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RESEARCH ARTICLE .

Social Communication is an Emerging Target for Pharmacotherapy in Autism Spectrum Disorder – A Review of the Literature on Potential Agents

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Abstract

Objective: To review the published literature and registered clinical trials on pharmacologic interventions targeting social communication impairment in Autism Spectrum Disorder (ASD). **Methods:** A comprehensive search of several databases (PubMed, MEDLINE, PsycINFO, Clinical trials.gov) was conducted to identify pharmacologic agents that have been, or will be, tested as treatments for social communication impairment in individuals with ASD. Evidence from basic science research supporting rational drug discovery is surveyed. **Results:** Data from animal models and early clinical trials suggest that novel and existing compounds, including N-methyl-D-aspartate (NMDA) modulators, **γ**-aminobutyric acid (GABA) agonists, metabotropic glutamate receptor (mGluR) antagonists and neuropeptides, may enhance social communication/function in ASD. Results from numerous Phase 2 and Phase 3 clinical trials are expected in the near future. **Conclusions:** Recent evidence suggests that social communication may be an appropriate target for pharmacologic manipulation. It is hoped that, in combination with behavioural interventions, novel therapeutics may soon be clinically available to help improve social outcomes.

Key Words: *autistic disorder, psychopharmacology, oxytocin, social behaviour*

Résumé

Objectif: Effectuer une revue de la littérature publiée et des essais cliniques enregistrés sur les interventions pharmacologiques ciblant la déficience de la communication sociale dans les troubles du spectre de l'autisme (TSA). **Méthodes:** Une recherche exhaustive de plusieurs bases de données (PubMed, MEDLINE, PsycINFO, Clinical trials.gov) a été menée afin d'identifier les agents pharmacologiques qui ont été ou seront mis à l'essai comme traitements de la déficience de la communication sociale chez les personnes souffrant de TSA. Les données probantes de la recherche scientifique fondamentale soutenant la découverte rationnelle d'un médicament sont examinées. **Résultats:** Les données de modèles animaux et des premiers essais cliniques suggèrent que des composés nouveaux et existants, notamment les modulateurs de N-méthyl-D-aspartate (NMDA), les agonistes de l'acide gamma-aminobutyrique (GABA), les antagonistes du récepteur métabotropique du glutamate (mGluR) et les neuropeptides, peuvent améliorer la communication/fonction sociale dans le TSA. Les résultats de nombreuses phases 2 et 3 d'essais cliniques sont attendus bientôt. **Conclusions:** Les données probantes récentes suggèrent que la communication sociale peut être une cible appropriée pour la manipulation pharmacologique. Il est à espérer qu'en combinaison avec les interventions comportementales, de nouvelles thérapies puissent bientôt être cliniquement disponibles pour contribuer à améliorer les résultats sociaux.

Mots clés: *trouble autiste, psychopharmacologie, oxytocine, comportement social*

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Introduction

Autism is a neurodevelopmental disorder characterized by deficits in social communication and restricted or repetitive interests and behaviours. Viewed on a spectrum of severity, 'autism spectrum disorder' (ASD) encapsulates diverse clinical presentations, including patients with mild functional deficits to those requiring very substantial support given comorbid intellectual and/or language impairment (Abrahams & Geschwind, 2008; American Psychiatric Association, 2013). The current prevalence of ASD is estimated at one in every 88 individuals (CDC, 2012). Patients with ASD are predisposed to emotional and behavioural problems; increasingly psychotropic medications are being prescribed to address associated symptoms (Tsiouris, Kim, Brown, Pettinger, & Cohen, 2012). Many traditional psychiatric medications are effective, but do not target the core features of the ASD phenotype (Chadman, Guariglia, & Yoo, 2012). Accordingly, behavioural/psychosocial interventions that address social communication are currently the mainstay of treatment (Bishop-Fitzpatrick, Minshew, & Eack, 2012).

