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Rationale, Design, and Methods of the Autism Centers of Excellence (ACE) Network Study of Oxytocin in Autism to improve Reciprocal Social Behaviors (SOARS-B)

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Abstract

Objective—To describe the rationale, design, and methods of the Autism Centers of Excellence (ACE) network Study of Oxytocin in Autism to improve Reciprocal Social Behaviors (SOARS-B).

Method—This phase 2 clinical trial was designed to evaluate the use of intranasal oxytocin treatment to improve social difficulties in individuals with autism spectrum disorder (ASD). In total, 290 participants ages 3 to 17 years with a DSM-5 diagnosis of ASD were enrolled to receive 24 weeks of treatment with either oxytocin or a matched placebo. Participants were subsequently treated with open-label oxytocin for 24 additional weeks. Post-treatment assessments were done 4 weeks after treatment discontinuation. Plasma oxytocin and oxytocin receptor gene (*OXTR*) methylation level were measured at baseline, week 8, 24 and 36 to explore potential relationships between these biomarkers and treatment response.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees at the collaborating sites and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results—This report describes the rationale, design, and methods of the SOARS-B clinical trial.

Conclusions—There is a tremendous unmet need for effective pharmacological treatment options that target the core symptoms of ASD. Several studies support the hypothesis that intranasal oxytocin could improve social orienting and the salience of social rewards in ASD, thereby enhancing reciprocal social behaviors. However, due to conflicting results from a number of pilot studies on the prosocial effects of exogenous oxytocin, this hypothesis remains controversial and inconclusive. SOARS-B is the best powered study to date to address this hypothesis and promises to improve our understanding of the safety and efficacy of intranasal oxytocin in the treatment of social deficits in children with ASD.

Keywords

Autism Centers of Excellence (ACE); Autism spectrum disorder (ASD); oxytocin; clinical trials

INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition with core symptoms of persistent challenges in socialization and communication, and restricted, repetitive patterns of behavior or interests (1). These symptoms manifest early and are found throughout development, as evidenced by impairments in joint attention and social orienting across auditory and visual modalities (2–5).

ASD appears to be related, at least in part, to impairments in social processing and social motivation (6–9). Youth with ASD show slower processing of social versus nonsocial stimuli and the rate inversely correlates with the magnitude of social impairments (3). Individuals with ASD appear to experience reduced rewards from interpersonal interactions relative to other activities. They fail to activate the ventral striatum, the center of the brain's reward circuit, in response to social rewards; whereas high levels of activation are evoked by social rewards in typically developing children (10). Further, when presented with social stimuli, children with ASD show reduced activity in the prefrontal cortex, which assesses the relative value of a reward (11). The extent of this reduction also correlates with the severity of social and communication impairments in children with ASD (2, 12).

There is an increasing interest in developing pharmacologic treatments to modulate the biological mechanisms of social behavior and motivation. Current FDA-approved medications treat irritability associated with ASD, but there are no approved pharmacological treatments for the core social symptoms of ASD. To that end, the neuropeptide oxytocin is of particular interest given its role in the brain's social reward circuit. For example, oxytocin increases the amount of dopamine released from the ventral tegmental area to the ventral striatum, amygdala and hippocampus, key components for eliciting feelings of social reward. In animal models, including primates, oxytocin has been demonstrated to increase social approach, social recognition, social memory, and generosity, while reducing stress responses (13–15). Similarly in humans, exogenous oxytocin has been shown to increase gaze to eye regions, social cognition, social memory, positive communication, empathy, perceptions of trustworthiness, and cooperation within one's own group (16–31). Allelic variants in the oxytocin receptor gene (*OXTR*) have also been

correlated with infant attachment, social auditory processing, empathy, and prosocial decision-making (32–34)).

The role of the oxytocin system in social function across species has led multiple groups to investigate whether it may contribute to ASD risk, with suggestive but inconclusive results. Multiple genetic variants in the oxytocin signaling system have been associated with ASD relative to typically developing controls, while others have been associated with cognition or functioning within ASD; although none of these findings have reached genome-wide significance (32, 35–45). Modestly greater (~20-40%) *OXTR* methylation relative to controls has been reported in two small, independent ASD samples (46). Reduced plasma oxytocin in individuals with ASD have been reported in a few studies but not in others, with little consistency across studies(45–53).

METHODS

Study Rationale

Interest in the oxytocin system in ASD has extended to experimental paradigms testing its impact in either laboratory or real-world settings. Multiple studies have shown that single-dose administration of intranasal oxytocin, in comparison to placebo, impacts social behavior in ASD, particularly on tasks that index social attention/motivation (39, 56, 57) or social cognition (29, 58). These results are supported by functional magnetic resonance imaging studies showing differential brain response to social stimuli following intranasal oxytocin administration (58–61); however, these observations have been inconsistent between all studies (62). Repeated administration of intranasal oxytocin has now been investigated in several small randomized, controlled trials, with sample sizes ranging from 13-53 individuals with ASD per treatment group. Individual studies have reported benefit for social function (63–65) or social attention/cognition (66, 67); whereas meta-analyses suggest no significant benefit for social function or social cognition (68–70) despite a limited ability to draw conclusions due to differing study designs, including oxytocin formulation, participant age, duration of treatment, primary outcome measure, and statistical analysis.

Building off of previous biomarker and experimental results, we developed a working model (Figure 1) for the potential therapeutic role of intranasal oxytocin in ASD based on the impairments in social orienting and social reward in ASD and oxytocin's role in social orienting and social motivation across species. We propose that the pathophysiology of ASD fundamentally alters social orienting and decrease the relative value ascribed to social rewards, resulting in limited social motivation. Reduced social motivation leads to a cycle of reduced social opportunities, reduced learning from social feedback, reduced skills and functional abilities, and worsening of ASD's core social communication symptoms, which further reduces social motivation. In our working model, intranasal oxytocin could improve social motivation to promote a competing cycle of increased social engagement and social learning, thereby improving social communication deficits in ASD.

Based on this working model, we developed the Study of Oxytocin in Autism to improve Reciprocal Social Behaviors (SOARS-B) Network to test the chronic neurobehavioral effects of intranasal oxytocin on fundamental impairments in reciprocal social behaviors and

to identify factors that may differentially influence response to oxytocin treatment in ASD. Our central hypothesis is that intranasal oxytocin, given over a sustained period of time, will improve core social communication impairments in ASD, thereby enhancing reciprocal social behaviors. Sustained improvements in social motivation and social reciprocity are expected to facilitate communication and learning and ultimately improve functioning. We designed SOARS-B to harness a well-powered (n = 290), randomized, placebo-controlled design with a sustained (24-week), flexible-dose intranasal oxytocin treatment in children from 3- to 17-years-old with ASD, allowing us to examine clinical and biological factors that may predict or enhance response.

Design

SOARS-B is a randomized, double-blind, parallel-group, placebo-controlled trial of sustained flexible dose intranasal oxytocin treatment in 3- to 17-year-old children with ASD. As depicted in Figure 2, eligible participants were randomized to oxytocin or placebo for a 24-week double blind phase, followed by a 24-week open-label extension phase in which all participants received intranasal oxytocin.

