THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY

ACAMH THE ASSOCIATION FOR CHILD AND ADOLESCENT MENTAL HEALTH

Journal of Child Psychology and Psychiatry 56:4 (2015), pp 444–452 doi:10.1111/jcpp.12305

The effects of a course of intranasal oxytocin on social behaviors in youth diagnosed with autism spectrum disorders: a randomized controlled trial

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Background: There is increasing interest in oxytocin as a therapeutic to treat social deficits in autism spectrum disorders (ASD). The aim of this study was to investigate the efficacy of a course of oxytocin nasal spray to improve social behavior in youth with ASD. **Methods:** In a double-blind, placebo-controlled trial across two Australian university sites between February 2009 and January 2012, 50 male participants aged between 12 and 18 years, with Autistic or Asperger's Disorder, were randomized to receive either oxytocin (n = 26) or placebo (n = 24) nasal sprays (either 18 or 24 International Units), administered twice-daily for 8 weeks. Participants were assessed at baseline, after 4- and 8-weeks of treatment, and at 3-month follow-up. Primary outcomes were change in total scores on the caregiver-completed Social Responsiveness Scale and clinician-ratings on the Clinical Global Impressions-Improvement scale. Secondary assessments included caregiver reports of repetitive and other developmental behaviors and social cognition. Clinical trial registration: Australian New Zealand Clinical Trials Registry www.anzctr.org.au ACTRN12609000513213. **Results:** Participants who received oxytocin showed no benefit following treatment on primary or secondary outcomes. However, caregivers who believed their children received oxytocin reported greater improvements compared to caregivers who believed their child received placebo. Nasal sprays were well tolerated and there was no evidence of increased side effects resulting from oxytocin administration. **Conclusions:** This is the first evaluation of the efficacy for a course of oxytocin treatment for youth with ASD. Although results did not suggest clinical efficacy, further research is needed to explore alternative delivery methods, earlier age of intervention, and the influence of caregiver expectation on treatment response. **Keywords:** Social cognition, neuropeptides, developmental disorder, emotion recognition, placebo-controlled.

Introduction

Autism Spectrum Disorders (ASD) are a cause of lifelong disability, characterized by severe deficits in social interaction and communication, and the presence of repetitive or stereotyped behaviors (APA, 2000; Einfeld & Tonge, 1996). Although a number of evidence-based behavioral (Reichow, Barton, Boyd, & Hume, 2012) and pharmacological (Sharma & Shaw, 2012) treatments have established efficacy across a number of domains, no medication-based treatments have as yet managed to address the profound social interaction and cognition deficits at the core of the disorder.

The mammalian neuropeptide oxytocin has been identified as a key modulator of social behavior (reviewed in Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011). Oxytocin administration enhances social recognition, partner preference and bonding, and decreases anxiety associated with social threat in both animal models and humans (Meyer-Lindenberg et al., 2011). Most importantly, oxytocin seems to enhance performance in tasks that require social cognitive ability (Guastella & MacLeod, 2012), such as emotion recognition or theory of mind (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007). In adults with ASD, acute doses have demonstrated benefits on measures of repetitive behavior (Hollander, 2003), social memory (Hollander et al., 2007), eye-gaze, social interactions, and self-report measures of trust (Andari et al., 2010). We reported the first evidence in younger ASD populations, demonstrating that oxytocin enhanced emotion recognition, compared to placebo (Guastella et al., 2010). Recently, a meta-analysis examining these studies together reported that autism appears to be the disorder that may exhibit the most benefit from oxytocin administration, compared to other studied psychiatric disorders (Bakermans-Kranenburg & Van IJzendoorn, 2013).

Two repeated administration studies in ASD have exhibited mixed effects. The first reported significant benefits on secondary measures of repetitive behavior, social cognition, and quality of life after 6 weeks of twice-daily administration, with no effects on the primary outcome measure (Anagnostou et al., 2012). A second study in children (n = 35; aged between 8

Conflict of interest statement: See Acknowledgements for disclosures.

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and 16 years) with autism recently failed to show benefit, but the complicated design, small number of drug administration (four doses in total), and large age range limits generalizability of these findings (Dadds et al., 2014).

