A SYSTEMATIC REVIEW ON THE EFFICACY OF THE NEUROPEPTIDES OXYTOCIN AND VASOPRESSIN IN THE TREATMENT OF AUTISM SPECTRUM DISORDER

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Approval

The thesis/project titled "A systematic review on the efficacy of the neuropeptides Oxytocin and Vasopressin" submitted by Saba Nawreen (19146005) of Spring, 2023 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This project does not involve any kind of animal and human trial.

Abstract

The aim of this review is to examine the efficacy of neuropeptides OXT and Vasopressin administration on amelioration of core symptoms of ASD as a pharmacological treatment. The objectives are to assess the effect of the mentioned two neuropeptides on the ASD core symptoms, to provide an understanding of the hypothetical neural mechanism underlying the action of OXT and Vasopressin, and to critically evaluate existing data from RCTs to interpret efficacy compared to placebo among individuals with ASD. The search methodology for RCTs were supplemented from PubMed and from manual searching in the bibliographies of relevant papers. 9 RCTs were included in this review which examined social cognition and repetitive behavior as target symptoms of ASD. In terms of oxytocin, only 2 studies reported improvement in key symptoms and for vasopressin, one study used arginine-vasopressin and demonstrated a trend of improvement while the outcomes from rest 3 studies that utilized vasopressin antagonist as treatment intervention suggested minor advancements in social communication but no significant between group differences. The studies included in this paper had a medium to high risk of bias. Our review yielded mixed findings about the efficacy of vasopressin and oxytocin, and due to the small number of RCTs included, our findings should still be seen as tentative.

Keywords: Autism spectrum Disorder; Oxytocin; Arginine Vasopressin; Clinical trial; Neural Mechanism; Efficacy

Dedication

I dedicate this thesis to my sister.

Acknowledgement

All honors belong to the Almighty for giving me strength to finally complete my project work and all other courses required for the completion of the Bachelor of Pharmacy (B. Pharm) program.

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List of Acronyms

OXT	Oxytocin
AVP	Arginine Vasopressin
ASD	Autism Spectrum Disorder
VAS	Vasopressin
IN-OXT	Intranasal Oxytocin
INT-VP	Intranasal Vasopressin
PL	Placebo
RCT	Randomized Controlled Trials
fMRI	Functional Magnetic Resonance Imaging
AMG	Amygdala
CNS	Central Nervous System
SRS-2	Social Responsiveness Scale – 2nd edition
RBS-R	Repetitive Behavior Scale-Revised
ADOS-2	Autism Diagnostic Observation Schedule-2nd edition

Chapter 1

Introduction

Autism spectrum disorder is recognized as a neurobehavioral and developmental disorder affecting approximately 1 in 36 children in 2023, U.S. reported by CDC's network for ADDM (Autism and Developmental Disabilities Monitoring) (*Data and Statistics on Autism Spectrum Disorder | CDC*, 2023). The recent modification of DSM-5 (Diagnostic and Statistical Manual 5th Edition) describe ASD associated disabilities into two core domains: 1) social communication impairment with difficulties in developing, reciprocating and having an understanding of social emotion and relationships, and 2) repetitive behavioral pattern characterized by unusual repetitive motor movements or ritualized use of object or repetitive word phrases, as well as sensory challenges (Aishworiya et al., 2022; Chu et al., 2022). However, the range of symptoms and severity varies with age, gender or may intensify with any other co-existing mental health condition such as ADHD (Attention Deficit Hyperactivity disorder), intellectual disabilities which makes diagnosis and management of ASD more intricate and difficult (Chu et al., 2022).

As per the DSM-5 criteria, signs of autism must be identified in early childhood encouraging better diagnosis of ASD in younger children (Aishworiya et al., 2022). The rating assessment scales validated for diagnosing ASD are: Autism Diagnostic Interview-Revised (ADI-R), the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2), among them the Autism Behavior Checklist (ABC) and the Childhood Autism Rating Scale (CARS) are most commonly used Aishworiya et al., 2022; Manohar et al., 2019). Reports suggests that in children with ASD, early diagnosis and commencement of suitable therapies provide an optimal outcome and reduce symptom progression (Manohar et al., 2019). For the etiology of ASD, a wide range of genetic factors including various gene variations, chromosomal

abnormalities and environmental effects that produce physiological changes among genetically sensitive individuals, coupled with mitochondrial dysfunction have been reported in 10-20% cases of ASD (Hodges et al., 2020). Non-genetic factors such as parental age, maternal infection and nutritional deficit and exposure to teratogenic substance or drugs also imposes potential risk in ASD development (Sauer et al., 2021).

Currently, there is no one standard treatment option for ASD, as it is viewed as a disorder with little scope for 'cure'. However, there are ways that can provide better outcomes in terms of improving independent living of individuals with ASD. The wide range of symptoms of ASD reflects that the difficulties and challenges vary greatly from person to person and thus, require different treatment approach as per need (*Treatment and Intervention Services for Autism Spectrum Disorder*, 2022). For pharmacological treatment of ASD, only two atypical antipsychotics (aripiprazole and risperidone) are approved by US. FDA till date, although these drugs do not address the core symptoms of ASD, they are effective to manage aggressive and irritable behavior (Pistollato et al., 2020). Other classes of drugs such as psycho-stimulants, anticonvulsants, antipsychotics and glutamate antagonists are also tested for the treatment of ASD, however they do not have any significant evidence of social development and may also cause side effects. Thus, as an alternative to pharmacological intervention, current research evidence solely supports behavioral (non-pharmacological) therapy as the mainstay of management of ASD primary symptoms (Pistollato et al., 2020; Aishworiya et al., 2022). Non-pharmacological intervention, known to be the most effective approach, mainly includes behavioral therapy based on applied behavioral analysis (ABA), occupational therapy, speech & physical therapies that emphasize on skill development for better functioning in daily life, enhance their ability to communicate and improve motor movements that may enable them to perform activities independently (Autism Science Foundation, 2023). While non-

pharmacological therapies have been found to be helpful, they are often time intensive and maintenance is also expensive in the long run (Guastella et al., 2022).

As per researchers, oxytocin which is an anterior pituitary hormone, is expected to be used as a potential breakthrough to seek the medical treatment of autism core symptoms, since this neuropeptide can regulate social cognition and information processing (Yamasue & Domes, 2017). Findings from a meta-analysis of 31 studies suggests that, significantly lower level of oxytocin was found in autism children compared to neurotypical subjects and this is an indication to the connection of oxytocin system in the etiology and associated social deficits of ASD (Glock, 2022). Previous systematic reviews and meta-analyses showed empirical evidence of improvements in measure of irritability, social cognition, repetitive behavior, eye gazing, facial expressions following administration of intranasal oxytocin in adults with ASD (Tachibana et al., 2013; Shahrestani et al., 2013). The mechanistic effect of oxytocin is yet unclear, but studies have reported that it promotes social interaction and behavior by regulating functional activity of the amygdala and medial pre-frontal cortex brain regions involved in social processing (Procyshyn et al., 2022), participants in studies were reported to have better behavioral improvement with stronger attenuations in amygdala-activity (Bernaerts et al., 2020). The long-term prosocial effects of oxytocin are not yet fully understood and require future research with rigorous study design. Despite having the proximity of beneficial outcome, the age, gender and other genetic factors affecting the efficacy of OXT is unclear and there remains a lack of conclusive evidence for its use as a single treatment option.

1.1 Traditional Mechanism of Action of Oxytocin

Oxytocin, a neuropeptide, plays a crucial role in regulating various physiological processes and behaviors related to reproduction, as well as a range of social and nonsocial behaviors. The effects of oxytocin are facilitated by a single G protein-coupled receptor that is found in

numerous peripheral tissues and specific regions of the brain. When released into the bloodstream, oxytocin stimulates uterine contractions and milk production. In monogamous species, oxytocin plays a role in pair bonding as well as in the regulation of social recognition, childcare, and maternal bonding. Oxytocin also influences hunger, mental state, and stress levels. The release of the processed oxytocin (OT) peptide into the bloodstream systemically occurs in reaction to various stimuli, including suckling, labor, and specific types of stress. This release takes place from the posterior pituitary. These stimuli also result in the intranuclear release of oxytocin (OT). The classical physiological action of oxytocin (OT) include the facilitation of uterine smooth muscle contractions during the process of labor and the promotion of milk ejection during lactation (Roopasree et al., 2019). Upon activation of the mammary glands due to stimuli, tactile receptor stimulation at that place sends sensory impulses from the nipples to the spinal cord and eventually to hypothalamic oxytocinergic neurons. After secretion, those neurons exhibit synchronous high-frequency bursting activity, which consists of a rapid but intermittent (every 5-15 min) release of action potentials. After each surge, the bloodstream is flushed with OT, which is then sent to the breasts for lactation. The myoepithelial cells lining the lactiferous ducts and breast tissue alveoli contract as a result, leading to milk ejection, also known as the let-down reflex. Upon binding to its receptor, oxytocin initiates further downstream signalling that ultimately triggers the activation of the enzyme Phospholipase-C, which further generates ITP (inositol triphosphate) and DAG (1,2-diacyl glycerol), while also triggering the release of intracellular Ca++ and subsequently initiating diverse cellular processes. Calmodulin is a protein in the myometrium that binds to calcium (Ca++) and forms a complex with it. Later on, this complex activates the Myosin Light Chain Kinase (MLCK) enzyme, which induces myometrial smooth muscle contraction causing the fetus to be expelled (Uvnäs-Moberg, 2023).

