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Are We There Yet? The Clinical Potential of Intranasal Oxytocin in Psychiatry

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Abstract: The hormone oxytocin plays a major role in relationship formation and social functioning in animals and humans. We review theory and research examining the potential for intra-nasal oxytocin as an adjunctive medication for several mental health problems and risks: autism, schizophrenia, developmental precursors of psychopathy, social phobia, anorexia nervosa, obsessive compulsive disorder, depression (especially postnatal) and impaired maternal-infant bonding. Initial findings suggest that oxytocin administration may alleviate symptoms of autism and social phobia, but current evidence is insufficient to recommend oxytocin as a standard treatment. Despite reasonable theoretical indications, there has also been no systematic examination of oxytocin effects with psychopathy, anorexia, depression, or in mothers with problems bonding with their infants. Findings in patients with obsessive compulsive disorder suggest that oxytocin administration may not be beneficial in this group. Overall, there are good reasons to suggest that intra-nasal oxytocin may be a promising adjunctive treatment for specific mental health problems that involve impairments in engaging comfortably with other people; however, research is in its infancy; the specificity and durability of effects remain unknown, and issues of safety and modes of delivery have yet to be addressed.

Keywords: Oxytocin, Anorexia, Autism, Depression, Maternal-infant bonding, Obsessive compulsive disorder, Psychopathy, Schizophrenia, Social phobia.

INTRODUCTION

The hormone oxytocin is renowned for its effects on the peripheral nervous system, inducing contractions during labour and facilitating lactation [1]. Oxytocin also has effects on the central nervous system through receptors distributed through the hypothalamus, lateral septal nucleus, periaqueductal grey, Broca's area, nucleus basalis of Meynert, locus coeruleus, vagus, solitary tract, trigeminal nerve, and lateral reticular formation [2-4]. This paper will review research on oxytocin's central effects in healthy adults, then explore whether there is a role for oxytocin administration in the treatment of mental health problems.

For exogenous oxytocin to exert central effects, a form of administration is required that allows either direct access to the central nervous system (CNS) or evidence that oxytocin passes through the blood-brain barrier to the brain. One such delivery route is intra-nasal administration of oxytocin: research has shown that the neuropeptides melanocortin, vasopressin, and insulin are able to cross the blood-brain barrier when administered intra-nasally – evidenced by a resultant increase in peripheral plasma measures of oxytocin between 10-30 minutes following delivery [5]. Others have argued that intranasal delivery offers a privileged route directly into cerebral spinal fluid in the epithelium, 'bypassing' the blood brain barrier and exerting central effects on the brain by moving through the subarachnoid space [6]. Furthermore, this delivery method has had no negative reported side effects when delivered between 18-40IU in short term research settings [7]. The proceeding discussion will focus on intranasal administration as a delivery method by which oxytocin can cross the blood-brain barrier, exerting central effects through brain oxytocin receptors.

CENTRAL EFFECTS OF OXYTOCIN: THE SOCIABLE HORMONE

Research suggests an important role for oxytocin in promoting social relationships. Convergent evidence from animal studies using knockout models, oxytocin agonists, and oxytocin antagonists, have found that oxytocin facilitates: (i) *social approach* or willingness to make contact with a new conspecific (as opposed to avoiding the conspecific); (ii) *social memory* or ability to remember a conspecific previously encountered, and finally (iii) *bond formation*, resulting in long-lasting attachment to one animal over other conspecifics (for a review, see [8]).

Initial research with healthy adults suggests that the social effects of oxytocin also generalise to humans. For example, oxytocin could encourage social approach to strangers by: decreasing amygdala activation and the stress response associated with social threat [9-12], increasing accuracy in reading others' emotions [13], increasing eye-contact [14], and increasing trust and cooperative behaviours [15, 16]. As with animal research, oxytocin has also been found to increase human memory for strangers [17, 18]. Finally, in humans oxytocin also improves *evaluation* of strangers: following oxytocin administration, strangers are deemed to be more attractive and trustworthy [19], and negative experi-

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ences with a stranger are negated [20]. For a review of oxytocin's effects in humans, see ref. [21].

OXYTOCIN IN THE TREATMENT OF MENTAL HEALTH PROBLEMS

Given these effects, attention has turned to a potential role for the administration of oxytocin in the treatment of mental health problems. Of particular interest has been the suggested use of oxytocin with problems that involve or lead to impairments in social engagement with other people. For oxytocin administration to have clinical utility for these problems, it must be shown to first, alleviate symptoms beyond the half-life of the drug (e.g., by influencing a learning process), and second, make symptomatic changes that are clinically significant (i.e., that will change the quality of the patient's life). We evaluate this potential role of intra-nasal oxytocin as an adjunctive medication for: (i) autism, (ii) schizophrenia, (iii) developmental precursors of psychopathy psychopathy, (iv) social phobia, (v) anorexia nervosa, (vi) obsessive compulsive disorder, (vii) depression (especially postnatal), and (viii) impaired mother-infant bonding.

