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Potential of Oxytocin in the Treatment of Schizophrenia

Paul D. Shilling and **David Feifel**

Department of Psychiatry, University of California, San Diego, La Jolla, CA 92093

Abstract

Schizophrenia is a heterogeneous, debilitating disorder characterized by three distinct sets of clinical features: positive symptoms, negative symptoms and cognitive deficits. Extant antipsychotic drugs have been most successful at treating the positive symptoms of patients that suffer from schizophrenia but have minimal therapeutic effects on negative symptoms and cognitive deficits, which are the symptoms that best predict the poor prognosis of these patients. Therefore, there has been a major effort towards identifying compounds that alleviate these symptoms.

Oxytocin (OT) is a nonapeptide that regulates peripheral reproductive-relevant functions, and also acts as a neurotransmitter in the brain. Converging evidence from both preclinical and clinical research suggests that OT may have therapeutic efficacy for the positive symptoms, negative symptoms and cognitive deficits of schizophrenia. In the majority of the small-randomized placebo controlled clinical trials conducted to date, OT has shown particular promise in its potential to treat the intractable negative symptoms and social cognitive deficits exhibited by most of the patients with this debilitating disorder.

In this leading article, we summarize the clinical evidence relevant to 1) endogenous OT and schizophrenia, and 2) the putative therapeutic effects of OT on each of the three clinical domains.

Keywords

oxytocin; schizophrenia; positive symptoms; negative symptoms; cognitive deficits; antipsychotic

Introduction

Schizophrenia (SCZ) is a heterogeneous, debilitating disorder characterized by positive symptoms, negative symptoms and cognitive deficits. Positive symptoms comprise perceptual aberrations such as auditory and visual hallucinations, delusions such as fixed or false beliefs, and disorganized behavior or speech. Negative symptoms include deficits in motivation (avolition), anticipation of pleasure (anhedonia), social interaction (asociality), verbal communication (alogia), and affect. In addition, most people with SCZ also exhibit

Correspondence to: David Feifel, MD, PhD, Department of Psychiatry, University of California, San Diego Medical Center, 200 West Arbor Drive, San Diego, CA 92103-8218, (619) 543-2485 [Telephone], (619) 543-3738 [FAX], dfeifel@ucsd.edu.

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deficient cognitive processing further impairing their ability to function. Seven specific domains of cognitive impairment were identified by NIMH-MATRICS initiative in patients with SCZ including working memory, attention/vigilance, visual and verbal learning and memory, information processing speed, reasoning and problem solving, and social cognition [1]. Although positive symptoms are required for a diagnosis of schizophrenia, a subset of patients do not exhibit negative symptoms and/or cognitive deficits consistent with substantial clinical heterogeneity among patients meeting the diagnostic criteria for SCZ [2].

When taken consistently by patients with SCZ, current antipsychotic drugs (APDs) provide substantial relief from the positive symptoms. The mechanism of this effect is the ability of these drugs to bind and reduce neural transmission through D2 receptors in the mesolimbic pathway. Whereas this is considered the sole mechanism of action for first generation or 'typical' APDs (e.g., haloperidol), second generation atypical APDs (e.g., clozapine) have an additional mechanism of binding serotonin-2A (5HT2A) receptors and these newer APDs are associated with reduced extrapyramidal side effects and possibly modest increased efficacy against negative symptoms and cognitive deficits [3–8]. Unfortunately, current APDs have, at best, have produced minimal therapeutic effects on the negative symptoms and cognitive deficits associated with poor functioning and prognosis [9, 10]. Therefore, the development of medications aimed at alleviating the negative symptoms and cognitive deficits of SCZ, highly chronic disabling symptoms of this disorder, are of highest priority.

Recently, converging results from preclinical and clinical studies suggest that activation of the oxytocin (OT) system may produce therapeutic effects on all three of symptom domains of SCZ. OT is a nonapeptide released from the hypothalamus that is best known for its action on uterine contractions and lactation. Of relevance to its potential therapeutic effects in SCZ, OT exhibits neurotransmitter activity in the brain and recently has become strongly associated with positive regulation of affiliation and social cognition, in addition to its role in learning and memory, and stress [11].

In this article, we summarize clinical studies aimed at investigating 1) endogenous OT and SCZ, and 2) the potential for OT or OT-mimetics to provide relief from the positive symptoms, negative symptoms and the cognitive deficits that torment patients with this devastating disorder.