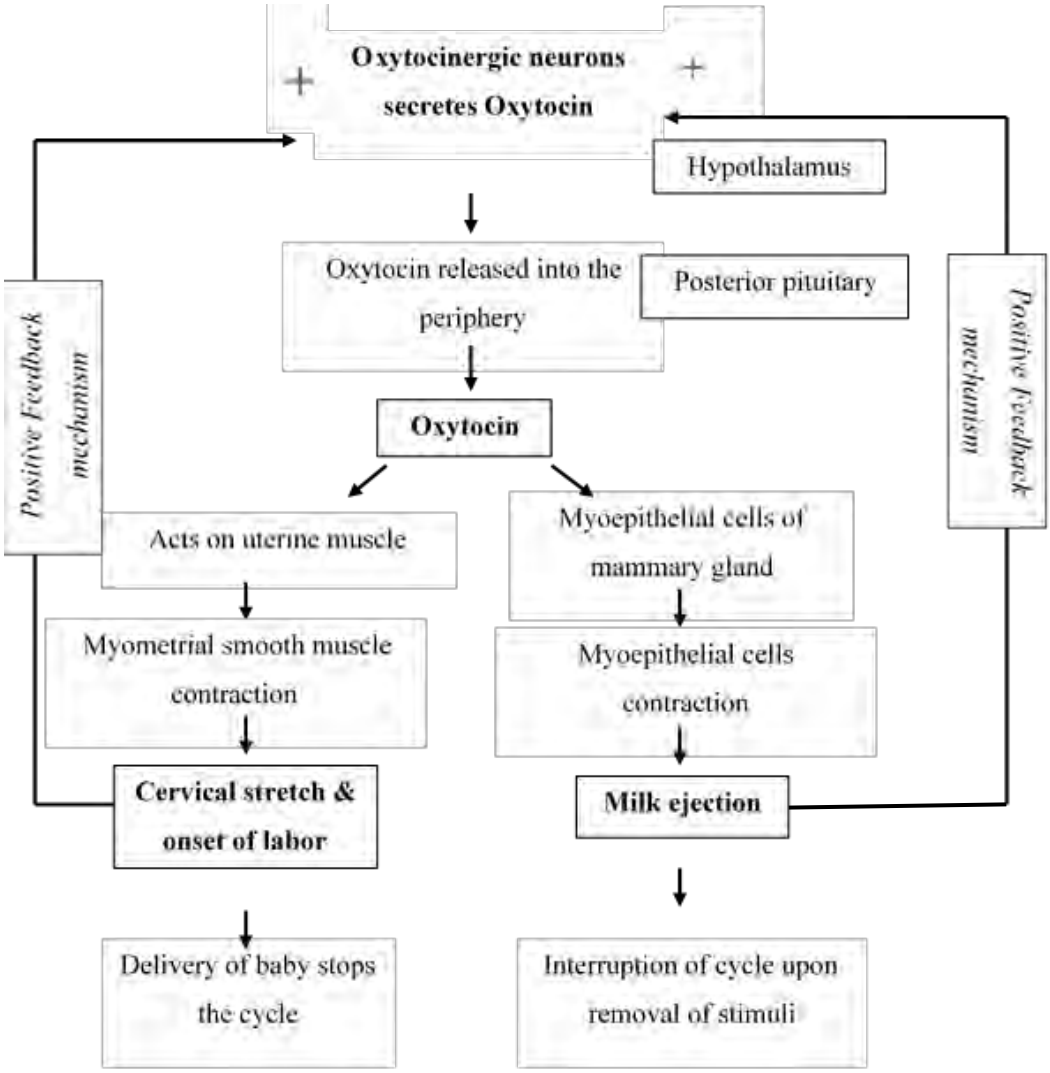


Figure 1: Regulation of Oxytocin during Labor and Breastfeeding

Vasopressin, closely similar to neuropeptide oxytocin, is also being studied with an aim to develop a new therapeutic approach for amelioration of the core deficits of ASD. Since Arginine Vasopressin (AVP) is thought to be a neuromodulator, that targets amygdala, hypothalamus, nucleus accumbens, it influences the repetitive behavior in ASD (Hammock et al., 2006). In animal model studies, intranasal AVP administration resulted in greater social proximity and interaction (Ramos et al., 2014), evidence from these studies led to few clinical trials of vasopressin in ASD subjects. A study conducted by researchers at Stanford University found that the social responsiveness measure was more in the group with AVP contrast to control group and decreased repetitive behavior was also reported (Hendaus et al., 2019).

Another study investigating the prosocial effect of vasopressin hypothesized a neurobiological mechanism that induce certain alteration in the connectivity of specific regional junction, i.e. temporal cortex in brain leading to the expression of prosocial neuropeptide effects and may enhance social familiarity (Zink et al., 2011). Furthermore, studies with intranasal administration of vasopressin summarizes, that low dose vasopressin is safe and may have positive effects like improvement in social responsiveness scale, greater prosocial effects and improvement in face processing, however, due to limitations larger controlled trials are required to explore its efficacy as a promising approach for enhancing social functioning in ASD (Hendaus et al., 2019; D'Arc et al., 2019).

1.2 Traditional Mechanism of Action of Vasopressin

Vasopressin, a nonapeptide hormone is also synthesized in the hypothalamus and released into the bloodstream from posterior pituitary. The primary physiological trigger for the release of vasopressin is an increase in plasma osmolality. However, substantial decreases in arterial blood pressure and volume of blood can also induce the secretion of vasopressin. Among vasopressin's many functions, its antidiuretic effect on the kidney's collecting ducts is an important one related to water homeostasis. A cascade of events occurs within tubular cells when vasopressin binds to surface V2 receptors, leading to the expression of aquaporin-2, a water channel. Preformed aquaporin-2 also moves to the luminal membrane of the tubule cells and inserts there. In this location, it functions as a conduit facilitating the reabsorption of water from the urine, traversing the cell, and ultimately returning it to the circulation. Consequently, there is a decline in the clearance of free water by the kidneys, an increase in urine concentration, and a decrease in urine volume (Guelinckx et al., 2016). The overall outcome is the process of water being reabsorbed into the bloodstream, which, in conjunction with the consumption of water due to thirst, results in the restoration of normal plasma osmolality.

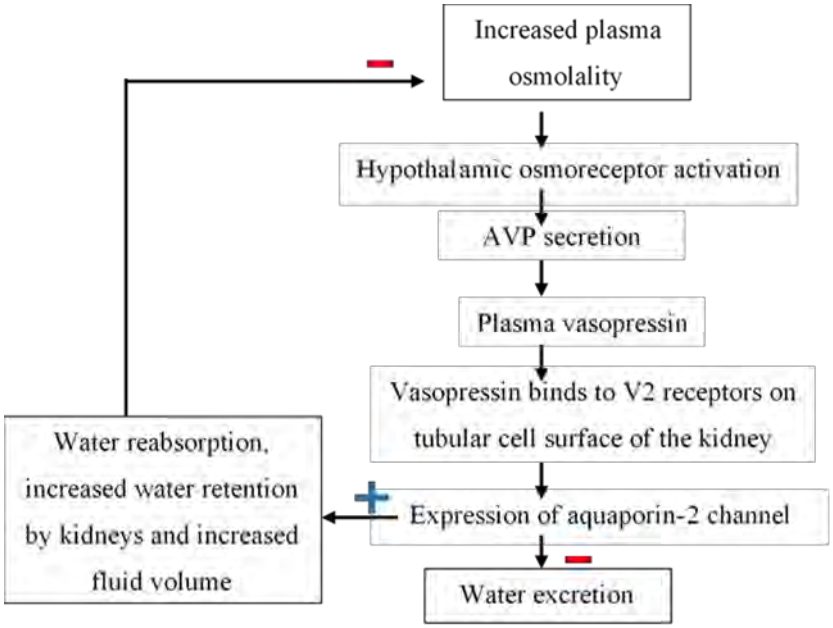


Figure 2: Feedback Loop Illustrating Regulation of Fluid Volume through Vasopressin Secretion

The regulating process of vasopressin secretion and its subsequent action is a crucial homeostatic mechanism that safeguards the osmotic balance within the body, hence enabling proper cellular functioning.

Findings from previous studies have shown that the oxytocin/vasopressin system has correlation with the etiology of ASD as the two hormone is responsible for regulation of social behavior. The data obtained implicates that plasma levels of OXT (Modahl et al., 1998) and AVP (Al-Ayadhi et al., 2005) was smaller in autistic children as opposed to normal developing children. Another study suggested role of OXT in vocal aspect of communication after reporting less impairment of verbal communication corresponding to higher OXT concentration (Theofanopoulou et al., 2017), while plasma levels of VP was found to be in positive correlation with brain morphological changes which indicates the impact of these structural alterations in the etiology of ASD (Shou et al., 2017). In the vasopressin-system, animal models demonstrated that AVP causes activation of specific brain regions such as, amygdala, hippocampus that coordinates a range of social cognition and behavior (Veenema

et al., 2010). Although much has been gleaned from studies investigating the oxytocin/vasopressin system, the exact pathway modulation behind their action is not fully elucidated yet but it is one of the most promising therapeutic strategy aiming the key symptoms of ASD (Veenema et al., 2010; Borie et al., 2021).

With an aim to add to the current literature, the purpose of this paper is to review randomized controlled trials of studies that investigated therapeutic efficacy of oxytocin and vasopressin respectively to improve core symptoms of ASD, particularly social responsiveness and repetitive behavior.

Chapter 2

Proposed Mechanism of Action of Oxytocin and Vasopressin

The neuropeptide oxytocin, well known for its physiological function, is also involved in regulation of socio-affective and cognitive processes due to its multifaceted role as a neuromodulator in the brain (Carter et al., 2014). It is synthesized mainly in the supraoptic and paraventricular nucleus (PVN) of the hypothalamus, where the magnocellular neurons of the PVN project to various core regions within the brain involved in social behavior and complex processes. Along with the release of oxytocin from the posterior pituitary into peripheral circulation, there is dendritic release of oxytocin which results in diffusion of OXT to other regions of brain circuitry such as amygdala, the nucleus accumbens (NA), hippocampus, the striatum, insula, caudate, bed of nucleus of stria terminalis- where it modulates the neurotransmission and induce a multitude of effects (Meyer–Lindenberg et al., 2011; Ludwig & Leng, 2006).

Previous studies involving intranasal oxytocin administration in humans has shown that it promotes social cognition (Riem et al., 2014; Bartz et al., 2010), enhances the development of positive social interaction (Ditzen et al., 2009; Heinrichs et al., 2009; Preckel et al., 2014) by modulating anxiety (Labuschagne et al., 2010; Riem et al., 2011; Sauer et al., 2013) and stress (Cardoso et al., 2012; Grimm et al., 2014). From the systemic review and meta-analysis of clinical trials of IN-OXT till 2021 (Huang et al., 2021), despite some mixed results, findings suggest that the role of oxytocin holds much promise in the treatment of ASD addressing its core symptoms due to observed beneficial improvement in social responsiveness and prosocial behavior such as cooperation (De Dreu et al., 2010; Declerck et al., 2010), trusting (Mikolajczak et al., 2010), and intentional moral judgement (Scheele et al., 2014; Shang et al., 2017). This evidence highlights the correlation of intranasal oxytocin administration with

prosocial behavior and thus require an understanding of the mechanism of OXT at the neural networks level in the brain, for further validation of the clinical findings involving core symptoms of autism.

2.1 Hypothesis for Prosocial Effects of Oxytocin

Based on clinical outcomes involving social and affiliative processes, authors have proposed few hypothetical underlying mechanisms for prosocial effects of OXT, which includes- 1) stress reduction or anxiolytic effect; 2) positive valence/ reward (affiliation-motivation); and 3) social salience (independent of valence) (Weisman & Feldman, 2013). Groppe et al. (2013), proposed a hypothesis that oxytocin exerts the salience effect by influencing the processing of socially relevant cues in the mesolimbic ventral tegmental area (VTA- a region implicated in social cognition and motivation) via interconnection with the dopaminergic neural pathways. Both oxytocin and dopamine receptors are located in mesolimbic region, as a result when exogenous oxytocin enters the VTA, dopamine release increases in other core region, the nucleus accumbens (NAc – region involved in responses emotionally relevant stimuli and receives projection from the VTA) (Weisman & Feldman, 2013). Another study in response to attachment related cues reported, mothers who exhibited higher degrees of social concurrence while interacting with their babies demonstrated increased activations in the nucleus accumbens (NAc) and these activations in the NAc were interrelated functionally to activations in socio-cognitive cortical circuits (Weisman & Feldman, 2013; Atzil et al., 2011). This study adjoined with that of Groppe et al. (2013), suggests that in response to socially relevant cues either social reward or punishment (friendly face or angry), oxytocin increases VTA site activation by enhancing the perceived salience(attention) of cues in that region (VTA-vental tegmental area) and thereby might play a role in triggering pro-social effects like- motivation

to react at any anticipated social cues, thus guiding social approach as per the “social salience” hypothesis (Weisman & Feldman, 2013; Groppe et al., 2013; Atzil et al., 2011).

