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Review article

Oxytocin therapy for core symptoms in autism spectrum disorder: An updated meta-analysis of randomized controlled trials

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ABSTRACT

Background: Evidence of oxytocin for treating core symptoms in autism spectrum disorder (ASD) across development remains mixed and establishing its role is critical for guiding therapy.
Aim: The current paper is aimed to include new studies and provide a stricter and updated meta-analysis to assess the oxytocin's effects on core symptoms in ASD.
Method: Computerized search was conducted in PubMed, EMBASE, Cochrane Library, PsycINFO, Web of Science Database and references in reviews from the earliest date available to September 2018. Randomized controlled trials (RCTs) were identified which evaluated the effectiveness of oxytocin on at least one of two domains in patients with ASD, namely social function and repetitive behaviors. Standardized mean difference (SMD) and 95% confidence intervals (CIs) were calculated, and heterogeneity was assessed using the I^2 test.
Results: Sixteen studies comprising 520 individuals with ASD were included in this meta-analysis. Results suggested that oxytocin had a small and non-significant effect on social function [SMD = 0.03, 95% CI (−0.19, 0.25), $p = 0.781$] and repetitive behaviors [SMD = 0.01, 95% CI (−0.26, 0.27), $p = 0.952$] compared with placebo. Studies included had a low heterogeneity ($I^2 = 46.4\%$, $p = 0.025$ in social function; $I^2 = 37.0\%$, $p = 0.123$ in repetitive behaviors).
Conclusions: The current meta-analysis demonstrated that oxytocin had a small and non-significant effect on core symptoms in ASD population. With the limited number of included studies, more large-scale, rigorously and multi-site RCTs are needed to confirm the effectiveness of oxytocin as a treatment of ASD to acquire more convincing conclusions in the future.

1. Introduction

Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental disorders, which is characterized by two core persistent deficits in social interaction and communication along with restricted, repetitive patterns of behaviors, interests or activities (American Psychiatric Association, 2013). The prevalence of ASD has ranged from one in 2500 in the late 1960s to 1–4% in recently (Carpenter et al., 2016; Fombonne, 2018). The pathogenesis of ASD remains unclear and the treatments for the disorder are limited. ASD is a lifelong disorder, contributing to a heavy financial burden and spiritual stress to their families (McGrew & Keyes, 2014; Parish, Thomas, Rose, Kilany, & Shattuck, 2012). Therefore, it is an emergency to develop efficient and economic interventions for individuals with ASD.

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To date, there are two evidence-based options for treating ASD, namely non-pharmacological and pharmacological interventions. Non-pharmacological interventions include applied behavior analysis, cognitive behavioral therapy, pivotal response training and so on (National Autism Center, 2015). Nevertheless, these interventions may be labor intensive and thus expensive, and need much time to see incremental benefits. Additionally, a wide range of studies has also investigated the effectiveness of pharmacological medications in the treatment of ASD. But pharmacological drugs are primarily targeted at alleviating some of the commonly associated symptoms of ASD, such as irritability, hyperactivity, inattention, sleep disorder as well as anxiety (Politte, Howe, Nowinski, Palumbo, & McDougle, 2015). Risperidone and aripiprazole, the only two drugs approved by the Food and Drug Administration (FDA), are consistently considered as the most effective treatment for irritability in children with ASD (individuals aged 5–16-year-old for risperidone and 6–17-year-old for aripiprazole) (Fung et al., 2016). However, because of the complex characteristics of ASD, there have been no approved medications anywhere in the world that existing for treating core symptoms of ASD so far.

During the last decades, accumulating studies have investigated the application of oxytocin as a novel method of improving social behaviors in humans. Oxytocin is a 9-amino-acid neuropeptide hormone, which is synthesized primarily in the paraventricular and supraoptic nucleus of the hypothalamus, and released into the bloodstream via axon terminals in the posterior pituitary (Insel, 2010). It is well known for its functions in facilitating uterine contractions during delivery and milk letdown reflex during lactation (Nielsen et al., 2017). Studies involving healthy individuals have found that oxytocin administration may produce a series of positive effects, including increases in levels of trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), eye gazing (Guastella, Mitchell, & Dadds, 2008), emotion recognition (Di Simplicio, Massey-Chase, Cowen, & Harmer, 2009) as well as the ability to infer others' mental and emotional states (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007).

Following many studies on the role of oxytocin in social function, a lot of studies have increasingly demonstrated its role in the etiology and potential treatment of the core impairments in ASD. Substantial studies have suggested that oxytocin system in individuals with ASD is disturbed. Children with ASD have lower levels of plasma oxytocin in comparison with the healthy subjects, and the levels of oxytocin are associated with the seriousness of core symptoms in ASD (Yang et al., 2015; Zhang et al., 2016). Additionally, emerging genetic data has suggested that the variations of the oxytocin receptor (OXTR) gene are linked with the development of ASD (Kranz et al., 2016; LoParo & Waldman, 2015; Yang et al., 2017). What's more, an explosion of promising results has indicated that oxytocin could promote eye contact (Andari et al., 2010; Auyeung et al., 2015; Domes, Kumbier, Heinrichs, & Herpertz, 2014), emotion recognition based on facial or affective speech (Guastella et al., 2010; Hollander et al., 2007), social judgment (Gordon et al., 2013; Watanabe et al., 2014), mentalizing abilities (Aoki et al., 2014; Kose, Fox, & Storch, 2018), and reductions in repetitive behaviors of individuals with ASD (Hollander et al., 2003). However, other studies found no significant improvements whether in social domain or repetitive behaviors (Dadds et al., 2014; Domes et al., 2013; Guastella et al., 2015; Munesue et al., 2016; Quintana et al., 2017; Yamasue et al., 2018). These contradictory findings could relate to variations in the characteristics of participants (e.g., gender, age) and administration (e.g., dosage, duration), as well as different outcome measures (Alvares, Quintana, & Whitehouse, 2016; Guoynes et al., 2018).