The aim of this study was to investigate the efficacy of a course of oxytocin nasal spray treatment on social behaviors in youth with ASD. It was hypothesized that oxytocin would result in significant improvements in caregiver-ratings of social functioning, and that any improvements would be maintained at follow-up assessment.

Materials and methods

Study design

Patients were enrolled in a double-blind, randomized, controlled trial at one of two Australian sites: the Brain & Mind Research Institute, University of Sydney, and the Centre for Developmental Psychiatry & Psychology, Monash University, recruited between 2009 and 2011. All participants were screened for eligibility at initial phone contact with a parent or other primary caregiver. Screening for eligibility involved the primary caregiver providing evidence of a previous diagnosis of an ASD from a pediatrician, developmental psychiatrist, or other allied health professional, as well as any recent cognitive assessments conducted within the past 2 years.

At initial visit, written consent was obtained from participants over the age of 14 with a confirmed mental age above 12, with additional consent obtained from caregivers for all participants under the age of 18. Participants aged 18 years signed a separate consent form. Ethical approval was provided by the University of Sydney Ethics Committee (11269) and the Monash University Human Research Ethics Committee (CF09/1574 – 2009000856). The trial was registered with the Australian Clinical Trials Registry (ACTRN12609000513213). Further methodological details about the study protocol can be found in the online supplementary Appendix S1.

Participants

Inclusion criteria were adolescents males aged between 12 and 18 years with a confirmed diagnosis of an Autism Spectrum Disorder (APA, 2000). Exclusion criteria included females, severe depressive or psychotic symptoms, including suicidal thoughts and/or actions, cardiovascular disease, kidney disease, smoking more than 15 cigarettes a day, substance dependence, or sensitivity to preservatives (in particular, E 216, E 218, and chlorobutanol hemihydrate).

Interventions and adverse event reporting

Nasal sprays were developed and randomized by a compounding chemist with an identical placebo containing all ingredients except the active oxytocin (all sprays contained sorbitol, benzyl alcohol glycerol, and distilled water, contained within an amber 7 ml glass nasal spray with metered dose pump). The first 17 participants (oxytocin $n = 9$, placebo $n = 8$) were assigned to a nasal spray bottle that administered each full dose in one spray to one nostril. Following an internal review after the trial commenced (Guastella et al., 2013), it was decided that subsequent participants (oxytocin $n = 17$, placebo $n = 16$) would be assigned to bottles that administered two sprays, each spray containing a half dose, one to each nostril. The older age group of participants (aged 16–18, oxytocin $n = 5$, placebo $n = 5$) received 24 International Units (IU), a dose used in most adult oxytocin nasal spray studies. Those aged between 12 and 15 years received 75% of the adult dose (18 IU; oxytocin $n = 21$, placebo $n = 19$). Our decision regarding dose was based on our previous study in the same age group (Guastella et al., 2010), which showed positive benefit of oxytocin on social cognition.

Parents or caregivers completed two side-effect assessments at each visit after the first nasal spray administration. A checklist of possible side effects was developed for this trial on which parents rated whether the symptom had been experienced in the last 4 weeks (none, mild, moderate, severe). Additionally, parents or caregivers were asked to report any side effects by free response at the end of each visit. Compliance was assured using a daily medication diary that recorded date and time of administration.

Diagnostic assessments

At the initial visit, participants and their caregivers completed a medical interview with the site psychiatrist (SLE, BJT) or psychologist (KMG) to confirm diagnosis using both DSM-IV-TR (APA, 2000) assessment criteria and case review. To assess symptom severity, the Autism Diagnostic Observation Schedule (ADOS) was used, consisting of a semistructured, standardized assessment of social interaction, communication, play, and imaginative use of material (Lord et al., 1989). The ADOS has excellent interrater reliability within domains and individual items and substantial internal consistency.(Lord et al., 2000) Participants were administered either Module 2 or 3, depending on verbal fluency by research-reliable ADOS administrators. A severity score based on norms was calculated based on the ADOS raw total using a revised algorithm (Gotham, Pickles, & Lord, 2009). Estimates of intelligence (IQ) were either collected from participants' cognitive assessments conducted within the last 2 years, which included either the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) or the Wechsler Intelligence Scale for Children (Wechsler, 2003). If no test results were available from the last 2 years, participants were assessed using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