AUTISM

As defined by the *Diagnostic and Statistical Manual of Mental Disorders(4th edition; DSM-IV-TR)*, autism is a neurodevelopmental disorder associated with impaired social interaction, impaired communication, and repetitive or stereotyped behaviour and interests [22]; these symptoms are evident by the age of two and persist into adulthood. In terms of pharmacological management, antipsychotics (e.g., Risperidone) have been found to be effective in decreasing aggressive or self-injurious behaviour associated with autism [23], and are the main class of medications prescribed. However, antipsychotics only address peripheral symptoms (aggressive or self-injurious behaviour), and do not target the primary component of autism – the social deficit symptoms that together form the bulk of the DSM-IV diagnostic criteria.

Theoretical Basis for Administering Oxytocin

Many of the social deficits associated with autism fall in the same domain as the social effects of oxytocin, suggesting that oxytocin administration may be able to reverse some of these deficits (e.g., by increasing eye-contact, facilitating bonding to important people, improving attributions made about others' motivations, and increasing empathy). This possibility is supported by observations that plasma oxytocin levels are lower in children with autism [24]. Further, variations in the oxytocin receptor gene (*OXTR)* have been found to relate to both the diagnosis and phenotype of autism ([25-27], but see ref. [28]).

Together, these findings associate autism with abnormalities in the oxytonergic system, and provide a theoretical basis for administering oxytocin to address the social symptoms of autism. On this basis, four placebo-controlled trials have examined the effects of oxytocin on: emotional understanding, social processing, and social learning in autism. (For detailed theoretical discussions on oxytocin and autism, see refs. [29-31]).

Clinical Studies

In one study on emotional understanding, Hollander *et al.* administered oxytocin or placebo intravenously to 15 adult participants (14 male, 1 female) diagnosed with an autism spectrum disorder (ASD; either Asperger's or autism) [32]. At test, participants were asked to identify the emotional intonation behind neutral sentences read aloud using emotional tones. Hollander *et al.* had previously reported that oxytocin reduced repetitive behaviour over the course of intravenous administration [33]. But more pertinent to emotional understanding, mere intravenous injection alone (either oxytocin or placebo) was found to increase participants' performance in emotional recognition; however, only oxytocin participants maintained this increased performance when tested again two weeks later (placebo participants dropped back to normal performance at this second session) [32]. While this suggests some positive effects of oxytocin on emotional understanding, the complex pattern of findings are difficult to interpret. Further, this study used intravenous (rather than intranasal) oxytocin administration, of which success in crossing the blood-brain barrier is unclear.

Stronger evidence on the role of oxytocin comes from a study by Guastella *et al.*, who gave intranasal oxytocin or placebo to 16 male ASD adolescents (aged 12-19) [34]. Participants were then shown photographs of strangers' eyes and asked to identify what the stranger was thinking or feeling. Participants performed better on this task when they had taken oxytocin than placebo, suggesting that oxytocin can ameliorate emotional understanding deficits associated with autism.

One way in which oxytocin might improve emotional understanding is by changing the way social information is processed. For example, Andari *et al.* found that oxytocin given to ASD adults (11 male, 2 female) via nasal spray increased gaze time to the eye region of strangers introduced through photographs [35]. Thus, oxytocin appears to normalise the way social information is processed in people with autism by modulating neural activity, attention, and eye gaze in response to human faces. Andari *et al.* also found that oxytocin improves social learning in autism [35]. That is, when asked to play a ball-tossing computer game, adults with ASD – unlike healthy adults – did not discriminate between a friendly stranger (who tossed the ball to them) from a non-cooperative stranger (who did not pass the ball to them). ASD adults reported that they liked and trusted both strangers equally, and when given the ball tossed it to both strangers equally often. However, when administered with intra-nasal oxytocin, ASD adults were then able to discriminate between the strangers – both in terms of self-reported attitudes (they reported liking and trusting the friendly stranger more), and in terms of ball-tossing behaviour (they threw the ball to the friendly stranger more).

Clinical Utility

Together, these preliminary results are promising, suggesting that oxytocin can improve social deficits of autism immediately following administration. However, it is not feasible for oxytocin to be administered on a continual basis, each time a social interaction occurs. The lack of information

Table 1. Catalogue of Double-Blind Studies Involving the Administration of Oxytocin in Clinical Populations

