sequencing; CGI, Clinical Global Impression; 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; hNP, human neurophysin; IU, International Unit; M, male; MDD, major depressive disorder; mPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; NOS, not otherwise specified; OCD, obsessive-compulsive disorder; OR, odds ratio; OT, oxytocin; *OXT*, oxytocin gene; *OXTR*, oxytocin receptor gene; PANSS, Positive and Negative Syndrome Scale; PD, personality disorder; PTSD, posttraumatic stress disorder; qid, four times daily; RMET, Reading the Mind in the Eyes Test; SNP, single nucleotide polymorphism; STAI-A, Spielberger State-Trait Anxiety Inventory–Anxiety scale; VABS, Vineland Adaptive Behavior Scale.

oxytocin levels in the cerebrospinal fluid (CSF) of 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 caused healthy controls with more anxious attachment styles to remember their mothers as less caring, whereas those with less anxious attachments remembered their mothers as more caring.²⁵ Also, in males classified as having “insecure” attachments, oxytocin increased the level of attachment

security in the majority of participants.²⁶ Clearly, the interrelationship between oxytocin and an individual’s experience of early childhood attachment is complex, and it remains unclear to what extent this connection influences the role of oxytocin in the pathophysiology of psychiatric disorders.

This review summarizes in detail the evidence of oxytocin dysfunction and its therapeutic potential in various neuropsychiatric disorders. Studies were found by performing a PubMed search using Boolean combinations of *oxytocin* with

the following search terms: anxiety disorders, autism, mood disorders, personality disorders, psychiatry, and schizophrenia. Abstracts were reviewed, followed by detailed evaluations of all relevant articles, whose references helped identify additional sources. Only human studies in the English language were included, and the date range was restricted to publications from 1970 to the present.

Due to space considerations, specific information about single nucleotide polymorphisms (SNPs) and allelic variations in the various genetics studies is included in the text only as it pertains to the discussion of similarities and differences between the various studies. This detailed information can be found in Table 1, however, which provides a comprehensive picture of what is known regarding oxytocin genetics in psychiatric disorders. Inconsistencies in the table reflect the inconsistencies in the reviewed studies. Also due to space considerations, specific methodological limitations of individual studies are not presented in detail. Instead, the authors' synthesis of broader limitations extending across studies will be presented in the concluding section.

This article discusses published research studies of oxytocin in psychiatric disorders. Oxytocin 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} which correlate with core deficits in autism spectrum disorders (ASD). Oxytocin has thus been investigated both for its role in the pathophysiology of ASD and as a potential therapeutic target for these disorders.

Plasma Levels

Modahl and colleagues²⁷ found lower mean plasma oxytocin levels in children with autism compared to age-matched healthy controls. Elevated oxytocin levels were associated with higher scores on the Vineland Adaptive Behavior Scale (VABS) for the typically developing children but with lower VABS 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 oxytocin—inactive forms of oxytocin derived from the same prohormone as oxytocin itself—indicating a defect in peptide processing of oxytocin.²⁸

In sharp contrast, Jansen and colleagues²⁹ compared adults with ASD and healthy controls, and found that adults with ASD showed increased basal plasma oxytocin levels. Differences in oxytocin levels between these studies may be related to differences in development (adults versus children), diagnostic subgroups, or intellectual development. In the adult study, oxytocin levels did not correlate with impaired social interaction, communication, or stereotyped behavior as measured by the Autism Diagnostic Interview–Revised.¹¹⁴

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

Genetic Studies

Several studies have investigated the association between autism and genetic variants in genes encoding oxytocin and the oxytocin receptor. Wu and colleagues³⁰ reported a family-based association test 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 family-based association tests 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 and colleagues³¹ attempted to replicate this finding in Caucasian autism proband-parent trios. They were able to detect an association at rs2254298, but a different allele was associated with autism at this location than in the study by Wu and colleagues.³⁰ The authors postulated that an undiscovered genetic variant associated with autism may be transmitted along with rs2254298 but with different alleles in different populations.