Primary Outcome Measure

Our primary hypothesis was focused on improvements in social behavior, but previous pharmacologic studies have failed to demonstrate any changes in this core symptom domain in their efforts to develop novel treatments for ASD. Our choice of primary outcome measure was therefore shaped by the expert consensus recommendations of the workgroup on social communication outcome measures empaneled by Autism Speaks (71). The workgroup concluded that no measures were broadly appropriate for use in clinical trials without conditions (71). They judged that six measures were “appropriate with conditions,” with the Aberrant Behavior Checklist (ABC) Lethargy / Social Withdrawal subscale (ABC-LSW) (72, 73) being judged as having “the most data to support its use in clinical trials in ASD.” (71) Notably, the ABC-LSW subscale is a brief, caregiver-reported measure of real-world social behavior with excellent internal consistency, reliability, and validity (71). However, it does not assess finegrained aspects of social communication, such as the quality of social initiations or reciprocal response to non-verbal cues. Based on publications subsequent to this consensus panel (74, 75), we made the decision to focus our primary analysis on a modified ABC subscale in which 3 items corresponding to absence of movement (lethargy) were eliminated (3, *Sluggish*; 32, *Stays in one place*; and 53, *Inactive*) to avoid potential confounding with sedating effects of medication or items that are not directly related to social function (75). The validation study done in 1893 children from the Autism Treatment Network found each of these items had factor loading values below 0.6, lower than all but one of the other items (43, *Does not communicate*, factor loading of .54) (76). We will refer to the modified subscale, comprising 13 items rated from 0-3, as the ABC Social Withdrawal subscale (ABC-SW). A sensitivity analysis is planned to assess the complete ABC-LSW subscale if a significant effect is observed on the modified ABC-SW subscale.

Sample Size and Statistical Power

We used a mixed longitudinal model for our primary analyses. Since some aspects of the model, such as covariance structure, were unknown, we performed the power and sample size calculations using a more conservative, simplified model that corresponded to a two-group t-test on change scores. SOARS-B was powered to independently evaluate the efficacy of intranasal oxytocin in youth with ASD who were either capable or incapable of verbally fluent speech.

Standard deviations of change scores for the ABC-LSW range from 5 to 9 in several large ASD intervention trials (77–82). We considered a between-group difference of 5 points in ABC-SW change scores to be clinically meaningful. In our power calculations, we used conservative estimates of 9 points for the SD of ABC-SW change and 5 points for between group differences in ABC-SW changes (representing a differential improvement on ~1/3 of the items). To achieve 90% power with an alpha of 0.05 on the ABC-SW, we required 71 participants in each treatment group within the two strata. Thus, our total required sample size to separately evaluate the ABC-SW separately in non-intellectual disability (ID) and ID strata was 284. A sample size of 300 allowed for a 5% attrition between the randomization and the first post-randomization visits. In March 2016, the study team reduced the estimated attrition rate to 1% based on the actual attrition rates observed during in the study, which led to a final sample size of 290. The primary analysis included all participants, which resulted in a much greater power than would have been the case for analyses in separate strata.

Participants

Individuals aged 3- to 17-years-old with ASD were recruited from clinical programs, research registries, and community referrals at each site. Most of the participants were in outpatient clinical care at the time of referral. The inclusion and exclusion criteria are described in Table 1. Notably, we did not include a minimum score threshold on any of the primary or secondary outcome measures as part of our inclusion criteria due to a desire to avoid inflated effects in the placebo group due to regression to the mean. Since impaired reciprocal social communication is an ASD diagnostic criterion, a minimum score threshold that excluded potential participants would also, by definition, be excluding youth with clinically meaningful impairment.

Study Procedures and Assessments

Participants were assessed at week 4, 8, 16, 20, and 24 during the double-blind phase and week 28, 36, and 48 during the open-label phase (Figure 2, Supplemental Table 1 for a schedule of procedures). Symptom assessment, side effect monitoring, and parent questionnaires occurred at each visit, with laboratory monitoring, electrocardiogram, and functional assessments scheduled during the course of the study. The following includes a description of diagnostic and outcome measures, safety monitoring, and biomarkers completed during the course of the study.

Diagnostic Measures

Autism Diagnostic Observation Schedule-2 (ADOS-2): The ADOS-2 is a semi-structured assessment used to assess and diagnose individuals suspected of having autism. It is applicable to individuals of varying ages, developmental levels, and language skills (from no speech to verbally fluent). A research reliable rater administered one of the four modules depending on the expressive language level and chronological age of the study participant. The rater used observations of social and communication behaviors during the appropriate module to assist with a clinical diagnosis of ASD.

Autism Diagnostic Interview-Revised (ADI-R): The ADI-R is a semi-structured, investigator-based interview for caregivers of children and adults who are suspected to have a diagnosis of autism. A research reliable rater completed the ADI-R at the screening visit at the discretion of the study physician.

DSM-5 Checklist: The diagnostic criteria of ASD were assessed according to DSM-5 criteria by the study physician at the screening visit.

Mullen Scales of Early Learning: The Mullen Scales of Early learning (85) was administered for nonverbal study participants or children younger than 5 years 9 mo assessed with the ADOS Module 1 or 2. The Visual reception, fine motor, expressive language and receptive language scales were administered.

Stanford Binet Intelligence Scales 5th edition: The Stanford-Binet intelligence scale (86) is a standardized test that assesses intelligence and cognitive abilities in children and adults aged two to 85+ years. The Stanford-Binet Scale tests intelligence across four areas: verbal reasoning, quantitative reasoning, abstract/visual reasoning, and short-term memory. The areas are covered by 15 subtests, including vocabulary, comprehension, verbal absurdities, pattern analysis, matrices, paper folding and cutting, copying, quantitative, number series, equation building, memory for sentences, memory for digits, memory for objects, and bead memory. The abbreviated IQ (ABIQ) was used for this study and includes non-verbal fluid reasoning and verbal knowledge subtests.

Outcome Measures

Aberrant Behavior Checklist (ABC): The 58-item caregiver rated ABC focuses on problem behaviors in five subdomains: irritability, lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech (72, 73). The study primary outcome, the ABC-SW score, was calculated by removing questions 3, 32, and 53, (which all assess reduced physical movement), from the ABC-lethargy/social withdrawal subscale and summing the remaining questions.

Social Responsiveness Scale-2: This 65-item, caregiver-rated scale measures the severity of autism spectrum symptoms as they occur in natural social settings (87). The SRS-2 provides an assessment of a child's social impairments, including social awareness, social information processing, capacity for reciprocal social communication, social anxiety/avoidance, and autistic preoccupations and traits. It is appropriate for use with children aged

2.5 to 18 years. The SRS-2 measures impairment on a quantitative scale across a wide severity range, which is consistent with recent research indicating that autism is best conceptualized as a spectrum condition.

Pervasive Developmental Disorders Behavior Inventory (PDDBI-Screening Version) -—The PDDBI-SV is a caregiver rated measure that examines both adaptive and maladaptive behaviors related to social behavior in ASD (88).

Caregiver Strain Questionnaire (CSQ): The CSQ assesses family stress and has been tested with caregivers of children with ASD (89).

Vineland Adaptive Behavior Scales (2nd edition, Parent/Caregiver Rating Form, VABS-II-PCRF (90)): The VABS-II-PCRF is completed by a parent or caregiver in a questionnaire format and is organized around four Behavior Domains: communication, daily living skills, socialization, and motor skills. For the purposes of this study, we did not assess the maladaptive behavior domain of the VABS-II-PCRF.