Ref.	Participants	Drug Manipulation	Dependent Variable(s)	Findings
Autism Spectrum Disorder (ASD)				
[32]	15 adult males and females with ASD	• Drug design: Within-subject (OT or P) • OT: Pitocin -Delivery: Intravenous -Dose: 10u/ml combined with 1.01 saline [First given at rate of 10ml/h, then titrated up every 15 min by 25ml (1st hr), 50ml (2nd hr), 100ml (3rd hr) & constant at 700ml/hr (4th hr)]	Emotion recognition: Accuracy of identifying emotions for neutral sentences read aloud in emotional intonations	• Mere injection (OT or P) ↑ accuracy • OT (but not P) sustains this increased performance after a delay
[33]	15 adult males and females with ASD	• Drug design: Within-subject (OT or P) • OT: Pitocin -Delivery: Intravenous -Dose: 10u/ml combined with 1.01 saline [First given at rate of 10ml/h, then titrated up every 15 min by 25ml (1st hr), 50ml (2nd hr), 100ml (3rd hr) & constant at 700ml/hr (4th hr)]	Repetitive behaviours: Frequency	• OT ↓ repetitive behaviors over time
[34]	16 adolescent males with ASD	• Drug design: Within-subject (OT or P) • OT -Delivery: Intra-nasal -Dose: 18 IU (participants aged 12-15); 24 IU (participants aged 16-19)	Emotion recognition / mentalising: Ability to recognize state of mind through photos of the eye region (Reading the Mind in the Eyes test)	• OT ↑ accuracy, particularly for easier test items
[35]	13 adult males and females with high-functioning ASD	• Drug design: Within-subject (OT or P) • OT: Syntocinon -Delivery: Intra-nasal -Dose: 24 IU	Discrimination in social choices: Reaction to good or. bad players in a ball-toss game (Cyberball game)	• OT ↑ discrimination between good and bad players: OT selectively↑ self-reported trust and preference, and ball-tosses to good players
			Eye-gaze: Gaze patterns to photographs of faces	• OT selectively ↑ eye-gaze to the eye-regions of faces
Schizophrenia				
[49]	19 adults with schizophrenia, all stabilised on antipsychotic medication(s) but with residual symptoms	• Drug design: Within subject (OT or P) • OT: Syntocinon -Delivery: Intra-nasal -Repeated administration: Daily for 3 weeks -Dose: 20 IU twice a day (1st week), 40 IU twice a day (2nd and 3rd weeks)	Clinical symptoms: Scores on the Positive and Negative Syndrome Scale (PANSS), and the Clinical Global Impressions scales (Severity, CGI-S; Improvement, CGI-I)	• OT ↓ clinical symptoms over time: at end-point, ↓ scores for OT group relative to placebo on PANSS (total score, positive subscale, negative subscale) and on CGI-I
[50]	20 adults with paranoid or undifferentiated schizophrenia, all stabilised on antipsychotic medication(s) but with residual symptoms	• Drug design: Between subject (OT or P) • OT: Syntocinon -Delivery: Intra-nasal -Repeated administration: Daily for 2 weeks -Dose: 24 IU twice a day	Clinical symptoms: Scores on the Positive and Negative Syndrome Scale (PANSS), and the Paranoia Scale Social cognition: Understanding of another person's state of mind (Brüne Theory of Mind Picture Stories Task), ratings of strangers' trustworthiness (Trustworthiness Task)	• OT ↓ clinical symptoms over time: at end-point relative to baseline,↓ scores for OT group on PANSS (total score, positive subscale, general subscale, and paranoia scale; no significant effect on negative subscale) • OT ↑ selected social cognition skills: at end-point relative to baseline, ↑ scores for OT in identifying second-order false beliefs (Brüne Task). No other significant effects on Brüne or Trustworthiness Tasks.

Table 1. Contd….

Ref.	Participants	Drug Manipulation	Dependent Variable(s)	Findings
[51]	14 adults with schizophrenia (5 with polydipsia, 9 without), all stabilised on antipsychotic medication(s); 11 healthy controls	• Drug design: Within-subject (10 IU OT, 20 IU OT, or P) • OT: -Delivery: Intra-nasal -Dose: 10 or 20 IU	Emotion recognition: Identification and intensity ratings of emotions in photographs of faces	• OT changed emotion recognition depending on dose and participant sub-group: • 10 IU OT ↓ emotion recognition (due to ↑ attribution of all emotions to the faces) • 20 IU OT ↑ emotion recognition for polydipsic group only (due to ↑ accuracy in identifying fear)
Social Phobia				
[63]	18 male adults with generalised social anxiety disorder; 18 healthy controls	• Drug design: Within-subject (OT or P) • OT: Syntocinon -Delivery: Intra-nasal -Dose: 24 IU	Brain activation: fMRI while matching emotional faces (emotional face matching task)	• OT ↓ typical heightened amygdala activation to fearful faces seen in social phobia group (relative to controls)
[64]	25 adult males with social anxiety disorder	• Drug design: Between subject (OT or P) • OT -Delivery: Intra-nasal -Repeated administration: Once a week for four weeks -Dose: 24 IU	Clinical symptoms: Responses to group exposure therapy	• OT ↑ self-appraisal during public performance tasks No effect of OT on self-reported social anxiety symptoms

OT = Oxytocin; P = Placebo.

about the depth and durability of changes in social functioning remains a serious limitation within the field, and several studies are underway to evaluate the nature of these changes. In particular, a priority should be studies that evaluate oxytocin as a synergistic adjunct to other cognate treatments; as an example, it would seem inappropriate for oxytocin to be administered to a person who then spends the next few hours in isolation, playing computer games alone in his or her room. Given that the effects of intranasal administration are probably short-lived and subtle, the aim should be for oxytocin to facilitate new learning or new patterns of interaction that become self-sustaining beyond the immediate treatment situation.

Improvements must also be shown to be clinically meaningful: beyond evidence that oxytocin can improve eye-contact or identification of emotions from photographs, oxytocin should also be shown to affect measures of the quality of social interaction with other people, and ideally generalise to broader measures of quality of life (e.g., clinician ratings on the Clinical Global Impressions Scale [36]) – as is expected of clinical drug trials for ASD (e.g., for risperidone [37]).

Finally, oxytocin administration for ASD must be considered within a developmental perspective, and it must be decided at what point in development oxytocin should be used. ASD has an early onset and in theory, oxytocin would most beneficially be used when the child is first involved in the establishment of social bonding and interaction with caregivers. However, little is known about the safety and effects of oxytocin administration with adolescents, let alone young children, and its role in altering developmental trajectories is completely unknown.