Along the same line, Domes et al. (2013) showed that, oxytocin administration modulates and enhances right amygdala activation towards facial stimuli- these results presented here align with the majority of human neuroimaging studies, which has shown that OT has a regulatory effect on the amygdala's reaction to social stimuli. This implies that the amygdala network might be a mediator of OXT effects on social salience and social reward (Weisman & Feldman, 2013; Domes et al., 2013). Consistent with the results presented in the study conducted by Groppe et al. (2013), Domes et al. (2013) also addressed that oxytocin influenced cognitive processing of social information in autism subjects, providing additional evidence in favor of the ‘social salience’ hypothesis as a key action underlying the pro-social effects of OXT. Besides, both the author highlighted another aspect of differential effect of OXT administration, that is, OXT was found to increase regional brain activity towards facial stimuli, specifically in Asperger syndrome group, whereas there was a reduction in brain activity in neurotypical individuals. The findings align with the concept that persons with lower levels of social competence may exhibit heightened sensitivity to the advantageous impacts of oxytocin (OXT) (Weisman & Feldman, 2013; Groppe et al., 2013; Domes et al., 2013).

2.2 fMRI Studies of Oxytocin

In order to elucidate the neural mechanisms that underlie the impact of oxytocin on social cognitive functions in humans, pharmacological functional magnetic resonance imaging (fMRI) studies have been conducted, a noninvasive technique that investigate brain regional activation to certain stimuli, tasks or during resting state by recording the blood oxygenation level-dependent (BOLD) signals (Zink & Meyer–Lindenberg, 2012). On the basis of evidences from earlier studies, (Weisman & Feldman, 2013; Domes et al., 2013), the fMRI studies under

oxytocin administration, mainly focused on the neural activity in amygdala due to the notion that amygdala reactivity is associated with social threat arousal from facial expressions (Zink & Meyer–Lindenberg, 2012; Williams et al., 2001). In addition, evidence supporting oxytocin release and binding in amygdala (Huber et al., 2005; Landgraf et al., 2004), and activation of oxytocin receptors in the same region seems to be responsible for the influence of oxytocin on specific aspects of social cognition – all sums up the reason for amygdala being the region of interest (ROI) (Zink & Meyer–Lindenberg, 2012; Ferguson et al., 2001).

These fMRI studies began with an initial investigation conducted by Kirsch et al. (2005) among men that involved the task of matching fearful or angry faces, in which results obtained showed significant attenuation of left amygdala activity by oxytocin upon exposure to negative emotions. The findings about attenuated amygdala, provide insight into the neural basis of mechanism for the ability of oxytocin to reduce aversion (Evans et al., 2010) and anxiety towards negative social stimuli that are perceived as threatening, since reactivity in the amygdala has been linked to perception of social threat arousal (Williams et al., 2011). Thus, Kirsch et al. (2005) study established the involvement of the amygdala associated with social behavioral effects of oxytocin. Although, their investigation exclusively employed negative valence stimuli, prompting the question whether these findings may be generalized to positive valence stimuli (happy faces). A subsequent study conducted an "implicit facial emotion processing" identification of gender task where it included both happy and fearful or angry faces of them (Domes et al., 2007). The study found that oxytocin had a diminishing effect on the amygdala's response to negative facial expressions in men. However, it was somewhat unexpected that oxytocin also reduced the activity in the right amygdala when processing positive happy faces in contrary to neutral faces. This suggests oxytocin could decrease the excited or arousal response to emotional social impulse in general by modulating overall activity of amygdala region (Zink & Meyer–Lindenberg, 2012; Domes et al., 2007). Another

oxytocin pharmacological fMRI study on explicit emotion classification found that oxytocin decreased amygdala reactivity to fearful looks but increased left anterior amygdala activity for happy expression (Gamer et al., 2010), contradicting previous findings (Domes et al., 2007) on positively valence social stimuli. Because the oxytocin-propelled reduction in amygdala reactivity to happy appearance was restricted to the right hemisphere (Domes et al., 2007), and noteworthy increase in amygdala activity only extended to the left hemisphere (Gamer et al., 2010), these discrepancies may point to a laterality-specific effect.

In the very first study of the impact of oxytocin on the brain pathways involved in the perception of social emotions in women, female participants were subjected to fMRI while evaluating the emotional intensity of facial expressions depicting fear, anger, and happiness. In comparison to findings from prior studies, in male participants (Kirsch et al., 2005; Domes et al., 2007; Gamer et al., 2010), the administration of oxytocin resulted in a remarkable increase in left amygdala responding to fearful looks, while having no impact on amygdala or brainstem activity in response to either angry or happy appearances (Domes et al., 2010). The findings of this study reveal a notable gender difference, where females exhibited heightened brain activity in response to oxytocin, while males reported a decrease in brain activation in regions such as the amygdala, brainstem, and temporal poles during the processing of emotional faces. Another pharmacological fMRI investigation using oxytocin found that women who had been given oxytocin showed decreased right amygdala activity when exposed to infants crying compared to those given a placebo (Riem et al., 2011). Although the impact of oxytocin on amygdala activity in females seems to vary depending on the task, it has been found that oxytocin enhances the responses of the insula and inferior frontal gyrus during emotional face processing (Domes et al., 2010) and exposure to infant crying (Riem et al., 2011). It is possible that women's increased insula responsiveness to oxytocin in these social

contexts represents a female- or paradigm-specific neurological discovery that underlies an affective empathy feedback (Fan et al., 2011).

2.3 Three Mechanistic Proposal of Oxytocin in ASD

From reviewing the fMRI studies reported evidence on neural basis, three mechanisms as a hypothesis underlying the effect of OXT in pro-social behavior had been suggested, they are- downregulation of negative effect, facilitation of rewarding experience derived from social interaction and an increased sensitivity or attention to social stimuli (Figure 1):

2.3.1 Downregulation of negative effect

Early animal studies have established oxytocin as a significant modulator of anxiety reactions due to its regulatory capacity on negative stimuli. Later on, evidence from human fMRI investigations suggested that in response to stimuli associated with negative emotional expression, including afraid (Domes et al., 2007; Gamer et al., 2010; Kirsch et al., 2005; Kanat et al., 2015), angry faces (Domes et al., 2007; Kirsch et al., 2005; Kanat et al., 2015), unpleasant images (Sauer et al., 2013; Petrovic et al., 2008), conditioned fear (Petrovic et al., 2008; Eckstein et al., 2015), and physical pain (Zunhammer et al., 2015), as well as towards negative social interaction such as, trust betrayal (Baumgartner et al., 2008), lack of reciprocation while trying to cooperate (Rilling et al., 2012), IN-OT was able to reduce amygdala activity. In addition to altering amygdala activity, oxytocin also affects other regions of the brain that controls how we feel and react to social & emotional stimuli (Ma et al., 2016). In specific areas of the brain that are linked in the processing of negative emotion, IN-OXT was found to decrease neural activity upon exposure to unpleasant emotions and these regions include thalamus (Domes et al., 2007), anterior cingulate cortex (Petrovic et al., 2008; Rilling e al., 2012; Preckel et al., 2015), anterior insula (Bos et al., 2015; Kanat et al., 2015) and orbitofrontal

cortex (Zunhammer et al., 2015; Singer et al., 2008; Preckel et al., 2015). On the other hand, studies suggests that, IN-OT might increase activity in the medial prefrontal cortex (mPFC) (Petrovic et al., 2008; Grimm et al., 2014), the ventral lateral prefrontal cortex (vlPFC) (Domes et al., 2010; Petrovic et al., 2008; Rilling et al., 2012; Singer et al., 2008), and the dorsal lPFC (Domes et al., 2010; Eckstein et al., 2015) as an underlying mechanism with enhanced ability for regulation of negative social cues, since, these are regions of the brain associated to the neural circuit that control emotion automatically (Figure 1) (Kupfer et al., 2012; Goldin et al., 2008).

Overall, these findings emphasize dual effect of IN-OXT on negative affect: 1) reducing brain reactivity or responsiveness to negative emotions (e.g., AMG, ACC, AI) and 2) increasing the activity of the automatic emotion regulation network (e.g., mPFC, vIPFC) (Ma et al., 2016). Consequently, these effects may have positive implications on social behavior, by diminishing the tendency of social withdrawal or isolation, enhancing engagement in their social surroundings, and more likely to initiate conversations with other people and such outcomes may promote their sociability.

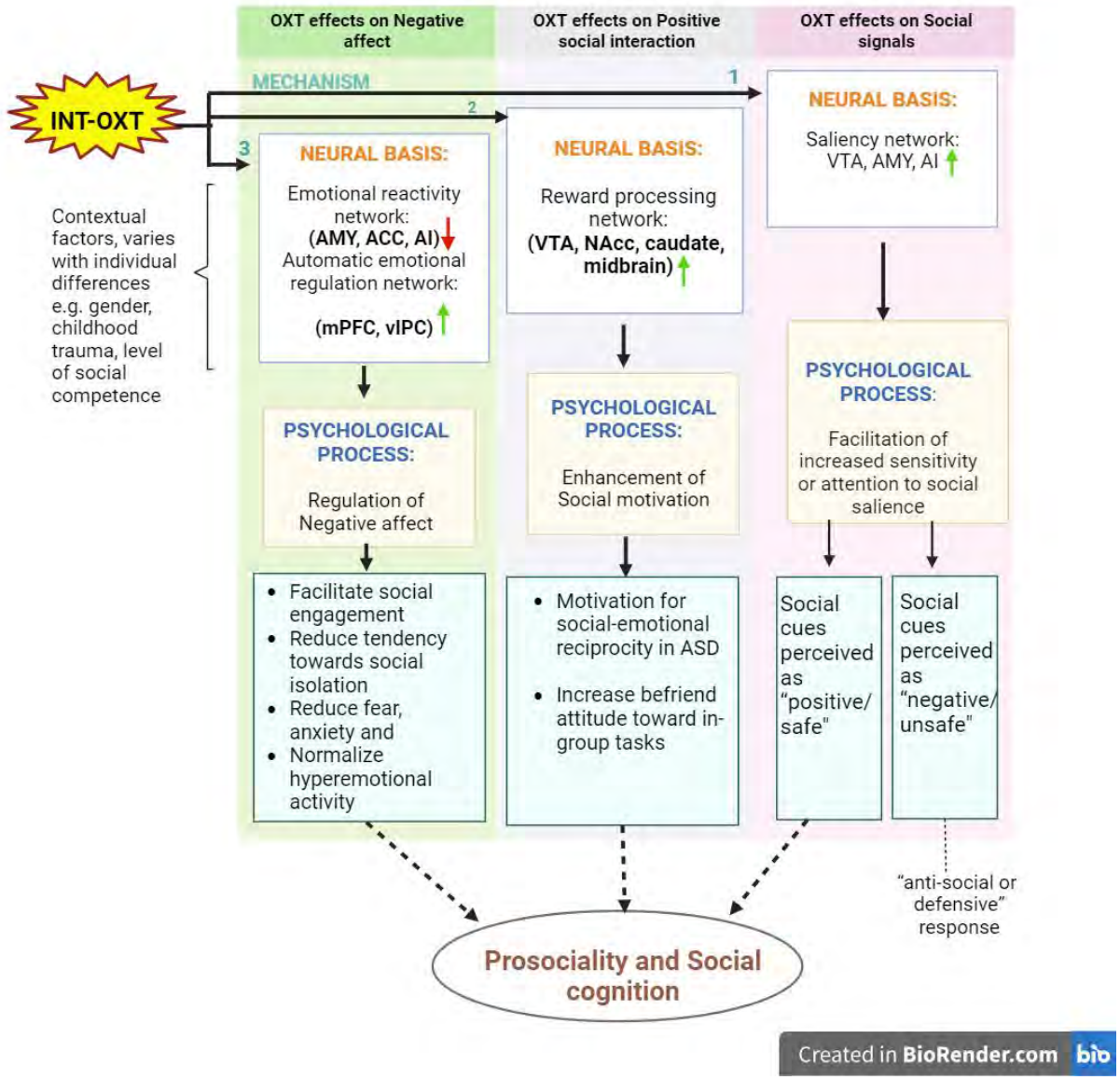


Figure 3: Hypothesis of neural mechanism underlying OXT effect on ASD core symptom-social dysfunction. Oxytocin alters activity in the emotional reactivity network, reward and salience network in response to perceived stimuli, thus regulates negative affect, enhance motivation and increase social sensitivity in ASD. Collectively, these processes facilitate individuals in navigating social interactions, assimilating into intricate social contexts, and ultimately adjusting to the surroundings. ↑indicates increased activity and ↓indicates decreased neural activity by OXT. Abbreviations: AMY, amygdala; ACC, anterior cingulate cortex; AI, anterior insula; mPFC, medial prefrontal cortex; vlPC, ventral lateral prefrontal cortex; VTA, ventral tegmental area; NAcc, nucleus accumbens.