Child and Adolescent Symptom Inventory-Progress Monitor-Parent Form (CASI-PM-P): This is a 29-item caregiver rating scale that evaluates symptom change for common psychiatric disorders in children and adolescents (91). The parent form can be used for a global rating of anxiety, ADHD, behavioral disorders, and depression.

Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Improvement (CGI-I): These are 7-point Likert scale ratings that are completed by a study clinician (92), which allows for a general rating of ASD symptom severity and change over time.

Reading the Mind in the Eves Test (RMET): This test evaluates a participant's ability to identify the emotional state from four choices based upon expressive pictures of the upper face, primarily with a focus on the eyes and eyebrows (93, 94). Due to the verbal demands of the test, the RMET was only utilized for children and adolescents in the verbally fluent stratum (see below).

Safety Monitoring

Electrocardiogram (ECG): A 12 lead ECG was obtained on all participants at screening and week 24 and the reading was confirmed by a pediatric cardiologist.

Laboratory assessments: Non-fasting blood chemistries, liver enzymes, urinalysis, and urine pregnancy (in pubertal females) were obtained at screening, week 24 and week 36. Labs could be repeated at study physician discretion at week 48. A certified laboratory conducted the blood and urine analysis.

Suicidality Assessment: Suicidality was assessed by a study physician at each study visit._ The study physician utilized clinical judgment to determine if the study participant understood the concept of death and suicide and asked participants standardized questions about passive death wish, suicidal ideation, suicidal behaviors, and self-injury at each visit.

The caregiver was also asked about each item and if this was a significant change in severity of frequency from the participant's baseline. The study physician determined whether self-injurious behaviors were stereotypic or were not considered stereotypic.

Systematic Longitudinal Adverse Events Scale (SLAES): This measure was adapted from the Safety Monitoring Uniform Report Form [95,96] and allowed for continuous monitoring of adverse events from the initial visit. Medical and behavioral conditions were assessed at each visit and those that were present at screening and/or baseline were considered treatment-emergent if their severity increased significantly after the participant had taken at least one dose of the study treatment. Treatment-emergent adverse events were tracked and considered in the adverse event safety analysis. Severity of adverse events were categorized as mild, moderate, severe, life-threatening, or resulting in death, and the treating physician indicated if the adverse event was related or unrelated to study drug. Suicidal ideation or behaviors, and self-injurious behaviors were summarized at each time point, as well as if these represented a significant change in frequency or severity from the child's baseline level of functioning.

Vital Signs: Vital signs including heart rate, sitting blood pressure, and temperature were collected at each study visit.

Biomarkers

Oxytocin levels: Plasma and salivary oxytocin levels were assayed at weeks 0, 8, 24, and 36 using standard radioimmunoassays to describe potential relationships between baseline levels and treatment response.

Genetic markers: Methylation and mRNA expression studies were completed at weeks 0, 8, 24, and 36.

Serotonin levels: Serum serotonin levels were measured from whole blood samples at weeks 0, 8, 24, and 36.

Randomization

Participants eligible for this study were stratified by verbal fluency. To harness an easily operationalized measure, we used capacity to perform ADOS module 3 or 4 as an indication of verbal fluency in the social context. Participants were further stratified by age (three age groups) using a centralized, randomization scheme with permuted blocks of 4 or 6. The unblinded statistician generated a randomization plan for each of the 6 strata, using a permuted block algorithm with randomly selected block sizes of 2 and 4, using SAS. A randomization form was used to assign participants to the appropriate stratum. The database randomly assigned the treatment, generated an ID number, and sent an email to the appropriate site's research pharmacy. Enrollment within the two verbal fluency strata was monitored to ensure at least 142 participants in each. Participants were further stratified by age so that at least 21% of the participants within each stratum fell into each of the specified age groups 3-6, 7-11, 12-17 years to fully assess the potential moderating effects of age.

Interrater Reliability

Before the study was initiated, the investigators and site raters established interrater reliability for the ADOS-2, ADI-R, Stanford Binet, Mullen Scales of Early Learning, the CGI-I and CGI-S scales. ADOS-2 and ADI-R raters were trained by each site's independently reliable raters, completing a double-scored administration for at least one form of each scale, and observation on up to six administrations. The ADOS-2 and ADI-R raters reached 80% and 90% reliability, respectively. Consensus discussions occurred with a supervising psychologist. Cases were presented at investigator telephone conferences to address questions about ratings, diagnosis, and adverse events.

Medication Administration

Intranasal oxytocin was formulated for the study by the lead site and contained the synthetic oxytocin peptide in a formulation that was concentrated so that a higher dose could be administered with fewer insufflations, since only a limited volume can be sprayed into the nasal cavity. The matched placebo solution was the same formulation but did not include the synthetic oxytocin and was packaged in an indistinguishable amber nasal administration bottle. Detailed administration instructions were provided to the parent and the child to ensure that the drug was properly administered. Medication adherence was assessed by review of parent-completed medication diary.

The initial titration to the target dose was performed from baseline to week 8 and followed the suggested dosing schedule shown in Table 2. Dosing began at 8 or 0 (placebo) IU in the AM at week 0. The dose was increased to 8/0 IU twice daily (BID) at week 2. Dose was then increased by 8/0 IU twice daily (BID) at weeks 4 and 8. The dose could be reduced by 8/0 IU once or twice a day any time between week 2 and achievement of the target dose at the clinician's discretion, whether due to a clinically significant adverse event, poor tolerability of dosing, parent request, or CGI-I of 6 (much worse) or 7 (very much worse). The dose was not subsequently increased without reassessing the participant. Dosage was increased by 8/0 IU 1-2 x/day between scheduled visits in order to achieve the target dose of 24/0 IU twice daily or 48/0 IU total daily dose as close to the week 8 visit as possible. All dosing reductions were discussed with the site PI within 2 business days and reported to the lead site for discussion with treating site PIs. If the target dose was maintained for at least 7 weeks, the dose could be increased by only 8/0 IU 2x/day or 16/0 IU total daily dose. Thus, at week 16, the maximal possible dose was 32/0 IU BID or 64/0 IU total daily dose. At week 20, the dose could also be increased again by only 8/0 IU 2x/day or 16/0 IU total daily dose. If there had been no prior increase at week 16, then the week 20 dose could be increased to 32/0 IU BID or 64/0 IU total daily dose. If the dose had been increased at week 16, then the week 20 dose could be increased to 40/0 IU BID or 80/0 IU total daily dose. Increases were not required and only made with the agreement of the parent, child, and clinician in instances where the CGI-I was not a 1 and there was no evidence of clinically significant adverse events.

Every effort was made to achieve the target daily dose of 48 IU unless a child was unable to tolerate it. Table 3 shows the suggested dosing titration schedule to reach target dose. Dose titration was flexible and could not proceed more rapidly than stated below, but it could

proceed more slowly based on clinician judgment. At week 24 participants began the open-label dosing schedule.