Over the past several decades, autism has become an increasing focus of scientific scrutiny. Numerous candidate genes have been identified, which suggest a role for multiple gene interactions, and/or gene by environment interactions (Kumar & Christian, 2009). Chromosomal microarray testing is receiving widespread acceptance as a first-tier diagnostic investigation (Miller et al., 2010). Approximately 10-15% of cases can now be attributed to a known genetic variant or syndrome (Kumar & Christian, 2009). For example, fragile X syndrome (FXS) is a genetic condition that is comorbid with ASD in 20-30% of cases, and accounts for 1-5% of autism (Bailey, Raspa, Olmsted, & Holiday, 2008; Kaufmann et al., 2004). Recent investigations in murine models of specific genetic subtypes of ASD (FXS and Rett syndrome) have shown that cellular and behavioural pathology can be reversed with exogenous compounds even after established symptom onset (Guy, Gan, Selfridge, Cobb, & Bird, 2007; Henderson et al., 2012). These exciting discoveries provide hope for the role of novel therapeutics in this disorder.

Despite known genetic risk factors, less is certain with respect to an overall mechanism of disease. Evidence of an imbalance between excitatory and inhibitory (E/I) signals leading to an abnormal signal-to-noise ratio (Rubenstein & Merzenich, 2003) provides a rational for targeting the glutamate and gamma-aminobutyric acid (GABA) systems. Taken together with hormonal theories of social affiliation (Modi & Young, 2012), these models present potential targets for drug development.

This review is intended to summarize emerging pharmacologic interventions targeting social communication impairment in ASD for a clinical audience. We will review the neurobiology of proposed drug targets. Preliminary human data and upcoming clinical trials will also be surveyed. Current trends in the literature suggest that medications may soon be available targeting the core features of ASD, including social communication impairment. This represents a paradigm shift for treatment providers, provides hope for patients and families, and may have implications for other neuropsychiatric conditions.

Defining and measuring social communication impairment in ASD

In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), ASD is defined by the following:

a) persistent deficits in social communication;

b) restricted or repetitive interests and behaviors; and,

c) symptom onset early in the developmental period (American Psychiatric Association, 2013).

Social communication impairment includes:

1) deficits in social-emotional reciprocity (e.g. in conversation, sharing of interests);

2) deficits in nonverbal communication behavior (e.g. eye contact, facial expression, body language, and gestures); and,

3) deficits in developing and maintaining relationships (e.g. making friends, interest in peers, imaginative play).

This marks a shift from DSM-IV (text revision), where social and communication deficits had been defined under separate symptoms categories, and verbal language delay had been included as a component of the condition (American Psychiatric Association, 2000). In addition, subtypes of ASD (including Asperger's syndrome and Pervasive Developmental Disorder not otherwise specified) are no longer defined in DSM-5, although remain pertinent upon review of the literature prior to 2013.

A diagnosis of ASD is achieved via consensus between experts through clinical interview and interactive assessment. Standardized tools such as the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) and the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) have helped to structure and validate the parent interview and clinical assessment, respectively.

For clinical trials, there is significant variability in the field with respect to instrument selection for outcome measurement; on review, an average of 11.4 different research tools were employed per study (Bolte & Diehl, 2013). In addition, many studies use investigator-designed or adapted assessments. The reliability and validity of these instruments continues to be investigated (Norris & Lecavalier, 2010).

With respect to social function, the Social Responsiveness Scale (SRS) (Constantino et al., 2003) and the Aberrant

Behavior Checklist (ABC) (Aman, Singh, Stewart, & Field, 1985) are caregiver-completed questionnaires frequently employed in medication trials measuring social communication in ASD. The SRS contains 68 items, and provides an overall quantitative score, as well as treatment specific subscores pertaining to receptive, cognitive, expressive, and motivational aspects of social behaviour. While this measure was developed specifically to evaluate social deficits in ASD, it has been shown to be influenced by age, IQ and presence of psychiatric comorbidities (Hus, Bishop, Gotham, Huerta, & Lord, 2013). Therefore, results from trials that employ this metric must be interpreted in light of these possible confounding factors.