Therefore, there is a necessity to conduct a meta-analysis to examine the effects of oxytocin on social function and repetitive behaviors in ASD. The results of the most recent meta-analysis (Ooi, Weng, Kossowsky, Gerger, & Sung, 2016) showed that oxytocin had no significant effect on the core symptoms of ASD. However, due to limited sample size, lack of quality assessment or sensitivity analysis, these results remain to be further confirmed. Over the last couple of years, more and more RCTs have focused on the efficacy of oxytocin treating core symptoms of ASD (Munesue et al., 2016; Quintana et al., 2017; Yamasue et al., 2018; Yatawara, Einfeld, Hickie, Davenport, & Guastella, 2016).

Hence, we presented a stricter and updated meta-analysis of randomized controlled trials based on the current evidence to examine the effectiveness of oxytocin therapy on core symptoms of individuals with ASD. Compared with the most recent meta-analysis (Ooi et al., 2016), there are several difference in our meta-analysis as follow: (1) we included more RCTs in the meta-analysis (Aoki et al., 2014; Kosaka et al., 2016; Munesue et al., 2016; Quintana et al., 2017; Watanabe et al., 2015; Yamasue et al., 2018; Yatawara et al., 2016); (2) we used the Cochrane risk of bias tool to evaluate the methodological quality of each included study in the meta-analysis; (3) we performed the sensitivity analysis to examine the stability of results; (4) we excluded the study sharing the same population (Domes et al., 2014). As such, the results of our study might more accurately reflect the actual effects of oxytocin therapy for ASD. Additionally, continuous updates can aggregate data from new studies, as well as provide more robust information for physicians to determine the most appropriate therapies.

2. Method

The current study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Moher et al., 2009).

2.1. Literature search and inclusion criteria

We identified studies evaluating the effectiveness of oxytocin administration for individuals with ASD by searching the following five electronic databases: PubMed, EMBASE, Cochrane Library, PsycINFO and Web of Science. Searches were limited to English-language articles published from inception until September 2018. Search terms included the following: autis*, Asperger disorder, pervasive developmental disorder, oxytocin and random*. After the electronic search, we conducted manual searches in the lists of reference from review articles.

All studies included in this meta-analysis met the following inclusion criteria using the PICOS strategy: P (Population): The studies that were conducted in ASD population groups; I (Intervention): oxytocin administration; C (The comparison group): Participants that received placebo intervention; O (Outcome): Interventions that led to at least one of the core symptoms. RCTs that included scales/ tasks assessing any components related to social function (e.g., emotion recognition, face processing, nonverbal information-based judgments) were identified. And RCTs that included measurements examining the overall severity of repetitive behaviors or higher-order repetitive behaviors (e.g., ritualistic, sameness, compulsive, and restricted behaviors) were included.

2.2. Data extraction

Two authors independently read the full text of each included articles. The information extracted were as follows: first author, publication year, country, study design, characteristics of individuals with ASD (sample size, age, gender, diagnosis) and oxytocin administration (type, dosage and duration), outcome measures (components related to social function, repetitive behaviors), corresponding measuring methods, main findings as well as adverse effect. If there were any discrepancies between the two authors during the screening process, a third author was consulted to determine the final result.

2.3. Assessment of risk of bias

The Cochrane risk of bias tool was used to evaluate the methodological quality of each included study in the meta-analysis. The tool was consisted of five evaluation elements: random sequence generation (selection bias), allocation concealment (selective bias), blinding of participants (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attribution bias), selective outcome reporting (reporting bias), and other potential bias to validity. The terms 'low', 'unclear' and 'high' referred to low, uncertain and high risks of bias respectively. Studies were defined as 'high risk' when at least three criteria were met as unclear risk and/or high risk. In contrast, studies were defined as 'low risk' when less than or equal to two bias criteria met as unclear risk and/or high risk (Higgins et al., 2011). REVIEW MANAGER 5.3 was used to present the results graphically.

2.4. Data analysis

In this study, meta-analysis was performed using STATA 12 software. Measurement data was used for statistical efficacy analysis using Cohen's standardized mean difference (SMD) with 95% confidence intervals (CIs). In order to calculate the effect size, means and standard deviation (SD) were obtained for each study group and the outcome of interest. If the direction of the used outcome measures was the opposite, the mean value of the included study would be multiplied by negative one to ensure that all points of measures were in the same direction (Higgins & Green, 2014). Forest plot was used to graphically present the pooled SMD and the 95% CI. Each study was represented by a square in the plot, proportional to the study's weight in the meta-analysis. The pooled effect sizes could be interpreted as a small effect (SMD ≤ 0.20), a medium effect (0.20 < SMD < 0.80) and a large effect (SMD ≥ 0.80) (Cohen, 1988). Two-sided *p*-values lower than 0.05 were considered statistically significant. In each meta-analysis, the Chi-square and I^2 tests were used to examine statistical heterogeneity. Benchmarks of I^2 could be categorized as having low (25–50%), moderate (50–75%) and high (≥75%) heterogeneity (Liu, Du, Zhang, & Zhou, 2019). Chi-square test was viewed as significant if $p < 0.10$. Given that the variation of study characteristics (e.g., sample size, country, age, gender, dosage), we assumed that the effect size might vary from study to study. Therefore, effect estimates were pooled using a random effects model. Egger's test and contour-enhanced funnel plots were used for evaluation of publication bias with *p* value < 0.05 indicating the presence of bias. Funnel plots are either symmetrical or asymmetrical and if the funnel plot is found to be asymmetrical, a 'Trim and Fill' procedure is used to determine and adjust an effect size by the number of studies to balance the plot. Sensitivity analysis was performed to further examine the stability of the estimated results by excluding sequentially each study and rerunning the meta-analysis.