Lerer and colleagues³² performed family-based association tests on all 18 identified SNPs within the *OXTR* region in Israeli participants with ASD, their parents, and unaffected siblings. They also evaluated how *OXTR* variants were associated, if at all, with intelligence quotient (IQ) and Vineland Adaptive Behavior Scale scores. SNP analysis revealed 2 SNPs associated 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 associated with ASD, IQ, and VABS scores.

Yrigollen and colleagues³³ 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 family-based association tests of 11 SNPs within *OXTR*; however, in a population-based, case-control analysis, differences were observed in allelic frequencies of 4 SNPs. Tansey and colleagues³⁵ 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 and colleagues³⁶ performed single-marker and haplotype family-based association tests 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, compared to noncarriers, in social interaction and communication as assessed with the Autism Diagnostic Interview–Revised. 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 and colleagues³⁷ performed family-based association tests on 25 SNPs in *OXTR* in over 1000 families. They reported association of 3 SNPs previously implicated in prior studies, and these markers were associated with various measures of social-communication dysfunction as assessed by the Autism Diagnostic Interview–Revised, Autism Diagnostic Observation Schedule,¹¹⁵ and Social Responsiveness Scale.¹¹⁶

Table 1 demonstrates the lack of consistency among 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. Given the heterogeneous nature of ASD, however, the associations with *OXT* and *OXTR* that are found across multiple studies indicate that this hormone system may indeed play some role in the pathophysiology of ASD.

Epigenetics

Gregory and colleagues³⁸ studied an autism proband containing an inherited deletion in chromosome region 3p25.3, which includes the oxytocin receptor gene. Interestingly, the proband had a brother with autism who did not inherit the deletion; however, bisulfite sequencing analysis demonstrated that a critical region previously shown to regulate expression of *OXTR*¹¹⁷ was heavily methylated in the affected sibling. The authors also performed bisulfite sequencing 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 postmortem temporal cortex from individuals with autism and age- and sex-matched controls. Again, hypermethylation was seen in the autism cases compared to healthy controls. Thus, even when no direct genetic evidence indicates alterations in oxytocin-related genes, the expression of these genes may be affected by epigenetic modification, providing 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 and colleagues^{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 four hours on the first day of testing, and received the other on the second testing day. In the first experiment,³⁹ severity of six repetitive behaviors was assessed at baseline and at several points during the infusion. A greater reduction in repetitive behaviors over time was present 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 \times treatment \times order effect for the comprehension of affective speech. During the first testing day, participants improved from baseline to endpoint regardless of whether they received placebo or oxytocin. During the second testing day, those who had received oxytocin the first day retained their high performance at baseline, and their performance did not change from baseline to endpoint. Those who received placebo during the first day first showed a drop in score at baseline, which then improved again over the course of oxytocin infusion. The authors interpret this result as demonstrating that oxytocin increases retention of social cognition.

Guastella and colleagues⁴¹ 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), which involves identifying emotion based on the 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 healthy adult males,⁹ intranasal oxytocin (24 IU) improved scores on difficult RMET items more than the easy items and showed a ceiling effect in the healthy controls. Bartz and colleagues⁴² measured baseline social competency in healthy adult males with the Autism Spectrum Quotient (AQ) and then, after administering intranasal oxytocin (24 IU) or placebo to participants, measured their empathic accuracy by having them rate the emotions of individuals in a video. 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 the low AQ and high AQ participants showed no difference in scores.