The role of OT in the CNS

Oxytocin a nine-amino acid peptide that is highly conserved across a wide variety of species [12, 13] and is best known for its role in regulating peripheral reproductive-relevant functions such as uterine contractions in parturition and lactation [14, 15]. In the mammalian brain, OT is also both a neurohormone and neurotransmitter [16]. It is structurally very similar to its sister peptide vasopressin, differing by only two amino acids in humans. OT is synthesized in distinct neurons in the paraventricular and supraoptic nucleii of the hypothalamus and released into portal circulation via hypothalamo-neurohypophyseal fibers terminating in the posterior pituitary and into specific brain regions such as the nucleus accumbens, and amygdala [17, 18] via axonal transport. In addition to its binding and subsequent action via the oxytocin receptor (OXTR), OT also has lower but functionally

significant affinity for vasopressin receptors, including the AVP-1A (V1A) receptor (the AVPR most abundant in brain) and AVP1B receptors [19]. In fact, OT binding to AVP1AR can contribute to OT's CNS relevant effects [20], and sometimes, is solely responsible, [21, 22]. In clinical or preclinical studies related to SCZ spectrum disorders the relative role of OXTR versus AVPRs has not been well elucidated. Readers should take note, that the experimental effects of OT described in this lead article, may be mediated by OXTR, one of the AVPRs, or both.

In addition to its well-known action as a neurohormone, OT also acts as a peptide neurotransmitter in the brain. However, the mechanisms of its central action differ somewhat from that of classical neurotransmitters. For example, in contrast to classic neurotransmitters, OT produces its effects via both axonal release from parvocellular neurons in the hypothalamic paraventricular nucleus into specific brain regions as well as through somatodendritic release into the CSF and subsequent diffusion (volume effects) in the brain. Neuropeptides such as OT unlike neurotransmitters do not have a reuptake system and can produce variety of effects via short-range diffusion in CSF and extracellular fluid [23, 16]. OT receptors have been localized to several areas associated with SCZ including subregions of the basal ganglia, central nucleus of the amygdala, substantia nigra, and lateral septal nucleus [24–26].

The functional significance of OXTRs was brought to light by [27] their discovery that the distribution and density of OXTRs in the ventral striatum (nucleus accumbens) contributed to contrasting social attachment styles (monogamous vs. promiscuous) in voles. This finding has significant translational relevance as differential distribution and density of OXTRs in reward relevant brain regions in humans may help to explain individual differences in social attachment behaviors. Dolan et al. using an oxytocin antagonist demonstrated that OT acts as a social reinforcement signal within the nucleus accumbens core in mice, where it elicits presynaptically expressed long-term depression of excitatory synaptic transmission in medium spiny neurons. This study also established a key role for serotonergic transmission via 5-HT1B receptors in the nucleus accumbens, in the processing of OT-mediated social reward [18].

Converging evidence suggests that OT interacts with several neurotransmitter systems in the brain including dopamine [28–30], glutamate [31–33] and serotonin [34] to produce some of its antipsychotic drug relevant behavioral effects. The preclinical studies supporting these interactions are reviewed elsewhere [57]. Clinical studies relevant to the potential role of OT in the etiology of SCZ are described in the next section.

Endogenous OT and Schizophrenia

Evidence for an inverse relationship between plasma OT (pOT) levels and symptom severity suggests that OT may contribute to the etiology of SCZ. For example, low pOT levels have been associated with more severe symptoms in all three domains of SCZ, although these findings have been most consistent for the negative symptoms and cognitive deficits. However, it is not completely clear if this relationship is causal, a consequence of the disease or a response to APD treatment. In addition, there is controversy regarding the relevance of

peripheral OT to OT in the CNS. Some reports do not support CSF OT concentrations as related to pOT levels bringing into question the potential relevance of peripheral OT levels to the behaviors of interest [35, 36]. But see [37] and for reviews see [38, 23]. Of particular interest, Quintana et al. cite evidence that activation of OT receptors in the heart by peripheral OT can moderate the effects of intranasal OT on social behaviors. [39].

In regards to the positive symptoms, there have only been a few reports and the findings have not been completely consistent. For example, female patients who had less severe positive symptoms and overall pathology also had higher pOT levels ([40] (Table 1). In contrast, the same group reported more recently, that more severe positive symptoms were related to higher pOT [41].

As opposed to the positive symptoms, many studies have addressed the relationship between the severity of negative symptoms and pOT levels and they have consistently found an inverse relationship between the severity of negative symptoms and levels of pOT and OT levels in CSF cerebrospinal fluid. For example, Jobst et al. [42] and Sasamyama et al. [43] reported more severe negative symptoms were related to lower pOT and lower CSF OT levels, respectively. In a more recent study, Strauss et al found that the severity of asociality in patients with SCZ can be predicted by lower pOT levels [44]. Consistent with these findings, Keri et al. reported that flattened affect and social withdrawal may be associated with decreased trust-related OT levels in SCZ [45]. Several genetic studies have provided further support that the OT system may contribute to the negative symptoms of SCZ. For example, Souza et al. 2010 [46] reported nominal association with the negative symptoms in patients with SCZ and an OT gene variant (rs2740204). More recently, Montag et al. detected significant association with negative symptom scores (PANSS) and OXTR variants rs53576 and rs237885 [47]. Furthermore, Haram et al. [48] found significant association between emotional withdrawal and the OXTR gene variant rs53576. It is very compelling that two independent genetic studies found significant association between negative symptoms and the same OXTR gene variant (rs53576).