3. Results

3.1. Trial flow and study characteristics

The flowchart of the study selection process was illustrated in Fig. 1. In this meta-analysis, the computerized search of databases generated a total of 530 potentially eligible studies and one additional article from the lists of references in the past systematic review and meta-analysis. 245 articles were duplicated and 260 did not meet our inclusion criteria after screening the title and abstracts (e.g., non-ASD, non-human, meeting abstracts, reviews or meta-analysis). We obtained the full text of the remaining twenty-six articles. Ten papers were excluded for the following reasons: the data of the four studies were incomplete and authors did not provide further supplementary data (Gordon et al., 2013; Hollander et al., 2007; Kanat et al., 2017; Parker et al., 2017); five studies merely reported data of changes in Skin Conductance Response (Lin et al., 2014) and different brain regions (Althaus et al., 2015, 2016; Aoki et al., 2015; Gordon et al., 2016) instead of behavioral changes; Two studies shared the same sample (Domes et al., 2013, 2014) and we excluded the one lack of adequate data measuring social function (Domes et al., 2014). Therefore, sixteen eligible RCTs involving 520 participants ($N_{\text{male}} = 497$ and $N_{\text{female}} = 23$) were included for this meta-analysis (Anagnostou et al., 2012; Andari et al., 2010; Aoki et al., 2014; Auyeung et al., 2015; Dadds et al., 2014; Domes et al., 2013; Guastella et al., 2010, 2015; Hollander et al., 2003; Kosaka et al., 2016; Munesue et al., 2016; Quintana et al., 2017; Watanabe et al., 2014, 2015; Yamasue et al., 2018; Yatawara et al., 2016).

The basic characteristics of included sixteen studies were summarized in Table 1. These studies were from seven different

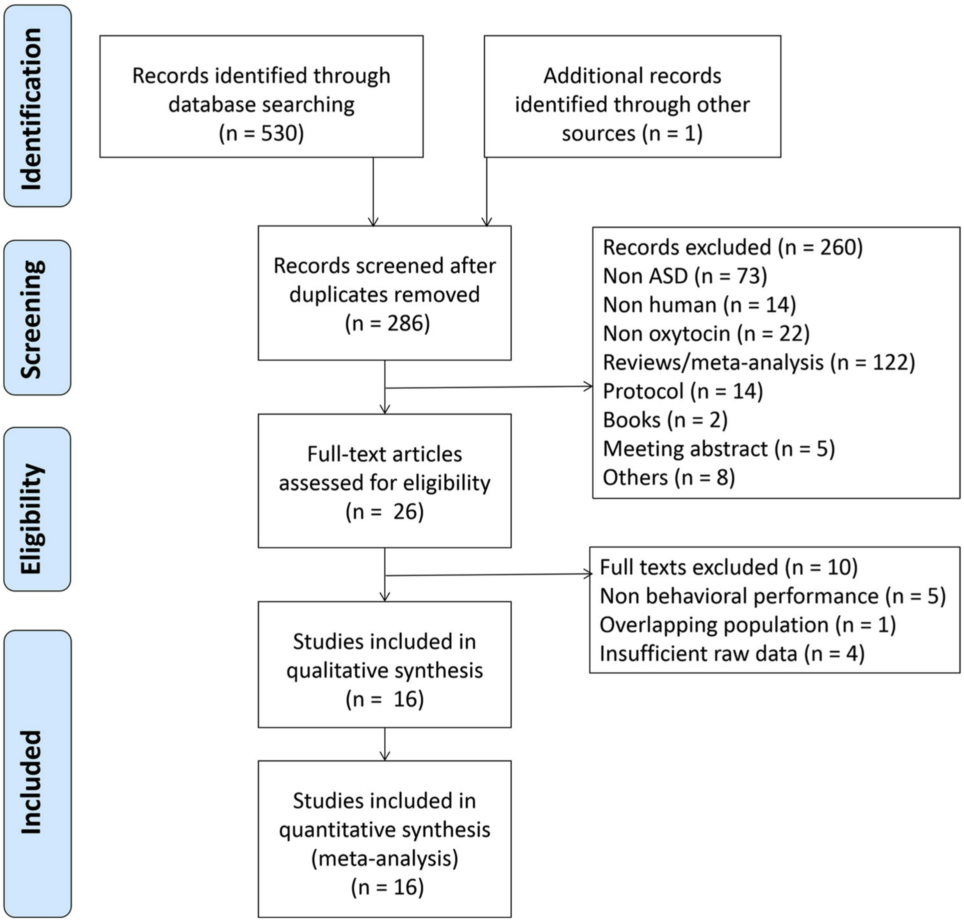

Fig. 1. Flowchart presenting RCTs selection process.

countries: USA, Japan, Australia, Norway, Germany, France and the UK, and published between 2003 and 2018. The sample size ranged from 13 to 106 and the mean age ranged from 6.2 to 35.1 years old. Seven studies involved diagnoses of Asperger disorder; eleven studies involved diagnoses of functioning autism; two studies involved diagnoses of pervasive developmental disorder; and three studies did not indicate specific types of ASD. Nasal spray administration of oxytocin was used in fifteen studies and intravenous administration was used in the remaining one. The dosage changed from 8 IU to 24 IU and the duration of oxytocin administration ranged from 4 h to 12 weeks. Several different tasks/scales of included studies were used to assess the effect of oxytocin on the social domain (e.g., Reading the Mind in the Eyes Test: the theory of mind; Face Discrimination Task: face processing; Emotional Recognition Task: emotion recognition; The Sally–Anne Task: comprehension of affective speech) and repetitive behaviors (e.g., Repetitive Behavior Scale, the Yale Brown Obsessive Compulsive Scale and Aberrant Behavior Checklist) in ASD. Of sixteen included trials, twelve RCTs reported adverse events, whereas four did not. Several common adverse outcomes were reported after oxytocin administration, such as tired, sweating, moderate irritability and headache.