Andari and colleagues⁴³ performed a series of elegant experiments, reported together, with adults with ASD and healthy controls. The participants played a computerized ball-toss game with computerized players A, B, and 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 24 IU oxytocin or placebo prior to playing the game. In healthy participants more balls were thrown to player A than to 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 the ratings of healthy controls 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, whereas those classified as actively rejecting social contact tended to show little response to oxytocin. In a second experiment, 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 (i.e., computerized ball toss) were only weakly correlated with effects on face-perception tasks (i.e., the eye gaze), indicating that a different cohort of individuals tended to respond to oxytocin in the respective tasks. Oxytocin's effects therefore appear to differ across individuals and may have beneficial effects on different aspects of social functioning in different individuals.

Few reports have been published on the long-term daily administration of oxytocin in individuals with ASD. Kosaka and colleagues⁴⁴ reported the case of a 16-year-old female with ASD receiving 8 IU of intranasal oxytocin 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 and colleagues.⁴⁵ Nineteen adults with ASD (16 males aged 33.20 ± 13.29 years) received intranasal oxytocin (24 IU twice daily; $n = 10$) or placebo ($n = 9$) for six weeks. Oxytocin participants had a significant improvement in Reading the Mind in the Eyes Task 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 difference in Clinical Global Impression–Improvement or Social Responsiveness Scale scores in groups receiving oxytocin or placebo.

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 to date have been of single-dose administration. The one longer-term study shows some promise of a positive clinical effect, but the study was not appropriately powered to detect small to medium effect sizes. 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

Given that oxytocin affects cognition, memory, and social functioning, it has long been studied as having a potential role in the pathophysiology of schizophrenia. Preclinical mouse models have demonstrated that oxytocin has a 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 (hNP II) rather than oxytocin. hNP II 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 and colleagues⁴⁶ found greater CSF levels of hNP II in individuals with schizophrenia than in age-matched, nondepressed neurological controls. Beckmann and colleagues⁴⁷ reported similar findings of increased CSF oxytocin levels in adult males with paranoid schizophrenia compared to controls with nonspecific neurological symptoms. Likewise, Legros and colleagues⁴⁸ found increased basal levels of serum hNP II in male patients with schizophrenia compared to healthy male volunteers. Also, no change in hNP II levels was found in patients after an apomorphine (dopamine agonist) challenge compared to a twofold increase in hNP II in healthy volunteers. Importantly, basal hNP II was higher in the paranoid subgroup than in the nonparanoid subgroup. In contrast to the above findings, several studies reported no differences in CSF⁴⁹ or plasma⁵⁰ oxytocin concentrations between patients with schizophrenia and healthy controls.

Some studies have measured associations of plasma oxytocin levels with clinical measures in schizophrenia. Keri and colleagues⁵¹ measured plasma oxytocin levels in patients and controls after neutral and trust-related interpersonal interactions. No difference in oxytocin levels was identified 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 and colleagues⁵³ also found that plasma oxytocin levels were negatively correlated both with the use of second-generation antipsychotics and with negative symptom scores on the PANSS.

Rubin and colleagues⁵² measured plasma oxytocin levels and PANSS scores in patients with schizophrenia and in healthy controls. No difference in oxytocin levels was found between the groups or across phases of the 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 scores, and with a trend toward association with lower negative symptom scores. In all patients, higher oxytocin levels were associated with better prosocial scores on the PANSS.

In general, these studies present conflicting data about whether or not differences in oxytocin levels are 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 oxytocin levels (because of the blood-brain barrier), 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 *OXT* and *OXTR* variants with schizophrenia. Souza and colleagues⁵⁴ 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 and colleagues⁵⁷ also performed a case-control analysis of individuals with schizophrenia and healthy controls, 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 group⁵⁵ evaluated *OXT* and *OXTR* variants for association with symptom severity and response to clozapine in individuals with schizophrenia treated for a minimum of six months. One variant within *OXT* was associated with treatment response and nominally associated with negative symptoms. Variants in *OXTR* were associated with the severity of overall symptoms and with the improvement of positive symptoms on clozapine. The *OXT* variant had also been previously associated with stereotyped behaviors in autism.³³

Finally, Teltsh and colleagues⁵⁶ 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 large clan study, 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 *OXT* and *OXTR* 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 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 oxytocin levels and the inconsistent findings in genetic studies, the evidence is weaker for a clear dysfunction in the oxytocin system in patients with schizophrenia than it is for ASD.