Relevant to cognition, higher pOT levels have been associated with enhanced social cognition including more prosocial behavior in males and females [40], superior emotion recognition [49], perception of faces as happier by female SCZ and controls [50]. Also consistent with a role for endogenous OT in social cognition, higher pOT levels in patients with SCZ were associated with more avoidance of angry faces in an Approach-Avoidance task [51], better emotion recognition in controls and SCZ (females only) [52] and more accurate encoding of socially relevant information in SCZ [53]. Although they did not detect differences in pOT levels between SCZ and controls, Frost et al. reported that in addition to social cognition, superior processing speed and working memory were also associated with higher levels of pOT [54]. However, Rubin et al. reported that OT levels in patients with SCZ were not related to clinical symptoms or cognition [55, 41].

Findings from genetic studies have also consistently detected endogenous OT as a potential contributor to social cognitive deficits. In this respect, worse social perception, mentalizing and poorer performance on a social cognition index in patients with SCZ were significantly

associated with OXTR (rs2268493) variant [56] and the OXTR variant rs22544298 was significantly associated with empathic concern [57].

Preclinical Models of OT and Schizophrenia

Animal models of relevance to SCZ have limitations in their ability to model the disorder, especially the positive symptoms such as hallucinations and delusions. However, animal models have been an invaluable tool for identifying novel compounds with APD potential. In addition, animal models allow investigators to utilize powerful techniques that would be too invasive (e.g., in vivo brain sampling) in humans. A variety of animal models have been utilized to investigate the potential therapeutic–like effects of OT against all three symptom domains of SCZ. These studies have been reviewed elsewhere. Please see [58] for a recent review.

Therapeutic Effects of Exogenous OT on Schizophrenia

Initially a potential role for OT in alleviating the positive symptoms of SCZ was supported by the converging preclinical evidence that OT may counteract central hyperdopaminegia and hypoglutamatergia [59, 31]. In subsequent studies in healthy subjects administration of a single intranasal (IN) dose of OT was reported to enhance trust of strangers by healthy subjects [60, 61].

More recently, several small clinical trials designed primarily to investigate the potential of IN OT as to reduce SCZ symptoms have been published. However, each of these studies has investigated IN OT as add-on to standard APDs or non-pharmacological treatments aimed at improving social behavior. Thus, the gold standard approach to assessing the efficacy of a putative drug, a monotherapy randomized, controlled clinical trial has yet to be conducted, limiting the ability of the field to truly determine the inherent therapeutic properties of OT for SCZ.

To date, four small clinical trials designed primarily to investigate the potential of IN OT as an adjunct medication to stable doses of APDs, to further attenuate psychosis in SCZ, have been published (see Table 2 for a summary of OT clinical trials in SCZ). In the initial clinical trial, Feifel et al. performed a clinical proof-of-concept study of the therapeutic potential of OT by employing a randomized double blind placebo-controlled crossover design. IN OT given twice daily to patients with SCZ for three weeks significantly decreased positive subscale scores on the Positive and Negative Symptoms Scale (PANSS) [62]. The clinical significance of their findings was demonstrated by significant improvement in the Clinical Global Impression (CGI) scores. In addition, OT improved learning (California Verbal Learning Test) but not working memory (Letter Number Sequence) after 3 weeks of treatment [63]. In contrast, Michalopoulou et al. 2015 recently reported that a single dose of OT improved the “executive” component of working memory in patients with SCZ [64].

In a subsequent clinical trial by Pedersen et al [65], twice daily IN OT given to patients with SCZ for 2 weeks significantly reduced the PANSS positive subscale scores compared to IN placebo and produced a nearly significant reduction in the PANSS negative subscale ($P < 0.08$). This treatment regimen also improved cognitive deficits, i.e., identification of second

false beliefs and trends toward significant improvement in accurate recognition of deception and rating untrustworthy faces as trustworthy (Brune task). Modabbernia, et al. [66], In the largest human trial to date, reported that administration of twice daily IN OT to SCZ for eight weeks significantly improved PANSS total, positive and negative sub scores as early as 4 weeks after the initiation of OT treatment.

In the fourth trial, Lee, at al. [67] did not detect a significant change in Brief Psychiatric Rating Scale (BPRS) in patients with SCZ after administration of twice daily IN OT for three weeks. These negative findings, which were not consistent with the first three clinical trials could be related to the use of the BPRS. The overall score of this 18-item scale represents a summation of various aspects of psychosis. The 30-item PANSS, considered the gold standard in SCZ research, was used in the three studies reporting positive findings. In contrast to the BPRS, the PANSS items are readily categorized into separate subscores for positive, negative and general symptoms of SCZ. In contrast to their negative findings on the therapeutic effects of OT on positive symptoms, Lee et al. found that negative symptoms improved in a small group of patients, 3 weeks after the start of OT treatment. Neither Lee et al. nor Modabbernia et al. investigated the effects of OT on cognitive deficits.