Mandatory dose reductions were in place for any of the following events: the clinician judged an adverse event (AE) to require immediate reduction, the CGI-I score was 6 (much worse) or 7 (very much worse), or if the two consecutive CGI-I scores at in-person visits were worse than the preceding two CGI-I scores and the treating clinician was comfortable with the decrease. Optional dose reductions occurred in the blinded phase by 8 IU once or twice daily due to a clinically significant adverse event, poor tolerability of dosing, or parent request. Dose increases above the target dose of 48 IU per day occurred if there was no evidence of clinically significant AEs, and parents and clinician were in agreement. During the follow-up phase, the oxytocin was tapered off over the course of 1-3 weeks. The down titration schedule depended on the total daily dose (TDD) at week 48. Participants receiving 72 IU TDD at week 48 were tapered off over the course of 3 weeks, participants receiving 48 IU TDD took 2 weeks, and participants on 24 IU TDD stopped after 1 week.

Administration of oxytocin could be interrupted on rare occasions due to other clinical conditions that temporarily prevent nasal administration (i.e., nasal injury or temporary severe nasal congestion), poor compliance with administration directions, or significant adverse events or acute worsening of symptoms or functioning. The treating clinician could restart treatment at the same or a lower dose after assessment of the participant.

Concurrent Medications and Therapies

Children with ASD are likely to be on concurrent medications, such as risperidone for irritability, divalproex for co-occurring seizure disorder, or methylphenidate for Attention Deficit/Hyperactivity Disorder (ADHD) symptoms. Thus, we felt that it was reasonable to allow concomitant medications in order to best represent a real-world sample. When SOARS-B began, serotonin reuptake inhibitors were not permitted due to concern that they might mask an anxiolytic effect of oxytocin, and potential participants were tapered off these medications prior to randomization. These guidelines changed in version 5.0 of the protocol (2015), in response to concerns with recruitment and the generalizability of the sample.

All concomitant medications were recorded at each visit. Medications that were used as needed (PRN) were not recorded unless they were taken for a period of 2 weeks or more and were taken more than 57% of the time, unless the clinician felt there was a valid reason to document them. All changes to the participants' medications from baseline were recorded.

Concurrent allied health therapies were recorded at each visit, including speech or occupational therapy, applied behavior analysis, psychotherapy, and social skills therapy. No changes in therapies were permitted within the 2 months prior to randomization.

Human Subjects Protections

SOARS-B was reviewed and approved by the institutional review board at each site. Written parental consent and participant assent (when clinically appropriate) was obtained for all of the participants. The UNC Tracs Data Safety Monitoring Board (DSMB) reviewed the safety data throughout the study.

Study Modifications

Several protocol modifications were instituted based on clinical and/or regulatory changes during the course of the study. See Supplemental Table 1 for a summary of protocol changes.

DISCUSSION

As a phase 2 study, SOARS-B was designed be an adequately powered test of the hypothesis that sustained administration of intranasal oxytocin improves social function in ASD, while evaluating its safety and tolerability. Prior trials have been underpowered, and, while individual studies have suggested that intranasal oxytocin may benefit social function (63–67), meta-analyses have found no significant benefit across studies (68–70). The variability in these studies makes it difficult to draw conclusions, including differences in dose or duration of treatment as well as participant characteristics, such as age or cognitive function. To address this in SOARS-B, we used an extended period of dosing to allow for detection of both potential early- or late-emerging benefits from intranasal oxytocin. While we targeted 24 IU twice daily as the most commonly used dose in previous studies, we also used flexible dosing to allow for selection of the most efficacious and well-tolerated dose, including allowing clinicians and caregivers/participants to increase beyond the target dose in the later portions of the trial. In this way, we are prepared to evaluate response at different time points or dose levels, thereby informing future studies.

Given the variability in prior studies and our desire provide a comprehensive evaluation of intranasal oxytocin as a potential treatment, we included a diverse population of both children and adolescents. We defined strata by both age and communication ability, allowing us to capture the full spectrum within ASD. Beyond establishing a generalizable population, we aimed to generate a well-powered primary analysis as well as adequate power to explore key subpopulations, which has not previously been possible in prior studies of intranasal oxytocin. Young children were included in SOARS-B because they could potentially demonstrate significantly greater functional improvements than older children as a result of greater brain plasticity. Children and adolescents of all functioning levels were included in SOARS-B to ensure that those with lower communication ability are not neglected in studies of novel treatments that could have a disproportionately large impact on those who are most affected. We also chose to be inclusive at the level of concomitant treatments, including both behavioral and medical treatments. Between 30-60% of children with ASD are prescribed a psychotropic medication (95, 96). To avoid excluding this large proportion of individuals with ASD from our analyses, we chose to include participants that were taking these medications, which also improves our generalizability. Instead, we will perform secondary post-hoc analyses of various clinical and biological factors that might typically be excluded (e.g. concomitant medication treatment) will be performed instead. Using these approaches will let us provide the greatest amount of clinically relevant information regarding sustained intranasal oxytocin treatment and do so in an expeditious manner.

The absence of any definitive evidence that current treatments, whether behavioral or medical, improve social function in ASD makes it difficult to identify outcome measures that are sufficiently sensitive to detect changes in social behavior. We selected the ABD-SW

subscale as the primary outcome measure based on consensus recommendations as previously described (71). This measure also has the advantage of being validated for individuals with and without ID, an important consideration in our broad, generalizable population (71). As appropriate for a phase 2 study, however, we included multiple secondary outcome measures to evaluate whether a different measure might be a better indicator of change in reciprocal social behavior with intranasal oxytocin. While we would have preferred to include additional direct assessment measures of social cognition and function, budgetary constraints prevented extensive video monitoring or eye tracking. The Reading the Mind in the Eyes Test allowed an assessment of social cognition in the stratum of children with high communication ability but was not well-suited to those who required ADOS-2 modules 1 or 2.

As in any phase 2 study, priority was also given to identifying potential safety signals in this large population. To date, adverse event monitoring in pediatric trials of oxytocin have used a variety of methods, which is a prevalent issue across pediatric clinical trials in general (97). The SOARS-B trial therefore moved to standardize AE monitoring by using a prospective systematic (body systems approach) elicitation of adverse events using the Systematic Longitudinal Adverse Events Scale (SLAES), complemented by both physical exam and monitoring of safety labs and ECG over the course of the trial. We also used the clinical global impression of improvement assessment to flag participants whose behavior appeared to be worsening over the course of treatment with oxytocin or placebo, regardless of whether this corresponded to a specific adverse event. This trial will be the largest and most generalizable pediatric cohort using systematically elicited AEs assessed during sustained oxytocin treatment.