3.2. Risk of bias of eligible studies

Seven of sixteen included studies reported appropriate sequence generation methods for randomization by a computer-generated list. Methods of sequence generation in the remaining studies were unclear, as authors merely suggested that allocation was randomized in their research. Twelve studies reported concealment of allocation by sequentially numbered drug containers. In addition, ten studies used participants and personnel blinding methods, and the other six studies described outcome assessment blinding. Two RCTs did not explain the risk of bias for participants dropped or withdrawn in the results (Munesue et al., 2016; Watanabe et al., 2015). In general, twelve studies were rated as a low risk of bias, whereas the remaining four studies were rated as a high risk of bias. More details about the risk of bias were shown in Table 2. The risk of bias summary and bias graph were presented in Figs. 2 and 3 respectively.

Table 1
Characteristics of RCTs included in the meta-analysis.

Study (author/ year)	Country	Design	M/F	Mean age (SD) Range	Diagnosis	Type of administration	Dosage	Duration	Outcome measures	Measuring methods	Main findings	Side effects
Hollander	USA	DB, within-subject	M = 14 F = 1	32.9 19.4–55.6	HFA AS	Intravenous	4 h period 1st: 10 ml 2nd: 50 ml 3rd: 100 ml 4th: 700 ml	4 h	RBs	RBS	Oxytocin significantly reduced RBs.	Well-tolerated
Andari	France	DB, within-subject	M = 11 F = 2	26 17–39	HFA AS	Intranasal	24 IU	1 week	SF	PANAS	Oxytocin significantly enhanced the trust and preference, and eye gazing.	–
Guastella (2010)	Australia	DB, within-subject, crossover	M = 16	14.88 (2.42) 12–19	HFA AS	Intranasal	Different ages: 16–19: 24 IU 12–15: 18 IU	1 week	SF	RMET	Oxytocin significantly improved emotion recognition.	Well-tolerated
Anagnostou (2012)	USA	DB, parallel	M = 16 F = 3	33.2 (13.29) 18–60	HFA AS	Intranasal	24 IU	6 weeks	SF, RBs	SRS, YBOCS	Oxytocin significantly improved social cognition and quality of life instead of RBs.	Well-tolerated
Domes (2013)	Germany	DB, within-subject, crossover	M = 14	24 (6.9) –	AS	Intranasal	24 IU	1 week	SF	Face Discrimination Task	Oxytocin did not significantly improve the social cognition but significantly increased the activity of right amygdala to facial stimuli.	–
Aoki (2014)	Japan	DB, within-subject, crossover	M = 20	30.8 (8) 24–41	HFA AS	Intranasal	24 IU	1 week	SF	The Sally–Anne Task	Oxytocin significantly increased the correct rate in inferring others' social emotions and enhanced the activity of the right anterior insula.	–
Dadds (2014)	Australia	DB, parallel	M = 38	11.23 (2.6) 7–16	ASD	Intranasal	Different weights: 40 + kg: 24 IU 40-kg: 12 IU	5 days	SF, RBs	Facial Emotion Task, Social Reciprocity Scale autistic mannerisms	Oxytocin did not significantly improve emotion recognition, social interaction or general behavioral adjustment.	Well-tolerated
Watanabe	Japan	DB, within-subject, crossover	M = 40	28.5 (5.9) ≥20	HFA	Intranasal	24 IU	1 week	SF	Friend or Foe Task	Oxytocin significantly increased the non-verbal judgments and enhanced the activity of in the MPFC, functional coordination area.	–
Auyeung	UK	DB, within-subject	M = 32	34.23 (9.36) 18.5–56	HFA	Intranasal	24 IU	1 week	SF	Numbers of eye contact	Oxytocin significantly enhanced gazing behaviors.	Well-tolerated
Guastella (2015)	Australia	DB, parallel	M = 50	13.92 (1.54) 12–18	ASD AS	Intranasal	The same as Guastella (2010)	8 weeks	SF, RBs	SRS, RBS	Oxytocin did not significantly improve social cognition and RBs.	Well-tolerated
Watanabe (2015)	Japan	DB, crossover	M = 20	32.2 (7.24) 24–43	HFA	Intranasal	24 IU	6 weeks	SF, RBs	SRS, RBS	Oxytocin significantly increased social reciprocity and functional connectivity between ACC and DMPFC.	Well-tolerated
Kosaka (2016)	Japan	DB, parallel	M = 47 F = 13	24 (6.09) 15–20	HFA	Intranasal	16 IU/32 IU	12 weeks	SF, RBs	IRSA, ABC III-stereotype behavior	Oxytocin significantly improved clinical global impression in the high-dose group.	Well-tolerated

(continued on next page)

Table 1 (*continued*)