Three additional clinical trials also measured changes in psychosis but as a secondary measure. These studies were designed to investigate the effects of IN OT on social cognition in SCZ. In the first of these studies, Gibson, et al. [68] found no improvement in PANSS positive scale scores after six weeks of twice daily IN OT compared to IN placebo. On the other hand, OT reduced fear recognition and the perspective-taking component of empathy (ER-40), as well as, PANSS negative subscale scores.

Based on converging evidence consistent with OT's potential as a "cognitive/plasticity enhancer," [69], the benefits of OT added to a potent psychosocial treatment has been investigated by a couple of research teams. For instance, Cacciotti-Salja, et al. reported adding twice daily IN OT or IN placebo to six weeks of social cognitive training in patients with early psychosis did not increase the positive effects of SCT beyond the effects of placebo. They also found no improvement of positive symptoms (measured with the Scale for the Assessment of Positive Symptoms, SAPS) beyond the social cognition training alone [70] and daily OT added to SCT did not add to the improvement in SANS scores after placebo. However, there was a positive correlation between the reduction of negative symptoms as measured by the Scale for Assessment of Negative Symptoms (SANS) and the volume of IN OT (total number of OT IN treatments) but not placebo, administered by patients with SCZ. In the second study, Davis et al. reported that OT given just before twice weekly sessions of a 6-week social cognitive training enhanced social cognitive benefits greater than placebo and this improvement in empathic accuracy lasted at least one month. However, they did not detect improvement in BPRS [71] or negative symptoms (CAINS) beyond those produced by SCT alone. As in all the studies reviewed here, these contrasting results may be due to different dosage or duration of OT treatment employed (see study details in Table 2), highlighting the great need for more studies aimed at identifying the optimal dose and time course of OT treatment.

In addition, a single dose of IN OT has been reported to enhance performance of patients with SCZ on many social cognitive tasks including deception, sarcasm, recognition of emotion, and empathy [72–77]. The effects of IN OT on social cognition in healthy subjects are reviewed in Evans et al. [78]. In these studies, a single administration of IN OT consistently enhanced the processing of social stimuli.

Recently, Shin et al. [79] in the first report of OT effects on neural activity associated with social cognition (facial emotion recognition) in SCZ found that a single dose of IN OT increased activity (FMRI) for happy faces while decreasing amygdala activity for fearful faces. These results are consistent with many other reports of alterations in amygdala activity in normal controls during emotional recognition tasks [80].

In summary, the robust ability of OT to facilitate trust toward strangers provides a potential mechanism for its therapeutic action on paranoid delusions (positive symptom). OT reduced positive symptoms in three out of four clinical studies designed to measure the effects of IN OT on psychosis in SCZ. However, OT-improvement of positive symptoms was not detected in three other studies aimed at testing the ability of OT to enhance social cognitive training or to improve social cognition. Importantly, six of the seven clinical studies that measured the effects of OT on negative symptoms provided evidence that OT may reduce negative symptoms. In the lone study that did not provide such evidence, Davis et al. [71], the lack of an effect of OT on the negative symptoms could have been due to the minimal OT treatment regimen (2 times per week), in contrast to the daily OT treatment regimen used in the other six studies. It is noteworthy that in contrast with animal studies [81–84], where chronic OT administration produced either no benefit or exacerbation of social interaction in rodents, these clinical studies reveal very promising effects of chronic daily OT on negative symptoms. Finally, both acute and chronic OT administration has consistently improved social cognition in both controls and patients with SCZ.

Conclusions

Patients with SCZ desperately need more effective treatments, especially for the negative symptoms and cognitive deficits that are incompletely treated by current APDs. The findings described in this review from the recent small randomized double blind placebo controlled add-on clinical trials and studies of the endogenous OT system in patients with SCZ are encouraging, though not completely consistent. Together, they suggest that OT may reduce the currently treatment resistant debilitating negative symptoms and social cognitive deficits, as well as the more treatment responsive positive symptoms. IN OT produced no significant adverse effects and was well tolerated across clinical studies. Despite these encouraging preliminary findings, many issues, still need to be addressed while optimizing OT or OT-mimetics to alleviate symptoms of SCZ-spectrum disorders.

The extant clinical trials collectively do not represent an adequate test of the therapeutic potential of OT for SCZ. For example, each trial has been small and only one dose of OT (range 48 – 80 IU/day) was administered as an adjunct therapy to already stable regimens of APDs. Therefore, the optimal time course, therapeutic OT dose, and dosing regimen for optimal treatment of all three clinical domains of SCZ has yet to be identified.

Significant limitations are inherent to add-on trials (see [85, 86]), and especially problematic is their inability to test the hypothesis that the added drug is an effective treatment for the clinical disorder of interest. Add-on trials are limited to testing whether the add-on drug plus the primary drug are more effective than the primary drug alone. Of particular concern, were studies in which OT was given as an adjunct to non-pharmacological interventions such as social cognition training, while patients were also on stable regimens of APDs, making it even more difficult to detect a therapeutic effect of OT.

