Effects of oxytocin on empathy, introspective accuracy, and social symptoms in schizophrenia: A 12-week twice-daily randomized controlled trial

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ABSTRACT

The effects of intranasal oxytocin, a neuropeptide involved in prosocial behavior and modulation of neural networks underlying social cognition and emotion regulation, have been studied in schizophrenia. We tested the hypothesis that twice-daily intranasal oxytocin administered for 12-weeks would improve tertiary and exploratory outcomes of self-reported social symptoms, empathy and introspective accuracy from the Jarskog et al. (2017) randomized controlled trial. Sixty-eight stable outpatients with schizophrenia or schizoaffective disorder were randomized to receive oxytocin (24 IU twice daily) or placebo. Introspective accuracy was assessed with the Specific Level of Functioning Scale and the Interpersonal Perception Task. Empathy was assessed with the Interpersonal Reactivity Index (IRI), and social symptoms were assessed with the Liebowitz Social Anxiety Scale and the Green et al. Paranoid Thoughts Scales. Outcomes were assessed at baseline, six, and twelve weeks. Results demonstrated limited effect of oxytocin with some improvement on the IRI Perspective-Taking Subscale. No additional between-group differences emerged on self-reported symptoms, empathy, or introspective accuracy.

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1. Introduction

A promising psychopharmacological intervention for schizophrenia is the neuropeptide oxytocin (Rosenfeld et al., 2011). Oxytocin modulates networks involved in social cognition and emotion regulation and is shown to play a key role in social behaviors (Lee et al., 2009; Meyer-Lindenberg et al., 2011; Rosenfeld et al., 2011). Several studies have investigated the effects of adjunctive intranasal oxytocin in schizophrenia with mixed findings (Bradley and Woolley, 2017; Burkner et al., 2017; Cacciotti-Saija et al., 2015; Feifel et al., 2016; Mercedes Perez-Rodriguez et al., 2015; Oya et al., 2016).

To address heterogeneity in findings and the file drawer effect (Rosenthal, 1979), especially as documented in oxytocin treatment research (Lane et al., 2016), the present study presents tertiary (i.e., self-report measures) and exploratory outcomes (i.e., introspective accuracy or IA) from Jarskog et al. (2017). Previously, Jarskog et al. (2017) found limited effects of oxytocin on the secondary outcomes of social functioning (i.e., improvements in social skills) and negative symptoms but not on the primary outcomes of social cognition (i.e., emotion perception, theory of mind, attributional style). Given mixed findings and no

previous research of oxytocin effects on IA, investigation of self-report and IA outcomes in the present study are exploratory.

2. Methods

2.1. Study design, participants, and randomization

Individuals with a diagnosis of schizophrenia or schizoaffective disorder participated in a double blind, randomized treatment study between June 2011 and September 2014. Participants completed screening, baseline, and assessment visits at six and 12 weeks. Participants were randomized to twice-daily intranasal oxytocin or placebo stratified by sex and total PANSS score. The Institutional Review Board at the University of North Carolina at Chapel Hill approved all procedures. Participants were compensated for participation. See Jarskog et al. (2017) for a comprehensive description of study methods, adverse events, and tolerability.

2.2. Intervention

Participants continued established medication regimens and administered intranasal spray twice daily before morning and evening meals for 12 weeks (see Jarskog et al. (2017) for drug and dosage details). To

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assess adherence, study drugs were weighed prior to dispensing and upon return and participants completed a daily medication diary.

2.3. Introspective accuracy measures

IA is the ability to accurately judge one's own performance or impairment in terms of symptoms, cognition, functioning, and potential for achievement, and is a better predictor of functional outcomes compared with cognitive or functional performance in schizophrenia (Gould et al., 2015; Harvey and Pinkham, 2015; Harvey et al., 2017). Measures with two informant sources (e.g., self and an informant report or objective performance on a task) were considered sources of IA. Differences between self and informant assessment or task performance were calculated with lower difference scores reflecting better IA. The present study included two IA outcomes.

Individuals and an informant source completed the Specific Level of Functioning Scale (SLOF; Schneider, 1983) with higher scores reflecting better functioning. Between and within-group differences on SLOF scores are presented in Jarskog et al. (2017).The difference between self-reported SLOF scores and informant SLOF scores measured IA.

