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A Double-Blind Randomized Controlled Trial of Oxytocin Nasal Spray and Social Cognition Training for Young People With Early Psychosis

Cristina Cacciotti-Saija[1], Robyn Langdon[2], Philip B. Ward[3], Ian B. Hickie[1], Elizabeth M. Scott[1], Sharon L. Naismith[1], Loretta Moore[1], Gail A. Alvares[1], Marie Antoinette Redoblado Hodge[4], and Adam J. Guastella[*,1]

[1]Brain & Mind Research Institute, University of Sydney, Sydney, Australia; [2]ARC Centre of Excellence in Cognition and its Disorders (CCD), Macquarie University, Sydney, Australia; [3]School of Psychiatry, University of New South Wales, Sydney, Australia; [4]Child Development Unit, The Children's Hospital at Westmead, Sydney, Australia

*To whom correspondence should be addressed; Brain & Mind Research Institute, University of Sydney, Building F, 94 Mallett Street, Camperdown, NSW 2050, Australia; tel: +61-2-9351-0539, fax: +61-2-9351-0855, e-mail: adam.guastella@sydney.edu.au

Social-cognitive deficits contribute to poor functional outcomes in early psychosis; however, no effective pharmacological treatments exist for these problems. This study was the first to investigate the efficacy of an extended treatment of oxytocin nasal spray combined with social cognition training (SCT) to improve social cognition, clinical symptoms, and social functioning in early psychosis. In a double-blind, randomized, placebo-controlled, between-subjects trial, 52 individuals (aged 16–35 years) diagnosed with an early psychosis schizophrenia-spectrum illness were recruited. Participants received oxytocin (24 International Units) or placebo nasal spray twice-daily for 6 weeks, combined with group SCT (2 × 1 hour weekly sessions for 6 weeks). An additional dose of oxytocin was administered before each weekly session. Assessments were conducted at baseline, post-treatment, and at 3-month follow-up. Primary outcomes included the Reading the Mind in the Eyes Test, the Scale for the Assessment of Positive and Negative Symptoms, and the Social Functioning Scale. Secondary outcomes included self-report and behavioral assessments of social cognition, symptom severity, and social functioning. Results showed that on all primary and secondary outcomes, there was no benefit of oxytocin nasal spray treatment in comparison to placebo. Exploratory post hoc analysis suggested that increased use of nasal spray was, however, associated with reductions in negative symptoms in the oxytocin condition only. This study represents the first evaluation of oxytocin treatment for early psychosis. Although results suggest no benefit of oxytocin treatment, results also highlight an urgent need to consider nasal spray delivery and dose-related variables for future clinical trials.

Key words: neuropeptides/emotion recognition/social behavior/schizophrenia

Introduction

Schizophrenia is characterized by a heterogeneous presentation of positive, negative, and disorganized symptoms.[1] In its most common form, schizophrenia presents with paranoid delusions, auditory hallucinations, and social deficits, such as poor theory of mind, emotion recognition, and attributional style.[2] Schizophrenia affects approximately 0.7% of the world's population,[1] with an onset typically between 18 and 24 years of age. The majority of clinical and psychosocial deterioration occurs within the first 5 years of onset, which can be exacerbated when left untreated.[3] As critical neurodevelopmental changes occur during late adolescence and early adulthood, there exists greater opportunities at this developmental point for effective intervention[4] to reduce illness recurrence and persistence[5] and disease burden.

First-line treatments for early psychosis combine pharmacological and psychosocial intervention. These include first-generation ("typical") and second-generation ("atypical") antipsychotic medications, effective in approximately 87% of first-episode patients.[6] These interventions, however, show little impact on negative symptoms and social functioning.[7] It has been suggested that this reduced efficacy may be due to a lack of influence of these interventions on social cognition.[8]

The neuropeptide and hormone oxytocin may provide a candidate treatment to treat social dysfunction in psychosis populations.[9] In nonhuman mammals, oxytocin administration facilitates social recognition, bonding and partner preference, and reduces anxiety associated with social threat.[9] In humans, a single dose of intranasal oxytocin enhances performance on a broad range of tasks associated with social cognition.[10] In schizophrenia, single-dose studies have demonstrated enhanced effects on

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facial emotion recognition[11,12] and higher level of social-cognitive task performance (eg, tasks assessing sarcasm, deception, and empathy)[13] in doses ranging between 10 and 40 International Units (IU). Benefits have also been reported after a course of oxytocin in schizophrenia. For example, 14 days of 24-IU oxytocin improved performance on a theory of mind task but not on other tests of social cognition.[14] Oxytocin also significantly reduces psychotic symptoms when administered over periods ranging from 2 to 7 weeks, in doses varying between 24 and 40 IU in chronic psychotic populations.[14–16] Furthermore, plasma oxytocin concentrations are lower in schizophrenia patients, correlating negatively with psychotic symptoms.[17,18] Lastly, oxytocin has demonstrated antipsychotic-like effects in preclinical investigations.[19]

Oxytocin may provide therapeutic benefit via 2 treatment methods. Firstly, psychiatric symptoms and social disability may improve directly through daily administration in this population. Secondly, oxytocin may combine with learning about social information to enhance outcomes of social cognition and skill development. In support of this approach, single doses of oxytocin in rodents[20] and humans[10] improve retention of social information.

