Psychoneuroendocrinology (2011) xxx, xxx—xxx

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journal homepage: www.elsevier.com/locate/psyneuen

REVIEW

A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research

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Received 6 December 2010; received in revised form 6 February 2011; accepted 26 February 2011

KEYWORDS
Intranasal;
Oxytocin;
Safety;
Side-effects;
Drug awareness;
Social behaviour

Summary
Background: Human research investigating the impact of intranasal oxytocin on psychological processes has accelerated over the last two decades. No review of side effects, subjective reactions and safety is available.
Method: A systematic review of 38 randomised controlled trials conducted between 1990 and 2010 that investigated the central effects of intranasal oxytocin was undertaken. A systematic search for reports of adverse reactions involving intranasal oxytocin was also completed.
Results: Since 1990, research trials have reported on $N = 1529$ (79% male) of which 8% were participants with developmental or mental health difficulties. Dosages ranged from 18 to 40 IU, mainly in single doses but ranged up to 182 administrations. Diverse methods have been used to screen and exclude participants, monitor side effects and subject reactions. Side effects are not different between oxytocin and placebo and participants are unable to accurately report on whether they have received oxytocin and placebo. Three case reports of adverse reactions due to misuse and longer-term use of intranasal oxytocin were reported.
Conclusions: The evidence shows that intranasal oxytocin: (1) produces no detectable subjective changes in recipients, (2) produces no reliable side-effects, and (3) is not associated with adverse outcomes when delivered in doses of 18—40 IU for short term use in controlled research settings. Future research directions should include a focus on the dosage and duration of use, and application with younger age groups, vulnerable populations, and with females.
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0306-4530/$ — see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2011.02.015

Please cite this article in press as: MacDonald, E., et al., A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research. Psychoneuroendocrinology (2011), doi:10.1016/j.psyneuen.2011.02.015

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Dating back to the 1950s, oxytocin was the first peptide hormone to be purified, synthesised, and made available for pharmacologically defined studies (Du Vigneaud et al., 1953a,b). Synthetic oxytocin, also known as 'pitocin' and 'syntocinon', is widely used for inducing labour, postpartum care and for enhancing lactation (Gimpl, 2008). The administration of oxytocin in neonatal settings has been predominately via intravenous infusion, although nasal delivery is used in many countries for enhancing lactation. It is also becoming increasingly accessible via the internet and is produced regularly by research pharmacies for use within clinical trials.

Comprehensive product information describing the pharmacology and possible side effects of intravenous infusion of synthetic oxytocin is accessible from Novartis pharmaceuticals (Novartis, 2011). Moreover, safety information regarding adverse reactions is reported on regulatory databases worldwide, for example the Foods and Drugs Association in the United States (Foods and Drugs Association, 2011) or the Therapeutic Goods Association in Australia (Australian Government Department of Health and Aging Therapeutic Goods Association, 2011). The European Medicines Agency lists all individual European National regulatory authorities (European Medicines Agency, 2011). Specifically, Novartis reports that cardiovascular changes including tachycardia and bradycardia can be common. Nausea, vomiting and headaches have also been reported to occur with intravenous infusion. Less frequent reactions from intravenous infusion include water intoxication and associated neonatal hyponatraemia, skin rashes and anaphylactoid reactions (Novartis, 2011).

Safety information regarding the use of intranasal oxytocin is available from European countries such as the Netherlands where it is marketed for improving lactation (CBG Medicines Evaluation Board, 2011). Product information from the Netherlands lists headaches, nausea and allergic dermatitis occurring rarely ($>1/10{,}000$, $<1/1000$) and abnormal uterine contractions known to occur sometimes ($\geq 1/1000$, $<1/100$). Previous research studies investigating the role of oxytocin in enhancing lactation have reported no safety concerns (Newton and Egli, 1958; Huntingford, 1961; Fewtrell et al., 2006). There are, however, special warnings for prolonged use of excessive doses together with large volumes of fluid as this has been known to cause water intoxication with hyponatraemia (Hubner-Mayer, 1996).

Although detailed information is available regarding the oxytocin system (see Gimpl and Fahrenholz, 2001; Holmes et al., 2003, 2004) the underlying mechanisms of reported side-effects are not always clear. It is widely accepted that the rare adverse reaction of water intoxication following oxytocin administration is thought to be related to the close similarity in chemical structure between oxytocin and the antidiuretic hormone, vasopressin (Potter, 1964; Legros, 2001; Brunton et al., 2006). The pharmacokinetics of intranasal oxytocin are also not fully understood. It is known that the half-life when administered IV is about 3 min (Brunton et al., 2006) and current evidence has found reliable central effects when administering vasopressin nasal spray (Born et al., 2002). In relation to general intranasal drug delivery it has been suggested that pathways of action involve the vasculature, cerebrospinal fluid, and lymphatic system (Hanson and Frey, 2008).

