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Combined Oxytocin and CBSST for Social Function in People with Schizophrenia

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Abstract

Background: A significant proportion of people with schizophrenia are characterized by impaired ability to socially engage with others. The development of effective interventions for social functioning remains a central therapeutic challenge. Cognitive Behavioral Social Skills Training (CBSST) has been found to improve social functioning in schizophrenia, but with only medium effect sizes. Intranasal oxytocin also has pro-social effects, but also only with modest effect sizes. This study assessed whether the addition of intranasal oxytocin to CBSST can strengthen their impact on social function.

Methods: Participants (N=62) with schizophrenia or schizoaffective disorder entered a 24-week, double-blind, placebo-controlled, randomized clinical trial with a 3-month follow-up evaluation at two sites: Maryland and San Diego. Participants were randomized to either intranasal oxytocin 36 I.U. (3 sprays) BID (n=31) or intranasal placebo-oxytocin (3 sprays) BID (n=31). All participants received CBSST plus a social cognition skills training module (48 total sessions).

Results: There were no significant treatment group differences in social functioning, positive symptoms, negative symptoms, defeatist beliefs, or asocial beliefs. The interpretation of treatment effects was complicated by site effects, whereby participants in San Diego began the trial with greater severity of impairments, and subsequently showed greater improvements than participants in Maryland.

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Conclusions: The results did not support the utility of add-on intranasal oxytocin to psychosocial rehabilitation interventions like CBSST for improvement in social function. (clinicaltrials.gov trial number: NCT01752712)

Keywords

oxytocin; cognitive behavioral therapy; social skills training; social function; schizophrenia

Introduction

A significant proportion of people with schizophrenia are characterized by impaired social function, which may reflect decreased motivation for social interactions, impairment in the normal reinforcement value of social interactions, and/or increased social aversion secondary to the presence of defeatist beliefs (1,2). Impairments in social function have also been shown to be associated with social skill deficits, including the ability to initiate and sustain conversations, affective expression (1–5), and social cognition (e.g., empathic accuracy, facial affect perception, emotional memory) (1–7). Unfortunately, pharmacological interventions have limited benefits for impaired social function (8), whereas psychosocial interventions provide only partial benefit for this critical aspect of the illness (9). The development of an effective intervention for social function remains a central therapeutic challenge.

Oxytocin plays a major role in the regulation of non-human and human social behavior, including social affiliation, pair bonding, maternal behavior, and social memory (10–13). Oxytocin is hypothesized to enhance social function through: 1) reduction of anxiety or social risk aversion; 2) enhancement of motivation for prosocial approach or affiliative behavior; and/or 3) increased modulation of the salience and processing of social cues (14–24). These three processes may act independently or synergistically with each other (24).

A series of studies have demonstrated that oxytocin is able to enter into the central nervous system through intranasal administration (25); in combination with the role of oxytocin in the regulation of human social behavior, this observation has led to examination of whether intranasal oxytocin can modify social behavior. In healthy controls, oxytocin has been shown to enhance various social cognitive processes. Specifically, studies have demonstrated that single-dose intranasal oxytocin: 1) increases the amount of time spent gazing at the eye region (17); 2) improves the ability to infer the internal mental state of another person through processing affective eye expressions (18); 3) enhances the ability to recognize facial expressions (19, 26–28), with a differential effect observed for rapidly presented happy facial expressions (19,27,28); 4) increases the perception of attractiveness and trustworthiness in the faces of others (20); 5) reduces arousal ratings to negative or threatening human visual stimuli (29); and 6) decreases the likelihood that positive or neutral facial emotions will be misclassified as negative emotions (21). In addition, single-dose intranasal oxytocin may diminish the affective response to fear-associated facial stimuli (14); reduce cortisol excretion and decrease anxiety levels during stressful social interactions (15); and increase trust behavior (16). Finally, oxytocin may enhance the ability to encode social versus non-social stimuli (22) and to encode positive (happy) facial stimuli, which

may increase the likelihood that the person will remember the face on subsequent exposures and may also reflect the action of oxytocin on reward circuits (23).

In light of the behavioral properties of oxytocin, the present two-site study was conducted to examine whether the long-term administration of intranasal oxytocin could be used to enhance the therapeutic effects of a psychosocial intervention for social function, cognitive-behavioral social skills training (CBSST; 30). In several previous clinical trials, CBSST was found to improve functioning in participants with schizophrenia through social skills training and challenging defeatist performance beliefs, which interfere with the community practice of social behaviors, but effect sizes were small to medium (31,32). We hypothesized that the addition of oxytocin, whose behavioral effects compliment the mechanisms of action of CBSST, would markedly enhance the therapeutic effect of CBSST. Specifically, we hypothesized that the addition of oxytocin to CBSST would: 1) further reduce defeatist performance beliefs by decreasing social risk aversiveness and avoidance; 2) enhance social skill acquisition through improvement of proximal social behaviors, e.g. making eye contact and attending to the facial expressions of social partners; and 3) facilitate the translation of learned social skills into community practice through its effects on prosocial attachment behaviors, reduction in social disinterest, and effects on distal behaviors, e.g. initiating conversations and responding to social invitations. These interactive effects would subsequently lead to a substantial improvement in CBSST efficacy for social function.