The ABC, on the other hand, was developed to track behavioural symptoms in individuals with developmental delay (Aman et al., 1985). It contains 58 items completed by a caregiver, including 16 items pertaining to social withdrawal (ABC-SW). Although its psychometrics are very good and it has proven assay sensitive, interpretation of this measure is limited by the scope of the contained questions which target primarily symptoms of social engagement/withdrawal, while providing little information on other DSM-defined aspects of social communication. Despite these limitations, a recent psychometric analysis comparing the ABC-SW subscale to other outcome measures of social communication (Vineland Adaptive Behavior Scale and the Child Symptom Inventory) found moderate correlations across scales, and concluded the ABC-SW to be a sensitive endpoint for treatment response in medication trials (Scahill et al., 2013). An alternative approach was employed by Sansone et al. (2012), using exploratory factor analysis of ABC items in a population of patients with FXS. They described a potentially more sensitive and specific combination of ABC items with respect to social function in a population of patients with FXS, termed the ABC-social avoidance subscale (ABC-SA) (Sansone et al., 2012), which has been used in recent drug trials for these patients (Berry-Kravis et al., 2012). This scale is limited however, by the small number of included items.

There are several other instruments designed to assess or track behaviour in children, which incorporate aspects of social communication and have been applied to populations with ASD. The Behavior Assessment System for Children (BASC-2), for example, includes parent report scales with items pertaining to social withdrawal, social skills and functional communication. These scales were highly sensitive in differentiating children with high functioning autism from typically developing children, although they have not been employed extensively in medication trials to date (Volker et al., 2010). Similarly, the Social Skills Improvement System (SSIS) contains parent, teacher and student surveys and has been used to track social skills acquisition (Gresham, Elliott, & Kettler, 2010). The Vineland Adaptive Behavior Scale helps to quantify an individual's personal and social skills across the lifespan and across conditions, and is validated in children with ASD (Freeman, Ritvo, Yokota, Childs, & Pollard, 1988). This scale covers three domains (communication, socialization and daily living skills), and has been used in clinical trials in autism to track responses to pharmacotherapy (Klaiman, Huffman, Masaki, & Elliott, 2013). Lastly, the Childhood Autism Rating Scale (CARS) has utility both in diagnosis (Van Bourgondien, Marcus, & Schopler, 1992), and in monitoring response to therapeutics (Lemonnier & Ben-Ari, 2010). Each of these scales has items pertaining to social functioning, but a comparison of the reliability and validity of such measures for use in pharmacotherapy trials is beyond the scope of this review.

There have also been attempts to measure aspects of social cognition/perception in individuals with ASD. The Diagnostic Analysis of Non-verbal Accuracy (DANVA) and the Reading the Mind in the Eyes Test (RMET) are examples of such measures. The DANVA-2 is used to assess a subject's ability to recognize emotions (happiness, sadness, anger and fear) and the intensity of these emotions, in facial expression, language and posture (Nowicki & Duke, 1994). Likewise, the RMET is used to assess the participant's ability to recognize emotional states from eye expressions (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001).

While novel ways of measuring social communication/cognition continue to be studied and replicated, most trials, including those reviewed here, incorporate a combination of standardized psychometric measures completed by caregivers (e.g. SRS, ABC) and by research subjects (e.g. DANVA, RMET). The development, selection and interpretation of appropriate and rigorous tools are essential to infer accurate and meaningful improvement in social communication in response to treatment strategies.

Neurobiological models behind rational drug targets involving the glutamate and GABA systems

Excitatory and inhibitory signaling pathways are selectively strengthened (termed long-term potentiation, or LTP) or weakened (termed long-term depression, or LTD) throughout development. An imbalance between excitatory and inhibitory signals (E/I) leading to an abnormal signal to noise ratio has been suggested as an underlying mechanism in ASD (Rubenstein & Merzenich, 2003).