To summarise, oxytocin has a promising role as an adjunct in the treatment of autism. However, there is currently insufficient evidence of efficacy, durability, and significance of effects, as well as critical periods for its use.

SCHIZOPHRENIA

As with autism, oxytocin could have a role in addressing the social deficits of schizophrenia. Schizophrenia is characterised by positive symptoms – the presence of atypical experiences (e.g., hallucinations, delusions), and negative symptoms – the absence of normal functioning with regards to emotions and thought processes (e.g., flat or blunted affect, diminished desire to form relationships) [22, 38]. Whereas anti-psychotic treatments (e.g., haloperidol, risperidone) target positive symptoms, their effect on negative symptoms is modest at best; negative symptoms, in turn, have been associated with poorer social functioning and a decreased quality of life [39, 40].

Theoretical Basis for Administering Oxytocin

As early as 1974, Bujanow discussed whether oxytocin could be an "anti-schizophrenic hormone" [41]. One way in which this has been studied has been through animal models of schizophrenia (for a review, see [42]) – where, for example, chronic administration of the glutamate receptor antagonist phencyclidine (PCP) induces schizophrenia-like behaviour in mice [43, 44]. These studies suggest that oxytocin

may have a role in the observation of schizophrenia-like symptoms: for example, PCP was found to induce deficits in the pre-pulse inhibition response (characteristic of schizophrenia); however, this effect was observed only in oxytocin knockout mice (with a disruption to the oxytocin gene), and not to wild-type mice controls [45].

With regards to social functioning, administration of PCP has been found to impair social interactions in normal rats: compared to rats administered saline, PCP rats spent less time interacting with a novel conspecific, and a larger proportion of their total interaction time in non-contact rather than contact behaviours [46]. Critically, these social impairments were associated with decreased oxytocin gene expression and with alterations in oxytocin receptor binding. Conversely, administration of oxytocin was sufficient to reverse these impairments [46].

Taken together, animal research suggests that: (i) alterations in oxytocin are implicated in schizophrenia-like behaviours observed in rat models, and that (ii) oxytocin administration could reverse associated social deficits. Although human studies have not found a consistent relation between endogenous oxytocin levels and schizophrenia symptoms [47, 48], three placebo-controlled trials have investigated the clinical role of oxytocin administration in patients with schizophrenia.

Clinical Studies

In one study, Feifel *et al.* administered intra-nasal oxytocin to 19 adults with schizophrenia [49]. Participants had already been stabilised on antipsychotic medications (i.e., same dosage in the past month), but had residual symptoms as defined on the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions-Severity scale (CGI-S). With these participants, three weeks of daily oxytocin administration was found to reduce clinical symptomology over and above any effects of the antipsychotic medications: relative to placebo, oxytocin resulted in greater improvement scores on the Clinical Global Impressions-Improvement scale (CGI-I), and reduced total symptomology scores on the PANSS. Critically, at the end of the three weeks, oxytocin had reduced not only the positive symptoms of schizophrenia (PANSS positive scale), but also the negative symptoms (PANSS negative scale). Thus, this study suggests that oxytocin could serve as an adjunctive treatment to existing antipsychotic medications, and in particular that it could address negative symptoms (which current antipsychotic medications have shown limited effects on).

If oxytocin could target negative symptoms, could it reverse the social deficits associated with schizophrenia? Pedersen *et al.*[50] administered intra-nasal oxytocin to 23 adults with schizophrenia who had been stabilised on antipsychotic medications. After two weeks of daily oxytocin administration, participants were again found to have reduced symptomology scores on the PANSS (total and positive scale scores, but not on the negative scale). Extending the work by Feifel *et al.*, Pedersen *et al.* also found that oxytocin could improve one aspect of participants' social cognition – their ability to understand another person's state of mind, as defined by their accuracy in identifying second-order false beliefs; however, oxytocin did not have a significant effect on other aspects of understanding state of mind, nor on trustworthiness ratings of strangers.

Finally, Goldman *et al.* [51] reported that oxytocin could affect the ability of schizophrenia adults to recognise emotions in others – but that the effects may depend on drug dosage and participant phenotype. In this study, a standard dose of oxytocin (20 IU) ameliorated emotion recognition deficits associated with schizophrenia, particularly for the emotion of fear; however, this effect was only observed in participants with polydipsia (as compared to those without). Of interest was that a lower dose of oxytocin (10 IU) was found to impair emotion recognition in schizophrenia participants, regardless of polydipsia status.

Clinical Utility

Considered together, the three studies conducted to date suggest that oxytocin administration could have a beneficial effect on schizophrenia symptoms, over and above the effects of stabilised anti-psychotics. Of note, oxytocin effects were found on standard clinical measures used to evaluate treatments for schizophrenia (namely, the PANSS and CGI scales), suggesting clinical relevance for oxytocin. In particular, the possibility that oxytocin could reduce negative symptoms is promising: if supported, oxytocin could have a unique contribution as an adjunctive to prescribed antipsychotics. Nonetheless, although Feifel *et al.* found such an effect [49], Pedersen *et al.* did not [50]. Thus, further studies will need to explore whether oxytocin can indeed address the negative symptoms of schizophrenia. (It is possible that differences between the two studies – e.g., different oxytocin doses, within- vs. between-subject design – could account for the different findings reported.)