Primary outcomes

Outcome measures were obtained at baseline, 4 weeks, 8 weeks, and a follow-up of 3 months for caregiver-, participant-, and clinician-completed measures. The primary outcome measure was change in the caregiver-completeda Social Responsiveness Scale (SRS) over the four assessment time points. The SRS measures the severity of social interaction impairments in ASD populations, sensitive between 3 to 18 years of age (Constantino, 2005). It provides an impression of observed social impairments, assessing domains of communication, social interactions, and repetitive and stereotyped behaviors and interests. The second primary outcome measure, measuring global improvement, was the clinician-rated Clinical Global Impression-Improvements subscale (CGI-I; Guy, 1976). The CGI-I assesses how much the patient's condition has improved or worsened relative to a baseline state, ranging from 1 (very much improved) to 7 (very much worse), and is recommended for all clinical trials involving participants with ASD (Aman & Gharabawi, 2004). Improvement was defined as a score of 3 (minimally improved) or lower.

Secondary outcomes

Secondary caregiver-completed outcomes included the Developmental Behaviour Checklist (DBC) and the Repetitive Behavior Scale-Revised (RBS). The DBC assesses the presence of behavioral and emotional problems in children with developmental disorders, with well-established psychometric properties

(Tonge, Brereton, Gray, & Einfeld, 1999). The RBS measures severity and frequency of restricted and repetitive behaviors observed in ASD (Bodfish, Symons, Parker, & Lewis, 2000).

Participant-completed secondary outcomes were tests of social cognition conducted on participants who showed ability to understand and concentrate on the instructions of the test. The Adult and Child versions of the Reading the Mind in the Eyes Test (RMET-A and RMET-C), tests the ability to read emotions from photographs of eye regions of adult faces (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). The Diagnostic Analysis of Nonverbal Accuracy (DANVA) measures ability to identify four basic nonverbal emotions differing in intensity in two nonverbal social contexts (pictures of faces and audio of voices) across both young and adult males and females (Nowicki & Duke, 2001). Finally, Biological Motion assesses accurate identification of actions, emotion, subjective states, or objects from video clips of dynamic point light displays (Moore, Hobson, & Lee, 1997).

Statistical analyses

Given the limited number of studies examining oxytocin in this population prior to the beginning of the present study, sample size estimates were based on these few previous studies (Guastella et al., 2010; Hollander, 2003; Hollander et al., 2007) and recruitment feasibility within this population. It was estimated that approximately 48 participants, accounting for a 20% dropout, randomly assigned in a 1:1 ratio to oxytocin or placebo, would have a 95% power to detect an effect size as large as previously observed (Guastella et al., 2010) in a between-within design with four time points, with $p = .05$, using G*power (Faul, Erdfelder, Lang, & Buchner, 2007).

Baseline demographic and behavioral characteristics were tested using independent samples *t*-tests. Analysis of primary and secondary continuous outcomes were based on a 2 (Drug: Oxytocin, Placebo) x Time (4; pretreatment, midtreatment, posttreatment, 3-month follow-up) mixed-design ANOVA, with an intent-to-treat format and last-observations-carried-forward to replace missing data. For participants with missing baseline data, analysis for that measure was excluded listwise. Missing individual values for the SRS were replaced with the median value for that item, based on normative data (Constantino, 2005).

All outcome measures were examined to ensure violations were not met for linear model assumptions with adjusted degrees of freedom reported if Mauchly's Test of Sphericity was violated for mixed model ANOVA tests and Bonferroni adjusted *p*-values used for multiple comparisons. Pearson's chi-squared test was used for dichotomous outcome variables. Exploratory analyses were conducted using multivariate ANOVAs. Change scores on questionnaire and social cognition measures were separately analyzed as dependent variables, with caregiver guesses made at the end of the 8-week treatment and actual drug assignment used as the between-subjects factors.

A Reliable Change Index (RCI; Jacobson & Truax, 1991) was also applied to the primary continuous outcome measure as a measure of both statistical and clinical significant for individual participants. An RCI was calculated for each individual participant on each outcome measure and summed to assess how many participants in each group improved from baseline at each time point. Level of significance was set at $p < .05$ and effect sizes were calculated with the use of Cohen's d for continuous measures and relative risk ratios for dichotomous outcomes. Data were entered by research assistants blind to drug assignment and analyzed using SPSS 20.0 (SPSS Inc, Chicago, IL).