Methods

Participants.

Outpatient participants were recruited from two sites: 1) the Maryland Psychiatric Research Center; and 2) the University of California, San Diego. Participants between the ages of 18 and 55 years, who met DSM-IV-TR criteria for schizophrenia or schizoaffective disorder, were selected for study entry. They were diagnosed using a best estimate diagnostic approach, which utilized information from the Structured Clinical Interview for DSM-IV (33), direct assessment, family informants, and past medical records. They were required to be clinically stable, in the non-acute phase of their illness, and to have a minimum level of social function impairment defined by a score of ≥ 2 on the Scale for the Assessment of Negative Symptoms (SANS; 34) asociality item (i.e., a decrease in social interactions with others).

Participants could be treated with a first or second generation antipsychotic; they were required to be on the same antipsychotic for at least 2 months and to be on the same dose for at least one month. Participants who met DSM-IV-TR criteria for current alcohol or substance dependence (except nicotine) within the last 6 months or DSM-IV-TR criteria for alcohol or substance abuse (except nicotine) within the last month were excluded. Participants with mental retardation, a past history of polydypsic hyponatremia (defined by sodium levels less than 130 mmol/L) or a current sodium level below 135 mmol/L, or other uncontrolled medical condition were excluded. Participants with EKG evidence of any of the following cardiac arrhythmias were excluded: QTc prolongation (males: 450 msec or greater, females: 470 msec or greater), atrial fibrillation, ventricular or supraventricular

tachycardia, or 2nd or 3rd degree A-V Block. Pregnant and lactating female participants were excluded.

The study protocol and informed consent procedures were approved by the University of Maryland, Baltimore; the State of Maryland Department of Health; and VA San Diego Healthcare System Human Research Protection Program Institutional Review Boards. Written informed consent was obtained from all participants after full explanation of study procedures and prior to study participation. Participant ability to provide valid informed consent was documented using study-specific procedures. The study was registered with clinicaltrials.gov (NCT01752712) and was monitored by a Data Safety Monitoring Board.

Social Function Assessment.

The Birchwood Social Functioning Scale (BSFS; 35) total score was used to assess social function. The BSFS is designed to assess social function in people with schizophrenia across six domains of social function: 1) social engagement/withdrawal; 2) interpersonal communication; 3) independence-performance; 4) independence-competence; 5) recreation; and 6) prosocial activities. The BSFS occupation/employment domain was also assessed, but not included in the BSFS total score, since our emphasis was on the assessment of social functioning. The BSFS was administered at baseline and weeks 12, 24, and 36.

Social Attitude Assessments.

The Defeatist Performance Attitude Scale (DPAS; 36) and Asocial Beliefs Scale (ABS; 37) were used to assess the effect of CBSST on defeatist attitudes and asocial beliefs; these two measures have previously been shown to be related to poor social functioning and are hypothesized to mediate the therapeutic effects of CBSST. The DPAS is a 15-item self-report subscale, which measures the tendency to over generalize from past failure experiences and form defeatist beliefs about the ability to perform future goal-directed tasks. Items are rated on a 1–7 Likert scale with higher total scores indicating more severe defeatist performance attitudes. The ABS is comprised 15 self-report true/false items designed to assess social disinterest/amotivation (37). The DPAS and ABS were administered at baseline, and weeks 12, 24, and 36.

Clinical Assessments.

The four Brief Psychiatric Rating Scale (BPRS; 38) positive symptom items (i.e., conceptual disorganization, hallucinatory behavior, unusual thought content, and suspiciousness) were used to assess positive symptom change. The modified SANS total score was used to assess negative symptom change (34), and the expressive (blunted affect and alogia items) and experiential (avolition, anhedonia/asociality items) dimensions were evaluated as secondary outcome scores. The Clinical Global Impression (CGI; 39) severity of illness item was used to assess global changes. The Calgary Depression Scale (CDS; 40) total score was used to assess depressive symptom change. The BPRS, SANS, and CDS were administered at the beginning and end of the Evaluation Phase, every 4 weeks during the Double-blind Treatment Phase, and at the week 36 follow-up visit. The CGI was administered weekly during the Evaluation Phase to document clinical stability, every 4 weeks during the Double-blind Treatment Phase, and at the week 36 follow-up visit. Intraclass correlation

coefficients for these instruments ranged from 0.76 to 0.90. All raters were blind to treatment assignment.