The Interpersonal Perception Task (IPT; Costanzo and Archer, 1989; Dane and Mark, 1993) is a measure of social perception processes. Videos of common social interactions were shown followed by multiple-choice questions. IPT task performance outcomes are presented in Supplementary Table 1. Participants were asked to indicate how many items they answered correctly. The difference between number of perceived correct responses and number of correct responses measured IA.

2.4. Self-report measures

Self-report measures included a measure of empathy, Interpersonal Reactivity Index (IRI; Davis, 1980; Davis, 1983), as well as two measures assessing symptoms, Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) and the Green et al. Paranoid Thought Scales (GPTS; Green et al., 2008). All self-report measures demonstrate good validity and have been used extensively with schizophrenia populations (Davis, 1983; Green et al., 2008; Liebowitz, 1987; Pallanti et al., 2004). The reliability of self-report measures in the present sample ranged from acceptable to excellent (Cronbach's αs 0.74–0.96).

2.5. Statistical analysis

Individuals receiving at least one dose of study medication and a post-baseline assessment were included in the present analysis. The effect of oxytocin on outcomes was analyzed using mixed models with random intercepts for each participant and fixed effects of visit, treatment, and treatment-by-visit interactions. An unstructured covariance pattern modeled correlations within participants over time. Least squares means for change from baseline were estimated using full information maximum likelihood. Unadjusted means are presented in supplementary materials (S2 and S3).
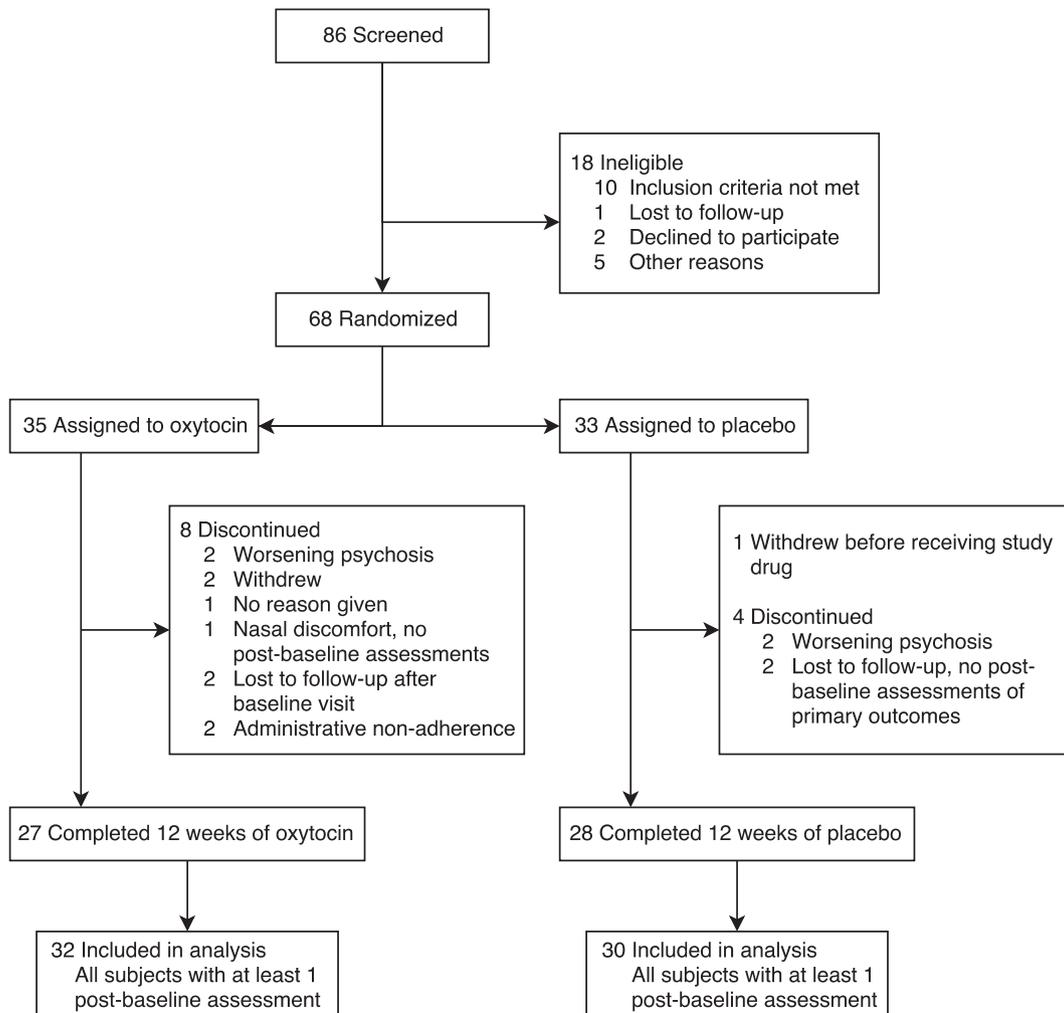
Fig. 1. Flowchart of study inclusion and data analysis adapted from Jarskog et al. (2017).