Response to Exogenous Oxytocin

Although the evidence for dysfunction in the oxytocin system in schizophrenia remains equivocal, a line of evidence supports the possible therapeutic use of oxytocin in these disorders. Nearly four decades ago, Bujanow^{122,123} reported that after giving patients daily injections of IV or intramuscular oxytocin (10–25 IU), therapeutic effects were “favorable” and “rapid,” and that hospitalization was prevented. A decade later, Bakharev and colleagues⁶⁰ ran 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. The authors 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. Averbek and colleagues⁶⁴ administered intranasal oxytocin (24 IU) or placebo in a randomized, double-blind, crossover study to individuals with schizophrenia and healthy controls 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. Although the overall performance was improved on oxytocin, the absolute effect was modest, and no improvement was seen in recognizing any particular emotion.

Goldman and colleagues⁶² performed a detailed study in which they administered two different doses of intranasal

oxytocin (10 IU, 20 IU) or placebo to three groups: healthy controls and 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, 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 (due to the small sample sizes), it appears that the effects of oxytocin on emotion recognition are dose-, emotion-, and patient characteristic-dependent.

Feifel and colleagues⁶¹ performed a randomized, double-blind, crossover study of patients with residual symptoms. Patients were given three weeks of daily intranasal oxytocin (40 IU twice daily) or placebo as adjunctive treatment to their stable psychotropic regimens. Oxytocin reduced scores on the PANSS total score, PANSS positive symptoms subscale, and PANSS negative symptoms subscale (effect sizes ranging from 0.40 to 0.50) and on the Clinical Global Impressions-Improvement scale (effect size = 0.74) compared to placebo at endpoint. Feifel and colleagues⁶⁵ also reported that patients receiving the same course of oxytocin improved 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 and colleagues⁶³ conducted a randomized, placebo-controlled, two-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 in the placebo group, and included 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 identifying second-order false beliefs and trends toward improvement in recognizing deception.

Finally, Modabbernia and colleagues⁶⁶ reported a double-blind, placebo-controlled, eight-week 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 oxytocin's clinical effect.

OXYTOCIN AND MOOD DISORDERS

Oxytocin inhibits stress-induced activity in the hypothalamic-pituitary axis in rats¹²⁴ and plays an important role in the response to stress through its close association with corticotrophin-releasing factor.¹²⁵ It has therefore 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 indicates 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 and colleagues⁶⁷ measured CSF hNP11 levels in patients with MDD and patients with BD, currently depressed. Levels in those with MDD were no different from neurologic controls, whereas the bipolar depressed group had higher levels (replicated in Linkowski and colleagues).⁴⁶ Several studies demonstrate consistently that patients with MDD do not differ from healthy controls in CSF hNP11 levels,⁴⁶ plasma hNP11 levels,⁷⁴ CSF oxytocin levels,⁶⁹ or plasma oxytocin levels.^{53,70} Plasma oxytocin levels were also not correlated with measures of motor activity⁷¹ or neuropsychological testing results.⁷²

In contrast to these findings, Frasch and colleagues^{68,126} compared nocturnal plasma oxytocin levels in patients with MDD and healthy controls. Eighty-three percent showed a reduction of plasma oxytocin compared to 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-Moberg⁷³ reported lower levels in female patients with both MDD and fibromyalgia than in healthy controls or patients with fibromyalgia without MDD. Low oxytocin levels 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 and colleagues⁷⁸ reported decreased serum oxytocin levels in inpatients with MDD or BD, currently depressed, compared to healthy controls. Levels were decreased both pre- and post-treatment with antidepressants or electroconvulsive therapy (ECT), and were unaffected by