Results

Participants

Participants were recruited to each site between January 2009 and December 2011. Sixty-five males were assessed for eligibility, with 57 invited to participate (see CONSORT diagram in Figure 1).

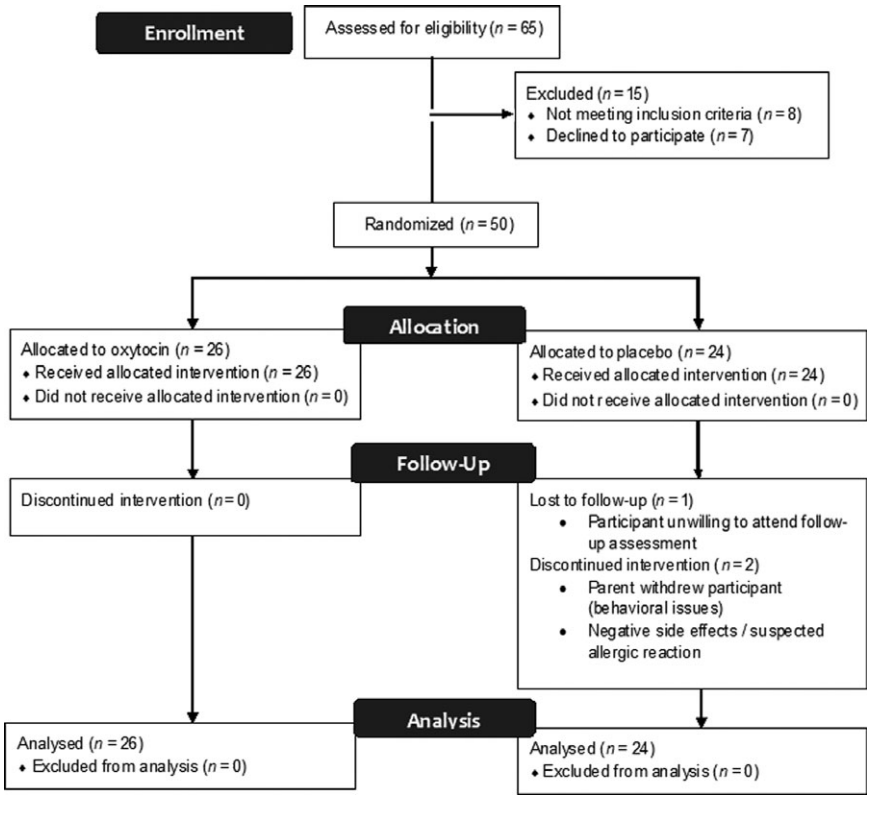

Figure 1 Study enrollment and randomization

Fifty participants were subsequently randomized (Oxytocin $n = 26$, Placebo $n = 24$), with a mean age of 13.92 years ($SD = 1.78$). Two participants, both randomly allocated to the placebo conditions, discontinued the intervention between their initial and midtreatment assessments (See Table S1).

Baseline characteristics

There were no significant differences between groups on age, ADOS severity scores or levels of social functioning or behavioral difficulties, as assessed by parent reports (Table 1). A significant difference in intellectual function indicated that those randomly assigned to oxytocin had lower overall full scale IQ, as well as lower verbal and performance IQ.

Adjunctive psychotropic medication use (oxytocin = 9, placebo = 9) included stimulants (35.7%), antipsychotics (28.6%), antidepressants (25%), mood stabilizers (7.1%), and benzodiazepines (3.6%). Medication use and number of medications taken was equal in both groups ($\chi^2 = 2.45$, df = 4, $p = .65$; Table S1). One participant was diagnosed with comorbid ADHD and one with Conduct Disorder and ADHD. Only one participant reported any physical health condition, Type I diabetes that was treated with insulin.

Primary outcomes

There was no significant interaction of treatment by time on primary outcome SRS ($F(3, 135) = 0.20$, $p = .90$); Table 2, or on any of its subscales (smallest p-value = .43; Table S2),b and when examining the clinically significant improvements using the RCI; smallest $p = .60$. There were also no significant differences between treatment group across any time point on the clinician-rated CGI-I; smallest $p = .43$. In terms of dosage effects, interpretations of these results did not change when analyses included dose as an additional factor (18 IU compared to 24 IU) or number of sprays per dose (one spray compared to two sprays per dose).