In addition to peripheral affects, oxytocin also acts as a neurotransmitter in the brain influencing many aspects of social behaviour (Landgraf and Neumann, 2004; Lee et al., 2009). The last two decades have witnessed a surge in research investigating the application of oxytocin as a method of enhancing psychological function in humans. Research involving healthy adults has linked oxytocin with a range of effects such as reducing levels of anxiety (Heinrichs et al., 2003), and increasing levels of trust (Kosfeld et al., 2005), gaze to the eyes (Guastella et al., 2008a), and accurate emotion processing (Di Simplicio et al., 2009; Fischer-Shofty et al., 2010). The vast majority of studies investigating oxytocin and social behaviour in humans has utilised nasal delivery as the administration method (MacDonald and MacDonald, 2010).

As noted above, current safety information regarding the use of intranasal oxytocin with humans is largely derived from usage by mothers to promote lactation. There is now an increased application of intranasal oxytocin in clinical trials for psychological problems, extending to use with children and young people. However despite recommendations (Loke et al., 2007), there is no available review into side effects and safety when used in these contexts. Evidence from intravenous infusion of oxytocin suggests possible cardiovascular effects and as previously reported there have been cases of water intoxication from intranasal oxytocin. Thus, it is essential to assess risk factors when

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administering to wider populations of differing participant profiles.

This article provides a systematic review from research studies investigating the central effects of intranasal oxytocin conducted between 1990 and 2010. Lactation studies were excluded to enable a clear focus on research investigating the central effects of intranasal oxytocin. A systematic review of case reports documenting adverse reactions following intranasal oxytocin was also undertaken.

1. Method

1.1. Selection criteria

The search, retrieval and screening of studies were undertaken by the first author. Data sources included regulatory websites, such as the Therapeutic Goods Association (TGA) and The Foods and Drugs Administration (FDA), Medline, the Cochrane Library, Google scholar and a general internet search. Key works used in this search included oxytocin, pitocin, syntocinon, intranasal oxytocin, nasal spray oxytocin, adverse reactions oxytocin, and side-effects oxytocin. A recent systematic review of intranasal oxytocin and its prosocial effects in humans (MacDonald and MacDonald, 2010) was included as a data source. Inclusion of studies was restricted to clinical trials conducted between 1990 and 2010. There was no restriction on study design, such that we included randomised, crossover designs, double blind and single blind. The rationale for the date restriction was based on information provided from Fehm-Wolfsdorf and Born's (1991) review which examined 30 studies published from 1980 to 1990 where intranasal or intravenous oxytocin and vasopressin was administered to humans. This review noted that sample sizes in all 30 studies were small and that there were some severe methodological shortcomings in the experiments. All case reports documenting adverse reactions in humans following intranasal oxytocin were included. No date restriction was imposed regarding adverse reactions from intranasal oxytocin to enable comprehensive reporting of such events. Two studies involving intravenous infusion of oxytocin with participants diagnosed with Autism Spectrum Disorders (ASD) were included to enable a review of all safety data available when administering to this clinical population. There were 38 studies identified for this review, all of which were peer-reviewed and three case reports. There are no adverse reactions from intranasal oxytocin listed on any of the regulatory databases. There were no prospective or retrospective observational studies found.

1.2. Data collection and analysis

A questionnaire was designed to gather specific information regarding occurrence of side effects, subjective awareness, methods for monitoring, recording and reporting side-effects, and general research methodology (available from first author by request). This questionnaire was designed based on recommendations from the 2007 Cochrane paper "Systematic reviews of adverse effects: framework for a structured approach" (Loke et al., 2007).

One reviewer, the first author, read each journal article and completed the questionnaire for each study from the available information. Each questionnaire was then sent to the corresponding author of all 38 identified studies. The authors were asked to check the questionnaire for accuracy, add any additional information and return for inclusion in this review. Information was extracted from the questionnaires and entered into an SPSS database and included; participant details; substance administration procedures; participant perception of drug allocation; and monitoring, recording and reporting of side-effect information. Of the three case studies reporting adverse effects information was extracted on the adverse reactions reported, participant details and dosage amounts.

2. Results

All studies collected data on side-effects for both oxytocin and placebo; in the results below, the term 'side effects' is thus used with reference to both unless otherwise specified. Questionnaires were returned from authors of 68% (26 out of 38) of studies, no corrections where made although additional information was provided by 21 authors. This additional information included, a statement highlighting that no side-effects occurred ($n = 13$), details regarding side-effects when they did occurred ($n = 7$); methods of monitoring and detecting side-effects ($n = 8$); and participant subjective effects ($n = 14$). The majority of studies reported no side-effects resulting in positively skewed and leptokurtic data; thus, descriptive statistics and non-parametric tests were conducted using SPSS 18 software to evaluate hypotheses. There were 12 studies whereby authors did not confirm the accuracy of the completed questionnaire or provide any additional information. The following results, however, include analysis of all 38 studies.

Table 1 presents detailed information regarding each of the 38 randomised controlled trials. In 76% of studies participants ($N = 1345$) were healthy adults aged between 20 and 30 years. In a total sample of 1529, 926 participants received oxytocin of which 735 (79%) were male. There were nine studies with a total of 182 participants that investigated the effects of intranasal oxytocin on individuals with a developmental, medical or mental health disorder. Of these clinical trials, 67% ($N = 6$) employed a within subject or crossover research design. Only one study recruited young participants under 20 years old, 16 participants diagnosed with ASD aged 12–19 years old (Guastella et al., 2010).