either treatment. The difference in oxytocin was also gender specific, with female patients having lower levels than female controls, whereas no difference was seen between the male groups. In this study, no difference was found between patients with MDD and those with BD, currently depressed. A single study⁷⁹ of small sample size (11 MDD, 19 healthy controls) reported an increase in nocturnal plasma oxytocin levels in patients with MDD compared to healthy controls, 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 and colleagues⁷⁶ found a negative correlation in patients with MDD between plasma oxytocin levels and Hamilton Depression Rating Scale 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 moderate the effects of oxytocin in depression. In a nuanced study of correlations with personality dimensions using the Temperament and Character Inventory in outpatients with MDD, Bell and colleagues⁷⁵ demonstrated a positive correlation of plasma oxytocin levels with the temperament dimensions of reward dependence and novelty seeking, indicating a relationship between temperament factors and oxytocin levels that may confound results in studies that fail to control for this relationship. Finally, using plasma levels, Cyranowski and colleagues⁷⁷ demonstrated that a group of women with MDD had greater variability in pulsatile oxytocin release during two one-hour experimental task sessions than a group of healthy controls, and greater oxytocin concentrations during a guided imagery task focused on attachment-related images. During this task, oxytocin concentrations were also positively correlated with clinician-observed depressive symptoms and with self-reported depressive and anxiety symptoms. These findings demonstrate that MDD may be associated with a dysregulation of oxytocin release that may be task dependent, with the consequence that measuring oxytocin levels at particular times or in different circumstances may produce conflicting results.

Response of Oxytocin Levels to ECT

In the wake of multiple reports that ECT for unipolar and bipolar depression increases oxytocin levels, researchers have been investigating the possible importance of oxytocin in the therapeutic response to ECT. Early reports identified an increase of approximately 50%–70% in plasma hNP11 levels within the first minute following seizure during ECT, with a return to baseline within 60 minutes.^{127,128} Scott and colleagues^{80,81} reported that peak plasma hNP11 response to ECT was greater in patients who recovered from depression than in those who did not, and that

the increase in hNP11 concentration correlated with improved scores on the HAM-D and Montgomery-Åsberg Depression Rating Scale. A later study by the same group replicated this effect,¹²⁹ which further demonstrated that it was the release of hNP11 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 hNP11 changed between the first and last treatment.

Studies of plasma oxytocin levels show an initial peak level after the first ECT, approximately ninefold higher than baseline^{83,84} and greater than the previously reported response of hNP11. In a study within the same group of patients, the initial increase in oxytocin level was approximately fourfold greater than the increase in hNP11.⁸² Also, unlike the response of hNP11, the increase of oxytocin was attenuated by the third treatment to an approximately fivefold increase over baseline.⁸⁴ Riddle and colleagues¹³⁰ demonstrated that the mean plasma oxytocin level shortly after ECT was greater after supra-threshold stimulation than after threshold stimulation. Similar to hNP11, no change was found in baseline plasma oxytocin 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 a study of patients with MDD,⁸⁴ no association was found between clinical outcome and either baseline plasma oxytocin levels or peak responses following ECT. In a larger study of patients with MDD,⁸⁵ peak responses of plasma oxytocin after the second treatment were not correlated with clinical response; however, a trend-level association was found 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 be partly modulated through its effects on the release of oxytocin and its related carrier protein, hNP11.

Neuropathological Correlations

Two studies^{86,87} have reported on neuropathological differences in oxytocin-related functioning in patients with mood disorders compared to healthy controls. Purba and colleagues⁸⁶ evaluated postmortem 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 and colleagues⁸⁷ performed quantitative oxytocin mRNA in-situ hybridization in the paraventricular nucleus of postmortem samples of patients with MDD and controls. They found an increase of oxytocin mRNA in melancholic depressive patients compared to nonmelancholic depressive patients and a trend toward higher oxytocin mRNA levels in the melancholic patients compared to controls. 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 and colleagues⁸⁸ studied *OXTR* in a cohort of adult patients with MDD, BD I, or BD II, and age-matched controls. No differences were identified between MDD patients and healthy controls in two SNPs that had previously been found to be associated with ASD. No difference was found between the BD group and the controls.