In schizophrenia, targeted psychosocial interventions, such as Social Cognition and Interaction Training (SCIT), aim to teach social-cognitive skill and improve social impairments.[21] Specifically, SCIT comprises 3 treatment domains: (1) emotion recognition; (2) attributional styles and theory of mind skills; and (3) integration and generalization of skills to everyday situations. Such group-based programs significantly improve social-cognitive ability, social relationships, quality of life and social functioning in schizophrenia[22–24] and recently in early psychosis.[25] However, it remains to be determined whether social cognition training (SCT) can be enhanced with novel psychopharmacological interventions that are also hypothesized to enhance social cognition.[26] A recent study combined a single dose of oxytocin with each of 6 sessions of social-cognitive training in 27 patients with chronic schizophrenia (13 patients given oxytocin).[27] Results suggested that these single doses did not enhance social cognition overall on the primary outcome measure, although 1 of 5 social cognition secondary measures as assessed by a new empathic accuracy test was reported to improve. It is unlikely this improvement would survive statistical correction for multiple tests, however. Failure to show an overall effect in this population may be due to the limited doses of oxytocin (6 in total) or the smaller sample size.

The aim of this study was to investigate the efficacy of an oxytocin nasal spray treatment course, combined with targeted SCT, in an early psychosis population. We hypothesized that oxytocin may provide therapeutic benefit, either by reducing symptoms of the illness through repeated administration morning and night over the course of 6 weeks or by enhancing learning of the social cognition intervention through an additional dose before each SCT intervention session. It was hypothesized that compared with placebo, 24 IU of twice-daily oxytocin administration, combined with an additional dose before each SCT session, would improve social cognition, clinical symptoms, and social functioning in individuals with early psychosis.

Methods

Study Design

Participants were enrolled in a double-blind, randomized, controlled trial at the Brain & Mind Research Institute, University of Sydney, allocated to receive either oxytocin or placebo nasal spray, plus SCT. The study was approved by The University of Sydney Human Research Ethics Committees (13166) and was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12612000190808).

Participants

Participants were outpatients recruited from specialized tertiary referral services for the assessment and early intervention of mental health problems in young people.[28] Inclusion criteria were as follows:(1) aged between 16 and 35 years; (2) current or past diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder and; (3) within the first 3 years of treatment for psychosis. Exclusion criteria included the following: (1) current substance dependence on alcohol or drugs, (2) insufficient English language skills, (3) intellectual disability (IQ < 70), (4) history of a significant neurological disorder, and (5) florid psychotic or related symptoms likely to require immediate intervention (eg, suicidality). Medication was stabilized for at least 8 weeks prior to entering the study, and participants were required to notify study personnel of any changes in medication during the course of the trial. After complete description of the study, written informed consent was obtained. Participants were concurrently in treatment as usual, including the continuation of any standard routine clinical care.

Interventions and Adverse Reporting

Social Cognition Training. Participants underwent a 6-week group-based, targeted SCT program. The manualized intervention was delivered weekly (2 × 1 hour consecutive sessions) in small groups of 6 to 8 participants for 12 sessions. Groups were led by a clinical psychologist (C.C.S. and A.J.G.) and facilitated with a training psychologist.

The intervention was based on previous research,[21,22,29,30] addressing 4 domains of social-cognitive impairment: emotion recognition, social perception, theory of mind, and attributional style. Three modules were the focus of

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4 sessions including: (1) emotion recognition training, involving identification of micro-facial expressions and vocal-cues in 6 basic emotions, while considering social context such as nonverbal cues; (2) understanding intentions, beliefs, and perspectives of others via intention-inference tasks (eg, false belief) and pragmatic language tasks (eg, faux pas); (3) correcting attributional biases by avoiding "jumping to conclusions" and making hostile attributions; and (4) skill integration and generalization to everyday life situations. Sessions involved a combination of group learning activities (70% of total session time) and computer-based training tasks (30% of session time) completed in pairs similar to those described elsewhere.[31] To ensure a youth focus, emphasis was placed on facilitating rapport and analyzing social behavior in popular film and culture. A treatment evaluation questionnaire was administered at the end of the group program assessing the extent to which participants found the intervention useful at improving their social understanding and behavior. Treatment acceptability and tolerability were examined using recruitment, attendance, and attrition rate data.

Nasal Spray Administration. Nasal sprays were developed and randomized by a compounding chemist with an identical placebo containing all ingredients except the active oxytocin (all sprays contained sorbitol, benzyl alcohol glycerol, and distilled water, contained within an amber 7-ml glass nasal spray with metered dose pump). Nasal sprays were labeled with sequential numbers; blocking was in sets of 6 (3 active and 3 placebo sprays) in a randomly generated order. Research staff conducting assessments, and participants, were blind to treatment allocation. Nasal sprays were allocated to participants sequentially and stratified according to gender by an independent research assistant (G.A.A.).