With respect to inhibitory signaling, GABA exerts an inhibitory effect via $GABA_A$ and $GABA_B$ receptor subtypes. A GABA related mechanism in ASD is supported by mouse models of FXS, where decreased GABAergic inhibition results in amygdala hyperactivity, repetitive behaviours, social anxiety and social withdrawal (Coghlan et al., 2012; Olmos-Serrano et al., 2010). Similarly, in humans, individuals with ASD have been shown to have lower levels of GABA in serum platelets, and lower GABA receptor expression in the brain (Fatemi, Reutiman, Folsom, & Thuras, 2009; Rolf, Haarmann, Grotemeyer, & Kehrer, 1993).

Patients with ASD may be more likely to have genetic changes involving GABA receptor subunits when compared to the general population (Collins et al., 2006). For example, recurrent microduplications at chromosome 15q11-q13 (OMIM #608636), encompassing a GABA receptor gene cluster, are well-established risk factors for ASD (Bassett, 2011; Hogart, Wu, LaSalle, & Schanen, 2010).

Excitatory signals involving glutamate act through fast acting ionotropic receptors (AMPA, Kainate, and NMDA) and G-protein linked metabotropic receptors (metabatropic glutamate receptors, mGluRs). mGLuRs in particular have been found to play an important role in mediating LTP and LTD by triggering receptor trafficking at the synapse (Neyman & Manahan-Vaughan, 2008; Xiao, Gustafsson, & Niu, 2006). This hypothesis has emerged from our growing understanding of the molecular etiopathogenesis of FXS (Bear, Huber, & Warren, 2004). The underlying genetic etiology in FXS is a triplet repeat expansion on the X chromosome, which interrupts the FMR1 gene resulting in impaired formation of the Fragile X mental retardation protein (FMRP). Data indicate that FMRP is an RNA-binding translational regulator, which serves to dampen protein synthesis triggered by mGluR1 or mGluR5 stimulation. Loss of FMRP in FXS results in exaggerated AMPA receptor trafficking, increased LTD, and dysfunctional synaptic plasticity, in keeping with a phenotype of developmental delay and motor impairment (Muddashetty, Kelic, Gross, Xu, & Bassell, 2007; Nakamoto et al., 2007).

In summary, molecules that have the ability to promote GABA activity or modulate glutamate receptors have the potential to treat ASD. These agents are reviewed below with respect to social communication.

mGluR antagonists and GABA agonists: arbaclofen, acamprosate, and novel compounds

Arbaclofen (previously known as STX209), is the R-enantiomer of baclofen, a clinically approved treatment for muscle spasticity. Arbaclofen is a $GABA_B$ agonist. Research in mice suggests that arbaclofen may also indirectly act as a negative modulator of mGluR (Henderson et al., 2012). Treatment of FMR1-/- knockout mice with arbaclofen reversed to some extent the underlying neuropathology, as evidenced by: (a) a normalized rate of protein synthesis in the mouse hippocampus; (b) a reduced rate of AMPA internalization in vitro; and, (c) a restoration of altered dendritic spine densities (Henderson et al., 2012). In an NMDA receptor knockout mouse model of ASD, treatment with arbaclofen normalized antisocial and repetitive behaviour, and improved E/I balance (Gandal et al., 2012). A recent randomized controlled trial of arbaclofen in 63 patients with FXS yielded no significant effects in the primary outcome measure of irritability. However, post hoc analyses demonstrated significant improvements in the ABC-SA, particularly for the subset of patients with more severe social communication impairment (Berry-Kravis et al., 2012). Currently, several trials are underway to study the potential for arbaclofen to enhance social communication in patients with ASD and FXS (see Table 1).

Acamprosate is a medication approved for treatment of alcohol dependence. Its exact mechanism of action remains unclear, although it has been shown to have a moderating effect on NMDA receptor activity, and may be a $GABA_A$ agonist (Mann, Kiefer, Spanagel, & Littleton, 2008; Mayer et al., 2002). Acamprosate is also proposed to act as an mGluR antagonist, specifically targeting the mGluR5 receptor subtype (Harris et al., 2002). A pilot, open-label study of acamprosate in six youth with ASD found significant improvements in social withdrawal and social responsiveness, with five out of six participants showing a positive change (Erickson et al., 2011). Likewise, recent data from an open label ten-week trial of acamprosate in 12 youth with FXS demonstrated improvement in Clinical Global Impression (CGI) scores for 75% of participants, with significant changes in the ABC-SA, ABC-SW and SRS (Erickson et al., 2013). There was also a measured reduction in hyperactivity. A placebo controlled trial of acamprosate in youth with ASD began recruiting participants in 2013, with CGI and SRS scores as primary outcome measures (NCT01813318).