2.1. Side-effects reported

Overall, there were minimal side-effects reported from all 38 randomised controlled studies (a complete list is available from the first author upon request). Table 2 presents information on side-effects reported by five or more participants. Of 1529 participants, mild side-effects were reported by 18% ($n = 279$). A Spearman correlation showed that there was almost a one-to-one relationship between the frequency of side-effects reported by oxytocin and placebo participants, $r_s = .903$, $p < .001$. Furthermore, a Wilcoxon signed rank test indicated that there was no significant difference between the frequency of side effects reported for oxytocin ($Mdn = 0$)

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Table 1 Safety data from 38 randomised controlled trials studying the effects of nasal delivery oxytocin in humans 1990—2010.

Study design and subject status	Subjects (*n*) and gender		Nasal spray			Total side effects		AR	Safety monitoring methods
	OT	OT & PL	Dosage details	Nasal spray supplier	PL ingredients	OT	PL		
Healthy: double blind with PL control									
Bruins et al. (1992)	11 M	23 M	20 IU single	Ingredients not reported	Not reported	0	0	0	Mood and physiological questionnaire; Medical assessment; BP & HR
Heinrichs et al. (2003)	19 M	37 M	24 IU single	Syntocinon: Novartis	All ingredients minus OT	0	0	0	Mood questionnaire Medical assessment
Heinrichs et al. (2004)	19 M	38 M	24 IU single	Syntocinon Novartis	All ingredients minus OT	0	0	0	Mood questionnaire Medical Assessment
Kosfeld et al. (2005)	89 M	178 M	24 IU single	Syntocinon Novartis	All ingredients minus OT	0	0	0	Mood questionnaire
Zak et al. (2007)	34 M	68 M	40 IU single	Syntocinon Novartis	Normal saline	0	0	0	Medical Assessment
Baumgartner et al. (2008)	25 M	48 M	24 IU single	Syntocinon Novartis	All ingredients minus OT	0	0	0	Mood questionnaire; Medical assessment
Guastella et al. (2008b)	35 M	69 M	24 IU single	Compounding chemist	All ingredients minus OT	13	12	0	Mood questionnaire; Medical assessment; self report; obs
Guastella et al. (2008a)	25 M	52 M	24 IU single	Syntocinon Novartis	All ingredients minus OT.	6	0	0	Mood questionnaire; checklist; Medical assessment
Petrovic et al. (2008)	15 M	27 M	32 IU single	Syntocinon Novartis	All ingredients minus OT	0	0	0	Checklist Medical Assessment
Unkelbach et al. (2008)	21 M	44 M	24 IU single	Compounding chemist	All ingredients minus OT	0	0	0	Mood questionnaire Medical Assessment
Rimmele et al. (2009)	22 M	41 M	24 IU single	Syntocinon Novartis	All ingredients minus OT	0	0	0	Mood questionnaire
Singer et al. (2008)	10 M	20 M	32 IU single	Syntocinon Novartis	All ingredients minus OT.	0	0	0	Mood and Physiological questionnaire; checklist; Medical Assessment; self -report &obs
Ditzen et al. (2009)	24 M 24 F	47 M 47 F	40 IU single	Syntocinon Novartis	Not reported	0	0	0	Physiological questionnaire; checklist Medical assessment; BP & HR
Di Simplicio et al. (2009)	14 M	29 M	24 IU single	Syntocinon Novartis	Not reported	6	6	0	Mood questionnaire; checklist Medical assessment
Guastella et al. (2009a)	36 M 17 F	71 M 33 F	24 IU single	Compounding chemist	All ingredients minus OT	0	0	0	Mood questionnaire Medical assessment
Gamer et al. (2010)	23 M	46 M	24 IU single	Syntocinon Novartis	All ingredients minus OT.	13	18	0	Mood questionnaire; Medical assessment; BP & HR; self report; obs
Theodoridou et al. (2009)	25 M 26 F	48 M 48 F	24 IU single	Syntocinon Novartis	All ingredients minus OT	41	31	0	Mood and physiological questionnaire; checklist; medical assessment; self report & obs