Study (author/ year)	Country	Design	M/F	Mean age (SD) Range	Diagnosis	Type of administration	Dosage	Duration	Outcome measures	Measuring methods	Main findings	Side effects
Munesue	Japan	DB, cross-over	M = 29	22.5 (5.9) 15–40	PDD	Intranasal	16 IU	8 weeks	SF, RBs	IRSA, ABC III-stereotype behavior	Oxytocin did not significantly improve SF and RBs.	Serious (2 subjects)
Yatawara	Australia	DB, crossover	M = 27 F = 4	6.2 (1.7) 3–8	Autism (*n* = 19) PDD-NOS (*n* = 12)	Intranasal	Morning: 12 IU Night: 24 IU	5 weeks	SF, RBs	SRS, RBS	Oxytocin significantly improved social responsiveness.	Serious (2 subjects)
Quintana	Norway	DB, parallel	M = 17	24.76 (4.75) 18–35	HFA	Intranasal	8 IU/24 IU	13 days	SF	RMET	Oxytocin did not significantly increase the social cognition.	Well-tolerated
Yamasue	Japan	DB parallel	M = 106	27.28 (11.03) 18–48	HFA	Intranasal	24IU	6 weeks	SF, RBs	ADOS, ADOS	Oxytocin did not significantly improve the social reciprocity and RBs.	Well-tolerated

Abbreviations: DB, double-blind; M, male; F, female; PDD-NOS, pervasive developmental disorder not otherwise specified; AS, Asperger disorder; HFA, high-functioning autism; SF, social function; RBs, repetitive behaviors; RBS, Repetitive Behavior Scale; PANS, Positive and Negative Affect Schedule; RMET, Reading the Mind in the Eyes Test; SRS, Social Responsiveness Scale; YBOCS, the Yale Brown Obsessive Compulsive Scale; IRSA, Interaction Rating Scale Advanced; ABC, Aberrant Behavior Checklist; ADOS, Autism Diagnostic Observation Schedule; MPFC, medial prefrontal cortex; DMPFC, dorsal medial prefrontal cortex; ACC, anterior cingulate cortex.

Table 2
Details about risk of bias.

Study	Sequence generation	Allocation concealment	Risk of bias
Hollander (2003)	Unclear	Unclear	High
Andari (2010)	Unclear	Unclear	High
Guastella (2010)	Unclear	Sequentially numbered drug containers	High
Anagnostou (2012)	Computer-generated	Sequentially numbered drug containers	Low
Domes (2013)	Unclear	Unclear	High
Aoki (2014)	Computer-generated	Sequentially numbered drug containers	Low
Dadds (2014)	Unclear	Sequentially numbered drug containers	Low
Watanabe (2014)	Unclear	Sequentially numbered drug containers	Low
Auyeung (2015)	Computer-generated	Sequentially numbered drug containers	Low
Guastella (2015)	Unclear	Sequentially numbered drug containers	Low
Watanabe (2015)	Computer-generated	Sequentially numbered drug containers	Low
Kosaka (2016)	Computer-generated	Unclear	Low
Munesue (2016)	Computer-generated	Sequentially numbered drug containers	Low
Yatawara (2016)	Unclear	Sequentially numbered drug containers	Low
Quintana (2017)	Unclear	Sequentially numbered drug containers	Low
Yamasue (2018)	Computer-generated	Sequentially numbered drug containers	Low

3.3. Outcome of meta-analysis

3.3.1. The effects of oxytocin on social function

Fifteen out of sixteen included studies examined the effects of oxytocin on social function in autistic individuals (Table 1). Results from the meta-analysis of the fifteen studies showed low between-study heterogeneity within the acceptable level ($I^2 = 46.4\% < 50\%$, $p = 0.025$). Results indicated that oxytocin had a small and non-significant effect on social function compared with placebo [SMD = 0.03, 95% CI (−0.19, 0.25), $p = 0.781$; Fig. 4].

3.3.2. The effects of oxytocin on repetitive behaviors

Nine out of sixteen included studies investigated the effect of oxytocin on repetitive behaviors (Table 1). Results from our meta-analysis showed low between-study heterogeneity within the accepted range ($I^2 = 37.0\% < 50\%$, $p = 0.123$). Pooled analysis using data from ASD samples in nine studies yield smaller effect size and indicted that oxytocin did not significantly relieve the severity of repetitive behaviors [SMD = 0.01, 95% CI (−0.26, 0.27), $p = 0.952$; Fig. 5].

3.4. Sensitivity analysis

In order to test the stability of the results, each study was excluded sequentially. Regarding the effects of oxytocin on social function, the results of our sensitivity analysis indicated that oxytocin had a small and non-significant effect on social function in individuals with ASD after excluding all studies separately except one (Quintana et al., 2017). Besides, the heterogeneity was relatively maximal decreased after excluding this study by Quintana et al. (2017), the recalculated SMD was −0.02 [95% CI (−0.20, 0.16), $p = 0.824$] with low heterogeneity ($I^2 = 17.5\%$, $p = 0.263$).

Regarding the effects of oxytocin on repetitive behaviors, the results of sensitivity analysis suggested that oxytocin had no effect on the domain of repetitive behaviors after excluding several studies respectively (Anagnostou et al., 2012; Munesue et al., 2016; Watanabe et al., 2015; Yatawara et al., 2016). Among these studies, after excluding the study by Yatawara et al. (2016), the heterogeneity disappeared ($I^2 = 0\%$, $p = 0.539$). It also demonstrated that the results of the effects of oxytocin on these two domains were unstable in our meta-analysis.

3.5. Publication bias assessment

Egger's funnel plot was performed to assess the publication bias of included studies regarding social domain (Fig. 6) and repetitive behaviors (Fig. 7). Although visual inspection of the funnel plot suggested publication bias might exist, Egger's test for bias indicated that publication bias was not significant ($p = 0.471$ in social function; $p = 0.459$ in repetitive behaviors). When Duval and Tweedie's trim-and-fill method was applied, no studies regarding the effects of oxytocin on social function and repetitive behaviors were trimmed or filled.