The inclusion criteria, which requires patients exhibit significant symptoms (i.e., PANSS score) after being stabilized on an established APD is another serious limitation of the add-on study designs for IN OT in SCZ. These subjects at best have had an incomplete response to the primary treatment, i.e. APDs, and at worst, no response to the primary treatment. The incomplete responders will have decreased symptoms at baseline and, therefore, a limited range of symptoms to exhibit improvement to the add-on therapy compared to untreated patients (celling effect). As non-responders are often treatment resistent they are less likely to respond to any drug treatment compared to most patients with SCZ. As expected, drugs that have been tested as both add-ons and as a monotherapy, reveal less therapeutic effect sizes as add-on medications (e.g., [87]).

The gold standard approach to assessing the efficacy of a putative drug, a monotherapy randomized, placebo-controlled clinical trial has yet to be conducted, limiting the ability of the field to truly determine the inherent therapeutic properties of OT for SCZ. The optimal clinical utility of OT for SCZ may ultimately be as an adjunct to conventional APDs as it may not possess sufficient efficacy on some of the core-features of this disorder (e.g., positive symptoms) to be used as a monotherapy alternative to conventional APDs. However in order to effectively characterize the inherent potential clinical effects of OT for the various clinical features of SCZ, a monotherapy trial of OT in SCZ needs to be conducted.

Although it would be optimal to perform OT monotherapy clinical trials designed to investigate the therapeutic efficacy of OT against SCZ, it is unlikely that many IRBs will approve outpatient placebo-controlled monotherapy trials of an investigational drug in subjects with SCZ. Regarding OT, IRBs are especially cautious since its mechanism of action remains to be fully elucidated and APD monotherapy trials usually require hospitalization of subjects, at least during the initial study phase and during the drug washout [88]. In this respect, gaps in our knowledge about the drug properties of OT, described above and in more detail in a previous paper [89], should be elucidated before conducting a monotherapy trial.

An adequately powered test of the efficacy of OT as an adjunct to APDs would require a larger sample size than an OT monotherapy trial due to the reduced effect size associated with add-on studies. Considering the previously described limitations inherent in their add-on design, and administration of only one OT dose and small sample sizes, it is very promising that 3 out of 4 clinical trials designed to test the anti-psychotic effects of OT (versus social cognition effects) found that OT exhibited therapeutic efficacy against the positive symptoms of SCZ [62, 65–67]. It is also not very surprising that three recent studies designed to specifically investigate the therapeutic effects of OT on social cognition did not

detect improvement in positive symptoms or negative symptoms. The most encouraging results suggest that OT consistently had therapeutic effects on negative symptoms and cognitive deficits, the symptoms most in need of effective treatments. In this respect, 6 out of 7 small clinical trials found evidence that OT had some therapeutic efficacy against the negative symptoms and social cognitive deficits. The lone study that failed to detect any therapeutic effects of OT against cognitive deficits was unable to detect an OT improvement in cognitive deficits beyond the improvement produced by social cognition training alone.

Therapeutic effects of OT consistent with some of the findings reviewed here, could provide much needed hope to patients with SCZ and their families that OT may provide relief especially from the poorly treated and debilitating negative symptoms and cognitive deficits. The effective treatment of these symptoms by OT would likely lead to improvement in the poor prognosis characteristic of this disorder, hopefully allowing those suffering from SCZ to lead more fulfilling lives.

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Key Points

1. Current antipsychotic drugs have produced their greatest benefit in treating the positive symptoms of schizophrenia but have limited therapeutic effects on the negative symptoms and cognitive deficits in patients who suffer from this devastating disorder.
2. The convergent findings from recent small clinical trials and studies of the endogenous oxytocin system in patients with schizophrenia are encouraging, although not completely consistent. Together, they suggest that oxytocin may reduce the currently treatment resistant debilitating negative symptoms and social cognitive deficits, as well as the positive symptoms.
3. Despite these encouraging preliminary findings, many issues still need to be addressed while optimizing oxytocin or oxytocin-mimetics to alleviate symptoms of schizophrenia.

Table 1

The endogenous OT system in patients with schizophrenia: relation to symptom domains. Adapted from [58].