2.3.2 Facilitation of social motivation

Another hypothesis put forward with regard to oxytocin's mechanism for prosocial effects is that it may enhance the capability to socially adapt by encouraging individuals to start and sustain social interaction by means of promoting intrinsic reward (Ma et al., 2016). Studies suggests, IN-OXT elicited heightened neural activity in reward processing brain regions- the ventral tegmental area (VTA), putamen, pregenual ACC (Phillips et al., 2003), insula, nucleus accumbens (NAcc), and midbrain (Figure 1). This effect was observed during the perception of positive social cues, such as a happy face (Domes et al., 2010; Gamer et al., 2010) or images of one's partner or child (Scheele et al., 2013). Additionally, IN-OXT was found to enhance neural responses when individuals anticipated social rewards (Groppe et al., 2013) and participated in positive social interactions (like working on cooperative tasks with others) (Rilling et al., 2012; Rilling et al., 2014; Feng et al., 2014).

The administration of OT resulted in hyperactivity in the reward system, provides a ground for OXT having a function in attaching reward value to social scenarios (Ma et al., 2016). This, in turn, may enhance motivation to engage in social interactions, maintain social-emotional reciprocity with surrounding people, and strengthen social bonds, and thereby alleviate the social deficits among individuals with ASD.

2.3.3 Enhancing social salience

Recent study has shown that the social effects of oxytocin (OXT) exhibit variability across different social circumstances, rather than consistently displaying favorable outcomes. For instance, the administration of IN-OT has been found to potentially contribute to the escalation of antisocial behaviors, such as violence (DeWall et al., 2014) and jealousy (Shamay-Tsoory et al., 2009). The contradictory results have been suggested to indicate a broader function of oxytocin (OT) in enhancing the significance i.e. salience of social cues, which is influenced by

social circumstances and variations among individuals (Olff et al., 2013; Bartz et al., 2011). In accordance with earlier findings that intranasally administered oxytocin increased VTA activity to stimuli showing social punishment (angry face) as well as social reward (friendly face), Groppe et al. (2013) had proposed the hypothesis of "social salience" mechanism of oxytocin. The amygdala's functional connection with the saliency network, which includes the insula and caudate, is likewise enhanced by IN-OT (Figure 1) (Rilling et al., 2012). Also, improved social learning has also been linked to an increase in functional connectivity between the amygdala and the insula/caudate, which OT has been shown to induce (Hu et al., 2015). There is an indication that the heightened prominence of social cues after administration of oxytocin (OT) is associated with improved attentional focus on social stimuli (Shamay-Tsoory & Abu-Akel, 2016) and this assertion is favored by previous research demonstrating improved attentional focus on the ocular regions (Tollenaar et al., 2013) following IN-OXT via alteration of amygdala activity (Gamer et al., 2010).

Intranasal oxytocin (OT) enhances social salience by increasing attention to social stimuli and this makes people with ASD more sensitive to social signals. This heightened sensitivity aids in the dealing of social information and facilitates individuals in effectively preparing for community involvement and anticipating associated outcome (Ma et al., 2016). Consequently, this adaptive response allows individuals to efficiently navigate and adjust to various social contexts.

The absence of any impact of oxytocin on social interactive behavior makes it challenging to interpret the neural changes induced by oxytocin. Nevertheless, these findings are significant as they suggest that certain neural structures and circuits can be influenced by oxytocin during specific social interactions.

2.4 fMRI Studies of Vasopressin:

Currently, there is a scarcity of pharmacological fMRI studies that have examined the influence of vasopressin on neural activity associated with social cognition. In comparison to oxytocin, the number of such studies is significantly lower. However, a limited number of studies have conducted experimental designs, to investigate the effects of vasopressin in men with an aim to reveal distinct patterns of neural activation. There are currently no approved therapeutic uses of AVP (Arginine Vasopressin) for CNS disorders, despite the widespread distribution of peripheral V1AR and V1BR and the essential reactions that can be elicited after activation or inhibition of these targets (Cid-Jofré et al., 2021). However, AVP has shown promise as a treatment alternative for social behavior defects in animal research where Magel2 KO adult male mice with autism showed social deficits due to improper AVP activation in LS (lateral septum) projection neurons and optogenetic stimulation or AVP administration restored social deficits in Magel2+/−p mice (Borie et al., 2021). Positive effects from administering IN-AVP to children with ASD were found in a placebo-controlled pilot study. Improvements in social skills, as judged by the Social Responsiveness Scale, were observed after 4 weeks of IN-AVP administration in 30 children aged 9.6 to 12.9 (Parker et al., 2019).

Among the limited number of studies investigating how AVP affects social behavior, a study following intranasal administration of AVP demonstrated an increase in mild frowning, as measured by the activity of the corrugator supercilii muscle (Thompson et al., 2004). This finding implies an intensified negative emotional reaction to ambiguous social cues, including neutral facial expressions. It is worth noting that there exists data supporting the presence of sexually dimorphic outcome of intranasal AVP on social understanding. Specifically, the administration of intranasal AVP has been found to result in a decrease in the feeling of friendliness among males, whereas conversely, in females it has been seen to improve (Cid-

Jofré et al., 2021; Thompson et al., 2006). The limited existing research indicates that AVP may have contrasting effects to OXT concerning social stress and cognitive ability, particularly in males (Figure 4) (Cid-Jofré et al., 2021. Imaging studies of intranasal AVP are rare till now, unlike oxytocin, the first study of AVP administration revealed that, AVP had no evident impact on amygdala reactivity, but it inhibited the deactivation of subgenual cingulate cortex which regulates amygdala activation. In addition, structural equation modeling highlighted the consequence of AVP on the circuitry linked to emotion processing by showing that AVP influences the way the subgenual and supragenual cingulate connect with the amygdala (Zink et al., 2010). In the second study, during an implicit social recognition matching task, participants were presented with either familiar or unfamiliar faces after AVP administration, which resulted in a localized modification in the left temporoparietal junction, a crucial component of the mind network (Zink et al., 2011). Collectively, the results of these two studies point to the likelihood of amygdala as primary target of OXT's effect, while indicating a major cortical effect of AVP, with effects particularly on a core region essential for regulation of the limbic system, as well as on another crucial region responsible for social cognition (Meyer–Lindenberg et al., 2011; Zink et al., 2010; Zink et al., 2011). Combining the majority of brain imaging studies impart evidence that the impact of oxytocin and, to a lesser extent, arginine vasopressin (AVP) on social cognition is facilitated by limbic circuitry, with the amygdala serving as one of the central component (Meyer–Lindenberg et al., 2011).

2.5 Hypothesis of Vasopressin Interaction with Neural activity in ASD:

The amygdala-cingulate circuit and HPA axis (Hypothalamic-pituitary-adrenal axis) system is stimulated during social anxiety or stress, and further enhanced by AVP (arginine vasopressin). Among neurotypical subjects, stress or anxiety promotes prosocial behavior as a coping method, also enhances oxytocin release which further encourage social approach. OXT is a significant conciliator of the anxiety relieving and stress-shielding effects of positive

socialization (also known as "social buffering") because it lowers reactivity in the amygdala and the HPA axis in response to social stimulus causing stress or anxiety, as illustrated by the inhibitory arrow in the figure. Individuals with autism may benefit from the treatment approach of oxytocin or OXT receptor agonists and/or AVP antagonists.

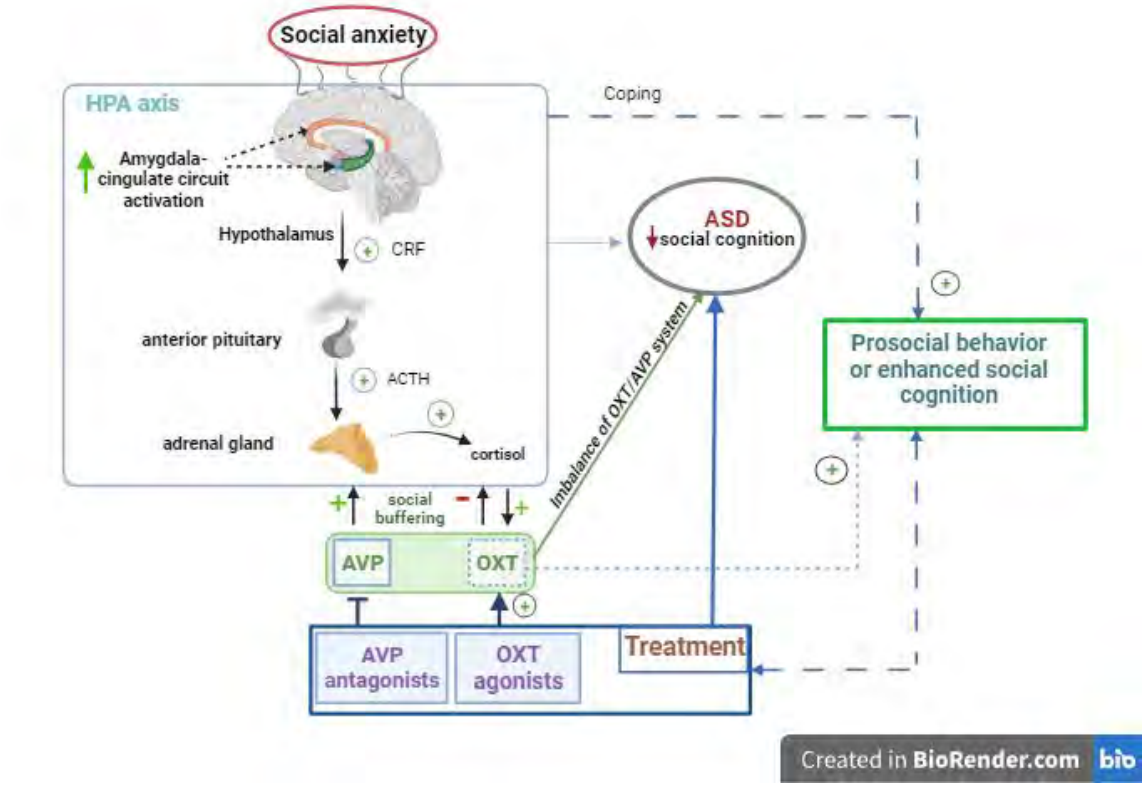


Figure 4: Interaction of OXT, AVP, Prosocial behavior and Social anxiety – A Conceptual Model

Children with autism spectrum disorder (ages 6-13) who received VP intranasally for 4 weeks reported decreased anxiety and some repetitive behaviors; increased social abilities as measured by the Social Responsiveness Scale. Conversely, after 12 weeks of treatment, high-functioning males with ASD showed improvements in socializing and communication with the AVPR1A antagonist balovaptan (Bolognani et al., 2019). It's interesting to note that both agonists and antagonists of VPRs had a positive effect. However, the ages of the patients in the

two groups are different, thus, additional research is needed to determine the optimal time to target the vasopressinergic system in order to improve the ASD symptoms.

