

## Article

## The Effect of Intranasal Oxytocin on Measures of Social Cognition in Schizophrenia: A Negative Report

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### ABSTRACT

Social cognition is impaired in patients with schizophrenia and is related to functional outcome. Neither current pharmacologic treatments for psychotic symptoms nor psychosocial interventions robustly improves measures of social cognition. Given this, the development of adjunctive treatments to improve functional outcome is a rational approach to treatment research in schizophrenia. The neuropeptide oxytocin is a candidate to treat deficits in social cognition due to its prosocial as well as anxiolytic effects. We report here results from a randomized, double-blind, parallel group 3 week clinical trial with daily administration of adjunctive intranasal oxytocin (20 IU twice daily) ( $n = 13$ ) or placebo ( $n = 15$ ). We examined the effect of oxytocin administration on measures of 4 domains of social cognition, as well as social functioning. After 3 weeks of oxytocin/placebo dosing, there was no significant difference favoring oxytocin between treatment groups in any outcome measure. These results add to the body of literature examining the effects of oxytocin on social cognition in schizophrenia. Further study is warranted.

### Open Access

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**KEYWORDS:** oxytocin; schizophrenia; social cognition

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### INTRODUCTION

Social cognition includes making inferences about other people's mental state, perception of emotions from facial cues, social cue perception, and reasoning about certain types of social information; all of these are impaired in persons with schizophrenia [1]. Social cognition

mediates the relationship between neurocognition and functional outcome in schizophrenia [2–6].

Current pharmacological treatments for symptoms of psychosis do not significantly impact social cognition. Therefore, targeting this domain with adjunctive treatments to improve functional outcome is a rational approach to treatment research in schizophrenia.

One candidate treatment in this regard is oxytocin (OT), a naturally occurring hormone, which has been associated with improving aspects of social cognition in humans, such as social bonding/positive interaction, trust, empathy, and emotional perception/memory [7,8]. Some studies have reported a positive relationship between plasma OT levels and social cognitive capacity such as prosocial behaviors or ability to perceive emotions in schizophrenia [9–15], while other studies reported no relationship between OT levels and social cognition measures [16,17]. Keri and colleagues [18] reported that schizophrenia patients exhibit a blunted OT response after trusting interaction compared to controls, suggesting a dysregulation of OT signaling in schizophrenia.

Clinical trials administering adjunctive OT to remediate symptoms and social cognition deficits have also yielded mixed outcomes [19–28]. Results from these studies overall show that OT may have some effect on negative symptoms, however our work found negative symptom improvement in inpatients only, suggesting the potential for contextual response or lack of adherence in the outpatient setting [25]. A recent meta-analysis of 12 randomized clinical trials of intranasal OT in patients with schizophrenia did not report overall improvements in social cognition or neurocognition [29]. However, a larger effect was found on high-level social cognition, such as theory of mind, compared with low-level social cognition such as social cue perception [29].

In addition, OT possesses anxiolytic, anti-stress effects [30,31], and exogenous administration may modulate anxiety symptoms and reduce fear and stress [32] in persons without schizophrenia. Although constructs separate from social cognition, it is well established that anxiety, stress, and poor social interaction are common in schizophrenia and predictive of poor functional outcomes. Therefore, studying the effects of exogenous OT administration on these symptoms would be valuable.

To this end, we studied the effect of repeated administration of OT on social cognition and social anxiety endpoints. We previously reported the results of this study with respect to the effect of repeated dosing of intranasal OT on positive and negative psychotic symptoms [25]. We explored four domains of social cognition capturing the breadth of this construct: Theory of Mind, emotion perception and recognition, attributional styles, and social knowledge.