Other mGluR antagonists (AFQ056, STX107 and RO4917523) are currently in the early phases of development as novel therapeutics for the treatment of FXS. AFQ056 restored the FMR1 knockout mouse's ability to inhibit a startle response, improved dendritic spine morphology and improved social behaviour (Gantois et al., 2013; Levenga et al., 2011; Pop et al., 2012). When tested in humans with FXS, the majority of 30 patients showed no clinical response to AFQ056. However, a subgroup of patients who had *complete* FMR1 mRNA suppression did indeed show statistically significant changes on the SRS, but not on the ABC-SW (Jacquemont et al., 2011). Phase 1-3 clinical trials of AFQ056 in FSX are currently under way. To date, AFQ056 has not been investigated in animal models or humans with ASD outside of FXS. Trials evaluating other mGluR5 inhibitors (STX107 and RO4917523) for safety and efficacy in FXS are currently under investigation, although no human or animal data are yet available, and application to other forms of ASD has yet to be investigated.

Agents targeting NMDA glutamate neuroreceptors: memantine and D-cycloserine

Congruent with imbalanced E/I signaling ratios, agents targeting NMDA neuroreceptors have also shown some treatment efficacy in addressing core features and associated symptoms in ASD. In an open label trial of memantine,

Table 1. Agents targeting social impairment in ASD (and FXS)

Molecule	Mechanism of action	Published human data measuring social communication (change in social communication)	Upcoming trials assessing social communication in ASD (Clinical Trial.gov ID)
Arbaclofen	$GABA_B$ agonist	† (Berry-Kravis et al., 2012) (+ in FXS)	NCT01288716
			NCT01706523
			NCT00846547
			NCT01282268
			NCT01325220 (in FXS)
			NCT01555333 (in FXS)
Acamprosate	NMDA moderator mGluR antagonist	‡ (Erickson et al., 2011) (+)	NCT01813318
		‡ (Erickson et al., 2013) (+)	NCT01911455 (in FXS)
Bumetanide	Enhanced GABA inhibition	‡ (Lemonnier & Ben-Ari, 2010) (+)	-
		† (Lemonnier et al., 2012) (+/–)	
AFQ056	mGluR antagonist	(Jacquemont et al., 2011) (+ in FXS subgroup)	NCT01348087 (in FXS)
			NCT01433354 (in FXS)
			NCT01253629 (in FXS)
			NCT01357239 (in FXS)
			NCT00718341 (in FXS)
STX107	mGluR antagonist	-	NCT00965432 (in FXS)
			NCT01325740 (in FXS)
RO4917523	mGluR antagonist	-	NCT01517698 (in FXS)
			NCT01015430 (in FXS)
			NCT01750957 (in FXS)
Memantine	NMDA antagonist	‡ (Owley et al., 2006) (+)	NCT01372449
		‡ (Chez et al., 2007) (+)	NCT01592773
		‡ (Erickson et al., 2007) (+)	NCT00872898
		Niederhofer, 2007 (– for social)	NCT01333865
		† (Ghaleiha et al., 2012) (– for social)	NCT01592747
			NCT01078844
D-cycloserine	NMDA partial agonist	(Posey et al., 2004) (+)	NCT00198120
		(Posey et al., 2008) (–) (unpublished data)	NCT01086475
			NCT00198107
Oxytocin	Acts on Oxytocin receptor	† (Hollander et al., 2003) (+)	NCT01417026
		† (Hollander et al., 2007) (+)	NCT01337687
		(Andari et al., 2010) (+)	NCT00490802
		† (Guastella et al., 2010) (+)	NCT01256060
		† (Anagnostou et al., 2012) (+)	NCT01624194
		‡ (Tachibana et al., 2013) (+/–)	NCT01308749
		† (Hall, et al. 2012) (+in FXS)	NCT01417026
		† (Dadds et al., 2013) (–)	NCT01914939
			NCT01944046
			NCT01945957
			NCT01931033
			NCT01788072
			NCT01908205
RG7314	Vasopressin receptor modulator	-	NCT01793441