In conclusion, SOARS-B was designed to meet the tremendous unmet need for accessible treatments that address core symptoms of ASD and are safe for sustained use. Several lines of evidence support the hypothesis that intranasal oxytocin could partially reverse the early pathophysiologic alterations in social orienting and the salience of social rewards present in ASD, thereby enhancing reciprocal social behaviors. The SOARS-B study will improve our understanding of the safety and efficacy of intranasal oxytocin in the treatment of reciprocal social behaviors in children with ASD. Regardless of the outcome, the results will significantly impact the care of people with ASD by definitively testing a very promising translational treatment strategy in a highly generalizable sample. The potential for subgroup and moderator analyses in this large sample may also help guide the therapeutic implementation of intranasal oxytocin to individuals that can benefit the most from it. Finally, future genetic and molecular studies of samples collected from the SOARS-B participants could enhance our understanding of the biological mechanisms that affect endogenous oxytocin signaling in ASD and identify new therapeutic targets to augment its prosocial effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES:

1. DSM-5. (DSM-5)Diagnostic and Statistical manual of Mental Disorders 5th edition. Association AP, editor 2013.
2. Dawson G, Meltzoff AN, Osterling J, Rinaldi J. Neuropsychological correlates of early symptoms of autism. Child Dev. 1998;69(5):1276–85. [PubMed: 9839415]
3. Dawson G, Webb SJ, Carver L, Panagiotides H, McPartland J. Young children with autism show atypical brain responses to fearful versus neutral facial expressions of emotion. Dev Sci. 2004;7(3):340–59. [PubMed: 15595374]
4. Sasson NJ, Turner-Brown LM, Holtzclaw TN, Lam KS, Bodfish JW. Children with autism demonstrate circumscribed attention during passive viewing of complex social and nonsocial picture arrays. Autism Res. 2008;1(1):31–42. [PubMed: 19360648]
5. Whitehouse AJ, Bishop DV. Do children with autism 'switch off' to speech sounds? An investigation using event-related potentials. Dev Sci. 2008;11(4):516–24. [PubMed: 18576959]
6. Waterhouse L, Fein D, Modahl C. Neurofunctional mechanisms in autism. Psychol Rev. 1996;103(3):457–89. [PubMed: 8759044]
7. Dawson G, Carver L, Meltzoff AN, Panagiotides H, McPartland J, Webb SJ. Neural correlates of face and object recognition in young children with autism spectrum disorder, developmental delay, and typical development. Child Dev. 2002;73(3):700–17. [PubMed: 12038546]
8. Grelotti DJ, Gauthier I, Schultz RT. Social interest and the development of cortical face specialization: what autism teaches us about face processing. Dev Psychobiol. 2002;40(3):213–25. [PubMed: 11891634]

9. Dawson G, Webb SJ, Wijsman E, Schellenberg G, Estes A, Munson J, et al. Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: implications for a model of abnormal development of social brain circuitry in autism. Dev Psychopathol. 2005;17(3):679–97. [PubMed: 16262987]
10. Scott-Van Zeeland AA, Dapretto M, Ghahremani DG, Poldrack RA, Bookheimer SY. Reward processing in autism. Autism Res. 2010;3(2):53–67. [PubMed: 20437601]
11. Greene DJ, Colich N, Iacoboni M, Zaidel E, Bookheimer SY, Dapretto M. Atypical neural networks for social orienting in autism spectrum disorders. Neuroimage. 2011;56(1):354–62. [PubMed: 21334443]
12. Ohnishi T, Matsuda H, Hashimoto T, Kunihiro T, Nishikawa M, Uema T, et al. Abnormal regional cerebral blood flow in childhood autism. Brain. 2000;123 (Pt 9):1838–44. [PubMed: 10960047]
13. Takayanagi Y, Yoshida M, Bielsky IF, Ross HE, Kawamata M, Onaka T, et al. Pervasive social deficits, but normal parturition, in oxytocin receptor-deficient mice. Proc Natl Acad Sci U S A. 2005;102(44):16096–101. [PubMed: 16249339]
14. Liu HX, Lopatina O, Higashida C, Tsuji T, Kato I, Takasawa S, et al. Locomotor activity, ultrasonic vocalization and oxytocin levels in infant CD38 knockout mice. Neurosci Lett. 2008;448(1):67–70. [PubMed: 18926879]
15. Insel TR. The challenge of translation in social neuroscience: a review of oxytocin, vasopressin, and affiliative behavior. Neuron. 2010;65(6):768–79. [PubMed: 20346754]
16. Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. Nature. 2005;435(7042):673–6. [PubMed: 15931222]
17. Domes G, Heinrichs M, Michel A, Berger C, Herpertz SC. Oxytocin improves “mind-reading” in humans. Biol Psychiatry. 2007;61(6):731–3. [PubMed: 17137561]
18. Zak PJ, Stanton AA, Ahmadi S. Oxytocin increases generosity in humans. PLoS One. 2007;2(11):e1128. [PubMed: 17987115]
19. Guastella AJ, Mitchell PB, Mathews F. Oxytocin enhances the encoding of positive social memories in humans. Biol Psychiatry. 2008;64(3):256–8. [PubMed: 18343353]
20. Petrovic P, Kalisch R, Singer T, Dolan RJ. Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. J Neurosci. 2008;28(26):6607–15. [PubMed: 18579733]
21. Savaskan E, Ehrhardt R, Schulz A, Walter M, Schachinger H. Post-learning intranasal oxytocin modulates human memory for facial identity. Psychoneuroendocrinology. 2008;33(3):368–74. [PubMed: 18221838]
22. Unkelbach C, Guastella AJ, Forgas JP. Oxytocin selectively facilitates recognition of positive sex and relationship words. Psychol Sci. 2008;19(11):1092–4. [PubMed: 19076479]
23. Di Simplicio M, Massey-Chase R, Cowen PJ, Harmer CJ. Oxytocin enhances processing of positive versus negative emotional information in healthy male volunteers. J Psychopharmacol. 2009;23(3):241–8. [PubMed: 18801829]
24. Ditzen B, Schaer M, Gabriel B, Bodenmann G, Ehlert U, Heinrichs M. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biol Psychiatry. 2009;65(9):728–31. [PubMed: 19027101]
25. Rimmele U, Hediger K, Heinrichs M, Klaver P. Oxytocin makes a face in memory familiar. J Neurosci. 2009;29(1):38–42. [PubMed: 19129382]
26. Theodoridou A, Rowe AC, Penton-Voak IS, Rogers PJ. Oxytocin and social perception: oxytocin increases perceived facial trustworthiness and attractiveness. Horm Behav. 2009;56(1):128–32. [PubMed: 19344725]
27. De Dreu CK, Greer LL, Handgraaf MJ, Shalvi S, Van Kleef GA, Baas M, et al. The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans. Science. 2010;328(5984):1408–11. [PubMed: 20538951]
28. Fischer-Shofty M, Shamay-Tsoory SG, Harari H, Levkovitz Y. The effect of intranasal administration of oxytocin on fear recognition. Neuropsychologia. 2010;48(1):179–84. [PubMed: 19747930]
29. Guastella AJ, Einfeld SL, Gray KM, Rinehart NJ, Tonge BJ, Lambert TJ, et al. Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. Biological psychiatry. 2010;67(7):692–4. [PubMed: 19897177]

30. Buchheim A, Heinrichs M, George C, Pokorny D, Koops E, Henningsen P, et al. Oxytocin enhances the experience of attachment security. Psychoneuroendocrinology. 2009;34(9):1417–22. [PubMed: 19457618]

31. Bartz JA, Zaki J, Bolger N, Hollander E, Ludwig NN, Kolevzon A, et al. Oxytocin selectively improves empathic accuracy. Psychol Sci. 2010;21(10):1426–8. [PubMed: 20855907]

32. Lerer E, Levi S, Israel S, Yaari M, Nemanov L, Mankuta D, et al. Low CD38 expression in lymphoblastoid cells and haplotypes are both associated with autism in a family-based study. Autism Res. 2010;3(6):293–302. [PubMed: 21182206]

33. Chen FS, Barth ME, Johnson SL, Gotlib IH, Johnson SC. Oxytocin Receptor (OXTR) Polymorphisms and Attachment in Human Infants. Front Psychol. 2011;2:200. [PubMed: 21904531]