Specific to social functioning, initial findings suggest that oxytocin could reduce schizophrenia-related deficits in understanding the thoughts or emotions of another person. However, the effects shown thus far are limited in domain (e.g., in [50], only for a measure of second-order false beliefs), by dose (e.g., in [51], only in standard, but not lower doses), and by patient sub-group (e.g., in [51], only for those with polydipsia). More research is needed to delineate the precise circumstances by which a patient with schizophrenia can benefit from oxytocin administration, and to advise on how oxytocin dosage may be titrated for beneficial effects.

Finally, it is unclear as yet how long the drug effects can last: both Feifel *et al.*[49] and Pedersen *et al.*[50] administered oxytocin twice daily for several consecutive weeks, and it is unclear what duration of administration is ideal and whether oxytocin effects could persist beyond this duration.

DEVELOPMENTAL PATHWAYS TO PSYCHOPATHY

Although not commonly acknowledged in the literature, oxytocin may have a role in the treatment of the development precursors of psychopathy. In the DSM-IV criteria [22], conduct disorder has as its core a chronic pattern of the violation of social norms and the basic rights of others (e.g., cruelty to people or animals), and usually begins in childhood and adolescence. Individual sufferers are not a homo-

geneous group however, and various methods exist for sub-categorising. In particular, there is increasing evidence of a subtype who display *callous-unemotional (CU) traits* – a fearless disregard of how others feel, and with impairments of guilt and empathy (see ref. [52] for a proposal to include this subtype descriptor in the upcoming *DSM-V*). CU traits are associated with an impaired ability to recognise other people's emotions, particularly fear and sadness [53]. Like autism, this impairment is accompanied by a lack of spontaneous eye-gaze to the eye regions of other people's faces, occurring both in computer-based facial recognition tasks [54, 55] and during natural interactions with attachment figures [56].

Theoretical Basis for Administering Oxytocin

Currently, psychosocial treatments, especially parenting and family interventions for young children, are the treatment of choice for conduct problems. In terms of medications, antipsychotics (e.g., risperidone, haloperidol) are only prescribed in extreme cases to reduce aggressive behaviour [57].

Like ASD, anti-social behaviour has also been linked to variations in the oxytocin receptor gene [58] and oxytocin antibodies [59]. Thus, administration of oxytocin might help to promote social understanding and behaviour – especially by increasing sensitivity to the emotions of others. For example, oxytocin has been found to increase healthy adults' attention to the eye region [14]. In boys with high CU traits, increase in the focus to the eye region temporarily reverses their emotional recognition deficits [54], suggesting one way by which oxytocin administration may promote social understanding and thus, interpersonal functioning.

Clinical Utility

While there is a theoretical basis for the use of oxytocin, there has been no published study on whether oxytocin can address these specific aspects of the development of conduct disorder and psychopathy. Thus, the clinical utility of oxytocin for this purpose remains at a theoretical stage.

SOCIAL PHOBIA

Social phobia is defined by the DSM-IV as a fear of situations involving social interactions or performance, and exposure to these situations cause anxiety. As a result, these situations are avoided or endured with distress [22]. The central feature of social phobia is fear associated with interactions with other people;in other words, as with autism and conduct disorder, social phobia is marked by significant impairment in social functioning.

Theoretical Basis for Administering Oxytocin

One way in which oxytocin administration may address symptoms of social phobia is by decreasing the stress response associated with threatening social situations. For example, encountering social threats (such as seeing fearful or threatening scenes, seeing angry or fearful faces, or seeing faces paired previously with aversive experiences) results in increased activation of the amygdala – a critical system of the brain for detecting and controlling fear; however, in healthy adults oxytocin has been found to attenuate amygdala responses to threatening faces [12, 20, 60] (but see ref. [61]). These responses are typically heightened in individuals with social phobia such that threat is over-detected and once detected, leads to exaggerated stress responses [62].

Supporting a role for oxytocin as treatment, Labuschagne *et al.* found in individuals with social phobia that oxytocin administration reduced the exaggerated amygdala activation to fearful faces [63]. The potential benefits of oxytocin administration are further supported by findings that in healthy adults, oxytocin administration also increased trust for strangers [15] and improved perception of how sympathetic someone was deemed to be after a threatening experience with him or her [20].

Clinical Studies

Thus far only one placebo controlled controlled trial has examined the effects of oxytocin in facilitating evidence-based psychotherapies (in this case exposure therapy) for social phobia. Before each of four weekly exposure therapy sessions, Guastella *et al.* administered either oxytocin or placebo to 25 males with social phobia [64]. Compared to taking placebo, as treatment progressed, participants who had taken oxytocin rated more positively their performance on the in-session public speaking tasks. However, oxytocin did not influence participants' self-reported anxiety during the public speaking task, nor did it influence symptoms of social anxiety (as measured by self-report questionnaires immediately and one month after treatment).

Clinical Utility

This preliminary data suggest that oxytocin can facilitate in-session progress on treatments for social phobia. However, there continues to be no available evidence that these effects will translate to improved coping abilities, or to fewer avoidance behaviours following treatment sessions. Future research will need to examine these oxytocin effects over a longer period of time, using different types of post-session measures of symptomatic improvement.