Limited clinical investigations have been undertaken to explore the administration of intranasal AVP. However, there is potential for the use of selective V1a and V1b receptor antagonists, as evidenced by their successful application in animal research (Griebel et al., 2005; Ferris et al., 2006). These antagonists hold promise as potential targets for human neuropsychopharmacology as they can reduce the anxiogenic and aggression-related effects of AVP. Antagonists of arginine vasopressin (AVP) have been under consideration as potential therapeutic agents for major depression and may be effective in the treatment of anxiety related symptoms of ASD. In 2019, the European Medicines Agency granted approval for the use of balovaptan (RG7314 or RO5285119), a selective V1AR antagonist, in the treatment of Autism Spectrum Disorder (ASD), following a series of clinical trials conducted in individuals with ASD (Cid-Jofré et al., 2021).

In brief, a number of oxytocin (OT) and arginine vasopressin (AVP) ligands have been created and have shown favorable outcomes, as demonstrated in both animal models and clinical environments in the management of autism and depression (Cid-Jofré et al., 2021). Specifically, OTR agonists and/or AVP antagonists targeting the V1AR and V1BR receptors appear to hold promise as a viable therapeutic approach for addressing various neuropsychiatric illness. Few researches have incorporated parts of prosocial behavior into their frameworks. However, our understanding of the impact of oxytocin and vasopressin on brain activity concerning social dysfunction treatment in ASD is constrained by the limited inclusion of social factors in neuroimaging investigations (Zink & Meyer–Lindenberg, 2012). The limitations of our knowledge of the molecular and cellular mechanisms of oxytocin/vasopressin in humans restrict the possible interpretations of the findings reported in this review. Although

these findings from fMRI studies along with the aforementioned hypothesis of neural mechanism, point to the involvement of oxytocin and vasopressin in specific parts of the brain, it still remains unclear whether these two neuropeptides are working directly on receptors there or if they are operating on these regions indirectly via interacting with dopaminergic system or any other mesolimbic pathway. Thus, further research are required to probe the interconnection among neuropeptide administration and neuronal systems in different age groups and gender, to fully understand the capacity of oxytocin and vasopressin to influence social cognition via modulation of behavior-related neural circuits in ASD.

Chapter 3

Methodology

3.1 Search Strategy

A structured literature search was conducted on PubMed using search terms and keywords which included oxytocin, autism spectrum disorder, autistic disorder, Asperger syndrome, treatment, intervention, therapy and efficacy. The search identified 349 results. After applying the 'randomized clinical trial' filter, the searches were limited to articles published in the last 5 years (2018-2023), thus, the number came down to 32 in the initial screening. In addition to that, we manually searched bibliographies of relevant articles to identify clinical trials of oxytocin. Then the suitability of eligible articles were reviewed with criteria that included full text, appropriate RCT study design and studies that focused particularly ASD and not other syndrome. We specifically included studies having a population diagnosed with ASD, and studies which assessed behavioral effects of oxytocin compared to placebo, in amelioration of the core symptoms of ASD. Articles that had RCT employed on animals and studies that did not assess any of the targeted core symptoms like- social recognition or repetitive behavior were excluded.

3.2 Inclusion Criteria

After abstract screening, full text articles were examined for eligibility and further reviewed based on following inclusion criteria:

a) subjects diagnosed with ASD as per the DSM-5 diagnostic criteria and of any age group

b) studies that employed RCT design and human data

c) assessed efficacy of oxytocin/vasopressin in comparison with a placebo group, irrespective of route of administration

d) studies that assessed targeted core symptoms (social recognition, repetitive behavior) as primary or secondary outcome measures

3.3 Exclusion Criteria

a) study conducted on animal model

b) evaluated other syndromes (e.g. Prader willi syndrome) that does not standardize with ASD

c) studies testing efficacy of combination therapy of oxytocin or vasopressin instead of OXT as a standalone

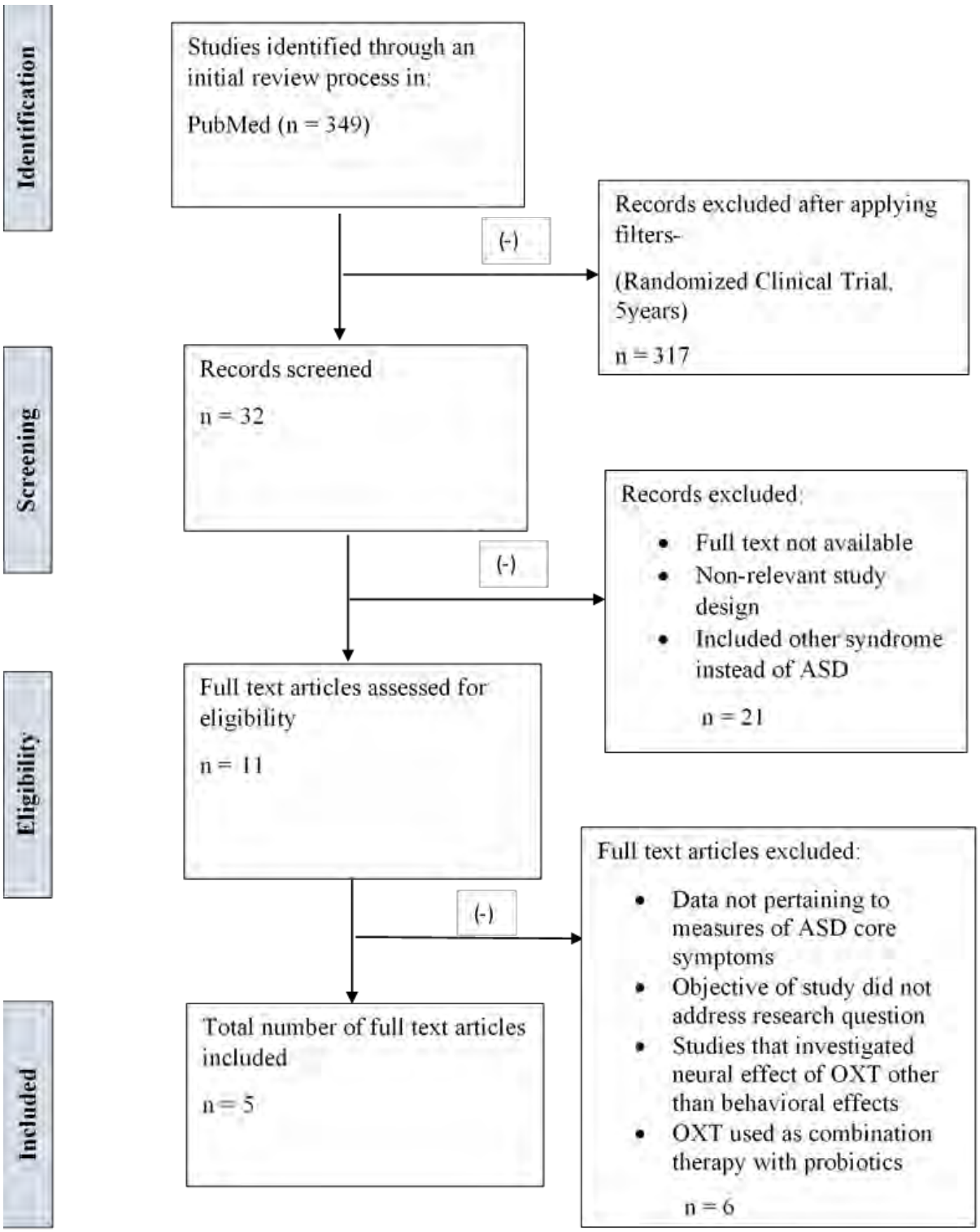
d)studies that investigated neural effect of OXT and not behavioral effect or core symptoms

Table 1: PICOS Table

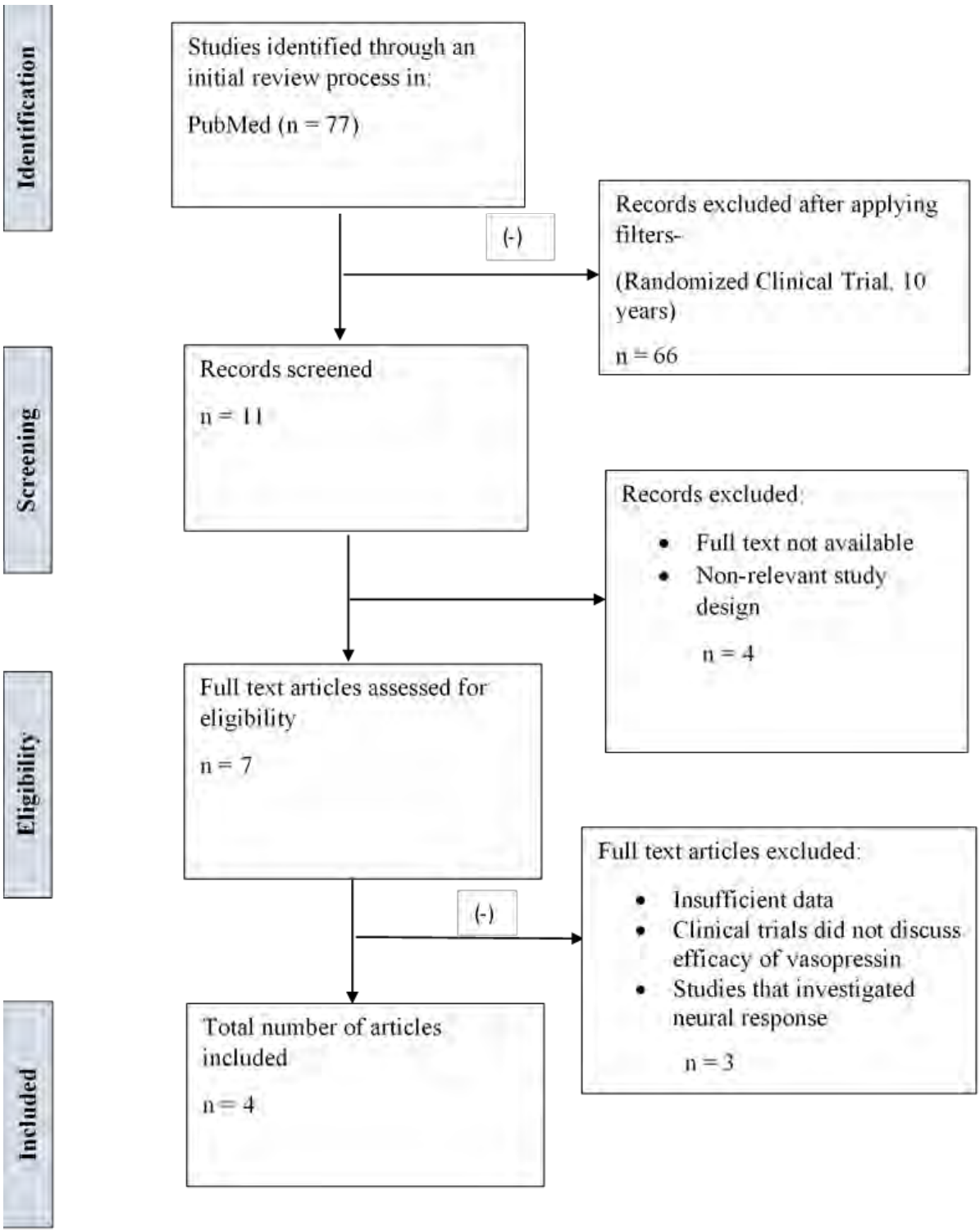
Parameter	**Inclusion criteria**	**Exclusion criteria**
Patients	Patients of any age group diagnosed with ASD	Diagnosed with others syndrome that differ from ASD
Intervention	OXT or Vasopressin as a standalone therapy regardless of route of administration	Combination therapy
Comparator	Placebo group	Lack of control group
Outcomes	Measure of behavioral effects on targeted core symptoms	Neural effect