## METHODS

The methods of this study have been outlined in detail in a previous publication [25]. Subjects: Twenty-eight participants with a diagnosis of schizophrenia or schizoaffective disorder (Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Axis I Disorders, Clinical version Structured Clinical Interview for DSM-IV (SCID) [33] who were inpatients or outpatients on a stable medication regimen participated in this clinical trial. Participants were excluded if they met DSM-IV criteria for substance dependence in last 6 months or DSM-IV criteria for substance abuse in past 30 days, were pregnant or lactating, had severe medical condition, history of polydipsia/hyponatremia, clinically significant rhinitis, or cognitive impairment severe enough to preclude informed consent as assessed by the Evaluation to Sign Consent(ESC) [34]. Participants were recruited from the Maryland Psychiatric Center's Treatment Research Program and Outpatient Research Program. This study was approved by the University of Maryland and National Institute on Drug Abuse Institutional Review Boards.

*Study Design/Experimental Procedures:* Following a two-week lead in phase, participants were randomized to three week treatment of adjunctive intranasal OT (20IU twice daily) ( $n = 13$ ) or matching placebo (PBO) ( $n = 15$ ), then followed with weekly study visits. Measures of social cognition and social outcomes were performed at baseline (BL) prior to study medication initiation and at endpoint (EP).

The Brief Psychiatric Rating Scale (BPRS), the Schedule for the Assessment of Negative Symptoms (SANS), the Clinical Global Impression (CGI), and the Calgary Depression Scale for Schizophrenia (CDSS) were performed to evaluate symptoms of psychosis, negative symptoms, overall function, and depressive symptoms. Symptom measures have been reported elsewhere [25].

Primary outcomes for social measures were the Mayer-Salovey Caruso Emotional Intelligence Test (MSCEIT) [35], Managing Emotions and Understanding Emotions components and the Maryland Assessment of Social Competence (MASC) [36]. The MSCEIT, Managing Emotions and Understanding Emotions components, have been used by others in schizophrenia research [37–39] and are the only social cognitive assessments to be a part of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery [40]. The MASC is a standardized evaluation that involves behavioral observation of role play tests in order to determine social competence in specific situations. In the role play test, the patient role plays for 3 min with a confederate who gives standardized responses. In the test, the responsibility to keep up the conversation and problem solve lies with the patient. The session is videotaped and rated for conversational content, nonverbal content and effectiveness (see Table 1). The MASC has been shown to have good discriminatory power for assessing overall social skill deficits among people with schizophrenia. Secondary outcomes included measures of

social cognition, quality of life, and social anxiety. These are listed in Table 1 with specification of the subtype of social cognition or anxiety measured.

*Data Analysis:* Analysis of covariance (ANCOVA) was used to compare changes between treatment groups at study end-point (EP) for social cognition and social functioning scores, controlling for age and baseline (BL) values in each treatment group, using the model. A mixed model was used controlling for age and BL values: outcome = BL primary outcome variable + age + treatment group. Since the only important difference between groups was mean age, with the OT group being significantly older ( $44.74 \pm 11.74$  vs.  $35.07 \pm 8.21$ ), age was used as a covariate in all analyses.

**Table 1.** Means (SD) for Measures of Social Cognition and Social Anxiety.

<b>Primary Social Cognition Assessments</b>						
<b>Assessment</b>	<b>Description of Test</b>	<b>BL OT</b>	<b>EP OT</b>	<b>BL PBO</b>	<b>EP PBO</b>	<b>Test</b>
<b>MSCEIT [35]</b>						
Managing Emotions Branch Score	emotional intelligence; ability to be open to feelings, modulation of emotions in self/others	87.1 (10.0)	85.1 (9.4)	80.7 (7.2)	80.7 (8.9)	$F = 1.64,$ $d_f = 1,23;$ $p = 0.21$
Understanding Emotions Branch Score	emotional intelligence; ability to understand emotional information	82.2 (12.4)	76.7 (9.2)	77.9 (9.8)	84.3 (10.4)	$F = 1.70,$ $d_f = 1,23;$ $p = 0.21$
<b>MASC [36]</b>						
Conversational Content	interpersonal social skill assessment; assess conversation	3.13 (0.75)	3.13 (0.76)	3.1 (0.71)	3.13 (0.77)	$F = 1.38,$ $d_f = 1,24;$ $p = 0.25$
Non-Verbal Content	interpersonal social skill assessment; assess non-verbal performance	3.13 (0.65)	2.92 (0.83)	2.93 (0.75)	2.98 (0.88)	$F = 1.66,$ $d_f = 1,24;$ $p = 0.21$
Effectiveness	Interpersonal social skill assessment; assess effectiveness performance	3.03 (0.62)	2.97 (0.79)	2.98 (0.73)	3.13 (0.80)	$F = 4.86,$ $d_f = 1,24;$ $p = 0.037$

Table 1. Cont.