Thompson and colleagues⁸⁹ focused on the rs2254298 polymorphism because a previous study had shown an association between heterozygosity (AG) at this genetic site and 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 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 findings¹³¹ of different patterns of association between the rs2254298 genotypes and loneliness in adolescents compared to 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 administering oxytocin may have an effect on individuals experiencing depressive symptoms. Pincus and colleagues⁹⁰ enrolled adults with MDD and matched healthy controls in a double-blind, placebo-controlled, crossover trial with a wrap-around fMRI study. Each participant performed the Reading the Mind in the Eyes Task in the fMRI scanner. The experiment was repeated before and after administration of 40 IU intranasal oxytocin or placebo. Healthy controls showed decreased reaction time to the task after oxytocin administration, whereas patients with MDD had increased reaction time. No difference was found in the accuracy of response between groups or after administration of oxytocin. Oxytocin differentially activated the brain in the two groups during the RMET. In controls, oxytocin enhanced activation of the amygdala, caudate, inferior frontal, parahippocampal, and superior temporal regions. In individuals with MDD, oxytocin enhanced activation in the cingulate, inferior frontal, insula,

middle frontal, precentral, superior frontal, superior temporal, and supramarginal regions. This brief experiment found no effect of oxytocin on general mood state or depressive scores.

No randomized, placebo-controlled, long-term studies have been published on the effects of oxytocin on MDD. There is one case report of a 38-year-old man with MDD with multiple failed antidepressant trials who had a decrease in depressive and anxiety-related symptoms, as measured by a reduction in HAM-D and Spielberger State-Anxiety Inventory scores, during a three-week trial of adjunctive intranasal oxytocin (8 IU twice daily) while on escitalopram 20 mg daily.⁹¹

Given the suggestive preclinical evidence that oxytocin plays a role in the stress response, coupled with the evidence for a complex interrelationship of the oxytocin system and mood, larger clinical studies are needed on oxytocin in mood disorder patients. Currently, the lack of available data prevents any supposition about its potential role in treating 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 (OCD), and personality disorders.

Anxiety Disorders

Hoge and colleagues⁹² measured plasma oxytocin levels in patients with Generalized Social Anxiety Disorder (GSAD) and healthy controls. No difference in oxytocin levels was found between patients and controls. Within the GSAD sample, however, 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 group of healthy controls at baseline but lower oxytocin levels after completing a trust game with a partner.

Pitman and colleagues⁹⁴ 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. A trend toward lower physiological response to personal combat–related imagery was present 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 healthy males, 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 faces⁹⁶ and hyperactivity of the medial prefrontal cortex extending into the anterior cingulate cortex when viewing sad faces.⁹⁷ No differences between groups was found 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. No subjective change in mood or anxiety was reported by patients or controls following administration of oxytocin.

Guastella and colleagues⁹⁵ 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 five-session weekly group exposure therapy. Following each administration, the participants gave a speech in front of group members about increasingly difficult topics. In general, a reduction in self-reported symptoms was found 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 and no 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 healthy controls, 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 by administration in a broader array of contexts, potentially having an additive effect that more robustly alters overall symptoms and functioning.