Safety Assessments.

A standard blood chemistry panel, complete blood count, urinalysis, and EKG were obtained in the Evaluation Phase and every 4 weeks during the Double-Blind Treatment Phase. The Side Effect Checklist (SEC) was used to assess standard medication side effects commonly associated with pharmacological treatments and monitor vital signs. The SEC rates each side effect on a 4-point scale (0: none to 4: severe) and the extent to which the side effect is judged to be related to the experimental treatment (A: none to D: Probable). The Water Consumption Questionnaire (WCQ) was used to assess how much the participant drinks on a daily basis; what the participant regularly drinks; and whether there has been any change in thirst or drinking behavior over the last week. The SEC and WCQ ratings were conducted at baseline, then weekly throughout the 24-week Double-Blind Treatment Phase by a non-blinded pharmacist.

Study Design.

The study consisted of a 2-week Evaluation Phase, a 24-week Double-Blind Treatment Phase, and a week 36 follow-up evaluation visit, which was completed 12 weeks after the last CBSST session to assess the persistence of any observed treatment effects. Participants who met inclusion criteria for asociality entered the Evaluation Phase, during which they underwent medical screening and baseline symptom, safety, and cognitive assessments. Participants who continued to meet inclusion criteria entered the 24-week Double-Blind Treatment Phase and were randomly assigned to intranasal oxytocin (36 IU, BID) or placebo intranasal oxytocin using a permuted block randomization system. All participants received extensive education and training to ensure the proper use of the intranasal oxytocin. If a participant could not tolerate their study medication, they were instructed to skip a dose and then resume treatment with the prescribed dose. If the participant was still unable to tolerate their study medication, then the dose could be lowered to alleviate side effects.

We used several procedures to enhance adherence with the study medications and to monitor treatment compliance. First, at the beginning of the study, each participant was provided an information sheet with strategies to help the participant to remember to take their medication. Second, we used an Ohaus AV313 Adventurer Pro scale to measure the Oxytocin intranasal spray metered-dose dispensers. The scale weighs objects to the nearest milligram. In the study, we were looking to measure the spray bottles to the nearest 100mg, which is the weight of one metered spray from our spray device. Therefore, the scale was sensitive enough to allow us to measure the amount of solution used over the course of each two-week period. The difference in grams gives us the weight of the solution used and extrapolating into the number of doses. Third, a chart was provided to each participant to document their administration and compliance. If a participant had a hard time remembering whether or not a dose was taken, they were provided with a plastic pill reminder box containing candy or nuts. They were instructed to spray the dose and then remove the physical reminders from the pillbox to signify that the dose was

administered. All participants who received 75% or more of their assigned study medication were considered compliant.

All participants received CBSST, with participants randomized to oxytocin and placebo-oxytocin attending the same therapy groups. The following modifications were made to the standard version of CBSST (30) to enhance the treatment focus on social functioning, social cognition, and adherence to oxytocin use: 1) to facilitate adherence to oxytocin between sessions, we incorporated behavioral tailoring interventions, including reminders, self-monitoring and reinforcement; 2) the focus on using corrective feedback from successful social interactions was strengthened to challenge social disinterest and defeatist performance beliefs; 3) motivational interviewing techniques were added to the initial session of each module to promote treatment engagement, reduce social aversion and focus on socialization goals; 4) eye contact and attending to facial affect was emphasized more extensively in behavioral role plays in the social skills training module, and 5) a Social Cognition Skills module was added, which trained skills for thought checking in ambiguous social situations, perspective taking, and facial affect recognition and expression (adapted with permission from Social Cognition and Interaction Training or SCIT; 41). CBSST was delivered in four 6-session modules (i.e., Cognitive Skills, Social Skills, Problem-Solving Skills, and Social Cognition Skills). The modules were delivered twice, to compensate for cognitive impairment and to improve sense of mastery and self-efficacy, for a total of 48 sessions. There were two ongoing groups at each site. We used a modular rolling admissions approach, whereby participants could enter groups at the start of any new module, which limited the maximum group entry wait time to 4 weeks. The CBSST groups met 2 times per week; on the CBSST session days, oxytocin was administered 45 minutes before the session, with direct observation of participant administration of intranasal oxytocin by the non-blind pharmacist.