Study Design	Randomized control trial (RCTs)	Literature review, case studies, non-controlled designs

3.4 PRISMA Flowchart for Oxytocin



3.5 PRISMA Flowchart for Vasopressin



Chapter 4 Result

Table 2: Results of Randomized Placebo Controlled Trials on the Efficacy of OXT on ASD

Author	Study design	Subjects/ no. of participants	Age	IQ scale	Route of adminis-tration	Dose/Intervention	Outcome value		Comment/ findings
Bernaerts et al., 2020	RCT, double-blind, placebo controlled	N=40, adult male	18-35 years old	Total IQ: OXT: 102.27 ± 12.45 PL: 104.61 ± 21.59	Intranasal	Daily dose of 24IU either of oxt or placebo (for 4 weeks) N= 22 (OXT) N= 18 (PL group)	Primary endpoint T1: OT group: **SRS-A** ***T value***: -2.28 ***p value***: 0.033 PL group: ***T value***: -0.45 ***p value***: 0.66 **Cohen's d(Between group difference): -0.42**	Secondary Endpoint Multiple dose effect, T1: OT group: **RBS-R**, ***T value***: -3.46 ***p value***: 0.002 PL group: ***T value***: -1.53 ***p value***: 0.15 **Cohen's d(Between group difference): -0.63**	The analysis comparing the primary outcome between groups showed no statistically significant effect of the treatment, nor was there a significant interaction effect between treatment and session. This suggests that the improvement in self-reported social responsiveness post-treatment were not substantially greater in the group receiving OT contrast to placebo. In terms of secondary outcome measure, the analyses conducted on different groups revealed a significant overall impact of OT (but no indication of an

							T2(one month retention effect): <u>OT group</u>: SRS-A ***T value:*** -2.10 ***p value:*** 0.048 <u>PL group:</u> ***T value:*** -2.69 ***p value:*** 0.015 **Cohen's d(Between group difference):** 0.22 **T3(one year retention effect):** <u>OT group:</u> SRS-A ***T value:*** -1.92 ***p value:*** 0.07 <u>PL group:</u>	**T2(one month retention effect):** <u>OT group</u>: RBS-R, ***T value:*** -3.64 ***p value:*** 0.002 <u>PL group:</u> ***T value:*** -2.83 ***p value:*** 0.012 **Cohen's d(Between group difference): -** 0.50 **T3(one year retention effect):** <u>OT group:</u> RBS-R, ***T value:*** -2.43 ***p value:*** 0.02 <u>PL group:</u> ***T value:***	interaction between treatment and session), suggesting that the amelioration in repetitive behaviors from pre- to post-treatment were remarkably greater in the oxytocin group, which demonstrates promising long lasting progress of moderate to large magnitude in repetitive behaviors & avoidant attachment.

							T value: -1.36 ***p value:*** 0.19 **Cohen's d (Between group difference):** -0.12 no significant between-group difference (p = .37)	-0.40 ***p value:*** 0.70 **Cohen's d (Between group difference):** -0.98	
Yamasue et al., 2018	RCT, double blind, placebo controlled, parallel design	N= 53, adult male	18-48 years old	Full IQ: **OXT group**-106.4 (13.8) **PL group**-108.5 (14.4)	Intranasal	48IU/day; or placebo for 6 consecutive weeks	**ADOS reciprocity** scores-decreased from baseline in both the <u>OXT group</u>: P = .0009 and <u>PL group:</u> P = .0003 [no major in-between group difference (effect size −0.08; 95%CI−0.46 to 0.31;	**ADOS repetitive behaviors**-greatly reduced from baseline in <u>OXT group:</u> P < .0001 <u>PL group:</u> P = .43 (effect size, 0.44; 95% CI, 0.05 to 0.83; P = .026).	Here. the primary endpoint and many of the secondary endpoints conducted in a wide-scale experiment showed no statistically substantial difference among intranasal oxytocin or placebo effects during the 6 weeks treatment duration. Despite the exploratory nature of the analyses, those receiving oxytocin showed improved ADOS repetitive behavior along with enhanced eye area focus when interacting than those who received placebo. Findings suggest that the dose given in this trial, in addition to

							P = .69)]		duration of intranasal oxytocin intervention alone are not optimal for reducing primary social symptoms of autism among adult males.
Sikich et al., 2021	RCT, double blind, placebo controlled	N=125 assigned in each group	3 to 17 years childr en and adole scent	Abbrevia ted IQ, mean: OXT group: 85.4±23. 7 PL group: 81.8±22. 8	Intranasal	24IU twice daily for 24-weeks, flexible dose that could be amplified by 16 IU every 4 weeks or can be reduced as per dose-adjustmen t schedule. Mean maximal daily dose: **OXT-** 67.6±16.9 IU **PL-** 69.5±16.1 IU	**ABC-mSW score**- least-squares mean (LSM), change from baseline OXT group: −3.7 PL: −3.5 (difference: −0.2 points; 95% confidence interval [CI], −1.5 to 1.0; P value, P = 0.61)	**SRS-2-SM**, T-score- least-squares mean (LSM), change from baseline OXT group: −4.5 PL: −5.4 (difference: 0.9 points; 95% CI, −1.0 to 2.9 [In this sensitivity analyses, the baseline plasma oxytocin level was incorporated as a covariate]	In the present trial examining individuals diagnosed with ASD who were in the age range of children and adolescents, it was observed that a 24-week intervention involving daily administration of intranasal oxytocin did not provide significant improvements in social interaction or other indicators of social functioning associated with ASD, as compared to placebo.

Zhang et al., 2022	A randomized, double-blind, crossover design trial (Placebo-Placebo/Oxytocin-Washout period-Placebo-Oxytocin/ Placebo- 6 months follow-up)	N=46, 23 in each group	Autistic childr en from 3-8years		Intranasal	a 6-week infrequent dose regime – average dose: quarter and half of 24IU twice daily intranasal oxytocin; every two days	**Improvement among OXT** receiving group compared to placebo was **significantly greater** for ADOS-2 score: (chi-square = 7.2, P value, p = 0.007) & SRS-2 score (chi-square = 11, $p < 0.001$) **6-months follow up**: the SRS-2 score continued to be noticeably better compared to the placebo phase conclusion	**Repetitive behavior scale measure, RBS-R**: RBS-R scores (pFDR = 0.033) [Improvement among OXT group as opposed to placebo] The ADOS-2 and SRS-2 subscales of restricted & repetitive behavior under OXT demonstrated an upward slope towards improvement but only the more comprehensive RBS-R measure reached significance	This crossover trial's outcome indicates that administering oxytocin intranasally every other day, rather than daily, followed by a period of positive social engagement can lead to a significant enhancement in social symptoms among young children diagnosed with autism.
AJ. Guastel	Randomized, double	OXT (n=49)	Children	Average full-scale	Intranasal	Oxytocin nasal	**SRS-2**:	No total scores of secondary	The outcome indicate that the administration of oxytocin did

la et al., 2023	blind, controlled, placebo lead-in, oxytocin trial [four time factors for evaluation (at baseline, week 3 after placebo lead in, week 15 after randomized intervention, week 27 follow-up]	PL (n=48)	aged between 3 and 12 years of age	IQ (SD, range) OXT group: 95.47 (16.12, 68–139) PL group: 98.00 (14.98. 68–131)		spray; 32IU per day; morning and night	no treatment condition main effect (p = 0.133) or time by treatment condition interaction, (p = 0.686) 3–5 year age group under OXT: **significant change** in SRS-2 total scores from Visit 1(baseline) to V3 (post treatment) (indicating improvement) compared to those given placebo, p = 0.029. 6–12 year age group: SRS-2 total scores from V1 to V3, p = 0.116, as well as from V1 to	outcomes were significantly impacted by treatment condition, nor were there any interactions between age group, treatment intervention and time	not yield a significant overall advantage for autism children. Although, there was some possibility that younger children exhibited more pronounced improvements in social responsiveness after oxytocin treatment was over, as compared to those who received a placebo. Nevertheless, the efficacy of oxytocin treatment in older autistic children remains inconclusive, since no empirical data has been found to support its benefits, also there is a lack of evidence suggesting that any evident benefits in the younger age group persist after discontinuation of treatment.

							V4, p = 0.189; did not vary significantly		

Abbreviations; ADOS-2(Autism Diagnostic Observation Schedule-2nd edition), SRS (social responsiveness scale) RBS-R(repetitive behavior scale-revised), ABC-mSW(ABC modified social withdrawal scale; assesses social interaction), SRS-2-SM (Social responsiveness scale-2-social motivation subscale)

Table 3: Results of Randomized Placebo Controlled Trials on the Efficacy of VAS on ASD

Author	Study design	Subjects/ no . of participa nts	Age	IQ scale	Route of adminis-tration	Dose/Interve ntion	Outcome value		Comment/ findings
Hollan der et al. 2017	randomized, double-blind, placebo-controlled, crossover design trial of RG7713 (balovaptan, an oral selective vasopressin 1a receptor antagonist)	N=19; high-functioni ng adult male subjects	18–45 years	Full scale IQ > 70	Intravenous	A single 20 mg dose of balovaptan or placebo: 2h infusion to each participant on two period - visits 1 and 2; washout pf 7–14 day in between	**Primary outcome** Under balovaptan, a substantial statistically meaningful increase in biological orientation of eye tracking result (ES = 0.8, p =0.047) and An insignificant enhancement in the composite score (ES =0.2, p =0.29)	**Secondary outcome** Balovaptan showed minor, insignificant improvements in RMET performance, and cumulative evaluation of ASD with the CGI-I (mean ±SD = 3± 0.8, barely improved vs placebo: mean ±SD = 4± 0.5, no change)	Although the positive changes seen in RMET in this study were not remarkably significant, they may point to elevating social interaction. The results of this pilot investigation suggest that persons with high-functioning ASD who are treated with the antagonist balovaptan, show minor advancements in social communication substitutes like eye tracking, ASR, RMET.
J. Parker	Phase 2 clinical trial;,	N=30 children	6 to 12.9 years		Intranasal	6 to 9.5yrs-maximum daily target	Under AVP treatment condition,	**Repetitive Behaviors Scale**–Revised (RBS-R; ηp	These preliminary results show AVP

et al. 2019	randomized, placebo-controlled, parallel design	with ASD				dose of 24IU AVP 9.6 to 12.9yrs-maximum daily target dose of 32IU for 4 weeks	subjects **showed substantial improvement** in the **Social Responsiveness Scale** 2nd Edition total score, SRS-2; P = 0.0052; Cohen's d = 1.40 [level of improvement was positively correlated with greater initial blood concentrations of AVP]	2 = 7.8%; equivalent Cohen's d = 0.58); no significant reduction of repetitive behavior by AVP in contrast to placebo but there was noticeable decrease in total repetitive behaviors among AVP group having highest blood AVP levels before treatment (F1,19 = 18.57; P = 0.0004) **CGI-I scale** indicated higher clinician-rated social communication improvement in AVP group vs placebo (P = 0.0145; equivalent Cohen's d = 1.16)	given intranasally could be a promising medicine for amelioration of core social dysfunctions in children with autism, as treatment with AVP for 4 weeks improved social abilities. AVP treatment improved basic social skills regardless of the amount of AVP in the blood before treatment. However, only people who had raised levels of blood AVP before treatment showed improvements in intricate social functioning and a decrease in repeated habits.
Bologn ani et al. 2019	randomized, double-blind, placebo-	N= 223 partcipan ts meeting	18-45 years of age	IQ range: 95.5 to 98.5	Orally	Stage 1: Participants were randomized	At 12-week**, No substantial variations** in change from	**Vineland-II Adaptive Behavior composite score**- improvements rising	Daily balovaptan did not significantly modify the SRS-2 score from baseline at