4. Discussion

In this meta-analysis, sixteen RCTs were included, covering a total of 520 participants that involved comparison of oxytocin with placebo for the treatment of core symptoms in ASD. Overall, mixed findings from our study indicated that oxytocin had a small and non-significant effect on social function (SMD = 0.03, $p = 0.781$) and repetitive behaviors (SMD = 0.01, $p = 0.952$) in patients with ASD.

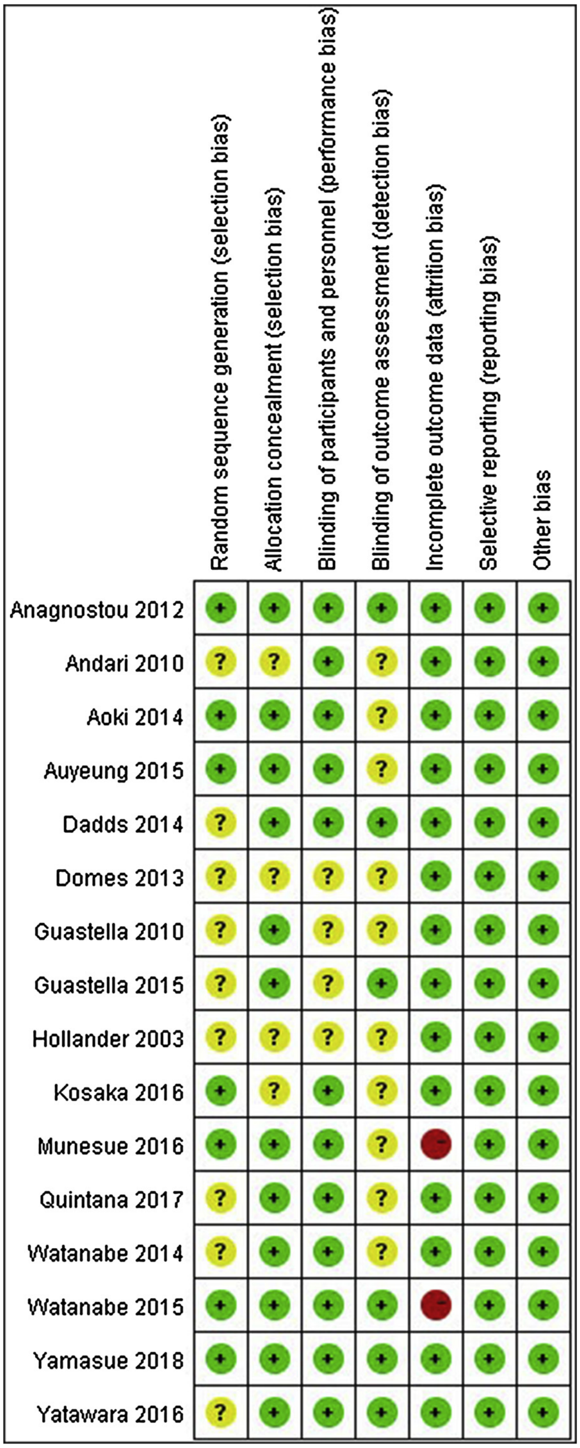

Fig. 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

4.1. Oxytocin and social function in individuals with ASD

A large number of studies have demonstrated that ASD individuals exhibited a marked withdrawal from interactions with others (Frye, 2018; Kasari & Patterson, 2012). It is often seen as difficulties in three domains: social–emotional reciprocity; nonverbal communicative behaviors such as eye contact, facial expressions and body postures; developing, maintaining and understanding relationships (American Psychiatric Association, 2013). Over the past decades, oxytocin has been considered as a potential

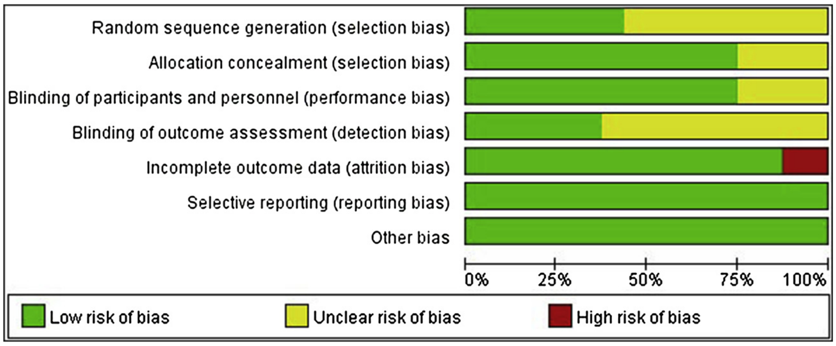

Fig. 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

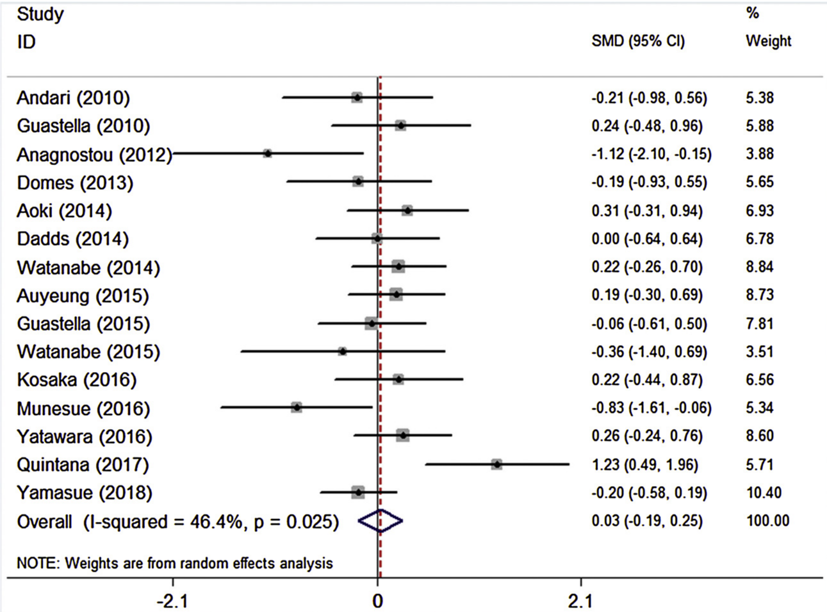

Fig. 4. Forest plot to analyze the effects of oxytocin on social function in ASD.