Obsessive-Compulsive Disorder

Swedo and colleagues⁹⁸ found that CSF oxytocin concentration was positively correlated with depressive symptoms in children with severe obsessive-compulsive disorder. Comorbid anxiety disorder was also associated with increased CSF oxytocin levels. No correlation was found between oxytocin concentrations and OCD symptoms. Leckman and colleagues⁹⁹ compared patients with OCD, patients with Tourette’s syndrome, and healthy controls. They found increased CSF oxytocin levels in the patients with OCD compared to the other two groups, but the elevation was significant only 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 no correlations were found between ratings of

depression or anxiety and oxytocin levels. Altemus and colleagues¹⁰⁰ also measured CSF oxytocin levels in patients with OCD and healthy controls, and found no differences between the groups. The differences between these studies may have been due to small sample sizes, differences in participants, 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 four weeks of daily intranasal oxytocin therapy (14.4 IU).¹⁰¹ However, this patient also developed psychotic symptoms in the context of emerging 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 presented in two 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 None of these studies identified any effect on OCD symptoms, with only a small decrease in Beck Depression Inventory scores in the comorbid depression study. In short, no evidence supports the effectiveness of oxytocin in treating OCD, although the total number of patients studied is small ($n = 29$).

Personality Disorders

On the basis of animal experiments demonstrating a connection between socially aggressive behavior and oxytocin, Lee and colleagues¹⁰⁷ 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 healthy controls, 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 and colleagues¹⁰⁸ 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 healthy controls,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. Greater attenuation of stress-induced dysphoria was present in the BPD group relative to controls after oxytocin administration, and a trend toward greater attenuation of cortisol was present in the BPD group after oxytocin administration. In the combined sample the difference between stress-induced dysphoria after oxytocin versus placebo was predicted by the presence of childhood trauma, whereas the difference in stress-induced cortisol surge after oxytocin versus placebo was predicted by a measure of insecure attachment.

Bartz and colleagues¹⁰⁹ demonstrated that oxytocin may have very different, even opposite, effects in BPD patients than in healthy controls. It had been shown previously that in healthy controls, oxytocin administration increased trusting behavior in a social-dilemma game⁸ and increased the perceived trustworthiness of faces.¹³³ In healthy adults and adults with BPD, Bartz and colleagues 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 plays a game with a “partner.” BPD participants had decreased expectations of their partner’s cooperativeness following oxytocin administration (decreased “trust”), and they were more likely to defect in response to partner’s hypothetical cooperation even though their payoff would be less for defection. Healthy controls, by contrast, demonstrated increased “trust” and more cooperation in response to partner’s hypothetical cooperation following oxytocin administration, although neither of these comparisons reached statistical significance. Thus, whereas oxytocin in healthy controls 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 affects 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. The genetic risk associated with variations in *OXTR* also appears similar 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 to 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, whereas high-functioning adults with ASD have higher baseline levels, indicates that as yet poorly understood developmental and individual factors may 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 healthy controls. Likewise, oxytocin had differential effects in healthy controls on memories of maternal care and closeness, depending on the participant’s baseline level of anxious attachment.²⁵ 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, however, given the positive social response of oxytocin in individuals with ASD, who may be expected to be predisposed to have limited attachment capability. That said, even in ASD the evidence suggests 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 of some therapeutic benefit associated with the administration of oxytocin is heartening. Particularly in individuals with ASD and schizophrenia, some evidence suggests that oxytocin may affect the core deficits in these disorders, improving social cognition in autism and decreasing positive and negative symptoms in schizophrenia. More limited evidence is available indicating a 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. Given that intravenous dosing is not a practical clinical alternative, intranasal delivery is the only available method that allows for frequent dosing and a chance of crossing the blood-brain barrier. Nevertheless, 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 The matter of delivery is further complicated by the 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 (about 20 minutes); elevated levels of salivary oxytocin were measured for more than two hours after administration of a relatively small dose (16 IU) 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 such dosing results in pulsatile or sustained levels of oxytocin in the central nervous system. Critical research questions remain regarding the pharmacokinetics and pharmacodynamics of intranasal oxytocin that can be answered only 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—ones that 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 evidence suggests 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. These studies should provide a better 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. Nonetheless, the multiple studies indicating a possible link between polymorphisms and these disorders suggest 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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