	controlled, parallel design phase 2 trial (VANILLA trial)	criteria for ASD				at 2:1 to AVP antagonist balovaptan 1.5 mg, 4mg and 10 mg daily or placebo in stage 1, stage 2 and stage 3 respectively.	initial measurement in SRS-2 T scores under balovaptan treatment condition contrast to placebo across all evaluated doses: estimated treatment difference (Δ) and effect size (ES) versus placebo, in case of (1.5-mg dose Δ = 0.15, ES = 0.02, P = 0.96); (4-mg dose Δ = 0.56, ES = 0.07, P = 0.74); and for (10-mg dose Δ = −2.93, ES = −0.31, P = 0.25)	with dosage in group given balovaptan.vs placebo. Estimated treatment difference (Δ) and ES versus placebo with P values were as follows: 1.5 mg dose Δ = 1.96, ES = 0.24, P = 0.41; for 4 mg dose Δ = 3.95, ES = 0.59, P = 0.005; and 10mg dose Δ = 4.87, ES = 0.49, P = 0.074 **Vineland-II Adaptive Behavior socialization standard score**: For 1.5 mg dose Δ = 0.48, ES = 0.04, P = 0.897; 4mg dose Δ = 2.70, ES = 0.31, P = 0.135; 10mg dose Δ = 5.97, ES = 0.46, P = 0.093 [As per Vineland-II separate domain scores, higher standard scores in the sociability and	12 weeks. But the 4- and 10-mg balovaptan dosages improved the Vineland-II composite score clinically and dose-dependently driven by Vineland-II sociability and communication score compared to placebo. This shows that blocking vasopressin receptor Ia could progress prosocial behavior in ASD adult subjects and supports vasopressin's significance in human social interaction.

								communication domain was reported with balovaptan as opposed to placebo.	
Hollander et al. 2022	randomized, double-blind, placebo-controlled, parallel-design phase 2 trial	N= 167 Balovaptan 10mg = 86 Pl group = 81	children and adolescents aged 5 to 17 years	n IQ of 70 or greater	orally	Either 4-mg or 10-mg adult-equivalent AVP antagonist-balovaptan or placebo daily was given at random	**Vineland-II 2DC (two-domain composite; socialization and communication domains**) difference in LSM (adjusted least-squares mean), −0.16; and confidence interval 90% CI, −2.56 to 2.23; P = .91 at week 24 [no noticeable change between balovaptan and placebo from baseline score]	Vineland-II 2DC score: balovaptan: LSM, 1.88; SE 0.97 vs placebo: LSM, 1.87; SE, 1.00; difference in adjusted LSM, 0.01; 90% CI, −1.99 to 2.01; P = .99) no significant variation from baseline was reported between balovaptan and placebo treatment groups in any of the Vineland II domain or other secondary endpoint	Among children and adolescents with ASD, balovaptan failed to enhance social skills or communicative abilities in this trial. Primary end measures along with secondary in the balovaptan group did not show statistically significant improvement from baseline, suggesting that balovaptan was ineffective in this pediatric and adolescent population.

Abb: Clinical Global Impression–Improvement (CGI-I), Vineland-II Two-Domain Composite (2DC) and Vineland-II Adaptive Behavior Composite (ABC); Reading the Mind in the Eyes Test (RMET)

SRS-2: decreasing score = improvement; Vineland-II: increasing score = improvement; ABC: decreasing score = improvement; RBS-R: decreasing score = improvement; CGI-I: decreasing score = improvement;

Chapter 5 Risk of Bias

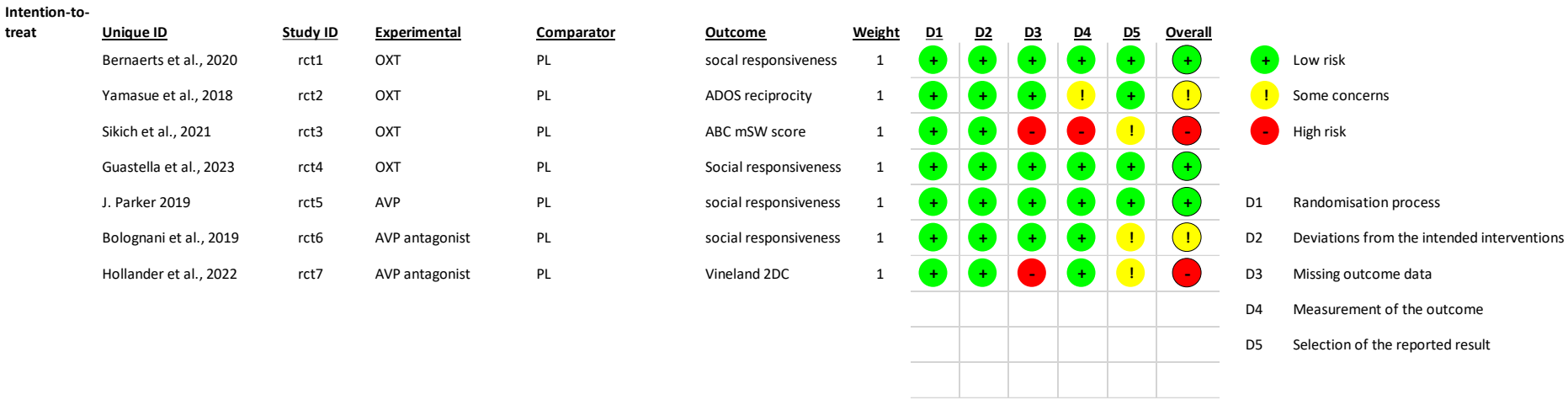


Figure 5: Risk of Bias figure for Randomized, Parallel design studies

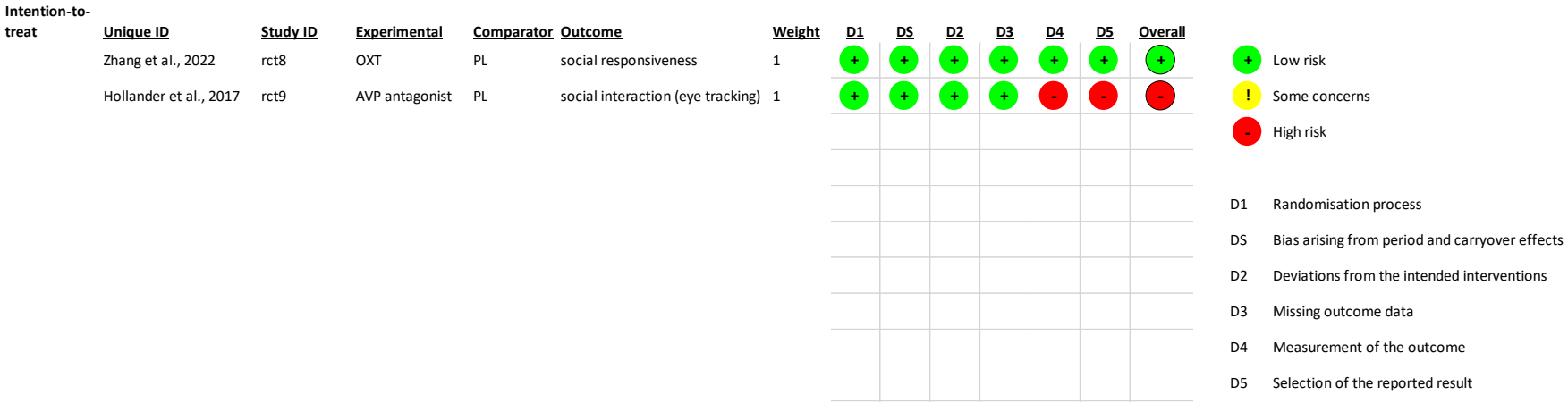


Figure 6: Risk of Bias figure for Randomized, Crossover design studies

Chapter 6 Discussion

The findings obtained from our systematic review demonstrated mixed efficacy outcomes in terms of oxytocin administration on alleviating primary symptoms of ASD, with 3 studies reporting no significant improvement (Yamasue et al., 2018; Bernaerts et al., 2020; Sikich et al., 2021) on social responsiveness assessed as the primary outcome measure, and among the remaining two studies, one of the trials pointed out a significant improvement (Le et al., 2022) of social symptoms in younger cohort, while the other one revealed (Guastella et al., 2022), no significant overall benefit of oxytocin, however it suggested, younger children compared to older ones may have greater chances of exhibiting improvements in the domain of social cognition. In terms of the effect of oxytocin on repetitive behavior, only 2 RCTs showed moderate to large size improvement (Yamasue et al., 2018 & Bernaerts et al., 2020) in the OT group and the remaining 3 reported no findings.

To begin with, Yamasue et al. (2018) in his large-scale 6 weeks single-dose intranasal oxytocin trial and Bernaerts et al. (2020) trial investigating the long-term behavioral impact of multiple dose oxytocin, both reported no significant between group difference (effect size 0.08; 95% CI, 0.46 to 0.31; P =.69) (Yamasue et al., 2018), that is, no specific advantage of oxytocin over the placebo on their common primary outcome measures assessing the social responsiveness in subjects with ASD. To assess these primary and secondary endpoints of core autism symptoms, self-report and informant rated questionnaires were used. These findings align with previous long-term oxytocin trial which also demonstrated no superior effect of oxytocin when assessed based on self-reports (Watanabe et al., 2015; Guastella et al., 2014), although few trials involving young children with autism have shown notable improvements in caregiver-rated social domain symptoms (Yatawara et al., 2015; Hollander et al., 2003). The lack of treatment specific effect observed might be due to the informants greater frequency and

duration of interactions with children than adults, they were more likely to notice changes in children's social functioning than with adults. This may result in more subtle improvements among adult subjects, which informants may not notice. In terms of secondary outcome, Yamasue et al. (2018) as well as Bernaerts et al. (2020), demonstrated positive effects of oxytocin in reducing RBS-R scores and ADOS repetitive behavior (2.0 to 1.5; P .0001) compared to placebo (2.0 to 1.8; P =.43; effect size 0.44; 0.05 to 0.83; P =.026) (Yamasue et al., 2018). Additionally, another secondary endpoint, the amount of time people spent looking (eye gaze fixation) at socially associated regions, was also found to be raised by oxytocin (41.2 to 52.3; P =.03) which may be reflective of the hypothesis that oxytocin modulates social functioning by increasing attention towards certain social stimuli.