Alvares et al. (2010)	17 M 18 F	35 M 39 F	24 IU single dose	Syntocinon: Novartis[a]	All ingredients in nasal spray minus active OT.	13	15	0	Checklist medical assessment
Kirsch et al. (2005)	15 M	15 M	27 IU single	Syntocinon: Novartis	All ingredients minus OT	0	0	0	Mood questionnaire; BP & HR self report; obs
Meinlschmidt and Heim (2007)	19 M	19 M	24 IU single	Syntocinon Novartis	Not reported	12	7	0	Physiological questionnaire
Burri et al. (2008)	10 M	10 M	24 IU single	Syntocinon Novartis	All ingredients minus OT	0	0	0	Medical Assessment BP & HR
Keri and Benedek (2009)	10 F	10 F	24 IU single	Syntocinon Novartis	All ingredients minus OT	2	3	0	Checklist; Medical assessment BP & HR; self report
Fischer-Shofty et al. (2010)	27 M	27 M	24 IU single	Syntocinon Novartis	Saline solution	1	0	0	Mood questionnaire Medical assessment; obs
Domes et al. (2010)	16 F	16 F	24 IU single	Syntocinon Novartis	All ingredients minus OT	0	0	0	Mood questionnaire Medical assessment
Healthy: single blind PL control									
Savaskan et al. (2008)	9 M 9 F	18 M 18 F	20 IU single	Syntocinon Novartis	Isotonic natriumchlorid	0	0	0	Medical Assessment BP & HR; self report & obs
Domes et al. (2007b)	30 M	30 M	24 IU single	Syntocinon Novartis	All ingredients minus OT.	0	0	0	Mood questionnaire Medication assessment
Domes et al. (2007a)	13 M	13 M	24 IU single	Syntocinon Novartis	All ingredients minus OT	0	0	0	Mood questionnaire Medication assessment
Shamay-Tsoory et al. (2009)	26 M 33 F	26 M 33 F	24 IU single	Syntocinon Novartis	Not reported	2	1	0	Mood questionnaire Medical Assessment; obs
Buchheim et al. (2009)	26 M	26 M	24 IU single	Syntocinon Novartis	All ingredients minus OT	0	0	0	Mood questionnaire; Medical Assessment; Self report; obs
Severe constipation: double blind PL control									
Ohlsson et al. (2005)	29 F	59 F	40 IU 182 doses (twice daily for 13 weeks	Syntocinon Novartis	All ingredients minus OT	20	23	0	Physiological questionnaire Medical Assessment; BP/HR; self report; obs
Post traumatic stress disorder: double blind PL control									
Pitman et al. (1993)	15 M	30 M	20 IU	Single dose: pitocin	Saline	0	0	0	Medical Assessment; BP/HR, self report; obs
ASD: crossover, double blind with placebo control									
Hollander et al. (2003)	14 M 1 F	14 M 1 F	10 U/ml	Infusion over 4 h	Not reported	8	3	0	Medical Assessment; BP & HR; self report; obs
Hollander et al. (2007)	14 M 1 F	14 M 1 F	10 U/ml	Infusion over 4 h	Not reported	Not known	Not Known	0	Medical Assessment; BP & HR; self report; obs
Guastella et al. (2010)	16 M	16 M	24 IU single	Compounding chemist	All ingredients minus OT	5	3	0	Side-effect checklist; Medical Assessment
ASD: within sub double blind with PL control									
Andari et al. (2010)	11 M 2 F	11 M 2 F	24 IU single	Syntocinon: Novartis	Not reported	0	0	0	Mood questionnaire Medical Assessment

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Table 1 (*Continued*)

Study design and subject status	Subjects (*n*) and gender		Nasal spray			Total side effects		AR	Safety monitoring methods
	OT	OT & PL	Dosage details	Nasal spray supplier	PL ingredients	OT	PL		
Trichotillomania: crossover, double blind PL control									
Epperson et al. (1996b)	2 F	2F	40 IU 28 doses:4 daily over 7 days	Syntocinon Novartis	Saline	0	2	0	Mood questionnaire BP & HR
OCD crossover, double blind PL									
Epperson et al. (1996a)	4 M 3 F	4 M 3 F	40 IU 28 doses: 4 daily over 7 days	Syntocinon Novartis	Not reported	Not known	Not known	0	Mood questionnaire medical assessment; HR/BP, self report
SAD double blind PL									
Guastella et al. (2009b)	12 M	25 M	24 IU (1 dose weekly for 4 wks)	Syntocinon: Novartis	All ingredients minus OT	7	6	0	Mood questionnaire Medical Assessment

ASD = autism spectrum disorder; SAD = social anxiety disorder; OCD = obsessive compulsive disorder.
[a] Oxytocin spray ingredients syntocinon: oxytocin, sodium phosphate, citric acid, sodium chloride, sorbitol, glycerol and preservatives; PL = placebo; OT = oxytocin; AR = adverse reactions; HR = heart rate; BP = blood pressure; Obs = observation.

or placebo participants (*Mdn* = 0), $z = .980$, $p = .327$, $r = -0.16$. The main categories of reported side-effects included, increased calmness/euphoria, feeling more comfortable or having more energy reported by 5% ($n = 78$); light headedness, drowsiness and/or headache reported by 6% ($n = 88$) and nasal irritation, dry mouth/throat reported by 3% ($n = 40$). Three female participants in a study that investigated the long term effects of oxytocin in treating chronic constipation (Ohlsson et al., 2005) reported severe vertigo on the first day of treatment, one of which had received placebo. All three participants withdrew on the first day, no other information was available. Five participants in this study also reported menstrual disturbances, four of those had received placebo.