All therapists at both sites had a master’s degree or higher level of education and had experience delivering group therapy for people with serious mental illness. Therapists at both sites attended the same two-day training workshop and attended the same weekly 1-hour video-conference supervision with the treatment developers, JH and EG. Supervision included discussion of groups at each site, weekly review of session recordings, and feedback of specific fidelity ratings. Eighty-four randomly-selected sessions across both sites were rated for intervention fidelity using the Cognitive Therapy Rating Scale for Psychosis (CTS-Psy; 42). The CTS-Psy total score (mean=41.6, SD=5.2) far exceeded the score (>30), which is typically considered to represent adequate fidelity for competent CBT for psychosis, used in previous clinical trials (e.g. 43). The two sites showed modest but statistically significant differences in fidelity on the total CTS-Psy score (San Diego: mean=42.9, SD=5.4; MPRC: mean=40.5, SD=4.9; $t(82) = 2.06$, $p=0.042$) and on CBT-specific skills (i.e., sum of Agenda, Feedback, Collaboration, Guided Discovery, Focus on Key Cognitions, Choices of CBT Interventions, Quality of Interventions, and Homework items) (San Diego: mean=31.2, SD=5.2; MPRC: mean=28.9, SD=4.6; $t(82) = 2.20$, $p=0.031$), with higher fidelity scores in San Diego. There were no site differences for the total of non-specific psychotherapy skills (i.e., sum of Understanding and Interpersonal Effectiveness items) (San Diego: mean=11.6, SD=0.6; MPRC: mean=11.7, SD=0.8; $t(82)=-0.17$, $p=0.87$).

The Comprehensive Modules Test (CMT; 43) total score was used to assess the extent to which participants were able to learn the information and specific skills taught in the CBSST sessions. The CMT was administered at baseline and weeks 12, 24, and 36.

There was one follow-up visit 12 weeks (week 36) after the last CBSST session to assess the persistence of any observed treatment effects.

Statistical Analyses.

The primary analytic approach for the efficacy measures was a linear mixed effect model. The change of BSFS total score from baseline was considered as the primary outcome measure. All participants who had at least one post-randomization efficacy measure were included in these analyses. The sites and time points were adjusted as covariates. We further investigated whether site or time moderated the treatment effect by examining the interaction terms. We treated the time effect as a categorical variable when the outcome variable was measured less than three times (the number of post-randomization visits), and otherwise a continuous variable. In addition, the persistence of any observed treatment effects was assessed by a mixed effect model for weeks 24 and 36.

We used Cohen's f^2 to estimate group differences associated with the primary outcome measure: BSFS total score. Cohen's f^2 is the standardized measure of effect size to characterize the association between the outcome variable and covariate of interest within the context of a multiple regression model. Cohen's f^2 can be considered as a counterpart of Cohen's d and Hedge's G within the context of two sample test.

Results

Eighty-three people were consented; 82 entered the Evaluation Phase; 66 participants completed the Evaluation Phase; and 62 participants underwent randomization: 31 participants were assigned to oxytocin and 31 assigned to placebo (see Supplementary Figure 1 for CONSORT flow chart). Two oxytocin participants withdrew prior to receiving study medication, because of loss of interest. Two oxytocin participants withdrew during the first 12 weeks of the study and 5 withdrew during the second 12 weeks. Eight placebo participants withdrew during the first 12 weeks of the study and 2 withdrew during the second 12 weeks. Forty-two participants (68%) completed the study. Demographic and baseline clinical characteristics are presented in Table 1. The two groups were comparable with respect to age, race, gender, and educational level.

Social Function Assessment (see Table 2).

In the final model for BSFS total score, there was a significant effect for site (t=2.32; df=58.4; p=0.02; Cohen's f^2= 0.09), but not for time (t=−1.38; df=58.4; p=0.17; Cohen's f^2= 0.03) or treatment (t=−0.84; df=58.4; p=0.41; Cohen's f^2= 0.01). There was a significant effect for the time x site interaction (t=2.09; df=39.7; p=0.04; Cohen's f^2= 0.07), but not for the treatment x time (t=1.50; df=39.2; p=0.14; Cohen's f^2= 0.04), treatment x site (t=−1.17; df=58.4; p=0.25; Cohen's f^2= 0.02), or treatment x time x site (t=−0.75; df=39.9; p=0.46; Cohen's f^2= 0.014) interactions. The significant site and time x site interactions reflect the greater improvement in BSFS total score over the course of the double-blind treatment

phase, in both the oxytocin and placebo groups, at the San Diego site (see Supplementary Figure 2). In the 12-week follow-up phase, there was a significant site effect (t=3.09; df=51.2; p=0.003; Cohen's f^2= 0.19), which reflects the continued difference in BSFS total score between the two sites. The BSFS subscale score analyses were largely consistent with what was observed for the total score, with improvements on most subscales across treatment groups, no significant group effects, and greater improvements in San Diego on some subscales (e.g., Prosocial Activities, Recreation, Independence), especially in the placebo group (data available upon request from the authors).

Social Attitude Assessments (see Table 2).