<b>Secondary Social Cognition and Functional Outcome Measures</b>						
<b>Assessments</b>	<b>Description of Measure</b>	<b>BL OT</b>	<b>EP OT</b>	<b>BL PBO</b>	<b>EP PBO</b>	<b>Test</b>
Facial Emotion Identification Test (FEIT) [41]	emotional perception	12.0 (2.1)	11.92 (2.22)	11.36 (2.65)	11.15 (1.95)	$F = 0.07$ , $d_f = 1,22$ ; $p = 0.80$
Profile of Nonverbal Sensitivity (Half-PONS) [42]	social perception through nonverbal cues	73.8 (11)	69.0 (11.5)	72.2 (11.7)	76.7 (8.5)	$F = 3.08$ , $d_f = 1,17$ ; $p = 0.10$
Personal and Social Performance Scale (PSP) [43]	socially useful activities, personal and social relationships, self-care and disturbing and aggressive behaviors to assess functioning	48.2 (8.5)	50.2 (7.7)	50.2 (8.8)	52.1 (10.1)	$F = 0.06$ , $d_f = 1,24$ ; $p = 0.81$
Attributional Style Questionnaire (ASQ) [44]	event valence (positive or negative) and cause of event (internal or external)	16.3 (2.5)	16.5 (2.2)	15.7 (1.7)	15.4 (2.1)	$F = 0.60$ , $d_f = 1,21$ ; $p = 0.445$
Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ) [45]	enjoyment and satisfaction in various areas of daily functioning	41.7 (6.4)	40.31 (7.5)	34.8 (10.8)	34.0 (10.3)	$F = 0.2$ , $d_f = 1,24$ ; $p = 0.66$
Reading the Mind in the Eyes (RMET) [46] % accuracy	theory of mind	60.7 (17.1)	56.2 (17.7)	57.3 (10.6)	54.4 (12.2)	$F = 0.11$ , $d_f = 1,23$ ; $p = 0.74$
<b>Social Anxiety Assessments</b>						
<b>Assessment</b>	<b>Description of Measure</b>	<b>BL OT</b>	<b>EP OT</b>	<b>BL PBO</b>	<b>EP PBO</b>	<b>Test</b>
Social Interaction Anxiety Scale (SIAS) [47]	general fear and attitudes of social situations	30.1 (14.4)	26.4 (12.1)	33.9 (17.8)	26.1 (14.2)	$F = 0.23$ , $d_f = 1, 24$ ; $p = 0.64$
Brief Fear of Negative Evaluation (BFNE) [48]	concerns of being negatively evaluated by others	18.8 (7.4)	17.4 (7.2)	22.3 (8.6)	19.6 (7.2)	$F = 0.04$ , $d_f = 1,24$ ; $p = 0.85$

## RESULTS

Participants were primarily male (69% oxytocin (OT) and 73% placebo (PBO)) and white (77% and 53%, respectively). Baseline demographics, including sex, race, education, marital status, schizophrenia symptoms, smoking status, and placement (inpatient or outpatient) were similar between the two groups, with the exception of age (44.74 (11.74) years vs. 35.07 (8.21) years respectively). Age was used as a covariate in all analyses. No significant treatment effects were found between the OT-treated and PBO groups at the end of study for any primary social cognitive (Mayer-Salovey Caruso Emotional Intelligence Test (MSCEIT), Maryland Assessment of Social Competence (MASC)) or secondary social cognition or anxiety outcomes. Primary and secondary social cognition outcomes as well as social anxiety outcomes are listed in Table 1. A significant change in the study favoring placebo was found for the MASC effectiveness measure ( $F = 4.86$ ,  $d_f = 1,24$ ;  $p = 0.037$ ), however, this would not survive correction for multiple testing.