Authors	N	OT Parameter	Main Findings	Implications
Positive Symptoms				
Rubin et al. 2010 [40]	50 SCZ (27 M, 23 F) 58 CTL	pOT	Female patients with higher pOT levels had less severe positive symptoms and overall psychopathology	Sex differences in clinical course of SCZ [90, 91]. Estrogen and prolactin regulate OT and OXTR expression [92–95]
Souza et al. 2010 [46]	140 M and F SCZ	OT and OXTR SNPs	Variants in the OXTR (rs237887) were nominally associated with positive symptoms	Supports a role for OT system in regulating positive symptoms
Rubin et al. 2013 [55]	38 SCZ (24 M, 14 F) 38 CTL	pOT	pOT did not differ between patients and CTL and were unrelated to severity of positive symptoms	Discrepant with [40]
Rubin et al. 2014 [41]	57 SCZ (M 35 F 22) 34 SCZA (M 15, F 19) 75 BP (M 24, F 8) CTL (M 28, F 14)	pOT	pOT did not differ between patients and CTL and were unrelated to severity of positive symptoms	Does not support a role of endogenous OT in manifestation of positive symptoms
Negative Symptoms				
Keri et al. 2009 [45]	50 SCZ (16M, 34 F) 50 CTL	pOT	Low pOT after trust-related interactions were associated with negative symptoms	Suggests endogenous OT counteracts negative symptoms
Souza et al. 2010 [46]	Vide supra	OT and OXTR SNPs	An OT gene variant (rs2740204) was associated with clozapine response and was nominally associated with negative symptoms	The endogenous OT system may mediate the effects of APDs [96, 97]
Sasayama *et al.* 2012 [43]	27 SCZ, 17 MDD 21 CTL	cOT	More severe negative symptoms (PANSS) related to lower cOT	
Montag et al. 2013 [47]	406 SCZ (285 M, 121 F) 406 CTL	OT and OXTR SNPS	Significant association between OXTR variant rs237902 and negative symptoms scores (PANSS), and OTR variants rs53576 and rs237885 and SCZ	
Haram, et al. 2015 [48]	265 SCZ (Sex not indicated) 412 CTL (208 M, 204 F)	OT, OXTR, AVP, CD38 SNPS	Significant association between OXTR risk allele A in rs53576 and emotional withdrawal No significant associations between OT pathway gene variants and SCZ	More evidence for role for OT in the negative symptoms of SCZ
Strauss, et al. 2015 [44]	39 SCZ (28 M, 11 F) 21 CTL (14 M, 7 F)	pOT	pOT levels higher in SCZ compared to controls. Lower OT levels associated with greater severity of asociality in SCZ	
Jobst, *et al.* 2015 [42]	41 M SCZ 45 CTL	pOT	More severe negative symptoms, e.g., emotional and social withdrawal (PANSS), related to lower pOT	
Cognitive Deficits				
Goldman et al. 2008 [49]	15 SCZ (6 PHS, 4 PNS, 5 NNS), 7 CTL	pOT	pOT increased in PHS patients compared to PNS or NNSA or controls, and higher pOT associated with greater accuracy in rating facial emotions. pOT inversely correlated with anterior hippocampal volume	Along with [73], indicates potential of differential role of OT in various subtypes, especially PHS. PHS also exhibit impaired hippocampal function and structural

Authors	N	OT Parameter	Main Findings	Implications
				pathology in amygdala, and anterior and lateral hippocampus
Keri et al. 2009 [45]	Vide supra	pOT	CTL subjects exhibited elevated pOT after trust related interactions, whereas SCZ subjects did not	Suggest a defect in OT systems ability to respond to interactions promoting trust consistent with OT effects on facial affect recognition [72–75, 65, 68]
Rubin et al. 2010 [40]	Vide supra	supra pOT	In both sexes, patients with higher pOT exhibited more prosocial behaviors (PANSS)	Suggests endogenous OT promotes pro-social behavior
Rubin et al. 2011 [50]	48 SCZ (26 M, 22 F) 57 CTL	pOT	Higher pOT related to perceiving faces as happier in both female patients and CTL	Sex differences reported in other studies of pOT [98, 99] and in [100] but not other studies of IN OT [101, 102]
Rubin et al. 2013 [55]	Vide supra	pOT	pOT unrelated to cognition in SCZ	Association of endogenous AVP and worse cognition in untreated female but not male patients
Walss-Bass et al. 2013 [103]	60 SCZ (45 M, 15 F) 20 CTL	pOT	Significant correlations between social cognitive bias and pOT in control group and SCZ with delusions. Social cognitive capacity correlated with pOT in SCZ with delusions, only	
Rubin et al. 2014 [41]	Vide supra	pOT	Higher pOT associated with better emotion recognition in healthy controls but not in proband or relative group	
Davis et al 2014a [56].	74 SCZ (M 53, F 21)	OXTR SNPs	OXTR variant (rs2268493) was significantly associated with poorer performance on a social cognition index, as well as tests of mentalizing and social perception	
Frost et al. 2014 [54].	31 SCZ (Sex not specified), 21 CTL	pOT	Higher pOT associated with superior processing speed, working memory, and social cognition	
Brown et al. 2014 [51]	28 SCZ M	pOT	In an approach-avoidance task, patients with SCZ with higher pOT levels exhibited increased avoidance of angry faces	Suggested elevated levels of endogenous OT increased social awareness in patients with SCZ
Strauss et al. 2015 [52]	41 SCZ (Sex not specified), 22 CTL	pOT	Higher pOT levels associated with better emotion recognition in CTL and SCZ (female only).	Individual differences in endogenous OT predict emotion perception accuracy
Strauss et al. 2015 [53]	40 SCZ (28 M, 12 F) 22 CTL	pOT	SCZ had higher pOT compared to CTL Fewer false positives for concrete items on SCRT associated with higher pOT in SCZ	In SCZ, accurate encoding of socially relevant information predicted by pOT
Montag et al. 2012 [57]	145 SCZ (91 M, 54 F),145 CTL (79 M, F 66)	OXTR SNPS	OXTR variant rs22544298 significantly associated with empathic concern	
Domain Not Specified				
Linkowski, et al. 1984[104]	12 SCZ (9 M, 3 F), 12 CTL (8 M, 4 F)	Plasma Np1	Basal NpI levels were decreased compared to CTL	
Beckman et al. 1985 [105]	28 M SCZ, 15 CTL	cOT	cOT increased in patients with SCZ and higher in patients on APDs (butyrophenones)	Relevance of cOT to central function in patients on APDs - see [106]
Legros et al. 1992 [106]	9 M SCZ, 14 M CTL	Plasma Np1	Basal NpI levels were decreased compared to CTL	