ANOREXIA NERVOSA

Oxytocin may also have a similar role in the treatment of anorexia nervosa. Although anorexia nervosa is defined on the DSM-IV by weight-related criteria (e.g., refusal to maintain normal body weight, intense fear of weight gain or becoming fat) [22], a recent review highlights a significant impairment of social functioning that is associated with anorexia nervosa: individuals with anorexia nervosa are socially withdrawn and isolated, with these deficits increasing the risk of death and persisting even after recovery [65].

In terms of pharmacotherapy, there is currently no drug that has been approved for the treatment of anorexia nervosa by the United States Food and Drug Administration (FDA); however, Olanzapine is commonly prescribed to increase weight and decrease obsessions related to anorexia nervosa [66]. Nonetheless, even with treatment, the prognosis of individuals with anorexia nervosa is poor: when these individuals come into contact with psychiatric services and are then followed-up over time, they show a high long-term risk of mortality. Less than 50% show full recovery on follow-

up, and there is a 20% rate of non-responding to treatment [67].

Theoretical Basis for Administering Oxytocin

One way of improving treatment for anorexia nervosa may be to address the social deficits that have been identified – an area traditionally under-targeted in treatment [65]. If so, then there may be a role for administering oxytocin to ameliorate the social deficits associated with anorexia nervosa. Support for this notion comes from findings that oxytocin levels in the cerebrospinal fluid are lower in women with restricting anorexia (that is, they primarily restrict food intake and do not induce food expulsion) than in healthy adult women [68]. Indeed, Odent likened the oxytocinergic profile for anorexia to that of autism, suggesting that anorexia may be the female variant of the autism spectrum [69]. Nonetheless, it is possible that social deficits associated with anorexia nervosa may be unrelated to levels of oxytocin, since oxytocin levels have been found to be normal in weight-matched individuals with binge/purge anorexia (who expulse their food or exercise excessively [68]), who also display similar social deficits. For a review of oxytocin and other neuropeptides in anorexia, see refs [70, 71].

Clinical Utility

To summarise, there is some theoretical basis for administering oxytocin as to treat anorexia nervosa. However, no clinical trials have been conducted to test oxytocin effects, and the efficacy of oxytocin as a form of treatment continues to be an empirical question yet to be addressed.

OBSESSIVE COMPULSIVE DISORDER

Another psychiatric condition for which oxytocin has been explored as a treatment is obsessive compulsive disorder (OCD). Based on DSM-IV criteria, the disorder is characterised by: (i) obsessions, that is, intrusive thoughts that cause distress, and (ii) compulsions, that is, repetitive activities employed to reduce distress associated with the obsessions [22].

Theoretical Basis for Administering Oxytocin

Up to this point, the theoretical bases for administering oxytocin have focused on the patient group meeting two conditions: 1) evidence of impairments in social engagement/social functioning, and 2) disturbances in oxytocin function (in terms of circulating oxytocin levels, variations in oxytocin receptor polymorphisms, or secondary responses to oxytocin action e.g., antibodies). However, with OCD, theoretical discussion of oxytocin has focused on its role in grooming behaviours.

In rats, oxytocin administration has been found to increase how much the animal grooms itself [72]. These grooming behaviours have in turn been compared to compulsive behaviours in OCD [73], and it is reasonable to hypothesise that some compulsive behaviours in OCD are associated with excessive oxytocin – as compared to the deficient oxytocin observed in other psychiatric conditions. In support of this notion, studies measuring baseline oxytocin levels have found that OCD patients have elevated CSF levels relative to healthy adults [74](but see ref. [75]).

With OCD patients believed to have excessive oxytocin, it is not clear why oxytocin administration has been proposed as treatment [76]. An argument can be made that even though oxytocin is deficient, administration may still be helpful. Such an argument is analogous to the case of Type 2 Diabetes, where insulin may be administered to alleviate symptoms even when the patient is not insulin-deficient. However, if oxytocin itself is thought to *induce* the compulsive behaviours, it is not clear how oxytocin administration might be conceived to *reduce* these very behaviours.

Case Studies

Nonetheless, there have been four publications on the use of oxytocin to treat OCD. In an early study, Ansseau *et al.* reported a case of a 55-year-old patient with OCD: compared to four weeks of placebo, four weeks of intranasal oxytocin resulted in decreased rituals, compulsive thoughts, and anxiety [77]. However, this patient simultaneously developed hallucinations and persecutory delusions, rendering the oxytocin effects difficult to evaluate. In another study, Salzberg and Swedo compared the effects of intranasal oxytocin and saline in three patients with OCD [78]. This time, they found no treatment effect on either clinician- or patient-rated symptoms of OCD, mood, or anxiety. Similarly, both den Boer and Westenberg [76], and Epperson, McDougle and Price [79] found that even when oxytocin was administered at very high dosages (160 - 528 IU a day), across a total of 21 male patients there was no effect of oxytocin on symptoms of OCD. Overall, these case report series provide no evidence for the therapeutic benefits of oxytocin in treating OCD.

Clinical Utility

Despite previous suggestions for the use of oxytocin in treating OCD, there is currently little theoretical basis and no scientific evidence that oxytocin can alleviate the symptoms of OCD. Conversely, if excessive oxytocin is indeed expressed in OCD symptoms, then treatment *reducing* oxytocin levels (e.g., administration of an oxytocin antagonist) may meet with better success.