2.2. Strategies for monitoring, recording and reporting of side-effects/adverse reactions

All studies included in this review ($N = 38$) reported methods for monitoring side-effects either in the review questionnaire or in the published article. Monitoring methods were categorised under seven headings. Table 1 presents monitoring methods used in each individual study. The most frequent methods included medical assessment reported in 84% of studies ($n = 32$) and mood questionnaires, such as the Multi-dimensional Mood Questionnaire (Steyer et al., 1997) and the positive and negative affect schedule (PANAS) (Watson et al., 1988), reported in 61% of studies ($n = 23$). Other methods used were non-standardised questionnaires aimed at gathering specific physiological/side-effect data (16%, $n = 5$), self-report and interviews (40%, $n = 15$), side-effect checklists (24%, $n = 9$) and observation (29%, $n = 11$). Monitoring of blood pressure and heart rate was reported in 37% of studies ($n = 14$).

The combination of monitoring methods varied between studies. Of the 21 studies that found no side-effects, 48% ($N = 10$) reported using only standardised mood questionnaires combined with a medical assessment to monitor participants' reactions. The remaining 52% of studies used a least one monitored method specifically targeted at recording information on side-effects, such as self-report, observation, physical symptoms questionnaire and monitoring of heart rate/blood pressure. Of the 16 studies that reported the occurrence of side-effects, 94% monitored participants' reactions through a least one targeted method. A Mann–Whitney-*U* test indicated there was a significantly higher frequency of side-effects reported in studies that used targeted methods (*Mdn* = 0.50) compared to those that used mood questionnaires and medical assessment (*Mdn* = 0), $U = 60.5$, $p = 0.002$, $r = 0.50$. Consistent with analyses above for the entire sample, however, there was no significant difference between the mean number of side-effects reported by participants who were administered oxytocin (*Mdn* = 0) or placebo (*Mdn* = 0), within studies using targeted methods, $z = 0.980$, $p = 0.327$, $r = -0.16$.

There were a small number of studies ($n = 6$; 16%) that used a medical practitioner to complete the medical assessment and 8% ($n = 3$) of studies reported having a medical practitioner present throughout the trial. Four of the former and one of the latter studies reported side effects, with no differences between oxytocin and placebo. These numbers of

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Table 2 List of side-effects reported by 5 participants or more from all 38 randomised controlled studies.

Symptom	Total # of times symptom reported			Onset				Duration			Severity		Final outcome	Participant status		
	Total N	PL	OT	Unknown	Immediate	Within 1st 2 h	Unknown	<4 h	<24 h	Mild	Moderate	Severe	Symptoms cleared	Healthy	ASD	Other[a]
Light headedness/vertigo	21	10	11	100%			100%			86%		14%	100%	76%		24%
Drowsiness/sleepy	38	22	16	53%		47%	50%	42%	8%	100%			100%	95%	5%	
Dry throat/mouth	12	6	6		100%			100%		100%			100%	100%		
Nasal irritation	14	8	6	60%	40%		60%	40%		100%			100%	40%		60%
Runny nose	13	6	7		100%			100%		100%			100%	100%		
Abdominal/stomach pain	8	3	5	100%			100%			100%			100%	13%	13%	74%
Anxious/worried/uncomfortable	18	11	7	100%			67%	16%	16%	100%			100%	56%	33%	11%
Euphoric/energised/uplifted	14	5	9	100%			64%	76%					100%	100%		
Calm, relaxed, comfortable	59	27	32	100%			93%	7%		100%			100%	78%	13%	21%
Headache		29	14	15	100%			45%		39%	100%		100%	52%	10%	38%

PL = placebo; OT = oxytocin.

[a] Other category included: obsessive compulsive disorder; social anxiety disorder; Trichotillomania; severe constipation and post traumatic stress disorder. ASD = autism spectrum disorders

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studies were too small to use for statistical comparisons, however they did not appear to differ from the other studies in terms of the occurrence of side-effects for either oxytocin or placebo.

Reporting methods on side-effect information within the published article for each of the 38 studies was also collated. Of the 21 studies where side-effects did not occur methods of reporting included; no information reported ($n = 5$; 13%); generic summaries providing a brief statement outlining that no side-effects occurred ($n = 9$; 24%) and generic summary combined with a table or statistical analysis ($n = 7$; 18%). Of the 16 studies where side-effects did occur reporting methods included; a detailed list specifying the type of side-effects ($n = 7$; 18%), a generic summary which stated that side-effects were minimal ($n = 2$; 5%), generic summary combined with a table or statistical analysis ($n = 6$; 16%) and no information ($n = 1$; 3%).

2.3. Exclusion criteria and concurrent use of medication

The process and content of exclusion criteria was highly variable across studies. The most frequently reported exclusion criteria was significant medical and mental illness ($n = 34$; 90% and $n = 33$; 87% consecutively); use of medication ($n = 28$; 72%); drug and alcohol abuse ($n = 25$; 66%); neurological disorders, including seizure activity, ($n = 21$; 55) and pregnancy/breastfeeding (37% — all studies with females participants). Other less frequently reported exclusion criteria included; endocrinological disorders ($n = 11$; 29%); heart disease and cardiovascular disorders ($n = 7$; 18%); kidney disease ($n = 6$; 16%); and allergy to preservatives ($n = 4$; 10%).