Authors	N	OT Parameter	Main Findings	Implications
Mai et al. 1993 [107]	11 SCZ (sex not indicated) 10 CTL	Neurophysin staining in post mortem brain samples	Altered neurophysin staining in PVN, globus pallidus, substantia nigra SCZ brains	Primarily untreated patients so not due to effects of medication
Glovinsky et al. 1994 [108]	40 SCZ (31 M, 9 F) 15 CTL	cOT	cOT levels did not differ within subjects based on APD status (treated or withdrawn), nor between SCZ and CTL	
Souza *et al.* 2010 [109]	179 SCZ, 358 CTL	OT, OXTR genes	OT variants rs4813625 and rs3761248 nominally associated with SCZ	
Watenabe et al. 2012 [110]	1) Case-Control 544 SCZ (M 290, 254 F), 674 CTL (341 M, 333 F) 2) 105 family based trios consisting of patients (59 M, 46 F) and both parents	OXTR	No significant associations in either the case control or trio study. Meta analysis detected nominal significance between rs9840864 and SCZ	
Teltsh et al. 2012 [111]	1) Extended pedigree 25 SCZ spectrum, 31 unaffected family members 2) 52 families (90 SCZ, 96 unaffected) 3) 272 SCZ (177 M, 95 F), 273 CTL	OT, AVP	1) Two OT variants (rs4813626, rs2740204) and one AVP variant (AVP3011589) significantly associated with SCZ 2) One OT variant (rs4813626) significantly associated with SCZ 3) One OT variant (rs4813626) significantly associated in male SCZ	One SNP (rs4813626) in OT gene significantly associated with SCZ in all three samples. However, its minor and major alleles in samples 2 and 3 were opposite to the extended pedigree in sample 1.

Abbreviations: APD, antipsychotic drug; AVP, arginine vasopressin; CTL, controls; NNS, normonatremic nonpolydipsic schizophrenia; NP1, neurophysin for oxytocin; OT, oxytocin; cOT, cerebrospinal fluid oxytocin; pOT, plasma oxytocin; OXTR, oxytocin receptor; pOT, plasma oxytocin; PANSS, Positive and Negative Symptoms Survey; PHS, polydipsic hyponatremic schizophrenia; PNS, polydipsic normonatremic schizophrenia; PVN, paraventricular nucleus; SCZ, schizophrenia;, SCRT; Social Cue Recognition Test; UPSIT, University of Pennsylvania Smell Identification Test

Table 2

Intranasal oxytocin treatment trials in patients with schizophrenia stable on antipsychotic drugs: effects on positive symptoms, negative symptoms and cognitive deficits[2]. Adapted from [58].

Author	N	Dosing/Duration	Results:Positive Symptoms	Negative Symptoms	Cognitive Deficits
Acute Studies		All study designs			
Averbeck et al. 2011 [72]	Exp 1: 30 SCZ (24 M, 6 F), 29 CTL, Exp 2: 21 SCZ M	24 IU, single dose	NA	NA	OT treatment improved ability of patients to recognize most emotions (hexagon emotion discrimination test)
Goldman et al. 2011 [73]	13 SCZ, 5 PS (3 M, 2 F), 8 NPS (4 M, 4 F) 11 CTL	10 or 20 IU, single dose	NA	NA	10 IU dose caused decreased emotion recognition due to emotion overidentification. 20 IU dose improved emotion recognition PS vs. NPS, specifically around fear recognition
Fischer-Shofty et al. 2013a [74]	35 SCZ (31 M, 4 F), 48 CTL	24 IU, single dose crossover design	NA	NA	OT improved recognition of kinship (Interpersonal Perception Task)
Fischer-Shofty et al. 2013b [112]	30 SCZ (27 M, 3 F) 35 CTL	24 IU, single dose crossover design	NA	NA	OT facilitated recognition of fearful facial expression in patients and controls
Davis et al. 2013 [75]	23 SCZ, OT 11 M, PL 12 M	40 IU, single dose	NA	NA	OT improved perception of sarcasm, deception and empathy (EPTT, Eckman Facial Recognition Task)
Horta de Macedo, et al., 2014[113]	20 SCZ M 20 CTL	48 IU, single dose	NA	NA	Facial affect processing not improved by OT
Woolley et al. 2014 [76]	29 SCZ M 31 CTL	40 IU, single dose	NA	NA	OT improved controlled (ability to comprehend indirect expression of emotion, thoughts and intentions) but not automatic (emotional cues in voices, faces and body language) social cognition in SCZ
Michalopoulou et al. 2015 [64]	21 SCZ OT 11 M PL 10 M	20 IU single dose,	NA	NA	OT improved the “executive component” of working memory (Digispan)
Shin et al. 2015 [79]	16 SCZ M 16 CTL	40 IU, single dose cross over design	NA	NA	OT decreased amygdala activity for fearful faces and increased activity (fMRI) for happy faces (Emotion recognition test)
Guastella 2015 [77]	24 SCZ M	24 IU, single dose, cross over design	NA	NA	OT improved higher-order social cognition such as appreciation of indirect hints and recognition of social faux pas
Clinical Trials					