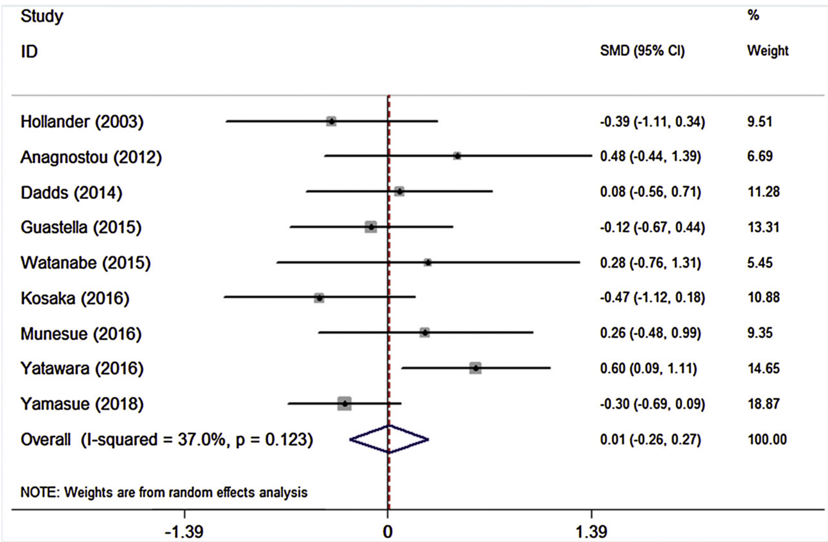

Fig. 5. Forest plot to analyze the effects of oxytocin on repetitive behaviors in ASD.

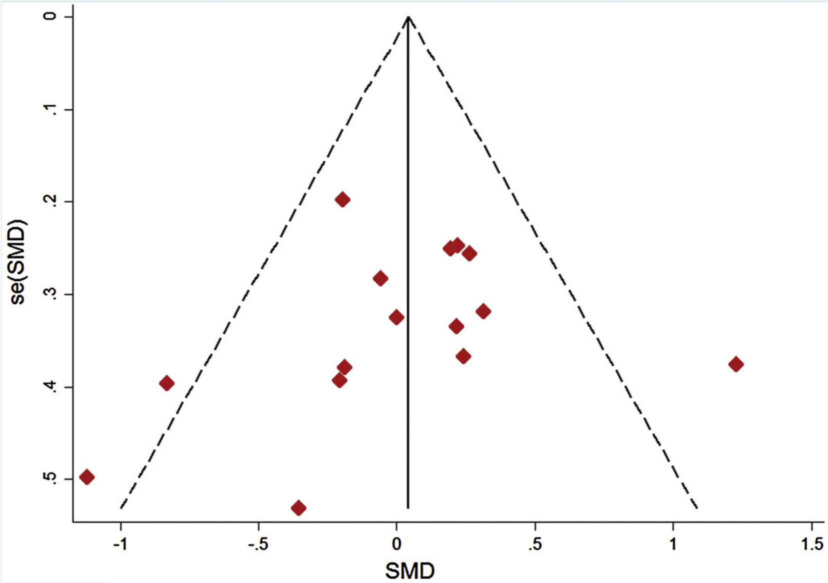

Fig. 6. Funnel plot to detect publication bias of the social function. The diamonds represent the studies in the analysis.

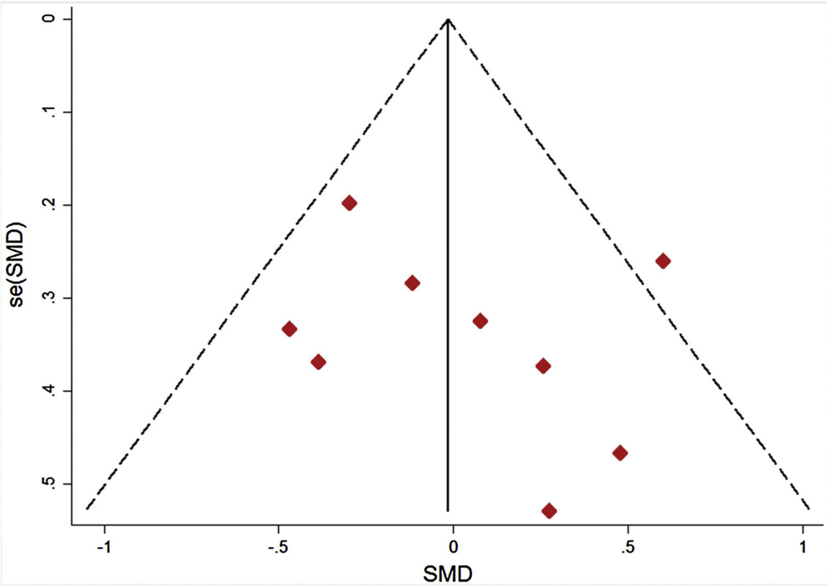

Fig. 7. Funnel plot to detect publication bias of the repetitive behaviors. The diamonds represent the studies in the analysis.

medication for treating social deficits of ASD. Extensive fMRI studies have found that the activity of certain areas associated with social impairments in the brain increased, such as right anterior insula, medial prefrontal cortex and anterior cingulate cortex (Aoki et al., 2014; Watanabe et al., 2014, 2015).