## DISCUSSION

No significant benefits in social cognition were found in this pilot clinical trial of 28 persons with schizophrenia treated with adjunctive intranasal oxytocin (OT) or placebo (PBO) for three weeks. These results add to the extant studies examining the use of OT for social cognitive endpoints in schizophrenia [19,20,22–24,26,27,49]. These previous studies used comparable doses of intranasal OT and had similar sample sizes, but focused on narrower measures of social cognition. The two largest trials ( $N = 52$  and  $N = 55$ ), used comparable doses of OT (40 IU twice daily for 6 weeks or 24 IU twice daily for 12 weeks). In one trial, OT was an adjunct to social cognitive therapy [20] and in the other it was an adjunct to antipsychotic treatment [27]. In both of these clinical trials, OT failed to improve social cognition measures [20,27].

The absence of an effect of OT on primary and secondary outcome measures may have been due to several factors including small sample size and a study population that was not selected for any particular level of social deficits. In addition, a three week study may have been inadequate to effect a change in these outcomes. However, the results of this study are important as they add to the extant body of literature examining the effects of intranasal OT on social cognition given the results of a recent meta-analysis suggesting that OT may not broadly improve overall social cognition or neurocognition, rather, it may improve more specific aspects of deficits in schizophrenia [29].

Single dose studies of intranasal OT have reported improvements in some aspects of social cognition [20,50–52]. However studies with repeated dosing of OT to patients with schizophrenia have not yielded robust improvements in social cognition [53,54]. Indeed, we did not see an effect in higher level social cognition as has been suggested in a

meta-analysis of randomized controlled trials of intranasal OT in schizophrenia [29]. The effect size reported in the meta-analysis was 0.2 (Hedges  $g$ ). Our power calculations were based on the MSCEIT and MASC. For our sample size enrolled we estimated in this pilot study a priori that with power=0.80 the effect size would need to be 0.84 to show group differences. For an effect size of 0.2, power was <0.80 and we were not powered to find between group treatment effects with this sample size. The calculated sample size for this power and effect size was 14 per group so we were not underpowered to detect an effect. A recent imaging study suggested that OT may improve social cognition in schizophrenia by reducing amygdala activation during emotionally-valenced social decision making [55]. Notwithstanding this, our findings added to the meta-analysis findings are highly suggestive of a lack of effect on repeated administration of OT in schizophrenia for robust improvements alone on any domain of social cognition. However, strategies to use OT with cognitive behavioral therapy or social skills training may be a more effective strategy [49]. These could be effective given the context dependent effect of OT [56] as well as the advances recently in cognitive behavioral therapy and other social skills strategies for schizophrenia [57]. Lastly, the optimal dosing of intranasal OT remains unknown. Endogenous OT receptor expression is altered in some brain regions such as the temporal cortex [58]. Repeated receptor activation often leads to receptor desensitization and or reduced membrane expression [59]. Therefore, the quantity delivered and its frequency may alter OT signaling in individuals with SZ who already have altered OT receptor expression in certain brain regions. More research needs to be done on how these variables affect behavioral outcomes.

#### **AUTHOR CONTRIBUTIONS**

MRL and HJW contributed equally to this work. They wrote the initial draft and managed the data analysis. RPM served as the statistician and helped in the design and analysis of the study. FL participated in the study design and the management and analysis of data. JL was the study coordinator and assisted in the design, implementation and dissemination. RWB was a coinvestigator that helped in the study design, implementation and writing. GPS and LHR were coinvestigators that helped with the study procedures and data analysis. DLK and MRL served as the study co-principal investigators and designed the study. DLK supervised all study activities and participated in the design, implementation and data analysis. All authors contributed to the paper writing and reviewed the final version.

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## CONFLICTS OF INTEREST

DLK has served as an advisor for XOMA and Lundbeck. RWB served on the advisory boards for Amgen, Astellas, Janssen Pharmaceuticals, Inc., NuPathe, Inc., Pfizer, Roche, and Takeda. He also serves as a DSMB member for Pfizer and Otsuka. RPM served as a consultant for Amgen. Other authors have no conflicts of interest to report.

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