Participants received 6 weeks of intranasal oxytocin (24 IU) or placebo, administered twice-daily. Participants were instructed to administer 2 sprays (1 per nostril) morning and night, with each spray containing 12 IU (50 µl of liquid), using published procedures.[32] An additional 24 IU was administered 15 minutes prior to each weekly session. To monitor compliance, participants were asked to keep a diary, to record date and time of each nasal spray administration, and return all used nasal sprays, for analysis of the amount of spray used. To assess for any adverse effects, a side-effects checklist was completed at the end of treatment, with any reported side-effects rated as none, mild, moderate, or severe. A safety medical monitoring board (comprising of I.B.H., P.B.W., and others) oversaw adverse events.

Diagnostic Assessments

The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision Axis I Diagnosis–Patient version was administered to confirm diagnosis.[33] To estimate full-scale IQ, the 2 subtest version of the Wechsler Abbreviated Scale of Intelligence was conducted.[34] The Opiate Treatment Index was used to screen for substance use and/or dependence.[35]

Outcomes

Outcome measures were obtained at baseline, post-intervention, and 3-month follow-up by assessors blind to treatment allocation. No assessments were conducted after drug administration on the same day.

Primary Outcomes. Primary outcomes assessed 3 domains (social cognition, symptom severity, and social functioning): the Reading the Mind in the Eyes Test (RMET),[36] the Scale for the Assessment of Positive and Negative Symptoms (SAPS and SANS),[37,38] and the Social Functioning Scale (SFS).[39] The RMET assesses one's ability to infer mental states from images of the eye regions of human faces[36]; from this, performance on easy and hard items is calculated. We have previously found the RMET as a sensitive measure for social cognition impairments in early psychosis[40] and demonstrated response to oxytocin.[41] SAPS and SANS total scores are generated by summing the respective global ratings, and the SFS total raw score is calculated by summing the frequency of self-reported social activities across 7 subscales.

Secondary Outcomes. Social Cognitive

1. Emotion Recognition: The Facial Expressions of Emotions Task (FEEST)[42] tests identification of 6 basic emotions (happiness, sadness, anger, fear, surprise, and disgust). The Movie Stills Task[43] requires identification of emotions (happy, surprised, afraid, angry, disgusted, sad, or neutral) from a complex movie scene, displayed both with and without the actors' facial expressions.
2. Theory of Mind: The False Belief Picture Sequencing Task[44] requires arrangement of picture-cards into a logical sequence of events to test the ability to go beyond objective information to reason that a story protagonist is acting on the basis of a false belief. The Faux Pas Task[45] was modified to include 10 items that require participants to identify when faux pas are present with the hit-rate and false-alarm rate calculated. The Empathy Quotient[46] is a self-report measure assessing the cognitive and affective aspects of empathy.
3. Attributional Bias: The Ambiguous Intentions Hostility Questionnaire[47] contains 5 short, written, second-person vignettes describing negative interpersonal events with ambiguous causality. This study focuses on the hostility, composite blame, and aggression bias scores.

General Neurocognition The Repeatable Battery for the Assessment of Neuropsychological Status is a brief

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test of basic neurocognitive function.[48] It generates 5 indexes for immediate memory, language, visuospatial/constructional, attention, and delayed memory.

Symptom Severity Secondary symptom severity measures include the Depression, Anxiety, and Stress Scale (DASS 21-item version),[49] Kessler Psychological Distress Scale (K-10),[50] and the Social Interaction Anxiety Scale (SIAS).[51] The DASS measures the tripartite negative emotional states of depression, anxiety, and stress experienced over the last week.[49] The K-10 measures levels of distress experienced over the past 4 weeks based on questions about anxiety and depressive symptoms.[50] The SIAS measures anxiety and distress associated with social interactions.[51] Additionally, the Clinical Global Impression-Severity scale (CGI-S) was employed as a clinician-rated measure of illness severity.[52]

Social Functioning Secondary social functioning outcomes included: the Social Skills Performance Assessment (SSPA),[53] Interpersonal Competence Questionnaire (ICQ),[54] and Sheehan Disability Scale (SDS).[55] The SSPA consists of two 3-minute role-play conversations assessing social skills.[53] The ICQ assesses 5 domains of interpersonal competence: initiating relationships, disclosing personal information, asserting displeasure with others, providing emotional support and advice to peers, and managing interpersonal conflict.[54] Lastly, the SDS measures the impact of symptomatology (here, social difficulties) on work, social, and family functioning.[55]

Analytic Methods A sample size of 48 participants, randomly assigned in a 1:1 ratio to oxytocin or placebo, was calculated to have a 95% power to detect an effect as large as previously observed,[41] with $P = .05$ based on a mixed-design ANOVA.[56] Baseline demographic and behavioral characteristics were assessed using independent samples *t*-tests or Pearson's chi-squared test for dichotomous outcome variables. Analysis of primary and secondary continuous outcomes were based on a 2 (drug: oxytocin, placebo) × 3 (time: pretreatment, post-treatment, 3-month follow-up) mixed-design ANOVAs, with an intent-to-treat format and last observations carried forward to replace missing data. For participants with missing baseline data, analysis for that measure was excluded listwise. All outcome measures were examined to ensure violations were not met for linear model assumptions, with adjusted degrees of freedom and significance levels reported if Mauchly's Test of Sphericity was violated for ANOVA tests, and Bonferroni-adjusted *P*-values used for multiple comparisons. Data were entered by research assistants, blind to drug assignment, and analyzed using SPSS (Version 20.0, SPSS Inc).