Table 1
Baseline demographic and clinical characteristics.

	Oxytocin N = 32	Placebo N = 30	p-Values
Age, years	41.4 ± 12.3	35.9 ± 12.5	0.09
Male % (N)	75 (24)	76.7 (23)	0.88
Education, years	12.6 ± 1.8	13 ± 2	0.41
Race % (N)			
White	46.9 (15)	53.3 (16)	0.61
Black	43.8 (14)	40 (12)	0.76
Other	9.3 (3)	6.7 (2)	0.70
Schizophrenia % (N)	59.4 (19)	65.5 (20)	0.55
Schizoaffective % (N)	40.6 (13)	34.5 (10)	0.55
WRAT standard score	93.63 ± 14.7	98.38 ± 14	0.20
PANSS			
Total	65.75 ± 13	68.5 ± 10.3	0.36
Negative	17.4 ± 4.6	18.67 ± 4.2	0.26
Positive	16.7 ± 4.7	17.2 ± 4.9	0.68
General psychopathology	31.7 ± 6.9	32.7 ± 5.8	0.54
Social[a]	10.5 ± 3.3	12.5 ± 3.6	0.03*
Medications % (N)			
1st generation antipsychotics	12.5 (4)	13.3 (4)	0.92
2nd generation antipsychotics	84.3 (27)	86.7 (26)	0.80
Antidepressants	46.8 (15)	33.3 (10)	0.28
Mood stabilizers	37.5 (12)	16.6 (5)	0.07
Benzodiazepines	18.7 (6)	30 (9)	0.30

Note: Data presented as mean ± standard deviation unless otherwise indicated. WRAT – wide range achievement test. PANSS – positive and negative symptom scale.

  * Significant differences between treatment groups on baseline demographics or clinical characteristics, $p < .05$.

  [a] PANSS items assessing social functioning: suspiciousness/persecution, hostility, passive/apathetic social withdrawal, uncooperativeness, and active social avoidance.

3. Results

3.1. Baseline characteristics, randomization, and treatment adherence

Fig. 1 provides a CONSORT flowchart of study screening and inclusion. Thirty individuals in the placebo group and 32 in the oxytocin group were included in the study.

Baseline demographic and clinical information are presented in Table 1. The placebo group had significantly higher levels of paranoia indicated by PANSS items assessing social functioning (i.e., suspiciousness/persecution, hostility, passive/apathetic social withdrawal, uncooperativeness, and active social avoidance) compared with the oxytocin group, $t(60) = 2.29$, $p = .03$. Age ($t(60) = 1.75$, $p = .09$) and taking mood stabilizers ($X^2(1) = 3.34$, $p = .07$) differed at a trend level. Subsequent analyses controlled for baseline PANSS social items and age given statistical and trend-level baseline differences. Mood stabilizers were not included in analyses given the relatively small proportion of the sample taking mood stabilizers. No additional significant between-group differences were observed at baseline.

Seventy five percent of individuals in the oxytocin group and 81.2% in the placebo group demonstrated excellent (80%–100%) or good (60%–80%) adherence to study drug based on bottle weights, adherence diaries, and any other available information. No significant between-group differences on adherence emerged.

3.2. Introspective accuracy

No significant differences on IA abilities measured by the IPT and the SLOF were observed between treatment groups (Table 2). However, improved IA, measured by the IPT task, was observed within the placebo group at 12 weeks ($M_{LS} = -1.7$, 95% CI $[-3.1, -0.3]$, $p = .02$).