In the final model for DPAS total score, the time (t=−1.31; df=38; p=0.20), treatment (t=−1.67; df=47; p=0.10), and site effects (t=−0.86; df=47; p=0.39) were not significant. The treatment x site interaction was significant (t=2.11; df=47; p=0.04); the treatment x time (t=1.50; df=38; p=0.14) and treatment x time x site (t=−0.77; df=38; p=0.45) interactions were not significant. The treatment x site effect was driven by the greater reduction in DPAS total score in the San Diego placebo group compared to the other three groups. Although participants randomized to oxytocin at both sites showed continued reduction in DPAS total score over the course of the 12-week follow-up period, there were no significant between group changes in DPAS total score from week 24 to week 36.

In the final model for ABS total score, the treatment, time, and site effects were not significant (all p values > 0.55). The treatment x time, treatment x site interaction, and treatment x time x site interaction were also not significant (all p values > 0.30). There were no significant changes in ABS total score between week 24 and 36.

Clinical Assessments (see Table 3).

BPRS: In the final model for BPRS total score, there was a significant main effect for site (t=−3.47; df=100.3; p=0.0008) and a trend for treatment (t=−1.70; df=100.5; p=0.09). The main effect for time was not significant (t=−0.15; df=227.6; p=0.88). The treatment x site (t=2.29; df=101.8; p=0.02) and treatment x time x site (t=−1.99; df=229; p=0.048) interactions were significant; the treatment x time interaction was not significant (t=1.07; df=227; p=0.29). The site main effect reflects the markedly greater reduction in BPRS total score, regardless of treatment assignment, at the San Diego site. The significant treatment x site and treatment x time x site interactions reflected the different patterns of treatment response between the two sites. Specifically, greater improvement was found for oxytocin relative to placebo early in treatment in Maryland, but benefits were reduced by the end of the treatment phase, whereas in San Diego both treatment groups showed rapid early improvement, but the oxytocin group continued to show greater improvement relative to placebo toward the end of the treatment phase (see Supplementary Figure 3). In the 12-week follow-up period, the improvement in BPRS total score was lost in the participants randomized to placebo at the San Diego site, but not in any of the other treatment groups (site: t=−2.76; df=38; p=0.009; time x site: t=2.43; df=35; p=0.02; see Supplementary Figure 3).

In the final model for BPRS positive symptom item score, the treatment, time, and site main effects were not significant (all p values > 0.20). There was a trend for the time x site interaction (t=−1.97; df=229.9; p=0.050). The treatment x time and treatment x time x site interactions were not significant (all p values > 0.35). The time x site interaction was driven by the greater reduction in BPRS positive symptom item score at the San Diego site, with improvements unrelated to treatment group (see Supplementary Figure 4). In the 12-week follow-up period, the BPRS positive symptom scores continued to decrease in both Maryland site treatment groups and in the San Diego oxytocin, but not placebo, group between weeks 24 and 36 (site: t=−2.96; df=58; p=0.004; time x site: t=2.88; df=38; p=0.006; and treatment x time x site: t=2.88; df=38; p=0.006; see Supplementary Figure 4).

SANS: In the final model for SANS total score, there was a significant site effect (t=−2.16; df=108.3; p=0.03), but the treatment effect (t=−0.89; df=109.9; p=0.38) and time (t=0.33; df=227.0; p=0.74) effects were not significant. The time x site effect was significant (t=−2.60; df=225.6; p=0.01); the treatment x site effect was not significant (t=1.40; df=109.8; p=0.16). There were no other significant interactions (all p values > 0.50). The significant site and time x site effects reflects the significant reduction in SANS total score in both treatment groups at the San Diego site, which occurred over the course of the double-blind treatment phase (see Supplementary Figure 5). The observed effects during the double-blind treatment phase persisted through the 12-week follow-up period, with greater reduction in the San Diego placebo group compared to San Diego oxytocin group (site: t=−4.06; df=54.9; p=0.0001; treatment x site: t=2.09; df=54.8; p=0.04).

In order to examine whether there was a selective effect of oxytocin on the expressive and experiential negative symptom subfactors, we examined the effect of oxytocin separately on the two SANS subfactors. There was a significant site effect (t=2.02; df=50.0; p=0.049) for the SANS expressive subfactor. The main effect for treatment and time and all two-way and three-way interactions were not significant (all p values > 0.15). The significant site effect reflects the improvement of this subfactor score in both of the San Diego treatment groups (see Supplementary Figure 6). There were no significant changes in the subfactor score over the course of the 12-week follow-up period.

There was a significant time x site effect (t=3.84; df=224; p=0.0002), with a marked reduction in the SANS experiential subfactor at the San Diego site. There were no other significant main, two-way, or three-way interaction effects (all p values > 0.17). The observed time x site effect reflects the significant reduction in subfactor scores in both of the San Diego treatment groups over the course of the double-blind phase (see Supplementary Figure 7). There were no significant changes in the subfactor score over the course of the 12-week follow-up period.