Results

Participants and Randomization

Participant recruitment occurred between January 2011 and March 2013 (figure 1) with 52 participants randomized (SCT + oxytocin $n = 27$, SCT + placebo $n = 25$). There were no significant differences between groups on any demographic, symptom severity, functioning level, medication use, or other outcome measure at baseline (table 1). Medications used are listed in supplementary table 1, with no participant reporting any change in medication use or dose during the trial.

Treatment Tolerability, Compliance, and Adverse Events

Participation rates were high, with 10 out of 12 sessions attended, on average (table 2). Participants reported a high degree of treatment acceptance, benefit, and generalization of skill for everyday life, with no differences on these measures between groups (table 2; supplementary table 3). No significant adverse events were reported in the oxytocin group and number of side-effects reported by checklist did not differ between groups, $t(33) = .09$, $P = 0.93$; (supplementary table 2), with no symptom exacerbations resulting in rehospitalization during the course of the trial. Compliance with nasal spray administration was high, with 84% of participants who completed the nasal spray administration phase ($n = 46$) returning intact nasal sprays for analysis. Of 41 participants who returned intact bottles, there were no significant differences between groups in the overall amount of spray used ($t(39) = -0.90$, $P = .38$; oxytocin $n = 21$; $n = 20$).

Primary Outcomes

There were no significant changes over time, or interaction with drug condition, on the RMET or the SFS (figure 2 and supplementary table 4). A significant main effect of time for both positive ($F(2, 100) = 5.77$, $P = .004$, $\eta^2_p = .10$) and negative ($F(2, 100) = 8.17$, $P = .001$, $\eta^2_p = .14$) symptoms indicated significantly fewer psychotic symptoms reported over time. A main effect of drug condition also indicated that the SCT + oxytocin group reported significantly higher ratings of positive symptoms compared with SCT + placebo, on average ($F(1, 50) = 5.58$, $P = .02$, $\eta^2_p = .10$), with no significant interaction with time. Post hoc pairwise comparisons, with Bonferroni corrections, suggested that this significant main effect was due primarily to the placebo group tending to decrease reports of positive symptoms over time, particularly between baseline and post assessments ($P = .03$), whereas there were no significant differences at any time point for the oxytocin group (supplementary table 3). There were no significant main effects of drug condition on negative symptoms ($F(1, 50) = 1.12$, $P = .30$, $\eta^2_p = 02$) or interaction between drug and time ($F(2, 100) = 0.23$, $P = .80$, $\eta^2_p = .01$). Comparison of effect sizes between baseline and post-treatment assessments, using Cohen's *d* for repeated measures,[57,58] on the primary outcomes revealed small to moderate effects