34. Tops M, van Ijzendoorn MH, Riem MM, Boksem MA, Bakermans-Kranenburg MJ. Oxytocin receptor gene associated with the efficiency of social auditory processing. Front Psychiatry. 2011;2:60. [PubMed: 22069391]

35. Green L, Fein D, Modahl C, Feinstein C, Waterhouse L, Morris M. Oxytocin and autistic disorder: alterations in peptide forms. Biol Psychiatry. 2001;50(8):609–13. [PubMed: 11690596]

36. Wu S, Jia M, Ruan Y, Liu J, Guo Y, Shuang M, et al. Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han population. Biol Psychiatry. 2005;58(1):74–7. [PubMed: 15992526]

37. Jacob S, Brune CW, Carter CS, Leventhal BL, Lord C, Cook EH Jr. Association of the oxytocin receptor gene (OXTR) in Caucasian children and adolescents with autism. Neurosci Lett. 2007;417(1):6–9. [PubMed: 17383819]

38. Yrigollen CM, Han SS, Kochetkova A, Babitz T, Chang JT, Volkmar FR, et al. Genes controlling affiliative behavior as candidate genes for autism. Biol Psychiatry. 2008;63(10):911–6. [PubMed: 18207134]

39. Andari E, Duhamel JR, Zalla T, Herbrecht E, Leboyer M, Sirigu A. Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. Proc Natl Acad Sci U S A. 2010;107(9):4389–94. [PubMed: 20160081]

40. Liu X, Kawamura Y, Shimada T, Otowa T, Koishi S, Sugiyama T, et al. Association of the oxytocin receptor (OXTR) gene polymorphisms with autism spectrum disorder (ASD) in the Japanese population. J Hum Genet. 2010;55(3):137–41. [PubMed: 20094064]

41. Munesue T, Yokoyama S, Nakamura K, Anitha A, Yamada K, Hayashi K, et al. Two genetic variants of CD38 in subjects with autism spectrum disorder and controls. Neurosci Res. 2010;67(2):181–91. [PubMed: 20435366]

42. Tansey KE, Brookes KJ, Hill MJ, Cochrane LE, Gill M, Skuse D, et al. Oxytocin receptor (OXTR) does not play a major role in the aetiology of autism: genetic and molecular studies. Neurosci Lett. 2010;474(3):163–7. [PubMed: 20303388]

43. Wermter AK, Kamp-Becker I, Hesse P, Schulte-Korne G, Strauch K, Remschmidt H. Evidence for the involvement of genetic variation in the oxytocin receptor gene (OXTR) in the etiology of autistic disorders on high-functioning level. Am J Med Genet B Neuropsychiatr Genet. 2010;153B(2):629–39. [PubMed: 19777562]

44. Campbell DB, Datta D, Jones ST, Batey Lee E, Sutcliffe JS, Hammock EA, et al. Association of oxytocin receptor (OXTR) gene variants with multiple phenotype domains of autism spectrum disorder. J Neurodev Disord. 2011;3(2):101–12. [PubMed: 21484202]

45. Riebold M, Mankuta D, Lerer E, Israel S, Zhong S, Nemanov L, et al. All-trans retinoic acid upregulates reduced CD38 transcription in lymphoblastoid cell lines from Autism spectrum disorder. Mol Med. 2011;17(7-8):799–806. [PubMed: 21528155]

46. Gregory SG, Connelly JJ, Towers AJ, Johnson J, Biscocho D, Markunas CA, et al. Genomic and epigenetic evidence for oxytocin receptor deficiency in autism. BMC Med. 2009;7:62. [PubMed: 19845972]

47. Modahl C, Green L, Fein D, Morris M, Waterhouse L, Feinstein C, et al. Plasma oxytocin levels in autistic children. Biological Psychiatry. 1998;43(4):270–7. [PubMed: 9513736]

48. Zhang HF, Dai YC, Wu J, Jia MX, Zhang JS, Shou XJ, et al. Plasma Oxytocin and Arginine-Vasopressin Levels in Children with Autism Spectrum Disorder in China: Associations with Symptoms. Neurosci Bull. 2016;32(5):423–32. [PubMed: 27342432]

49. Husarova VM, Lakatosova S, Pivovarciova A, Babinska K, Bakos J, Durdiakova J, et al. Plasma Oxytocin in Children with Autism and Its Correlations with Behavioral Parameters in Children and Parents. Psychiatry Investig. 2016;13(2):174–83.

50. Parker KJ, Garner JP, Libove RA, Hyde SA, Hornbeak KB, Carson DS, et al. Plasma oxytocin concentrations and OXTR polymorphisms predict social impairments in children with and without autism spectrum disorder. Proc Natl Acad Sci U S A. 2014;111(33):12258–63. [PubMed: 25092315]

51. Taurines R, Schwenck C, Lyttwin B, Schecklmann M, Jans T, Reefschlager L, et al. Oxytocin plasma concentrations in children and adolescents with autism spectrum disorder: correlation with autistic symptomatology. Atten Defic Hyperact Disord. 2014;6(3):231–9. [PubMed: 24989441]

52. Al-Ayadhi LY. Altered oxytocin and vasopressin levels in autistic children in Central Saudi Arabia. Neurosciences (Riyadh). 2005;10(1):47–50. [PubMed: 22473184]

53. Alabdali A, Al-Ayadhi L, El-Ansary A. Association of social and cognitive impairment and biomarkers in autism spectrum disorders. J Neuroinflammation. 2014;11:4. [PubMed: 24400970]

54. Feldman R, Golan O, Hirschler-Guttenberg Y, Ostfeld-Etzion S, Zagoory-Sharon O. Parent-child interaction and oxytocin production in pre-schoolers with autism spectrum disorder. Br J Psychiatry. 2014;205(2):107–12. [PubMed: 24855128]

55. Miller M, Bales KL, Taylor SL, Yoon J, Hostetler CM, Carter CS, et al. Oxytocin and vasopressin in children and adolescents with autism spectrum disorders: sex differences and associations with symptoms. Autism Res. 2013;6(2):91–102. [PubMed: 23413037]

56. Kanat M, Spenthof I, Riedel A, van Elst LT, Heinrichs M, Domes G. Restoring effects of oxytocin on the attentional preference for faces in autism. Translational psychiatry. 2017;7(4):e1097. [PubMed: 28418399]

57. Althaus M, Groen Y, Wijers AA, Noltes H, Tucha O, Hoekstra PJ. Oxytocin enhances orienting to social information in a selective group of high-functioning male adults with autism spectrum disorder. Neuropsychologia. 2015;79(Pt A):53–69. [PubMed: 26498227]

58. Watanabe T, Abe O, Kuwabara H, Yahata N, Takano Y, Iwashiro N, et al. Mitigation of sociocommunicational deficits of autism through oxytocin-induced recovery of medial prefrontal activity: a randomized trial. JAMA psychiatry. 2014;71(2):166–75. [PubMed: 24352377]

59. Gordon I, Vander Wyk BC, Bennett RH, Cordeaux C, Lucas MV, Eilbott JA, et al. Oxytocin enhances brain function in children with autism. Proc Natl Acad Sci U S A. 2013;110(52):20953–8. [PubMed: 24297883]

60. Gordon I, Jack A, Pretzsch CM, Vander Wyk B, Leckman JF, Feldman R, et al. Intranasal Oxytocin Enhances Connectivity in the Neural Circuitry Supporting Social Motivation and Social Perception in Children with Autism. Scientific reports. 2016;6:35054. [PubMed: 27845765]