CDS: The final model for CDS total score included a significant main effect for site (t=−2.61; df=94.1; p=0.01); there was trend for a significant treatment x site interaction (t=1.80; df=95.9; p=0.08). The time (t=−0.60; df=227.8; p=0.55), treatment x time (t=−0.03; df=227.9; p=0.98) and treatment x time x site (t=−1.52; df=229.0; p=0.13) effects were not significant. The observed site effect reflects the significant reduction in CDS total score in both of the San Diego treatment groups (see Supplementary Figure 8).

There were significant site (t=−2.85; df=47.6; p=0.006) and time x site (t=2.55; df=34.4; p=0.02) effects at week 36, which reflect the return to pre-treatment levels of the CDS total score in the two San Diego groups.

CGI: There were no significant main effects (all p values > 0.10) or interaction effects (all p values > 0.10) for the CGI severity item. There was no further change in the item score over the course of the 12-week follow-up period.

Comprehension Modules Test (CMT).

The final model for CMT total score included a significant main effect for time (t=2.22; df=35; p=0.03). There were no other significant main effects (all p values > 0.90) or interaction effects (all p values > 0.45). There was a slight, but not significant, decrease in CMT total score in all four groups during the 12-week follow-up period (time: t=−1.75; df=33; p=0.09), though the scores suggested that there was still a high level of retention of information.

Safety Measures.

There were two serious adverse events (SAE), both of which occurred in a single participant, who had been randomized to oxytocin. The participant was hospitalized one day for the treatment of sinusitis. The participant was treated with an antibiotic to which he responded. The SAE was judged to be probably not related to the study medication. The same participant was hospitalized again, when he reported an increase in voices telling him to harm himself. The participant was discharged after returning to baseline after treatment for insomnia. The SAE was judged to be probably not related to the study medication.

Twelve participants randomized to placebo had 39 adverse events; whereas, 7 participants randomized to oxytocin had 34 adverse events. There were no significant group differences in any of the adverse events. There were no significant group differences on any of the SEC medication side effects (data not shown).

There was trend for an increase in systolic blood pressure over the course of the study (F=3.85; df=1,955; p=0.05), but the treatment x time (F=0.63; df=1,955; p=0.43) effect was not significant. There was a significant treatment x time (F=5.09; df=1,956; p=0.02) effect for diastolic pressure, which reflected a slight increase in this measure with oxytocin and a slight decrease in the placebo group (data not shown). The time, treatment, and treatment x time effects were not significant for either pulse or weight (data not shown).

The only laboratory measure for which there was a significant treatment x time effect was for sodium (F=5.35; df=1,217; p=0.02); participants treated with oxytocin had a modest increase in sodium levels, whereas there was a small decrease in the placebo group. There was a significant time effect for chloride (F=4.34; df=1,217; p=0.01) and bilirubin (F=5.26; df=1,216; p=0.02), which reflected a small decrease in these levels over the course of the study. There was a significant time effect for glucose (F=6.79; df=1,216; p=0.04) and cholesterol (F=4.26; df=1,133; p=0.04), which reflected an increase in these levels over the course of the study. There were no significant effects for any of the liver enzymes group differences for any of the other laboratory measures.

There were small, but significant, increases in hemoglobin (F=6.48; df=1,217; p=0.01) and hematocrit (F=10.6; df=1,217; p=0.001) over the course of the study. However, neither the treatment or treatment x time effects were significant. The time, treatment, and treatment x time effects were not significant for white blood cell or platelet counts (data not shown).

Discussion

In contrast to our study hypothesis, the addition of intranasal oxytocin to CBSST did not significantly enhance social function on the BSFS. There were also no significant benefits for either of the two social attitude assessments: the DPAS and ABS. Consistent with several prior clinical trials (31,32), social functioning, experiential negative symptoms and defeatist performance beliefs improved in CBSST groups (primarily at the San Diego site), but oxytocin did not significantly enhance these effects at either site. Total BPRS symptoms also improved primarily at the San Diego site, but oxytocin did not add significant benefit. The results, therefore, did not support the utility of add-on intranasal oxytocin to CBSST for improvement in social function or other outcomes.