Table 1 Demographic and clinical characteristics of participants randomized to receive either oxytocin or placebo at baseline

	Oxytocin $n = 26$	Placebo $n = 24$	p-value
Age	13.85 (1.54)	14.00 (2.04)	.76
Full Scale IQ[a]	80.04 (19.18)	93.14 (21.11)	.03
Verbal IQ	75.19 (20.44)	92.00 (23.71)	.01
Performance IQ	88.58 (17.84)	99.77 (21.92)	.06
Autism diagnostic observation schedule (ADOS) severity	7.54 (1.70)	7.25 (2.54)	.64
SRS total[b]	109.15 (22.35)	107.83 (23.12)	.84
DBC total[b]	54.31 (23.03)	59.22 (20.34)	.44
RBS total[b]	29.50 (21.15)	28.61 (18.91)	.88

Values are means (*SD*). For the Social Responsiveness Scale (SRS), higher scores are indicative of better social responsiveness. For the Developmental Behaviour Checklist (DBC) and RBS, higher scores are indicative of greater reported incidence of problematic behaviors.
[a]Two participants' IQ scores were missing from the placebo group.
[b]One participant's questionnaire was missing at baseline.

Secondary outcomes

There were no differences due to drug assignment across the four time points for the caregiver-completed assessments; see Table S2. A significant interaction was observed for the restricted behavior subscale of the RBS ($F(3, 141) = 3.29$, $p = .02$, partial $\eta^2 = .07$) which did not survive correction for multiple comparisons (Bonferroni adjusted p-value $\leq .008$).

Five participants did not complete the experimental tasks of social cognition due to difficulty comprehending instructions or limited expressive language (final sample: Oxytocin $n = 22$, Placebo $n = 22$). A further three participants did not complete the RMET-A and Biological Motion (Oxytocin $n = 20$, Placebo $n = 21$). There were no significant interactions observed between drug group and time for either the version of the RMET, the DANVA or Biological Motion, $p > .05$ (see Table 2), or when RMET-A and RMET-C items were split into easy and hard categories, all p-values >.05 (See Table S2). Analyses were repeated with IQ entered as a covariate and excluding participants with a full scale IQ <70 (remaining sample: Oxytocin $n = 18$, Placebo $n = 17$). This did not alter the above interpretation of results.

Exploratory analyses

Parents or caregivers of participants in either condition equally believed their child had received oxytocin or placebo at any time point (largest $\chi^2 = 1.37$, $df = 1$, $p = .24$); Table 3. Exploratory analysis was then conducted to examine whether reported beliefs about treatment assignment moderated any outcome measure. A main effect of parent's reported beliefs was found for reported social responsiveness (SRS; $F(1, 43) = 9.16$, $p < .01$), as well as developmental behaviors and emotional problems (DBC; $F(1, 43) = 7.85$, $p < .01$); see Figure 2. That is, parents who believed their child was receiving oxytocin reported significantly greater reduction across symptom measures than those who believed their child had been receiving placebo. However, beliefs did not interact with actual drug assignment (all p-values > .05). These effects were also found across a number of subscales within each questionnaire; see Table S3. Parent guess, however, did not interact with any changes on any social cognition measures from pre- to posttreatment, all p-values > .05.