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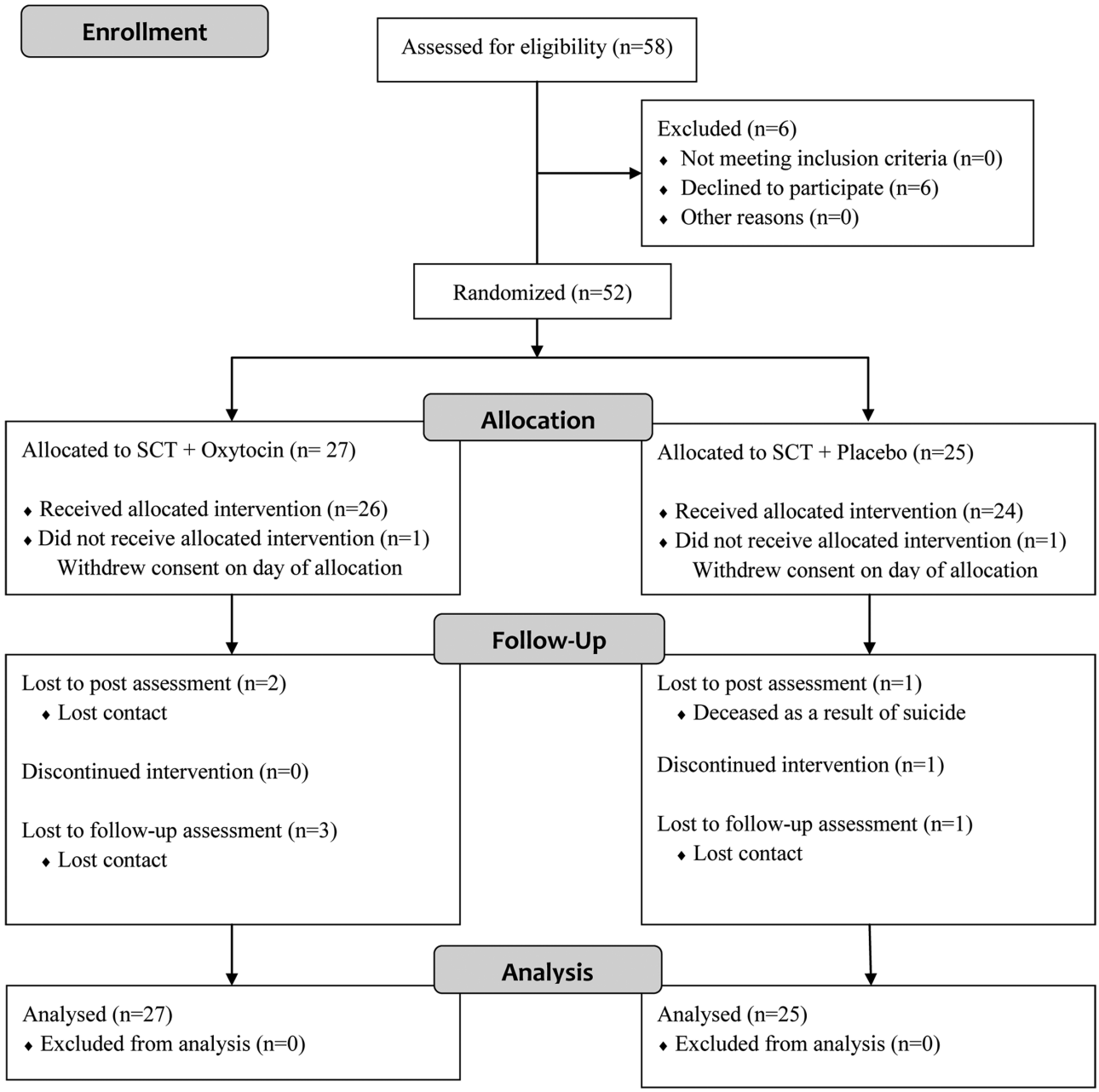

Fig. 1. Consolidated Standards of Reporting Trials flow diagram. A total of 58 participants with early psychosis were assessed for eligibility to participate in the trial. A total of 52 participants underwent randomization, with 27 allocated to the active treatment, oxytocin, and 25 allocated to placebo. Both groups received social cognition training. On the day of allocation, 1 participant in the active group and 1 participant in the placebo group withdrew consent to participate due to a change of mind. One participant discontinued in the placebo intervention due to study commitments. Two participants in the active and 1 participant in the placebo group were lost to post assessment. The participant allocated placebo, died due to suicide shortly after completion of the 6-week intervention. Three participants in the active and 1 participant in the placebo group were lost to follow-up. Using an intention-to-treat approach, all participants were included in the final analysis.

on both positive and negative symptoms in both groups (positive symptoms: oxytocin $d = 0.27$, placebo $d = 0.62$; negative symptoms: oxytocin $d = 0.31$, placebo $d = 0.53$). Smaller effect sizes were observed on the social cognition and functioning primary outcomes (RMET: oxytocin $d = 0.05$, placebo $d = 0.19$; SFS: oxytocin $d = .04$, placebo $d = 0.13$).

Secondary Outcomes

Across all secondary outcomes of social cognition, social functioning, and symptom severity, there were no significant interaction effects between drug condition and time point (supplementary table 3). A significant interaction effect for the SCT + oxytocin group compared with the

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Table 1. Baseline Demographic and Clinical Characteristics of Participants Randomized to Receive Social Cognition Training and Either Oxytocin or Placebo Intervention

	SCT + Oxytocin, n = 27		SCT + Placebo, n = 25		
Measure	Mean	SD	Mean	SD	P-Value
Age	21.52	4.22	22.32	4.43	0.51
Gender (male/female)[a]	18/9		18/7		0.68
Full-scale IQ	101.59	13.31	102.84	15.39	0.76
SAPS	5.56	4.23	4.08	3.56	0.18
SANS	9.41	4.47	10.92	3.74	0.19
DASS-D[b]	19.31	12.90	12.83	11.93	0.07
DASS-A[b]	12.77	9.73	9.58	9.87	0.26
DASS-S[b]	14.96	11.28	12.08	10.27	0.35
OTI	0.89	1.12	0.84	0.94	0.87
SFS[b]	119.38	30.67	112.71	25.49	0.41

Note: SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; DASS, Depression, Anxiety, and Stress Scale, 21-item version; OTI, Opiate Treatment Index; SFS, Social Functioning Scale. Significant values taken from independent sample's t-tests, with $P < .05$ (2-tailed).
[a]Chi-square test.
[b]DASS and SFS scores were missing from 1 participant in each group.