Considering that safety data available from intravenous infusion of oxytocin (TGA, 2010) points to the importance of heart disease, cardiovascular problems, and neurological conditions such as epilepsy in reactions to oxytocin, we tested the benefits of excluding participants with these conditions. A Mann—Whitney-*U* test indicated that studies that excluded participants with heart disease, cardiovascular or neurological disorders ($Mdn = 0$) did not report lower side effects than studies who did not exclude these conditions ($Mdn = 0$), $U = 149.0$, $p = 0.696$, $r = -0.06$, and again, there was no difference in side effects between oxytocin and placebo in these exclusion groups.

Two (22%) of the nine studies that investigated the effects of intranasal oxytocin on individuals with a developmental, medical or mental health disorders accepted participants who were regularly taking other medications. The first study which investigated the impact of oxytocin with youth diagnosed with ASD (Guastella et al., 2010) included 2 participants who were stabilised for over 8 weeks on psychotropic medications, including a 15 years old administering ecitalopram and paliperidone and a 17 years old stabilised on fluoxetine, risperidone and desmopressin. Frequency of side-effects reported by participants diagnosed with ASD ($Mdn = 1.5$) did not differ significantly from all other participants ($Mdn = 0$), $U = 61.00$, $p = 0.840$, $r = -0.04$. The second study examined intranasal oxytocin as an adjunct to exposure therapy for individuals with social anxiety and included four participants stabilised on anti-depressants and three participants taking cardiovascular medications (Guastella et al., 2009b). Individual participant information was not available. There was no difference in reporting of side-effects, however, when participants received oxytocin compared to placebo in both of these studies.

2.4. Pre-study instructions, administration procedures and subjective awareness of drug allocation

Information regarding pre-study instructions was available for 63% ($n = 24$) of studies. These used similar instructions prior to administering intranasal oxytocin: asking participants to abstain from caffeine, alcohol and nicotine 24 h prior ($N = 9$; 23%); 12 h prior ($N = 5$; 13%); or 2 h prior ($N = 10$; 26%). In addition 39% ($N = 15$) of studies recommended abstaining from food and drink, other than water, for 2 h prior the experiment. A Kruskal—Wallis test was conducted to evaluate differences among the three time points of abstaining from caffeine, alcohol and nicotine on the median change of the frequency of side-effects reported in each study ($N = 24$). There were no significant differences in the frequency of side effects for the three types of pre-study instructions, $H(2) = 1.090$, $p = 0.602$.

Table 3 presents information regarding administration procedures for intranasal oxytocin from 36 studies, excluding those that used intravenous infusion. The dosage amounts range from 18 IU to 40 IU, with 78% of studies administering 20—24 IU. There were four studies that administered oxytocin over an extended time period, with 66% of participants being female (Epperson et al., 1996a,b; Ohlsson et al., 2005; Guastella et al., 2009b). Three of these studies included clinical populations, with participants diagnosed with obsessive compulsive disorder (OCD) ($N = 1$) (Epperson et al., 1996a); social anxiety ($N = 1$) (Guastella et al., 2009b) and Trichotillomania ($N = 1$) (Epperson et al., 1996b). Of these studies, nine adults received four doses of 40 IU per day for one week (Epperson et al., 1996a,b) and 12 adult males received 24 IU once per week for four weeks (Guastella et al., 2009b). The longest intranasal oxytocin administration period was 13 weeks, with 40 IU administered twice daily to 29 female participants (30 received placebo) (Ohlsson et al., 2005). Participants in this study were questioned regarding side-effects on a weekly basis. At the end of the 13 weeks a total of 39 side-effects had been reported and were equally distributed between oxytocin and placebo participants. The total frequency of side-effects in this study was similar to studies involving the short-term use of intranasal oxytocin.

Subjective perceptions of drug allocation was provided by 74% of studies ($n = 28$). Of the 28 studies, 93% reported that participants ($n = 1115$) were unable to distinguish between oxytocin and placebo, χ^2 (2, $N = 28$) = 44.64, $p < 0.001$. Two studies (7%) reported that some participants were able to reliably detect when there had received oxytocin or placebo. This included a study with $n = 20$ males who received a single dose of either 24 IU oxytocin or placebo; 80—100% correctly guessed drug allocation reportedly on the basis of degree of sexual arousal after administration (Burri et al., 2008). The second study involved 27 male participants, two of whom were excluded from analysis because they reported during debriefing that they were certain of what substance they had received (Fischer-Shofty et al., 2010).

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Table 3 Intranasal oxytocin: dosage and time between administration and experimental tasks.

Dosage and waiting time	Total number of studies (N = 36)	Duration of study (no. of weeks)	Administration procedure	Total no. of participants receiving OT
Individual dose				
18 IU	1 (3%) [a]			
20—24 IU	28 (78%)	4 (N = 1)		
27—32 IU	3 (8%)			
40 IU	5 (14%)	1 (N = 3)		
		13 (N = 1)		
Total number of administrations				
1	32 (89%)	1 day (N = 32)	1 dose on 1 day	874
4	1 (3%)	4 (N = 1)	1 dose per week	12
28	2 (5%)	1 (N = 2)	4 doses per day	9
182	1 (3%)	13 (N = 1)	2 doses per day	29
Waiting time before exp. Tasks				
0—30 min	7 (20%)			
45—60 min	26 (72%)			
Unknown	1 (3%)			
Not applicable	2 (5%)			

N = number of studies (2 studies administered oxytocin via intravenous infusion not included in table).
[a] One study administered 18 IU to 11 participants aged 11—15 years old.