Table 2 Primary and secondary outcomes by treatment group and time

	Oxytocin $n = 26$	Placebo $n = 24$	Effect size
Primary Outcomes			
SRS[a]			Cohen's *d*
Baseline	109.15 (22.35)	107.83 (23.12)	0.05
Midtreatment	102.00 (22.00)	98.52 (27.28)	0.14
Posttreatment	97.08 (27.73)	95.43 (28.10)	0.06
3-Month follow-up	104.27 (27.62)	103.52 (27.43)	0.03
SRS[a] RCI – number improved (%)			
Baseline	–	–	Risk ratio (95% CI)
Midtreatment	3/23 (11.5)	3/21 (12.5)	0.92 (0.21–4.14)
Posttreatment	4/22 (15.4)	3/21 (12.5)	1.23 (0.31–4.94)
3-Month follow-up	2/24 (7.7)	1/23 (4.2)	1.84 (0.18–19.08)
CGI –I[b] – number improved (%)			
Baseline	–	–	Risk ratio (95% CI)
Midtreatment	6/15 (28.6)	5/16 (23.8)	1.20 (0.43–3.33)
Posttreatment	7/14 (33.3)	6/15 (28.6)	1.17 (0.47–2.89)
3-Month follow-up	3/19 (13.6)	5/17 (22.7)	0.60 (0.16–2.21)
Secondary Outcomes			
DBC[a]			Cohen's *d*
Baseline	54.31 (23.03)	59.22 (20.34)	0.26
Midtreatment	44.54 (20.01)	48.30 (23.07)	0.17
Posttreatment	42.31 (22.85)	47.87 (22.93)	0.24
3-Month follow-up	46.92 (21.30)	52.22 (26.36)	0.22
RBS[a]			
Baseline	29.50 (21.15)	28.61 (18.91)	0.04
Midtreatment	23.50 (17.46)	25.13 (20.53)	0.09
Posttreatment	22.77 (20.47)	25.17 (20.66)	0.12
3-Month follow-up	25.81 (19.59)	25.43 (21.29)	0.02
RMET-A[c]			
Baseline	16.35 (6.14)	18.48 (6.06)	0.35
Midtreatment	15.25 (7.67)	18.67 (7.30)	0.46
Posttreatment	17.70 (6.94)	18.95 (6.77)	0.18
3-Month follow-up	17.25 (7.45)	19.14 (8.37)	0.24
RMET-C[c]			
Baseline	15.64 (4.42)	17.59 (4.32)	0.45
Midtreatment	16.23 (5.15)	17.68 (5.63)	0.27
Posttreatment	16.55 (5.10)	18.86 (5.23)	0.45
3-Month follow-up	17.10 (6.00)	18.64 (6.17)	0.25
DANVA[c]			
Baseline	63.82 (14.79)	68.86 (17.61)	0.31
Midtreatment	63.59 (13.11)	69.36 (14.56)	0.42
Posttreatment	66.86 (13.11)	71.09 (15.27)	0.30
3-Month follow-up	65.82 (14.49)	72.95 (16.38)	0.46
Biological motion[c]			
Baseline	14.79 (3.14)	15.86 (3.53)	0.32
Midtreatment	16.53 (2.87)	16.67 (3.94)	0.20
Posttreatment	16.79 (3.15)	17.79 (4.00)	0.28
3-Month follow-up	17.89 (2.79)	18.10 (4.12)	0.06

Means (*SD*) depicted except for RCI and CGI-I which depict the number of participants that improved (%). For the SRS and social cognition tasks, higher scores indicate better social responsiveness, or better performance, respectively. For the DBC and RBS, higher scores indicate greater reported incidence of problematic behaviors. SRS, Social Responsiveness Scale; RCI, Reliable Change Index; CGI-I, Clinical Global Impression scale, Improvement subscale; DBC, Developmental Behaviour Checklist; RBS, Repetitive Behavior Scale; RMET, Reading the Mind in the Eyes Test, Adult and Child versions; DANVA, Diagnostic Analysis of Variance.
[a]One participant's data, in the placebo group, was missing at baseline, and thus excluded listwise from analysis.
[b]CGI ratings were missing for eight participants at mid and post assessments, six participants missing at follow-up.
[c]Of the sample that completed at least one of the social cognition measures, three participants were unable to complete the RMET-A, with one further excluded from the analysis of RMET-A due to difficulty with completion, and four did not complete the Biological Motion task.

Adverse events

The nasal spray was well tolerated by all participants, and the two trial withdrawals (one serious adverse event) were from participants randomly allocated to placebo. Number of side effects reported by checklist did not differ between groups at either mid- or posttreatment assessments ($F(1, 46) = 1.62$, $p = .21$; See Table S3).