Author	N	Dosing/Duration	Results:Positive Symptoms	Negative Symptoms	Cognitive Deficits
Feifel et al. 2010 [62]	15 SCZ 12 M, 3 F	40 IU twice daily 3 weeks/crossover design	OT improved PANSS positive subscale and CGI after 3 weeks	OT improved negative subscale after 3 weeks	See [63]
Pederson et al. 2011 [65]	20 SCZ OT 9 M, 2 F PL 8 M, 1 F	24 IU twice daily 2 weeks	OT improved PANSS positive subscale after 2 weeks	OT improved PANSS negative subscale	Improvement in identification of second false beliefs and trends toward significant improvement in accurate recognition of deception and rating untrustworthy faces as untrustworthy (Brune task)
Feifel et al. 2012 [63]	See Feifel et al. 2010 [62]	40 IU twice daily 3 weeks/crossover design	NA	NA	OT improved verbal learning (CVLT) but not working memory (LNS) after 3 weeks
Modabbernia et al. 2013 [66]	40 SCZ 20 OT 17 M, 3 F 20 PL 8 M, 1 F	40 IU twice daily 8 weeks	OT improved PANSS positive subscale starting at 8 weeks	OT improved PANSS negative subscale after eight weeks	NA
Lee et al. 2013 [67]	28 SCZ OT 9 M, 4F PL 8 M, 7 F Included schizo-affective	20 IU twice daily 3 weeks	Positive symptoms (BPRS) not improved vs. PL after 3 weeks	Negative symptoms (BPRS) improved in small group of inpatients patients after 3 weeks	NA
Gibson et al. 2014 [68]	14 SCZ OT 6 M, 2 F PL 5M, 1 F	24 IU twice daily 6 weeks	Both OT and PL groups exhibited significant improvement in PANSS positive subscale after 6 weeks	OT improved PANSS negative subscale after six weeks	OT but not PL decreased fear recognition and perspective taking component of empathy after 6 weeks (ER-40)
Cacciotti-Saija et al. 2014 [70]	52 SCZ SCT + OT M 18, F 9 SCT + PL 18 M, 7 F	40 IU twice daily 6 weeks	OT did not improve positive symptoms (SAPS) beyond SCT when given in combination with 6 weeks of SCT	Increased use of IN OT, but not PL was correlated with lower SANS scores	Six weeks of daily OT added to SCT did not enhance the SCT greater than PL
Davis et al. 2014 [71]	27 SCZ SCT + OT M 13 SCT + PL M 14	40 IU twice weekly 6 weeks	OT did not improve positive symptoms (BPRS) beyond SCT when given in combination with 6 weeks of SCT	Six weeks of OT added to SCT did not improve negative symptoms (CAINS)	Six weeks of OT added to SCT enhanced social cognitive benefits (empathic accuracy) greater than PL, lasting at least one month

Abbreviations: BPRS, Brief Psychiatric Research Survey; CAINS, Clinical Assessment Interview for Negative Symptoms; CTL, controls; CVLT, California Verbal Learning Test; EPTT, emotional perspective taking task; ER-40, The Emotion Recognition 40; LNS, Letter Number Sequence; NPS, non poydipsic; PANSS, Positive and Negative Symptom survey; PL, placebo; PS, polydipsic; SANS, Scale for Assessment of Negative symptoms; SAPS, Scale for Assessment of Positive Symptoms; SCT, social cognitive test; SCZ, schizophrenia

[2]Several decades ago, investigators in the USSR published two letters [114, 115] describing open-label experience using OT to treat patients with “SCZ” and a small randomized study [116] of OT in “SCZ” subjects. These reports suggested that OT had therapeutic effects. However, these reports contain clinical descriptions and terminology that do not correspond to contemporary concepts of SCZ. Furthermore, the rigor of methodology and reporting is well below accepted current standards. These shortcomings significantly limit the value of these early reports to shed light on the effects of OT in SCZ