Table 2. Adherence Data for the SCT Program for Participants Randomized to Receive SCT and Either Oxytocin or Placebo Intervention

	Total, n = 52	SCT + Oxytocin, n = 27	SCT + Placebo, n = 25	P value
Participants attending ≥6 sessions[a,b,c]	88.50%	92.60%	84.00%	0.26
Number of sessions attended[a,b]	10.12 (2.66)	9.77 (2.49)	10.50 (2.84)	0.34
Range of sessions attended[a,b]	4–12	4–12	4–12	

Note: SCT, Social Cognition Training. $P < .05$ (2 tailed). Numbers of sessions attended are means (standard deviations).
[a]Data were missing from 1 participant in the oxytocin group due to withdrawing on first day of treatment.
[b]Data were missing from 1 participant in the placebo group due to withdrawing on first day of treatment.
[c]Chi-square test.

SCT + placebo condition indicated improved recognition of disgust over time in the oxytocin group (supplementary table 3); however, this did not survive corrections for multiple comparisons.

Significant main effects of time on some social cognition outcomes suggested potential improvements on social-cognitive performance, averaged across drug condition. This included improved emotion recognition from faces using the FEEST ($F(2, 96) = 19.83$, $P < .001$, $\eta^2_p = .29$), recognition of emotions in scenes using the Movie Stills task ($F(1.77, 86.76) = 5.86$, $P = .01$, $\eta^2_p = .11$), and understanding of false beliefs ($F(2, 96) = 9.41$, $P < .001$, $\eta^2_p = .16$). Significant reductions were also observed in interpreting ambiguous situations as hostile ($F(1.69, 81.01) = 5.83$, $P < .01$, $\eta^2_p = .11$) and a trend towards less aggressive attributions ($F(1.77, 84.99) = 2.76$, $P = .07$, $\eta^2_p = .05$) over time.

On symptom severity measures, significant main effects were observed for depression, anxiety, and social interaction anxiety. Although SIAS scores significantly decreased over time ($F(2, 96) = 3.57$, $P = .03$, $\eta^2_p = .07$), depression and anxiety exhibited significant quadratic trends, indicating initial reductions in symptoms and then a return to baseline levels by the follow-up assessment (supplementary table 3). Assessor-rated severity of illness, using the CGI, also indicated significant reductions in the severity of illness over time ($F(2, 100) = 7.65$, $P = .001$, $\eta^2_p = .13$), with no differences between groups. Significant improvements in social functioning were observed on the SSPA ($F(2, 100) = 6.55$, $P < .01$, $\eta^2_p = .12$) and SDS ($F(2, 94) = 5.82$, $P < .01$, $\eta^2_p = .11$) that did not significantly interact with drug condition.

A significant main effect of time emerged on general neurocognition ($F(2, 100) = 20.63$, $P < .001$, $\eta^2_p = .29$), indicating improved cognitive performance over time.

Exploratory Analyses

A series of Pearson's correlations explored potential associations between change scores from baseline at post and

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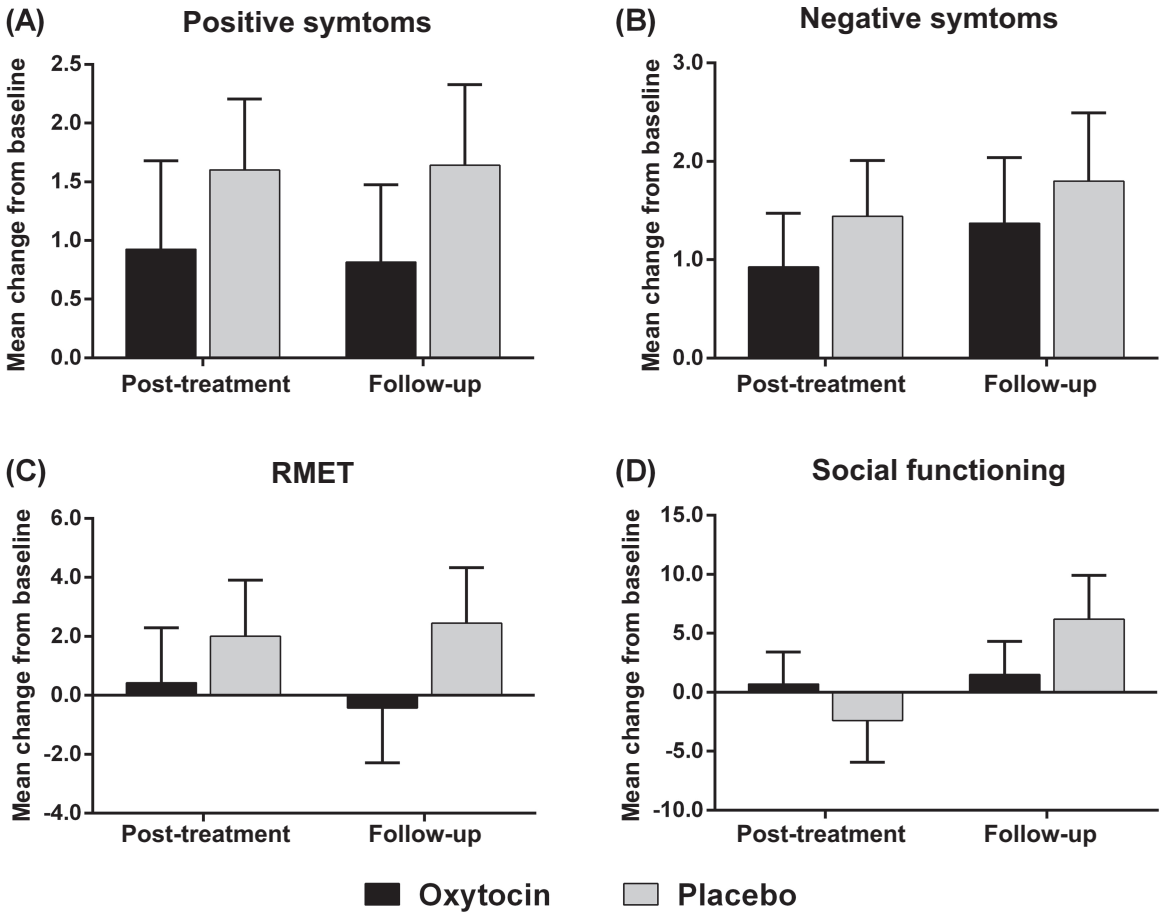