Discussion

This study represents the first test of the tolerability and efficacy of a course of oxytocin intranasal

Table 3 Percentage of parents who believed their child had received oxytocin

	Treatment guess: Oxytocin		
Actual drug assignment	Mid, %	Post, %	Follow-up, %
Oxytocin	26.92	38.46	38.46
Placebo	29.17	20.83	25.00

administration in adolescent males with ASD. Overall results suggest that oxytocin did not improve parent-reported symptoms of social and repetitive behaviors or social cognition. However, parents or caregivers who believed their child had been assigned the active treatment, regardless of drug assignment, reported greater benefit than those who believed their child received placebo. No serious adverse events, or additional adverse events, resulted from oxytocin treatment compared to placebo. The nasal spray delivery method was also well tolerated by participants. Given recent concerns about the use of oxytocin as a therapeutic (Miller, 2013), as well a recent surge in the number of registered studies examining the clinical potential of oxytocin across psychiatric disorders, such results have important implications for future work in this field.

A number of randomized controlled trials published recently have highlighted the potential positive benefits of oxytocin administration in ASD. Following on from the initial findings reported by Hollander and colleagues (Hollander, 2003; Hollander et al., 2007), in which intravenous oxytocin in adults with ASD reduce repetitive behavior and increased social cognition, a number of single-dose crossover studies have demonstrated benefits in emotion recognition, eye-gaze, and social behavior (Andari et al., 2010; Guastella et al., 2010). While these results are seemingly inconsistent with the present findings, it is worth noting that the only other published course of oxytocin treatment in autism failed to find a benefit from oxytocin nasal administration on primary outcomes, with some improvements in repetitive behaviors (Anagnostou et al., 2012). Thus, the evaluation of the therapeutic potential of oxytocin for autism treatment and disorders of social impairment remains in its early stages.

An interesting finding was that parent beliefs about treatment allocation were associated with an improved reported treatment response as assessed by parent or caregiver reports. Additionally, parents who believed their child was assigned to oxytocin were almost double the number in the oxytocin in comparison to placebo condition (although, due to sample size, this difference was not statistically significant). This suggests one of two possibilities. Parents or caregivers may have identified real treatment responders and perhaps a sub-group of children that did respond to oxytocin treatment. An alternative explanation is that expectancy biases from caregivers may have substantially influenced response when caregiver reports are relied upon as the primary measures of outcome. Expectancy biases and placebo-like effects have been noted previously many times in child (Birmaher et al., 1998) and autism treatment studies (King et al., 2009), and are potentially enhanced in this field where there much media hype about benefits of oxytocin to autism patients. Such factors have the potential to undermine clinical trials and confound investigations of critical markers of response to the actual oxytocin treatment.

As ASD is a heterogeneous disorder, the inclusion of participants across the spectrum in the present trial may have also contributed to these negative findings. Although participants in the oxytocin group had an overall lower IQ, this baseline difference did not appear to make an impact on the overall pattern of results. We also note that while we maintained the same dose throughout the trial, we did move from one to two sprays for delivery following a review of the absorption from nasal spray application (Guastella et al., 2013). However, results did not suggest that this change moderated treatment response.

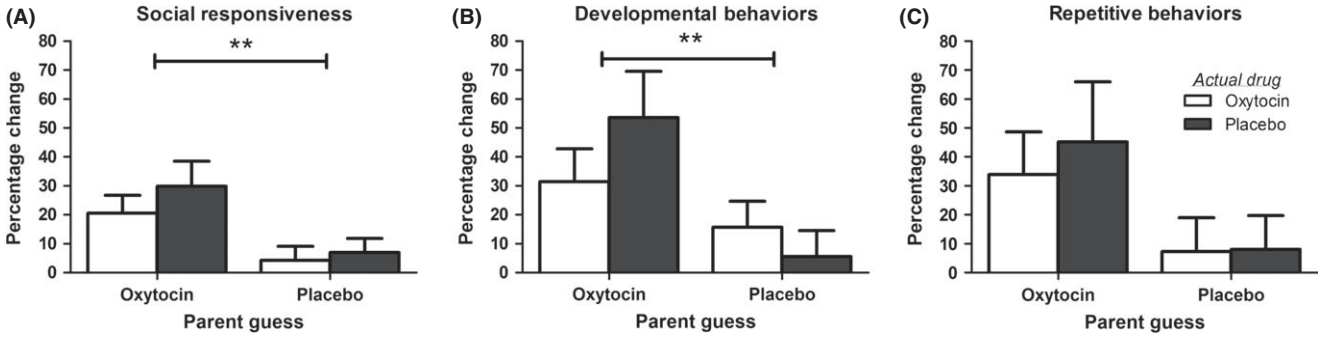

Figure 2 Change in parent reported symptoms from baseline to posttreatment according to caregiver beliefs of their child's drug assignment. Significant differences shown are between parents who believed their child received oxytocin against those parents who believed their child received placebo drug, regardless of actual drug assignment. These differences are shown for scores on the (A) Social Responsiveness Scale (SRS) and (B) Development Behaviour Checklist (DBC) but not (C) Repetitive Behaviour Scale (RBS). *Note*. Higher percentage change on outcomes was scored to indicate improvements at the posttreatment assessment, compared to baseline. $^{**}p < .01$