61. Kruppa JA, Gossen A, Oberwelland Weiss E, Kohls G, Grossheinrich N, Cholemkery H, et al. Neural modulation of social reinforcement learning by intranasal oxytocin in male adults with high-functioning autism spectrum disorder: a randomized trial. Neuropsychopharmacology. 2019;44(4):749–56. [PubMed: 30390065]

62. Greene RK, Spanos M, Alderman C, Walsh E, Bizzell J, Mosner MG, et al. The effects of intranasal oxytocin on reward circuitry responses in children with autism spectrum disorder. J Neurodev Disord. 2018;10(1):12. [PubMed: 29587625]

63. Parker KJ, Oztan O, Libove RA, Sumiyoshi RD, Jackson LP, Karhson DS, et al. Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism. Proceedings of the National Academy of Sciences of the United States of America. 2017;114(30):8119–24. [PubMed: 28696286]

64. Watanabe T, Kuroda M, Kuwabara H, Aoki Y, Iwashiro N, Tatsunobu N, et al. Clinical and neural effects of six-week administration of oxytocin on core symptoms of autism. Brain. 2015;138(Pt 11):3400–12. [PubMed: 26336909]

65. Kosaka H, Okamoto Y, Munesue T, Yamasue H, Inohara K, Fujioka T, et al. Oxytocin efficacy is modulated by dosage and oxytocin receptor genotype in young adults with high-functioning

autism: a 24-week randomized clinical trial. Translational psychiatry. 2016;6(8):e872. [PubMed: 27552585]

66. Yamasue H, Okada T, Munesue T, Kuroda M, Fujioka T, Uno Y, et al. Effect of intranasal oxytocin on the core social symptoms of autism spectrum disorder: a randomized clinical trial. Mol Psychiatry. 2018.
67. Anagnostou E, Soorya L, Chaplin W, Bartz J, Halpern D, Wasserman S, et al. Intranasal oxytocin versus placebo in the treatment of adults with autism spectrum disorders: a randomized controlled trial. Molecular autism. 2012;3(1):16. [PubMed: 23216716]
68. Wang Y, Wang M-J, Rong Y, He H-Z, Yang C-J. Oxytocin therapy for core symptoms in autism spectrum disorder: An updated meta-analysis of randomized controlled trials. Res Autism Spectr Disord. 2019;64:63–75.
69. Ooi YP, Weng SJ, Kossowsky J, Gerger H, Sung M. Oxytocin and Autism Spectrum Disorders: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Pharmacopsychiatry. 2017;50(1):5–13. [PubMed: 27574858]
70. Keech B, Crowe S, Hocking DR. Intranasal oxytocin, social cognition and neurodevelopmental disorders: A meta-analysis. Psychoneuroendocrinology. 2018;87:9–19. [PubMed: 29032324]
71. Anagnostou E, Jones N, Huerta M, Halladay AK, Wang P, Scahill L, et al. Measuring social communication behaviors as a treatment endpoint in individuals with autism spectrum disorder. Autism : the international journal of research and practice. 2014.
72. Aman MG, Singh NN, Stewart AW, Field CJ. The Aberrant Behavior Checklist: A behavior rating scale for the assessement of treatment effects. Am J Ment Def. 1985;39(5):485–91.
73. Aman MG, Singh NN, Stewart AW, Field CJ. Psychometric characteristics of the Aberrant Behavior Checklist. Am J Ment Def. 1985;89(5):492–502.
74. Scahill L, Hallett V, Aman MG, McDougle CJ, Eugene Arnold L, McCracken JT, et al. Brief Report: social disability in autism spectrum disorder: results from Research Units on Pediatric Psychopharmacology (RUPP) Autism Network trials. J Autism Dev Disord. 2013;43(3):739–46. [PubMed: 23104617]
75. Veenstra-VanderWeele J, Cook EH, King BH, Zarevics P, Cherubini M, Walton-Bowen K, et al. Arbaclofen in Children and Adolescents with Autism Spectrum Disorder: A Randomized, Controlled, Phase 2 Trial. Neuropsychopharmacology. 2017;42(7):1390–8. [PubMed: 27748740]
76. Kaat AJ, Lecavalier L, Aman MG. Validity of the aberrant behavior checklist in children with autism spectrum disorder. J Autism Dev Disord. 2014;44(5):1103–16. [PubMed: 24165702]
77. Shea S, Turgay A, Carroll A, Schulz M, Orlik H, Smith I, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Pediatrics. 2004;114(5):e634–41. [PubMed: 15492353]
78. McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med. 2002;347(5):314–21. [PubMed: 12151468]
79. Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. Pediatrics. 2009;124(6):1533–40. [PubMed: 19948625]
80. Marcus RN, Owen R, Kamen L, Manos G, McQuade RD, Carson WH, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. J Am Acad Child Adolesc Psychiatry. 2009;48(11):1110–9. [PubMed: 19797985]
81. King BH, Hollander E, Sikich L, McCracken JT, Scahill L, Bregman JD, et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism. Arch Gen Psychiatry. 2009;66(6):583–90. [PubMed: 19487623]
82. Aman MG, McDougle CJ, Scahill L, Handen B, Arnold LE, Johnson C, et al. Medication and parent training in children with pervasive developmental disorders and serious behavior problems: results from a randomized clinical trial. J Am Acad Child Adolesc Psychiatry. 2009;48(12):1143–54. [PubMed: 19858761]

83. Lord C, Rutter M, DiLavore PS, Risi S, Gotham K, Bishop S. Autism diagnostic observation schedule, 2nd edition (ADOS-2) manual (Part I): Modules 1-4. Torrence, CA: Western Psychological Services; 2012.
84. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview - Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. Journal of Autism and Developmental Disorders. 1994;24(5):659–85. [PubMed: 7814313]
85. Mullen EM. Mullen Scales of Early Learning (AGS ed.). Circle Pines, MN: American Guidance Service Inc.; 1995.
86. Stanford GHR Binet Intelligence Scales (5th ed.). Itasca, IL: Riverside Publishing; 2003.
87. Constantino JN, Davis SA, Todd RD, Schindler MK, Gross MM, Brophy SL, et al. Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. J Autism Dev Disord. 2003;33(4):427–33. [PubMed: 12959421]
88. Cohen IL, Schmidt-Lackner S, Romanczyk R, Sudhalter V. The PDD Behavior Inventory: a rating scale for assessing response to intervention in children with pervasive developmental disorder. J Autism Dev Disord. 2003;33(1):31–45. [PubMed: 12708578]
89. Khanna R, Madhavan SS, Smith MJ, Tworek C, Patrick JH, Becker-Cottrill B. Psychometric properties of the Caregiver Strain Questionnaire (CGSQ) among caregivers of children with autism. Autism : the international journal of research and practice. 2012;16(2):179–99. [PubMed: 21715548]
90. Sparrow SS, Cicchetti DV, Balla DA. Vineland adaptive behavior scales, (Vineland-II). Circle Pines, MN: American Guidance Services; 2005.
91. Lavigne JV, Cromley T, Sprafkin J, Gadow KD. The Child and Adolescent Symptom Inventory-Progress Monitor: a brief Diagnostic and Statistical Manual of Mental Disorders, 4th edition-referenced parent-report scale for children and adolescents. Journal of child and adolescent psychopharmacology. 2009;19(3):241–52. [PubMed: 19519259]
92. Guy W ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: United States Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976.
93. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The “Reading the Mind in the Eyes” Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry. 2001;42(2):241–51. [PubMed: 11280420]
94. Baron-Cohen S, Wheelwright S, Scahill V, Lawson J, Spong A. Are intuitive physics and intuitive psychology independent? A test with children with Asperger Syndrome. Journal of Developmental and Learning Disorders. 2001;5:47–78.
95. Rosenberg RE, Mandell DS, Farmer JE, Law JK, Marvin AR, Law PA. Psychotropic medication use among children with autism spectrum disorders enrolled in a national registry, 2007-2008. J Autism Dev Disord. 2010;40(3):342–51. [PubMed: 19806445]
96. Madden JM, Lakoma MD, Lynch FL, Rusinak D, Owen-Smith AA, Coleman KJ, et al. Psychotropic Medication Use among Insured Children with Autism Spectrum Disorder. J Autism Dev Disord. 2017;47(1):144–54. [PubMed: 27817163]
97. Coates M, Spanos M, Parmar P, Chandrasekhar T, Sikich L. A Review of Methods for Monitoring Adverse Events in Pediatric Psychopharmacology Clinical Trials. Drug Saf. 2018;41(5):465–71. [PubMed: 29318515]