Fig. 2. Change from baseline on primary outcomes. (A) Positive symptoms assessed using the Scale for Assessment of Positive Symptoms (SAPS), change in total score; (B) Negative symptoms assessed using the Scale for Assessment of Negative Symptoms (SANS), change in total score; (C) RMET: Reading the Mind in the Eyes Test, change in percentage correct; (D) Social functioning assessed using the Social Functioning Scale (SFS), change in total score. All primary outcomes are scored so that positive numbers indicate improvement compared with baseline. Error bars depict standard error of the mean.

follow-up assessments on the primary and secondary outcomes, across the 3 domains (social cognition, symptom severity, and social functioning). However, no significant differences in these associations emerged between drug groups. Further analyses examining the number of individuals who had positively responded to treatment on any of the primary outcomes at the post assessment also indicated no differences between drug groups, all *P*-values >.05.

We then examined the relationship between nasal spray usage and primary outcome change scores at post-treatment in treatment completers. Significant associations were found between spray usage and changes in negative symptoms in the oxytocin condition only (figure 3). This relationship was found when examining the amount of spray used (oxytocin: $r = .60$, $P = .004$, $n = 21$; placebo: $r = .33$, $P = .17$, $n = 19$) and the percentage of spray used (number of sprays relative to the actual number of days of administration; oxytocin $r = .53$, $P = .01$; placebo $r = -.17$, $P = .50$). These results suggest that greater reductions in negative symptoms post-intervention in the oxytocin group may be associated with greater use of oxytocin, but not for placebo-administered participants. No associations with spray compliance were found on any other primary outcome measure.

Discussion

This study demonstrates that oxytocin treatment, in comparison with placebo, did not improve social cognition, symptom severity, or social functioning at either post-treatment or follow-up in young people with early psychosis. Oxytocin was well tolerated, with no evidence of elevation of any reported side-effects or serious adverse events in the active treatment condition. Interestingly, use of nasal spray liquid was associated with reductions in negative symptoms within the oxytocin condition, but there was no significant association in the placebo condition. Although results do not support the efficacy of oxytocin specifically, improvements over time on specific symptom severity, social-cognitive and social functioning outcomes, and positive participant evaluations, may suggest benefit of social-cognitive training in this sample.

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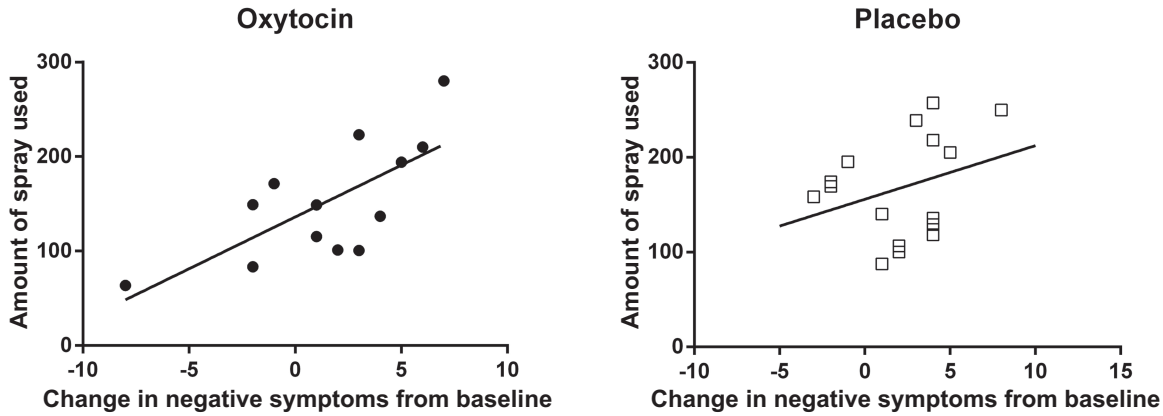

Fig. 3. Associations between nasal spray compliance and change in negative symptoms; oxytocin $r^2 = .36$, placebo $r^2 = .11$. A positive change in negative symptoms indicates a reduction in symptoms compared with baseline. A similar pattern of correlations was also found when assessing percentage of spray used (oxytocin $r = .53$; placebo $r = -.17$). Participants indicated here are treatment completers with available compliance data; oxytocin $n = 21$, placebo $n = 19$.