DEPRESSION AND SPECIFICALLY POSTNATAL DEPRESSION

Seventeen per cent of us will experience a major depressive episode (MDE) at some point in our lives [80]. To meet criteria for MDE no fewer than five symptoms must be present over a two week period and must include either depressed mood or a loss of interest or pleasure (or both), along with the following symptoms: weight changes, sleep disturbance, fatigue, cognitive impairment, psychomotor impairment, feelings of worthlessness or suicidal ideation [22]. Between 10-20% of mothers experience a major depressive episode following the birth of their child and this is termed Postnatal or Postpartum Depression (PND) [81]. When identified factors are controlled for, women who have given birth are 1.6 times more likely to develop depression compared to their nulliparous peers [82].

Theoretical Basis for Administering Oxytocin

Depressive symptoms have shown to be alleviated following delivery of selective serotonin reuptake inhibitors (SSRIs), the most frequently employed medication for de-

pression and postnatal depression [83]. In animal models, SSRIs have been found to increase plasma oxytocin levels and it has been speculated that the clinical outcomes of reduced stress and depression may be in part due to the hormone oxytocin [84], which has been found to have both anxiolytic and anti-depressant effects in animals [85, 86].Thus far in humans, analyses of resting plasma levels in people with varying levels of depressive symptomatology have not returned consistent results with both null findings and a positive correlation being reported [87-89]. A linear relationship between depression and oxytocin is therefore unlikely; however, due to the large body of evidence linking depression to HPA axis functioning [90], at the core of which is the pituitary gland which produces oxytocin,some relationship is anticipated with increased HPA axis activity in depression likely to be reducing oxytocin levels [91]. Cyranowski *et al*. [92] confirmed this when they found that depressed women did not display the same oxytocin release pattern as their non-distressed peers during emotional and stress-inducing tasks. A notable negative correlation between oxytocin levels and depression was returned in a study by Ozsoy, Esel, and Kula assaying plasma levels in both sexes. Interestingly only females demonstrated this relationship; the males in the study returned equivalent serum levels despite depressive symptoms. The authors appreciated that gender differences in HPA axis stress responsiveness may explain the variation here. Certainly gender differences are of importance here when examining a hormone noted for social, sexual and parenting behaviours [93].

For the first time the relationship between oxytocin levels and postnatal depression has been directly investigated. Skrundz *et al*. [94] predicted women's depression scores in the first two weeks post-partum (which is often an early indication of PND) from their oxytocin levels during the third trimester and found that women with the lowest levels of oxytocin at that time showed elevated depressive symptoms following the birth of their child. Thus, there is evidence to support a relationship between circulating oxytocin levels and depressive symptomatology, at least in females.

Clinical Utility

Thus far no controlled trials have been carried out using oxytocin nasal spray; however, researchers this year reported a case-study of a male aged 38, who had a history of non-response to various SSRIs and associated treatments, and when given intranasal oxytocin in addition to escitalopram, his depression rating fell below the clinical cut-off [95]. Inevitably, other researchers will move to replicate this finding and one could argue for RCTs comparing SSRIs with oxytocin-only treatments to determine the extent of oxytocin's anti-depressant effects in humans [96].

MOTHER-INFANT BONDING

Another clinical area in which oxytocin has been causally implicated is mother-infant bonding, critical for both physical and mental health. For the mother, bonding refers to a set of behavioural and emotional responses which include recognising the infant as her own, seeking proximity, and having feelings of closeness and love [97] [65]. For the child, differences in early bonding experiences can lead to poorer outcomes during childhood in social, behavioural, and cognitive domains [98, 99], predicting differing profiles of risk and resilience for psychopathology later in life [100]. Bonding difficulties are prevalent in mothers suffering from distress (e.g., depression and anxiety) in the postpartum period [101].

Theoretical Basis for Administering Oxytocin

While there are evidence-based interventions for supporting young mothers at risk [102], there are few empirically-validated interventions for repairing early bonding difficulties. Medication and cognitive behavioural therapy are reasonably effective in treating post-natal depression, but these treatments do not remediate the associated infant-bonding problems [103]. Currently, the only direct interventions for difficulties in mother-infant bonding are baby massage and interaction-coaching to improve maternal sensitivity [104, 105].

It is possible that oxytocin has a role in mother-infant bonding, as has been found in animals [106]. The evidence suggests that mothers who demonstrate more responsive, sensitive parenting and who report higher levels of bonding to their infants: predominantly carry the more efficient variant of the oxytocin receptor gene [107], have higher basal levels of plasma oxytocin [108], and show both increased oxytocin levels and greater activation of brain reward centres following play sessions [109].

Clinical Utility

To date, there is no published study on the use of oxytocin to improve mother-infant bonding; however, our research group in Australia (authors R.M and M.D) are currently exploring the effects of intranasal oxytocin when delivered alongside direct interventions for maternal bonding (e.g., baby massage and interaction-coaching) [110]. With these set-ups, oxytocin would be expected to potentiate effects of the interventions via increased eye gaze, affectionate touch, and positive vocalisations – behaviours found to be higher in women with elevated oxytocin levels [108].