2.5. Case reports of adverse reactions

A literature search located three case reports of adverse reactions (Seifer et al., 1985; Ansseau et al., 1987; Hubner-Mayer, 1996). Two of these reports were published in 1980s and one in 1990s. One involved a 55 years old man participating in the first trial of intranasal oxytocin as a treatment for OCD (Ansseau et al., 1987). Intranasal oxytocin was administered three times per day for four weeks, with the daily dose between 8.4 IU and 16.8 IU. The patient was reported to develop psychotic symptoms (hallucinations and delusions) and significant memory loss assessed through the visual motor gestalt test (Bender, 1938) and visual retention test (Benton, 1976). Although the explanation for the adverse reaction was unclear, there was a decrease in the patient's plasma sodium and osmolality levels, possibly an antidiuretic effect of long-term oxytocin administration.

The other case reports involved long-term use of intranasal oxytocin to facilitate lactation (Seifer et al., 1985; Hubner-Mayer, 1996). In both cases the adverse reaction was the development of severe water intoxication due to excessive water intake in combination with intranasal oxytocin. One female was hospitalized for a viral illness and given a large quantity of intravenous fluid, in combination with excessive self-administration of intranasal oxytocin. The second female was 33 years old and was administering oxytocin eight times or more a day (exact dose unknown) and drinking 5 l of herbal tea daily. Following a reduction in the patient's fluid intake she fully recovered back to normal.

3. Discussion

This paper reviewed side effects and safety data on the use of intranasal oxytocin in 38 controlled trials conducted over the last 20 years. To date, 1529 participants have received intranasal oxytocin or placebo, of which only 279 reported mild side-effects. The main categories included: (1) increased calmness/euphoria or more energy; (2) light headedness, drowsiness and/or headache and (3) nasal irritation, dry mouth/throat. No difference in the type, frequency and severity of side effects reported by placebo versus oxytocin recipients was found. Further, evidence from these trials shows that the short-term use of intranasal oxytocin administered to humans, both males and females, in dosage amounts up to 40 IU (per dose) has resulted in no adverse reactions.

It was clear from these data that people are unable to differentiate whether they have received placebo or oxytocin. This indicates that psychological and behavioural effects of intranasal oxytocin are unlikely to be due to subjects' awareness of physical sensations, relaxation levels, and other sensations cueing them to receipt of the hormone. It also indicates that the subjective-awareness effects of oxytocin are subtle if not non-existent, far from the hyped 'love drug' intervention of web-based fame.

Preliminary evidence shows that the short-term use of intranasal oxytocin is equally safe to use with clinical populations, such as individuals with ASD as with healthy adults. There has only been one study, however, with children and young people and there continues to be a predominate recruitment of male participants (Guastella et al., 2010). Future research should direct attention to clinical populations, including female participants and younger populations.

To examine in more depth factors contributing to participant safety this review analysed both research exclusion criteria and pre-study instructions. Firstly, there is no evidence supporting the requirement for participants to abstain from substances such as caffeine and nicotine longer than 2 h prior to receiving intranasal oxytocin. This is, however, safety orientated and does not consider factors such as the effects of nicotine on oxytocin levels. Research, for example, has shown that nicotine stimulates the production of adrenaline

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which inhibits oxytocin release (Cross, 1955), this may require consideration in terms of impact on experimental outcomes.

The relationship between exclusion criteria and side effects was more complex. Studies that excluded participants with conditions such as neurological disease, heart disease and cardiovascular disorders did not significantly enhance or decrease participant safety. Indeed, there was no evidence to suggest that any particular exclusion criteria enhanced safety or that certain participants were more at risk than others. Furthermore, we found no effects associated with the clinical status of the screener or evidence to support the need for a medical practitioner during administration of intranasal oxytocin and experimental tasks.

These results speak to the overall safety of short-term use of intranasal oxytocin. Minimal side effects have been reported and no difference has been found in side effects reported by placebo versus oxytocin recipients. The conclusion could be drawn that there are no participant risk factors associated with short-term use of intranasal oxytocin. The data, however, do not provide details on the presence or absence of specific exclusion criteria does not quantify how many participants met those criteria, remained in or were removed from the study, and reported side effects. Moreover, it is highly likely that authors of the original studies not only controlled for exclusion criteria based on possible interactions with oxytocin, but mainly with regard to their outcome criteria. Thus, we would benefit from specific detailed review of exclusion and inclusion criteria from future studies. This will be particularly important when studies use longer term administration of intranasal oxytocin.