Our meta-analytic findings showed that oxytocin had no significant effect on the social function of ASD, which were consistent with the most recent meta-analysis (Ooi et al., 2016). There might be several reasons why the effect was not significant. First, ASD is a highly heterogeneous population, all of the studies included a majority of males of varying age with high-functioning ASD; second, the dosage and duration of oxytocin administration are changeable; third, variations of OXTR gene might influence the effects of oxytocin administration. Watanabe et al. (2017) examined associations between oxytocin efficacy and genetic variability to identify genetic variants of OXTR that enhance/deteriorate oxytocin's beneficial effects on ASD. And the results showed that specific SNP sets accurately predicted behavioral/neural responses to oxytocin in ASD; last but not least, several studies included in our meta-analysis used different methods to measure changes in the social domain. Interestingly, the assessment results were inconsistent by using different evaluation methods in the same population. For example, Anagnostou et al. (2012) used clinical global impression-improvement rating and Social Responsiveness Scale-Revised to examine the effects of oxytocin administration on the social function of

ASD. The results showed that social function in ASD individuals was 30% improved in the former while no effects in the latter assessment tool. Therefore, more sufficiently pervasive studies based on larger cohorts should be designed for the effects of oxytocin on social function in individuals with ASD to rationalize our conclusions.

4.2. Oxytocin and repetitive behaviors in individuals with ASD

Another main finding in our meta-analysis was that oxytocin did not significantly ameliorate the severity of repetitive behaviors that was also consistent with the past meta-analysis performed by Ooi et al. (2016). So far, there were a fair bit of scientific studies specified for exploring the effects of oxytocin on the repetitive behaviors in individuals with ASD. Initially, Hollander et al. (2003) found that intravenous administration of oxytocin significantly reduced the repetitive behaviors (needing to know, needing to tell/ask, repeating, ordering, self-injury and touching) in adults with ASD compared with placebo during a four-hour period, and the outcome was measured by the Repetitive Behavior Scale (RBS). However, in the latest research, Yamasue et al. (2018) randomized 106 adults to a parallel placebo-controlled trial of six-week intranasal oxytocin (48 IU/day) and reported no significant reductions in repetitive behaviors as measured by Autism Diagnostic Observational Scale (ADOS). The reasons for the inconsistency of conclusions might be limited sample size, different types, dosage and duration of administration, as well as different tools of outcome measurements. Due to the conflicting results, additional RCTs regarding the effects of oxytocin on repetitive behaviors in patients with ASD are recommended to verify the conclusions in our meta-analysis.

4.3. The safety of oxytocin therapy

The safety of oxytocin administration is another significant issue that should be discussed. Of the sixteen studies included, only two trials in the meta-analysis reported the occurrences of serious adverse reactions. Yatawara et al. (2016) reported that three subjects experienced hyperactivity and aggression. Two out of three participants experienced these serious side effects in the first week of oxytocin phase; the remaining one occurred during the first week of placebo phase of the crossover trial. The study also added that all serious adverse reactions ceased when the administration was discontinued. Munesue et al. (2016) found that two participants in the crossover study experienced seizures. The first participant occurred during the period of follow-up. The researchers made an assumption that forgetting to take anti-epileptic medicine gave rise to the seizures. Although the epilepsy of the second participant was well controlled before, he still experienced seizures during the period of oxytocin and placebo administration.

Other ten studies included reported no severe adverse events in patients receiving oxytocin administration in the included RCTs (Table 1). All adverse events were mild to moderate in the short or long term administration of oxytocin, such as tiredness, shakiness, nausea and irritability, which was consistent with other trials (Lin et al., 2014; Parker et al., 2017). Furthermore, there was no significant or clinically important difference after individuals receiving the administration of oxytocin or placebo, which indicated that oxytocin was well-tolerated in the treatment of ASD. Consequently, future studies are needed to investigate the occurrences of adverse events during oxytocin administration, and the safety of oxytocin still requires further validation.

4.4. Limitation of the study

The present meta-analysis has several important limitations that required greater attention in the future. First, we could include only a relatively small sample of studies and several studies with high risk of bias (Andari et al., 2010; Domes et al., 2013; Guastella et al., 2010; Hollander et al., 2003), leading to low power to examine the effects of oxytocin administration on core symptoms in individuals with ASD. Second, the included studies employed heterogeneous methodologies with different levels of quality that may have impacted our ability to draw definitive conclusions. Studies selected showed variability in the duration of treatment ranging from continuous four hours to twelve weeks. Studies were also quite variable in the sample size, gender, age, diagnosis, the type and dosage of oxytocin administration. This heterogeneity may lead to the high variability between and within studies. Third, the sample size of included trials was limited and therefore small sample size effects may be generated. Finally, the language of studies included was restricted in English.

5. Conclusion

In summary, although our meta-analytic findings from RCTs suggested that oxytocin had a small effect on social function and repetitive behaviors compared with placebo, the difference was not significant. ASD is a complex disorder along with biologic and phenotypic heterogeneity, and the effects of oxytocin on core symptoms might be moderated by variable elements, including gender etc. that mentioned above. Moreover, due to lack of clearly established studies about efficacy and safety along with approved by FDA for its use as a drug to improve social function and repetitive behaviors, we should treat cautiously about the effect of oxytocin in treating core symptoms of ASD. In the future, more large-scale, rigorously and multi-site, randomized, double-blind, placebo-controlled trials should be employed to overcome the limitations of the current meta-analysis, and to acquire more convincing conclusions.

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