† Randomized controlled trial; ‡ Open label trial
+ = positive; – = negative

(an NMDA neuroreceptor antagonist used in the treatment of Alzheimer's disease), Chez et al. found that the majority of children improved on CGI pertaining to language, self-stimulatory and social behaviours (Chez et al., 2007). Likewise, an eight-week open label trial of memantine in 14 youth with Pervasive Developmental Disorder yielded significant improvements in multiple ABC subscales, including ABC-SW, despite a lack of improvement on CGI (Owley et al., 2006). Retrospective analysis of open label use of memantine in 18 children and adolescents with PDD found improvements on CGI pertaining to social withdrawal and inattention (Erickson et al., 2007). When applied as an adjunct to risperidone, memantine improved ABC scores related to hyperactivity, stereotypic behaviour and irritability, but not social withdrawal, when compared to risperidone alone (Ghaleiha et al., 2012). On a cellular level, Wei et al. found that treatment of cerebellar granule cells from FMR1-/- knockout mice with memantine promoted maturation and corrected synapse formation of dendritic spines (Wei et al., 2012). Upcoming human data comparing memantine to placebo for social communication impairment in ASD are anticipated in the near future (see Table 1).

D-cycloserine is an antibiotic approved for the treatment of tuberculosis. It is a partial agonist of the NMDA neuroreceptor and may have a moderating effect on receptor activity. It has been tested as a treatment for negative symptoms in schizophrenia (Buchanan et al., 2007). Additionally, D-cycloserine has shown the potential to address social impairment in animal models of autism. For example, prairie and meadow voles were more likely to select a partner when treated with D-cycloserine (Modi & Young, 2011). Similarly, multiple transgenic mouse models of ASD (including the balb/c mouse, the GluD1-/- knockout mouse, and the Shank2-/- mouse) responded to D-cyloserine treatment with improved social interactions and more frequent social approaches (Deutsch et al., 2012; Won et al., 2012; Yadav et al., 2012). Regarding human trials, Posey et al. compared three doses of D-cycloserine to placebo in a group of ten individuals with ASD (Posey et al., 2004). Statistically significant improvements in CGI as well as ABC-SW were noted in a dose dependent manner. A large-scale follow up study did not confirm a treatment benefit, however (Posey, 2008; personal communication, unpublished data, NCT00198120). Other trials looking at combining D-cycloserine with aripiprazole, or as an adjunct to social skills training, are currently underway (see Table 1).

Hormonal models of social affiliation: oxytocin and vasopressin

The oxytocin and vasopressin systems have generated significant interest as potential targets for pharmacotherapy to increase social communication. Oxytocin is a peptide hormone known for triggering uterine contractions during labour, and initiating milk letdown after birth. Arginine vasopressin (AVP), also known as antidiuretic hormone, is a closely related pituitary peptide involved in maintaining water homeostasis. Both hormones are structurally similar and have some cross reactivity at receptor sites. Recently, they have been found to play a role in social affiliation through imaging, genetic and animal studies (Modi & Young, 2011). In support of a hormonal contribution in ASD, children with autism have lower plasma oxytocin levels than controls (Modahl et al., 1998). Additionally, pharmacologic or genetic alterations in the oxytocin and vasopressin systems are associated with functional changes on functional Magnetic Resonance Imaging (fMRI) in brain regions implicated in autism (Sauer, Montag, Worner, Kirsch, & Reuter, 2012; Yamasue, 2012; Zink & Meyer-Lindenberg, 2012). With respect to genetic data, genes coding for oxytocin, the oxytocin receptor (OXTR), CD38 (an enzyme that regulates oxytocin secretion), as well as the vasopressin receptor (AVPR1A), may be altered in certain cases of ASD (Lerer et al., 2008; Sebat et al., 2007; Wermter et al., 2010; Yang et al., 2010; Yirmiya et al., 2006). Blood and tissue analysis has shown that patients with ASD express lower levels of OXTR in the brain, and less CD38 in peripheral blood cells (Gregory et al., 2009; Lerer et al., 2010).