The precise relationship between repetitive behaviors and challenges in social functioning remains uncertain. However, some research suggests that in certain individuals with Autism Spectrum Disorder (ASD), perceiving the social environment as unwelcoming or even threatening may lead to a heightened 'need for sameness' desire, as a means of maintaining a sense of control over the environment (Rodgers et al., 2012). The two RCTs conducted by Yamsue et al. (2018) & Bernaerts et al. (2020), provide initial evidence suggesting that administering multiple doses of oxytocin may alleviate this heightened desire for sameness and the inclination to engage in repetitive behaviors. Bernaerts et al. (2020) showed improvement in secondary outcome measure based on self-reports, however, studies that relied on informant-based reports of repetitive behavior do not indicate any significant beneficial effects (Guastella et al., 2014). Collectively, the mixed findings imply that self-reports, in contrast to reports from informants, might show more sensitivity in detecting subtle alterations in repetitive behaviors that are personally experienced by the individuals. The findings of these trials (Bernaerts et al., 2020 & Yamasue et al., 2018) are incongruent with those of prior trials that have shown enhancements in social responsiveness, although they suggest oxytocin's possibility to

improve repetitive behavior to some extent. The limitations common in these two RCTs include the possibility for subjective bias because they relied heavily on self-report questionnaires, and the observed significant placebo effect may be attributable to their parallel-design. Because, previous crossover experiments, as opposed to parallel design trials (Dadds et al., 2013; Guastella et al., 2014), have found substantial effects of long term oxytocin treatment on the primary endpoints evaluating social symptoms related to ASD (Yatawara et al., 2015). Another limitation in Yamasue et al. (2018) was the lack of adequate plasma oxytocin level required to induce a significant clinical improvement that could be seen at behavioral level.

In line with the aforementioned trials, Sikich et al. (2021) also yielded results indicating no statistically noteworthy difference between oxytocin and a placebo effect for primary endpoint on the modified Social Withdrawal scale of the Aberrant Behavior Checklist (ABC-mSW) assessing social interaction, as well as reported absence of in group difference in secondary outcome SRS-2 (Social responsiveness scale-2-social motivation subscale) T-score following exposure to a flexible-dose intranasal oxytocin intervention (8 to 80IU/day) for 24 weeks in 3-17 years children and adolescents. Based on a prior study analysis [116] that showed substantial improvement of intranasal oxytocin on the social responsiveness scale after including initial plasma level which is at basline, this trial also utilized baseline plasma oxytocin level however, no replicable positive effect of intranasal oxytocin was observed in ABC-mSW or SRS-2 total score. This study's limitation was using the unvalidated ABC-mSW as the major outcome measure and an adjustable dosing technique. Since a minimum ABC-mSW score wasn't required for inclusion, improvements in children with low baseline scores may go unreported.

Le et al. (2022) in his 6 weeks crossover trial involving 3-8 years children accompanied by a time of positive social engagement and Guastella et al. (2022) in a 3-week placebo lead in phase design reported statistically significant benefits for intranasal oxytocin compared to

placebo in primary outcome measures (total ADOS-2 and SRS-2 scores, *ps* < 0.001) (Le et al., 2022) and a notable correlation with age (p = 0.028) that indicates an observed treatment effect specifically among younger children between 3-5 years (Guastella et al., 2022) respectively. Also, considerable advantage of oxytocin over placebo was shown for secondary outcome measures-behavioral adaptation and repetitive behavior (Le et al., 2022). Two novel aspects of the study by Le et al. (2022), were the reduction in OXT intranasal dosing frequency to every other day and the incorporation of engaging/playing with children by caregivers under OXT treatment condition. Although, this trial's weakness was the lack of strictly regulated or structured duration of positive social contact amidst caregivers and children. Compared to the improvements seen in this trial (Le et al., 2022) with a new, less frequent intranasal oxytocin dose schedule, other treatment approaches may have led to mixed outcomes in other clinical trials by only focusing on increasing basal OXT levels through more frequent or higher dosages, without incorporating positive social interactions. Guastella et al. (2022) revealed in younger children, moderate development was found in the placebo lead-in phase and remained throughout oxytocin administration, but declined after termination. However, the placebo group showed a small improvement during the initial placebo phase, which was not sustained throughout the next phase, supporting its washout. The enrollment of people who were already on other psychiatric drugs which were stabilized prior to drug randomization and the caregiver or clinician rated bias on the outcome measures were based on reports from a caregiver and a clinician are some drawbacks in this RCT.

The vasopressin system is a possible therapeutic target for autism spectrum disorder (ASD) due to its role in social cognition and social signaling deficiencies which are associated with the core symptoms of autism. Among a handful of RCTs investigating efficacy of vasopressin as a pharmacotherapy for ASD, we reviewed 4 randomized placebo-controlled trials in our systematic review. In one of the RCT reviewed here (Umbricht et al., 2017), the result from

the composite score for eye-tracking effects revealed a reduction in aberrant eye-gaze patterns but it did not achieve statistical significance (ES =0.2, p=0.29) and also reported the positive trends seen in RMET (measures individual's capacity of recognizing socially relevant information during interaction) which may point to progress in social interaction after receiving 20 mg RG7713, an arginine vasopressin receptor 1A . In the phase 2 VANILLA trial of 12 weeks (Bolognani et al., 2019), a notable and consistent enhancement in the scores of the Social Responsiveness Scale (SRS-2), was seen across all participant groups, however, there was no major change between groups. Compared to placebo, the 4-mg dose of balovaptan improved the score on the daily living skills domain of Vineland II scale, whereas the 1.5-mg and 10-mg doses of Balovaptan (selective vasopressin V1a receptor antagonist) did not. Although this trial could not succeed to meet its primary goal of showing that balovaptan treatment was more effective than placebo on social responsiveness outcome measure, the Vineland-II Adaptive Behavior Scales aggregate data did show that balovaptan treatment was effective. The previous findings on intranasal vasopressin administration leading to increased threat perception among healthy subjects (Thompson et al., 2004), increased response to socially threatening stimuli (Zink et al., 2010) & impaired emotion recognition in adults (Uzefovsky et al., 2012), combined with the results of the two trials, provide evidence to the idea that antagonizing vasopressin receptors can have a prosocial effect by mitigating aggressive tendencies and decreasing the feeling of threat and this potential effect could be useful in the alleviation of symptoms associated with the social domain in adults with ASD. Hollander et al. (2022) conducted the most recent placebo-controlled phase 2 trial to determine whether the administration of 10-mg adult-equivalent balovaptan for 24-week lead to improvements in sociability and communication challenges among children and adolescents diagnosed with ASD. The primary end point Vineland-II 2DC score, did not significantly improve with balovaptan as opposed to placebo in children with ASD. The same was demonstrated for secondary and exploratory

endpoints; balovaptan failed to surpass placebo in any of them which indicates that blocking V1a receptors does not enhance children with ASD's social skills. The limitations noted in these trials include a very brief evaluation period, small sample size, possibility of selection bias, caregiver rated expectation bias on SRS-2 and the Vineland Adaptive Behavior Scales.

Lastly, the study of intranasal AVP treatment (Parker et al., 2019) employing a cautious approach to dose escalation gradually for 4 weeks in a cohort of 30 children with autism revealed that individuals who exhibited the highest levels of AVP in their blood prior to treatment saw more advancements in complex social behaviors in SRS-2 measure and a slight decrease in repetitive behavior. Given the ongoing debate surrounding the notion that lesser blood AVP concentrations could be a biomarker for distinguishing ASD individuals, it is plausible to consider that subjects with lower initial endogenous AVP concentrations may have received a suboptimal dosage or duration of treatment, potentially resulting in a diminished response to AVP administration compared to those with elevated endogenous AVP blood levels. The current pilot investigation ascertained that in comparison to a placebo, intranasal AVP resulted in improved social communication abilities, decreased sensations of anxiety, and reduced repetitive behaviors in children and the initial blood AVP levels may be a valuable indicator for defining dose guidelines, as those with the highest concentrations prior to treatment showed the greatest improvement on nearly all behavioral measures while on AVP. Outcome measures relying on parents' reports are likely to be influenced by subjective bias, and the use of subject’s concurrent medications throughout the intervention period are the drawbacks of this study since it wasn't known if these medications had an interaction with intranasal AVP.

Chapter 7 Conclusion

In our systematic review examining the influence of oxytocin and vasopressin on social cognition and repetitive behaviors, all of the studies predominantly consisted of males across a varied range of ages and cognitive functioning who were diagnosed with autism. As such, it is not feasible to analyze the potential moderating effects of these individual characteristics on the impact of oxytocin and vasopressin on core symptoms, hence, no firm conclusion can be drawn from these studies. The functional magnetic resonance imaging (fMRI) investigations discussed in the proposed mechanism of action the neuropeptides, consistently indicated a positive correlation between oxytocin levels and increased neural activity in specific zones related with socio-emotional processing, including the amygdala and prefrontal areas. Our systematic review on social cognition and repetitive behavior yielded results that appeared contradicting with those of fMRI studies; this discrepancy may suggest that oxytocin's subtle effects after administration can be observed at the functional level in certain regions of the brain, but they may not yet reflect visible improvements in behavioral traits. RCTs of intranasal oxytocin intervention in this review indicates that younger children could be more prone to improvements in social responsiveness compared to adults and positive effects of long term multiple dose oxytocin post treatment supports the hypothesis that prolonged administration may cause long-term adjustments in the regional brain circuits involved in social cognition, more likely in an experience dependent way. In terms of vasopressin, some of the reasoning behind giving an AVPR1A antagonist to people with ASD comes from early studies showing AVP makes healthy male rats more anxious & aggressive and healthy adult male volunteers more aware of threats. Hence, the current challenge lies in reconciling these apparently contradictory pharmacological strategies for the management of ASD. Nonetheless, Autism Spectrum Disorder (ASD) exhibits clinical diversity, suggesting that different therapeutic approaches targeting AVP (Arginine Vasopressin) may be effective in specific subgroups of

ASD. So, the vasopressin agonist employed in the aforementioned study and the AVPR1A antagonist investigated in the VANILLA trial could potentially demonstrate efficacy in separate ASD subgroups.

Chapter 8 Future Prospective

Extensive research is necessary due to the existence of significant knowledge gaps within this particular domain of ASD treatment using neuropeptides oxytocin and vasopressin (agonists or antagonists). Many studies, for instance, featured a limited sample size with predominantly male subjects. Large placebo effect observed in some studies limit the statistical power, thereby impeding the ability to identify meaningful clinical improvements. The majority of studies looked at the effects of a single dose of oxytocin, whereas, few investigations looked at the effects of prolonged dosing periods. There has been no comprehensive research into the optimal dosage or frequency of administration of oxytocin and vasopressin. In addition, the rating scales employed may also lack the necessary sensitivity to accurately determine the small alterations that occur in response to these neuropeptides. Given the unclear pharmacodynamics, further investigation is warranted about the precise mechanism through which oxytocin (OXT) and arginine vasopressin (AVP), as well as their respective receptor agonists and antagonists, traverse the blood-brain barrier subsequent to various modes of administration. Additional study should be conducted to explore the relationship between plasma oxytocin levels and symptomatology through the implementation of larger systematic trials and utilization of methodologies that could effectively influence elevated plasma oxytocin concentration and minimize the impact of placebo effect with a view to predict the capability of oxytocin and arginine vasopressin in alleviating social dysfunction. Besides, it is imperative for future research endeavors to diminish the influence of certain bias and to make coordinated efforts to include female participants in these investigations for more validating outcomes as the response of these neuropeptides may vary depending on the heterogeneity across individuals with autism. Such evidence would strengthen our knowledge of the probable underlying mechanisms in Autism Spectrum Disorder (ASD) and enable more comprehensive conclusions on the efficacy of oxytocin & vasopressin as a treatment addressing core dimensions of ASD.

Regardless of the outcomes of future research, it is improbable that it will serve as an ultimate "cure" for autism hence, researchers should also prioritize examining how oxytocin and vasopressin can be used as an adjunct to psychosocial interventions with an aim to enhance social functioning, independent living skills, as well as to improve overall well being and quality of life of individuals with ASD

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