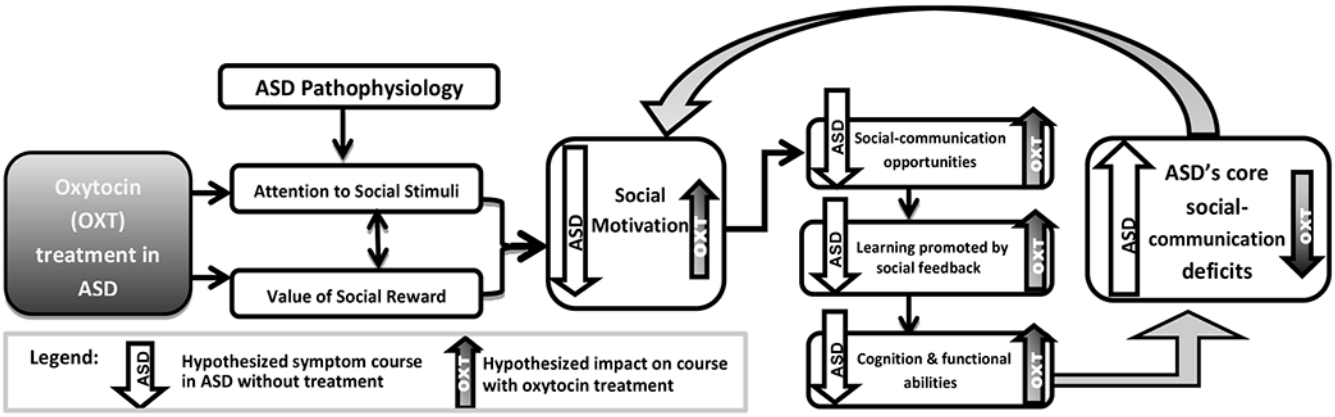

Figure 1:

Model of ASD Social Symptom Pathophysiology & Proposed Mechanism of Oxytocin Treatment

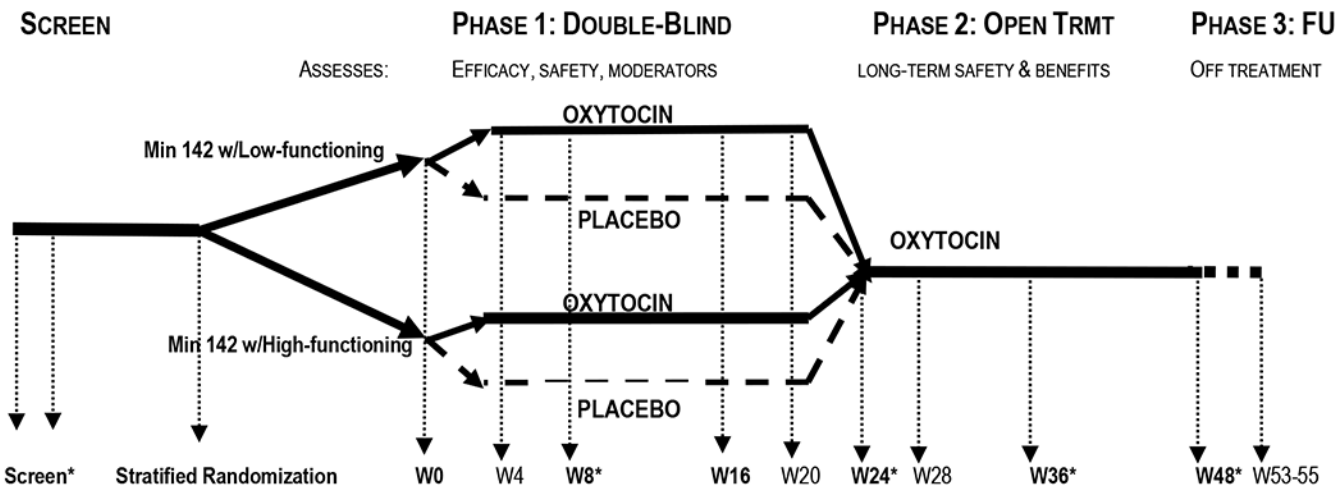

Figure 2: SOARS-B Study Design

*indicates safety labs and genetic sample taken. Primary outcome assessed at bolded time points.

TABLE 1.

SOARS-B Inclusion and Exclusion Criteria

Inclusion Criteria
3 years 0 months to 17 years 11 months at the time of randomization
Meet DSM-5 [1] criteria for autism spectrum disorder
Have a clinical diagnosis of ASD confirmed either using the Autism Diagnostic Observation
Scale-2 (ADOS-2)(83) or the Autism Diagnostic Interview-Revised(84). For participants who did not meet criteria on either but still had a clinical diagnosis of ASD, the Steering Committee (SC) was required to review and approve inclusion.
Have a guardian who is able to provide informed consent
If cognitively able, participant must provide informed assent/consent
Exclusion Criteria
A known diagnosis of Rett Syndrome or Childhood Disintegrative Disorder or have marked sensory impairment such as deafness or blindness.
Active cardiovascular disease or renal disease that is not controlled by medication
Pregnancy, lactation, or refuse to practice contraception if sexually active
Changes in allied health therapies, behavioral, or educational interventions within the two months prior to randomization other than those associated with school holidays
Changes in psychiatric medications within 4 weeks of randomization
Previous treatment with chronic intranasal oxytocin (daily dosing more than 1 month)
Caretakers who are unable to speak English, be consistently present at visits to report on symptoms, or are otherwise judged as unable to comply with the protocol by the data collection site team
Active seizures within the 6 months preceding screening or baseline. (This exclusion criterion was added during the study after a participant died from a seizure during the posttreatment period.

TABLE 2:

Dose Titration Schedules (Dose = Total IU/day)

Week 0	Week 2	Week 4	Week 8	Week 16	Week 20	Week 24	Week 28	Week 36
8/0 IU	16/0 IU	32/0 IU	48/0 IU	64/0 IU	80/0 IU	24 IU	48 IU	72 IU