Meta-analyses of randomized clinical trials (RCTs) of intranasal oxytocin in schizophrenia have primarily focused on symptom and social cognition outcomes (44–47). An earlier meta-analysis of 6 RCTs (44) found some benefit of oxytocin for the Positive and Negative Syndrome Scale general symptom subscale, but not for positive, negative or total symptoms; a subsequent meta-analysis of 8 RCTs (46) found that oxytocin did not improve any aspect of symptoms in schizophrenia. The most recent meta-analysis (47) of ten well-controlled RCTs of intranasal oxytocin (40–80 IUs/day) versus placebo over 2–16 weeks found no significant benefit for oxytocin for total, positive or negative symptoms, although a higher dose of 80 IU/day showed greater improvements in total and positive symptoms relative to placebo. The present clinical trial using a dose of 72 IU/day, did not find any benefit for any type of symptoms. A recent meta-analysis of 12 clinical trials focused on social cognition outcomes (45) found that oxytocin did not have significant effects on social cognition, although effects were greater for higher-level social cognitive abilities (e.g. theory of mind) than for lower level abilities (e.g. social cue perception). However, in a prior report on social cognition outcomes from the present clinical trial (48), we found that the addition of oxytocin to CBSST did not significantly enhance social cognition on either higher- or lower-level social cognition tasks (i.e., empathic accuracy task, trust game, facial emotion recognition test, or reading the mind in the eyes test). Thus, consistent with many RCTs focused on symptoms and social cognition, the present RCT, which was focused on social functioning as the primary outcome, did not support the utility of add-on intranasal oxytocin to improve symptom, social cognition, or social functioning outcomes in schizophrenia. The failure to find pronounced effects with multiple dose oxytocin, versus the results from single dose oxytocin challenge studies, raises the concern that the observed effects of single dose oxytocin may reflect the temporal association of oxytocin administration and outcome assessment, rather than the potential of any long-term benefits of oxytocin, which persist beyond the immediate central nervous system effects of oxytocin (17–23; 49–51).

Participants in San Diego showed better outcomes in several symptom and functioning domains relative to participants in Maryland. One possible explanation for these site

differences is that the CBSST intervention was more effective in San Diego, due to higher fidelity in the hands of the intervention developers in San Diego. Fidelity was significantly, but only modestly, higher on the CTS-Psy fidelity scale (only 2.4 of 54 items rated higher on average) in San Diego relative to Maryland, and the therapists at both sites received very high ratings and participated in weekly joint supervision with the intervention developers (EG and JH). Participants with schizophrenia at both sites also showed comparable significant improvements in CBSST skill knowledge on the CMT, suggesting therapists at both sites were able to train, and participants were able to learn, the CBSST skills to a comparable level. Another possible explanation for the site differences found in outcomes may be related to dramatic site differences in baseline level of functioning (see Supplementary Figure 2), such that participants in San Diego had much poorer functioning, and therefore, greater room for improvement. In order to increase sample heterogeneity in baseline level of function, we chose to conduct the study at two sites. Although we were able to successfully recruit a heterogeneous sample, the heterogeneity in functioning led to significant site differences, which may have complicated our ability to detect an effect of oxytocin on our primary outcome measure. However, when we included baseline BSFS total score in the analytic model, there were no longer any site differences (data available upon request from the authors), which suggests that the observed site differences were due to differential efficacy of CBSST in participants who were more severely functionally impaired.

There were relatively few adverse effects associated with the long-term administration of oxytocin. Although the only two SAEs were both observed in the oxytocin group, neither SAE was judged to be related to the study drug. There were no significant group differences in the occurrence of adverse events or in assessed medication side effects. Oxytocin had minimal effects on vital signs, blood indices or various laboratory measures. Of particular interest, despite the concern that oxytocin might cause lower sodium levels secondary to polydipsia, participants randomized to oxytocin actually had a modest increase in sodium levels. Thus, oxytocin was safely administered even at the relatively high daily dose over six months used in this clinical trial.

This RCT had several limitations. First, although we conducted extensive training with the study participants on how to properly administer nasal oxytocin, the effectiveness of the nasal route of administration may be compromised by issues related to nasal anatomy and individual participant characteristics, which could lead to inadequate dosing of oxytocin (52). Second, we did not obtain peripheral oxytocin levels to evaluate their role in treatment response or confirm an effect of treatment on changing endogenous oxytocin. This may be important given that prior studies have demonstrated that individual differences in endogenous oxytocin levels at baseline are a significant predictor of treatment response (53; however, see 54). The availability of regular oxytocin levels could also confirm proper administration of intranasal oxytocin and medication adherence. However, we used multiple procedures to enhance adherence to the study medication, including extensive participant education on how to administer the nasal spray; weighing the intranasal oxytocin dispenser on a weekly basis; and the provision of a chart to each participant to document their administration and compliance, which was reviewed on a weekly basis. Third, we did not control for antipsychotic treatment, which has been shown to have important moderating

effects on oxytocin treatment response in some studies (52). Finally, this was a pilot trial designed as a preliminary test of efficacy and safety. The study was not adequately powered if oxytocin only has small effects above and beyond the medium effects of CBSST on key outcomes like social functioning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Demographic and Baseline Clinical Characteristics