Unfortunately, we did not collect blood in this study and evaluation of relevant biological markers of response to oxytocin nasal spray would have enhanced this investigation. We also did not weigh nasal spray bottles upon return, which may have provided some insight into possible drug responders (Cacciotti-Saija et al., 2015). This trial was initiated before our associated guidelines and recommendations were written (Guastella et al., 2013). Future studies using within-subjects crossover designs may avoid the heterogeneity problems that exist in between-subject designs. Oxytocin interventions may be more effective when provided early and evaluation in a younger cohort if required. It may also be more effective to combine oxytocin treatment with a validated and efficacious social-learning package. The assessment of the impact of social contexts immediately following treatment with oxytocin requires further investigation. Lastly, although there exists substantial debate about optimal methods to assess change in autism treatment trials, we chose measures that have previously shown response to treatment, including response to oxytocin in repeated-measures designs (Guastella et al., 2010). Future research is, however, required to develop optimal methods for assessing change in treatment trials for patients with autism.

In conclusion, the present study observed that a course of oxytocin, compared to placebo, did not result in significant improvements on either parent reports of behavior or measures of social cognition in youth with ASD. Oxytocin as a nasal spray was well tolerated and safe to use within this sample. Given recent positive findings in this field, larger samples of longer dose duration, in younger samples, and in crossover designs, are urgently needed.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Study protocol methods and results.

Table S1. Number of participants taking concurrent psychotropic medication.

Table S2. Primary and secondary outcome subscales by drug condition and time.

Table S3. Change scores for drug groups split by parents' beliefs.

Acknowledgements

This study was funded by a National Health and Medical Research Council Project Grant to authors A.J.G., K.M.G., N.J.R., and S.L.E. (632625). The National Health and Medical Research Council had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

IBH is a Senior Principal Research Fellow of the Australian National Health & Medical Research Council (AppID 1046899). He is the executive director of the Brain and Mind Research Institute (BMRI), at the University of Sydney, which operates two early-intervention youth services under contract to headspace. He is a commissioner of the Australian National Mental Health commission and was previously the CEO of beyondblue: the national depression initiative and a director of headspace: the national youth mental health foundation until January 2012. Previously, he has led a range of community-based and pharmaceutical industry-supported depression awareness and education and training programs. He has led depression and other mental health research service evaluation or investigator-initiated research projects that have been supported by a variety of pharmaceutical partners. Current investigator-initiated studies are supported by Servier (manufacturers of agomelatine) and Pfizer. He has received honoraria for his contributions to professional educational seminars related to depression, youth mental health and circadian-rhythms research. He has received travel support from Servier to attend scientific meetings related specifically to circadian-rhythm disorders.

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Key points

- Previous research has demonstrated that oxytocin, a hormone and neuropeptide, enhances social cognition and social behavior in healthy and autism spectrum disorder (ASD) samples
- An 8-week double-blind trial of twice-daily intranasal oxytocin or placebo in youth with ASD did not improve any measure of social cognition or behavior
- Caregiver reports indicated that those who believed their child received oxytocin reported more significant benefits on behavioral measures, irrespective of actual drug received, suggesting a strong expectancy effect existed
- Although results did not support the efficacy of oxytocin treatment in this sample, increased clinical interest in oxytocin as a therapeutic supports the necessity for further clinical trials to determine optimal dose and duration of administration

Notes

[a]Despite best efforts to obtain responses, poor compliance/response rates from teachers left too much missing data (35%) to report the outcomes of these evaluations.
[b]Restricting analyses to absolute change scores, or alternatively percentage change from baseline, did not significantly change our interpretation of these findings.

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Accepted for publication: 11 June 2014
Published online: 2 August 2014