Major strengths of this study were the inclusion of a range of illness and social cognition measures and the recruitment of a larger sample size compared with previously published trials. Assessments covered many proposed important domains, from lower- and higher-order social cognition, positive and negative symptoms, and observational and self-report measures of social functioning. Some measures have demonstrated sensitivity to change from single doses of oxytocin (eg, RMET),[41] albeit in different target populations. Although existing evidence provides strong support that a single dose of oxytocin impacts favorably on domains of social cognition in humans,[41] the reliability of these effects across populations and contexts remains an ongoing issue. Some positive-extended treatment studies also show inconsistent positive effects across social-cognitive domains.[14]

In contrast to previous trials of oxytocin treatment in chronic schizophrenia, this study administered oxytocin to young patients with early psychosis. This population exhibits reduced illness persistence and is more likely to consist of heterogeneous presentations, with different trajectories of illness, compared with chronic schizophrenia.[5] These previous studies have shown likely benefits on negative symptoms of schizophrenia. If oxytocin provides benefit for patients with chronic schizophrenia, either the symptomatic benefits from oxytocin may be too subtle to detect in an early psychosis population, or benefit may be isolated to only those that go on to show severe and persisting psychotic symptoms.[4] The heterogeneous nature of schizophrenia has also led to speculation that subgroups of treatment responsiveness may exist, including patients with low basal plasma oxytocin, deficit syndrome, or polydipsia.[11,59] Evidence from imaging studies increasingly suggests that a variety of neurobiological predictors may determine pharmacological treatment response during the early stages of psychosis.[60] Further research is, therefore, needed to investigate whether these predictors may identify a cluster that responds to treatment or show neurobiological correlates underlying treatment response.

We have previously highlighted medication and delivery variables that may influence outcome in oxytocin trials.[32] On the basis of these recommendations, in this study we measured the amount of liquid in bottles returned and found an association between amount of use of oxytocin nasal spray and subsequent reductions in negative symptoms. This association was found when liquid used was considered as a total volume and also as a percentage of number of days allocated to drug. This may suggest that more frequent or higher dosing could reduce negative symptoms in psychosis. Alternatively, it may suggest that a subgroup of individuals benefit from oxytocin and these individuals may be more likely to comply with spray administration. Although we used the standard adult dose reported in the literature of 48 IU (24 IU twice-daily), this dose is lower than some other reports demonstrating positive effects of oxytocin.[15] Furthermore, and in accordance with our past recommendations, a greater understanding and execution of delivery variables and factors that influence deposition in the nasal cavity is needed for future research.[32] As we have argued elsewhere, delivery factors may substantially influence absorption across olfactory, trigeminal or peripheral pathways to effect bioavailability of oxytocin.[32] Finally, we provided an additional dose before treatment sessions in the hope of capitalizing on the proposed benefits of combining oxytocin with SCT. Although this was an important novel aspect of this study, this treatment may have the undesired effect of reducing capacity to show benefits from oxytocin alone (without psychosocial treatment). Indeed, placebo-like effects have been observed in adolescent treatment studies[2] and may hinder the detection of any potential benefits of active treatments.

We did not include a control group to evaluate the efficacy of our psychosocial intervention independent of drug treatment. Accordingly, firm conclusions about whether

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improvements in psychotic symptoms were related to the training itself rather than the effects of socialization or time cannot be made. Based on the existing evidence, we modified our program in a manner that we believed provided the best opportunity for young people with early psychosis to obtain benefit. It may be possible that oxytocin may enhance treatment components that were not included or not emphasized in our specific social cognition training package. However, participants reported the program to be both acceptable and tolerable, there was high attendance rates, and significant main effects of time may suggest improvements on a range of measures, including positive and negative psychotic symptoms, emotion recognition and theory of mind, hostile attributions and observational measures of social functioning, and self-reported functioning in work, social, and family domains. Many of these outcomes were specifically targeted by this program and would not normally be expected to change. Clinical trials using an active control group are now needed to evaluate the specific effects of the psychosocial program in early psychosis.

In conclusion, this study demonstrated that oxytocin, combined with SCT, did not result in significant improvements in social cognition, symptom severity, or social functioning, when compared with placebo. Although the results of this study do not support the efficacy of oxytocin nasal spray to treat early psychosis, either through its twice-daily administration over 6 weeks, or via enhanced learning and benefit from a social cognition intervention, more research in this area is needed to further explore optimal dosing and routes of administration to enhance efficacy.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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