3.3. Self-report measures

The oxytocin group ($M_{LS} = 0.4$, 95% CI $[-1.1, 1.9]$) exhibited improved IRI Perspective Taking at week 12 compared with the placebo group ($M_{LS} = -1.8$, 95% CI $[-3.3, -0.4]$, $F(1, 109) = 4.77$, $p = .031$) (Table 3). No other significant between-group differences were observed on the empathy subscales.

Significant within-group changes in empathy were only observed in the placebo group. The placebo group exhibited worse empathy abilities over time on the Emotional Concern Subscale of the IRI ($M_{LS} = -1.4$, 95% CI $[-2.7, -0.1]$, $t(109) = 2.2$, $p = .03$) at 6 weeks as well as on the Perspective Taking Subscale of the IRI ($M_{LS} = -1.8$, 95% CI $[-3.3, -0.4]$, $t(110) = 2.5$, $p = .02$) at 12 weeks.

No significant between-group differences were observed on self-reported symptom outcomes. Significant within-group changes in symptoms were only observed in the placebo group. Significantly better social avoidance measured by the LSAS Social Avoidance Subscale was observed in the placebo group at 12 weeks ($M_{LS} = -2.7$, 95% CI $[-4.6, -0.7]$, $t(106) = 2.7$, $p = .007$). The placebo group also demonstrated significantly better paranoia at 6 weeks measured by the GPTS Social Reference Subscale ($M_{LS} = -4.7$, 95% CI $[-8.2, -1.2]$, $t(108) = 2.7$, $p = .008$) and total score ($M_{LS} = -8.1$, 95% CI $[-14.6, -1.7]$, $t(108) = 2.5$, $p = .01$).

4. Discussion

Twice-daily administration of intranasal oxytocin showed limited evidence for improving self-reported symptoms, empathy, and IA in patients with schizophrenia. Individuals in the oxytocin group showed improvement on the Perspective Taking subscale of the IRI only but not on other self-reported outcomes and IA. Improvements in empathy in the oxytocin group extend findings from an oxytocin treatment study of a shorter duration (i.e., 6 weeks) where improvements on empathic perspective taking as measured by the IRI were also observed (Gibson et al., 2014).

No improvements in IA or self-reported symptoms of anxiety and paranoia were observed with oxytocin compared to placebo. These

Table 2
Change from baseline for introspective accuracy outcomes.

Introspective accuracy measure	Time point (wks)	LS mean change [95% CI]				Trt diff[b]
		Oxytocin N = 32		Placebo N = 30		
Interpersonal perception task	6	0.3	[−1.1, 1.7]	−0.5	[−1.9, 1.0]	0.8
	12	−0.5	[−1.9, 1.0]	−1.7[a]	[−3.1, −0.3]	1.2
Specific levels of functioning						
Interpersonal relationships	12	2.7	[−0.6, 6.0]	1.7	[−2.2, 5.6]	1
Social acceptability	12	−0.9	[−3.0, 1.1]	−0.5	[−2.8, 1.9]	−0.4
Activities	12	2.4	[−1.1, 6.0]	−2.0	[−6.4, 2.3]	4.4
Work skills	12	−0.01	[−2.2, 2.2]	−0.1	[−2.6, 2.4]	0.09
Total	12	4.6	[−1.6, 10.8]	−1.2	[−9.1, 6.6]	5.8

Note: Bold values indicate significant between group differences, $p < .05$.

  [a] Indicates significant within group differences, $p < .05$.

  [b] Values reflect differences between treatment groups, i.e., oxytocin group compared with the placebo group, at each time point. Models adjusted for baseline value, age, and baseline PANSS social items.

Table 3
Change from baseline for self-report outcomes.