	Oxytocin	Placebo
N	31	31
Age (years; ±S.D.)	42.8 (8.7)	40.7 (10.2)
Gender (N; % male)	18; 58.0%	20; 64.5%
Race (N)		
White	17; 54.8%	15; 48.4%
Black	9; 29.0%	7; 22.6%
Other	5; 16.1%	7; 22.6%
Education (years; ±S.D.)	13.0 (1.9)	13.4 (2.3)
Birchwood Social Function Scale (BSFS; ±S.D.)	120.0 (23.1)	115.8 (21.4)
Defeatist Performance Attitude Scale (DPAS; ±S.D.)	51.4 (19.2)	52.1 (15.3)
Asocial Beliefs Scale (ASD; ±S.D.)	6.8 (3.6)	5.5 (2.5)
SANS Total Score (±S.D.)	32.5 (8.5)	33.5 (7.8)
SANS Asociality Item Score (±S.D.)	3.1 (0.8)	3.2 (0.6)
BPRS Total Score (±S.D.)	38.2 (8.2)	40.0 (10.4)
BPRS Positive Symptom Item Score (±S.D.)	10.4 (4.9)	11.7 (6.0)
CDS Total Score (±S.D.)	3.2 (3.6)	4.5 (5.4)
CGI Severity of Illness (±S.D.)	4.2 (0.8)	4.5 (0.7)

Note: The two groups did not differ significantly on any variable.

Table 2:

Social Function and Attitude Scores by Week and Treatment Group

	Oxytocin Mean (±SD)				Placebo Mean (±SD)			
Week	**N**	**BSFS Total Score**	**DPAS Total Score**	**ABS total Score**	**N**	**BSFS Total Score**	**DPAS Total Score**	**ABS Total Score**
0	31	120.0 (23.1)	51.5 (19.2)	6.8 (3.8)	31	115.8 (21.4)	52.1 (15.3)	5.4 (2.8)
12	27	120.8 (21.9)	49.1 (19.0)	6.2 (4.0)	24	127.4 (22.2)	51.5 (15.3)	5.4 (3.4)
24	22	125.3 (20.3)	46.5 (18.1)	6.1 (3.1)	20	126.3 (17.4)	47.4 (16.8)	4.9 (3.6)
36	22	124.0 (20.2)	42.9 (18.2)	6.1 (3.6)	20	125.8 (21.4)	47.6 (16.8)	4.8 (3.9)
Week 24 change from baseline		5.0 (20.6)	−5.2 (13.4)	−1.4 (2.7)		10.2 (22.7)	−7.6 (10.7)	−0.8 (3.0)

Table 3:

Symptom Scores by Week and Treatment Group

	Oxytocin Mean (±SD)					Placebo Mean (±SD)				
Week	**N**	**BPRS Total Score**	**BPRS Positive Symptom Item Score**	**SANS Total Score**	**CDS Total Score**	**N**	**BPRS Total Score**	**BPRS Positive Symptom Item Score**	**SANS Total Score**	**CDS Total Score**
0	31	37.9 (8.1)	10.1 (4.0)	42.6 (16.0)	3.2 (3.6)	31	39.6 (10.1)	11.4 (5.2)	50.9 (16.5)	4.3 (5.0)
4	29	34.2 (6.8)	9.4 (3.7)	37.8 (14.2)	1.9 (3.0)	25	38.2 (9.0)	11.2 (5.0)	46.7 (14.0)	3.6 (4.1)
8	26	33.8 (8.8)	9.4 (3.9)	38.5 (14.5)	2.4 (3.0)	24	37.5 (8.3)	11.7 (4.5)	45.2 (13.3)	3.7 (4.5)
12	27	32.0 (6.2)	8.0 (3.4)	38.2 (13.1)	1.8 (2.4)	23	35.7 (7.8)	11.0 (4.0)	42.4 (15.3)	3.2 (4.0)
16	22	30.2 (4.4)	7.3 (2.8)	39.9 (11.6)	1.4 (1.8)	21	36.3 (10.4)	10.6 (5.2)	44.4 (17.8)	3.8 (4.6)
20	20	31.2 (6.7)	8.2 (3.6)	37.9 (12.3)	1.6 (2.4)	22	36.7 (10.1)	10.2 (5.1)	45.3 (17.7)	3.5 (4.7)
24	22	33.8 (7.0)	9.4 (3.5)	40.2 (13.1)	1.0 (1.8)	20	37.4 (9.6)	10.8 (4.6)	45.0 (14.1)	3.8 (4.5)
36	22	33.3 (5.6)	8.3 (3.1)	39.7 (12.9)	1.9 (2.0)	19	38.1 (8.6)	10.7 (4.6)	44.5 (15.0)	4.8 (4.8)
Week 24 change from baseline		−3.5 (8.3)	0.0 (3.4)	−4.6 (7.6)	−1.7(3.0)		−4.2 (8.5)	−1.2 (3.3)	−6.2 (12.5)	−0.1 (2.8)