IMPLICATIONS FOR PRACTICE AND RESEARCH

For oxytocin to serve as a useful adjunctive medication for psychiatric conditions, it should be able to improve symptoms beyond the half-life of the drug, and these improvements should have a distinct influence on the patient's quality of life. Based on these criteria, we reviewed evidence for the utility of nasal oxytocin as an adjunctive treatment in several psychiatric problems. Table **1** summarises the clinical trials we located that constitute the best sources of evidence. Initial findings suggest a promising role of oxytocin in targeting social deficits central to autism, schizophrenia, and social phobia; future research will need to explore whether these effects last long enough and have a large enough impact on daily life to warrant therapeutic administration. Despite good reasons for doing so, no controlled studies have examined the use of oxytocin in the developmental antecedents of psychopathy, anorexia nervosa, depression, and maternal-infant difficulties; thus, oxytocin remains a logical but unexplored form of treatment. Finally, several studies and case reports have found no effect of oxy-

tocin administration on OCD symptoms, suggesting that oxytocin may not be useful in the treatment of OCD. Aside from the disorders discussed within the current review, intranasal oxytocin is being explored as a potential therapeutic agent for trichotillomania, post-traumatic stress-disorder, and borderline personality disorder [111].

On a whole, the search for experimental evidence on oxytocin in psychiatric care is relatively new, with few studies published on the topic. As data from more placebo-controlled trials are collected, it will be important to evaluate whether any oxytocin effects are consistent: presently, every one of the published clinical studies has used different outcome measures from other studies. For example, the four published studies with individuals with autism have reported oxytocin effects on five separate outcomes (ability to identify emotions from voice tones, ability to recognise thoughts and feelings from pictures of eyes, functional imaging patterns, eye gaze patterns, and ball-tossing behaviour); this is promising in terms of the generalisation of treatment benefits but makes it unclear whether the findings for any one outcome are robust. This is further highlighted in studies involving participants with social phobia: with these studies, the observed oxytocin effects have been difficult to predict. For example, Heinrichs [112] and Guastella *et al*. [64] found that oxytocin increased self-reported confidence for social interactions and self-evaluation following public speaking, but had no effect on self-reported anxiety or symptoms of social anxiety. From these findings, it is unclear what exact domains oxytocin can influence in participants with social phobia; thus, future studies will need to replicate these findings and explore exactly what outcomes oxytocin can influence.

As more data are collected, the precise effects of oxytocin in psychiatric care should also be refined to address questions on the nature of treatment itself. For example, in terms of efficacy of oxytocin administration, what might be an optimal dosage of oxytocin, and for how many times or across what duration? Further, how might oxytocin compare to current best practice in treatments, rather than to a placebo control alone? (For example, how might oxytocin compare to psychosocial interventions for social impairments in autism?) Furthermore, as oxytocin and vasopressin are similarly structured nonapeptides which have some overlap in explaining animal and human social behaviour, could vasopressin act as a therapeutic tool (see ref [113] for the first study to examine the effects of vasopressin upon social behaviour in a non-clinical sample and [114] for a review of both neuropeptides)? Additionally, does oxytocin has a role as a stand-alone intervention, or as a synergistic adjunct to other cognate interventions? Basic animal and human research on oxytocin show that circulating levels of oxytocin and associated behavioural effects are observed during species-specific scenarios such as meeting a potential mate, being confronted with conspecific fear stimuli, and sharing valued resources with strangers. It is likely that oxytocin will develop as a useful intervention by being used to facilitate other powerful psychological experiences, such as those involved in existing psychotherapies.

With regard to mental health problems that have an early onset, a critical question will be if and when oxytocin can be used to alter growth trajectories of the disorder. For example, impairments in social engagement are a primary characteristic of autism as it emerges in the first years of life, and many of the impairments associated with psychopathy begin early in life [52]. At present, oxytocin is being evaluated as a temporary means of helping to overcome impairments that have been long established. A more appealing idea is that oxytocin (among other interventions) could remediate problems early in life while basic programmes of social interaction are being learned. Unfortunately, little is known about the developmental psychopathology of oxytocin systems and nothing about whether infants and children can be safely and effectively given oxytocin as an early-remedial measure.

Finally, if ongoing clinical trials find oxytocin a viable treatment in psychiatry, it will be useful to incorporate into clinical trials the current methods of genetic research on the oxytocin receptor. This would result in pharmacogenetic questions being asked, allowing, for example, an exploration of whether certain variations of oxytocin gene expression can predict an individual's response to oxytocin administration to treat the symptoms of autism. Such a programme of research will help clinicians make harm-benefit assessments as they formulate treatment plans for their patients.

CONCLUSIONS

In conclusion, the current review suggests that the administration of intra-nasal oxytocin has potential as an adjunctive form of psychiatric treatment – particularly for psychiatric conditions which hitherto have shown poor responding to pharmacological interventions. This is a relatively new area however, with little research done; future research will need to follow theory with well-controlled clinical trials in areas that have not yet been tested (as is the case with psychopathy, anorexia, depression and mother-infant bonding). In areas where initial data have already been collected (e.g., amongst patients with autism, schizophrenia, and social phobia), there is a need to replicate existing findings and refine questions being asked about oxytocin effects – both in terms of treatment and participant characteristics.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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