Self-report measure	Time point (wks)	LS mean change [95% CI]				Trt diff[b]
		Oxytocin N = 32		Placebo N = 30		
Interpersonal reactivity index						
Fantasy	6	−0.8	[−2.4, 0.8]	−1.5	[−3.1, 0.1]	0.7
	12	−1.3	[−2.9, 0.4]	−1.1	[−2.7, 0.5]	−0.2
Emotional concern	6	−1.2	[−2.5, 0.1]	−1.4[a]	[−2.7, −0.1]	0.2
	12	−1.2	[−2.5, 0.1]	−1.1	[−2.3, 0.2]	−0.1
Perspective taking	6	−0.4	[−1.9, 1.0]	−1.4	[−2.8, 0.1]	1
	12	**0.4**	[−1.1, 1.9]	**−1.8**[a]	[−3.3, −0.4]	2.2
Personal distress	6	0.6	[−0.9, 2.1]	−0.4	[−1.8, 1.1]	1
	12	0.2	[−1.3, 1.7]	−0.3	[−1.8, 1.1]	0.5
Lieberman anxiety scale						
Total	6	−0.3	[−8.3, 7.7]	−1.6	[−9.7, 6.4]	1.3
	12	−1.3	[−9.6, 6.9]	−8.0	[−16.1, 0.2]	6.7
Fear	6	−0.2	[−4.6, 4.2]	1.7	[−2.7, 6.0]	−1.9
	12	−0.7	[−5.2, 3.8]	−1.6	[−5.9, 2.8]	0.9
Avoidance	6	−0.1	[−4.3, 4.0]	−3.7	[−7.8, 0.5]	3.6
	12	−0.6	[−4.9, 3.7]	−5.4	[−9.5, −1.3]	4.8
Social fear	6	−0.1	[−2.4, 2.2]	−0.1	[−2.4, 2.2]	0
	12	−0.6	[−2.9, 1.8]	−1.4	[−3.7, 0.9]	0.8
Social avoidance	6	0.4	[−1.6, 2.3]	−1.2	[−3.1, 0.8]	1.6
	12	−0.1	[−2.0, 1.9]	−2.7[a]	[−4.6, −0.7]	2.6
Performance fear	6	−0.1	[−2.6, 2.3]	1.7	[−0.7, 4.2]	−1.8
	12	−0.2	[−2.7, 2.4]	−0.2	[−2.6, 2.2]	0
Performance av	6	−0.5	[−2.9, 1.8]	−1.1	[−3.4, 1.3]	0.6
	12	−0.6	[−3.0, 1.8]	−1.9	[−4.2, 0.5]	1.3
Green paranoid thought scale						
Social reference	6	−0.3	[−3.8, 3.2]	−4.7[a]	[−8.2, −1.2]	4.4
	12	−0.3	[−3.8, 3.3]	−3.5	[−6.9, 0.1]	3.2
Persecution	6	−0.2	[−4.1, 3.9]	−3.4	[−7.4, 0.6]	3.2
	12	−0.9	[−5.0, 3.3]	−2.1	[−6.1, 1.8]	1.2
Total	6	−0.4	[−6.9, 6.2]	−8.1[a]	[−14.6, −1.7]	7.7
	12	−1.0	[−7.7, 5.7]	−5.6	[−12.1, 0.8]	4.6

Note: Bold values indicate significant between group differences, *p* < .05.

[a] Indicates significant within group differences.

[b] Values reflect differences between treatment groups, i.e., oxytocin group compared with the placebo group, at each time point. Models adjusted for baseline value, age, and baseline PANSS social items.

findings contrast previous support for oxytocin as a potential anxiolytic in schizophrenia (Heinrichs et al., 2003; Pedersen et al., 2011); no other previous studies have examined the effects of oxytocin on IA.

The present study had a number of limitations. First, although Jarskog et al. (2017) is one of the largest treatment studies of oxytocin in schizophrenia to date, limited power precluded investigation of potential moderators such as age and psychotropic medication (Bradley and Woolley, 2017). Second, investigation of IA outcomes may be underestimated due to heterogeneity in informant source (e.g., roommate, friend, family member). Finally, adherence to study drug was carefully monitored with over 75% of participants demonstrating good or excellent adherence. However, intranasal delivery likely introduced individual variability in drug absorption dose (Guastella et al., 2013).

In summary, we found little support for the effect of twice-daily intranasal oxytocin on self-reported social symptoms, empathy and IA. Presentation of these tertiary and exploratory outcomes should contribute to any potential file drawer effect in oxytocin treatment research.

Contributors
CAP, DLP and LFJ designed the study and wrote the protocol. TFH wrote the first draft of the manuscript. TFH performed statistical analyses with support from the Odum Institute and certifies the accuracy of the results. All authors contributed to the data interpretation, meaningful manuscript revision, and all authors have approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.09.013.

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