Given that oxytocin can modify heart rate and cause cardiovascular effects (Petersson, 2002; Rasmussen et al., 2004), suggesting that people with heart and cardiovascular conditions may be more vulnerable to the effects of oxytocin. Moreover, the case reports of adverse reactions all related to longer term use of intranasal oxytocin and excessive fluid intake; an antidiuretic effect that could be associated with seizures (Ansseau et al., 1987; Seifer et al., 1985; Hubner-Mayer, 1996). Thus neurological disorders may be an extra risk factor. In addition, allergies are always an important consideration and screening for allergies to preservatives within the nasal spray is recommended. Overall, future studies should be explicit regarding their exclusion criteria and expertise of the screener. We recommend a standard general screening for allergies, significant heart disease, cardiovascular and neurological disorders.

The use of medication was an exclusion criteria applied across the majority of studies. Only two studies in this review recruited participants who were regularly taking other medication (Guastella et al., 2009b, 2010). No adverse effects were reported from these studies and interestingly three participants were taking cardiovascular medication. The current data provide no evidence to suggest that participants taking medication are at risk of adverse reactions to short-term use of intranasal oxytocins; however, the range of medications included in the current data was quite limited. Future research including participants on a broader range of medications is essential to clarify safety.

Processes of monitoring and reporting side-effect information hold the foundation for accurately assessing participant safety regarding pharmacological substances (Loke and Derry, 2001; Ernst and Pittler, 2001; Loke et al., 2007). Targeted monitoring tools previously recommended include the use of standardised tools for assessing side-effects, using open-ended questions, interviews, observations and reporting detailed information in the published article (Loke and Derry, 2001). We found that studies using more targeted monitoring tools reported a higher frequency of side-effects; however, there were no adverse reactions is any study, all studies reported no difference in frequency of side-effects between oxytocin and placebo participants and there were 29% of studies using targeting monitoring that still reported no side-effects.

Given that research with oxytocin is likely to expand into increasingly vulnerable clinical samples, there will be an increasing need for appropriate monitoring tools, such as specific side-effect checklists or interviews to enable a comprehensive assessment of all physiological reactions. Monitoring methods and outcome information should be clearly reporting in the published article for transparent distribution of safety data. Details regarding onset, duration, severity and final outcome are all important for inclusion in the published article. To assist this process there are some very useful guidelines currently available to assist with this monitoring and reporting process (Loke and Derry, 2001). It would also be useful for studies to collate information regarding the ease at which participants administer intranasal oxytocin. Information could include, whether participant presented with any nasal congestion, if sneezing occurred, and any other general observed details. This information is valuable as it is difficult to assess the exact quantity of substance each participant receives when administering intranasally compared to intravenous infusion.

Advancements into the clinical application of intranasal oxytocin will require higher-dose longer term use of this substance, the safety of which remains unknown (MacDonald and MacDonald, 2010). This review included one study that administered intranasal oxytocin over a 13 week time period with daily administration of 40 IU placebo or oxytocin to 59 females (Ohlsson et al., 2005). There were limited side-effects reported, equally distributed between placebo and oxytocin. Nevertheless, there are concerns regarding safety with females and the potential to cause electrolyte imbalances with chronic use (MacDonald and MacDonald, 2010). This review presented three case reports of adverse reactions linked to antidiuretic effects of oxytocin, two involved the excessive misuse of intranasal oxytocin and water intake and one involved long-term use (Seifer et al., 1985; Ansseau et al., 1987; Hubner-Mayer, 1996). Recommendations for higher-dose longer term use include the implementation of screening and exclusion criteria outlined above, appropriate monitoring of participants through targeting methods and clear advice/information regarding appropriate fluid intake.

In conclusion, this article conducted a systematic review of safety and side effects data in research investigating the central effects of intranasal oxytocin in humans. Evidence from 38 randomised controlled trials, nine studies in vulnerable groups, showed no side-effects specific to oxytocin versus placebo, and no adverse reactions. The most frequently reported sensation was a feeling of calmness, but again this did not differ between oxytocin and placebo. The short-term use of intranasal oxytocin (1) produces minimal side-effects (2) produces no detectable differences in side-

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effects reported by either placebo or oxytocin participants, (3) produces no detectable subjective changes in recipients and, (4) preliminary is equally safe to use with vulnerable populations as with healthy adults. A systematic search for adverse reactions found only three reported incidents, two due to misuse of the nasal spray oxytocin and one linked with long term application.

In order to safeguard further clinical applications of oxytocin, research should direct attention to the impact of intranasal oxytocin when applied in higher-dosage longer-term, when used with younger individuals, different clinical populations and concurrently with additional medications. Such research goals will advance the current understanding of the pharmacokinetics, pharmacodynamics and general safety of intranasal oxytocin when administered to humans.

Role of the funding source

The authors did not receive funding for this project and so there is no role to report.

Conflict of interest

The authors have no conflict of interest in providing an impartial report. The authors report no biomedical financial interest. The authors are conducting a clinical trial investigating the impact of intranasal oxytocin with youth within the autism spectrum.

Acknowledgements

We would like to thank the researchers who kindly provided additional information regarding the monitoring and reporting of side-effects from their studies.

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