Animal models of oxytocin and vasopressin disruption have highlighted the importance of these hormones in social behaviour. Knockout mice lacking oxytocin, OXTR and CD38 display decreased vocal communication, increased motor activity, impaired maternal nurturing behaviour and deficits in social recognition (Ferguson, Aldag, Insel, & Young, 2001; Higashida et al., 2010). Likewise, pharmacologic antagonism of AVP, and AVPR1A receptor knockout, yields rodents with impaired social recognition and impaired habituation when meeting unfamiliar peers (Egashira et al., 2007; Tobin et al., 2010). Many social deficits in animal models of ASD can be improved or restored following treatment with exogenous hormone (Ferguson et al., 2000; Jin et al., 2007; Sala et al., 2012). Natural animal models of social interaction also show increased socialization in response to oxytocin administration (Cho, DeVries, Williams, & Carter, 1999; Williams, Carter, & Insel, 1992).

In humans, oxytocin has been shown to facilitate trust and prosocial behaviour in typically developing individuals (Yamasue et al., 2012). To highlight a few interesting studies, Kosfeld et al. showed that in a monetary investment game, treatment with intranasal oxytocin made it more likely for participants to trust other players (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Similarly, Domes et al. found that oxytocin administration increased eye gaze directed at positive and neutral expressions, and decreased eye gaze towards angry expressions (Domes, Steiner, Porges, & Heinrichs, 2012). Guastella et al. demonstrated that treatment with oxytocin made it more likely for an individual to recall a previous social appraisal regarding pictures of facial expression (Guastella, Mitchell, & Mathews, 2008).

Preliminary data suggest that oxytocin can also alter social behavior in ASD. An initial trial by Hollander et al. in 15 individuals with autism revealed that oxytocin infusion decreased the severity and variety of repetitive behaviours compared to placebo (Hollander et al., 2003). A follow-up study by Hollander et al. looked at social processing in ASD in response to oxytocin (Hollander et al., 2007). Oxytocin administration resulted in improved recognition of affect in audio recordings of neutral sentences. This improvement was maintained following the infusion, while placebo recipients reverted to baseline scores. It was hypothesized that oxytocin facilitated social memory formation for individuals where this process is otherwise impaired.

Intranasal oxytocin administration was subsequently trialed as a more convenient method of medication delivery. Andari et al. administered intranasal oxytocin to patients with high functioning autism during a computer simulation of a ball-tossing game (Andari et al., 2010). Typically developing controls were able to distinguish which characters in the game were more likely to reciprocate the ball toss, and adapted their behavior accordingly. Participants with ASD who received placebo did not distinguish between the "good, neutral and bad" characters, while those who received oxytocin behaved like controls by selectively engaging with the "good" character. The same pattern held true regarding feelings of trust and preference towards the simulated players. Subsequent testing regarding facial scanning in this group showed that oxytocin administration increased gaze time directed at the eye area in photographs (Andari et al., 2010). Similarly, in a small study by Hall et al. (2012), eight males with low functioning FXS were treated with intranasal oxytocin and filmed during a standardized social interaction task. Compared to placebo, those who received oxytocin were observed to have an increase in frequency of eye gaze directed towards the experimenter (Hall, Lightbody, McCarthy, Parker, & Reiss, 2012).

Intranasal oxytocin was also able to increase affect recognition in visual stimuli. In a study by Guastella et al. (2010), males with ASD who received intranasal oxytocin were better able to infer emotion states from eye expression during the RMET. There were statistically significant differences compared to placebo regarding easier items, although neither treatment nor placebo group scored highly on difficult items (Guastella et al., 2010).

Pilot randomized controlled trial (RCT) data on 19 adults with ASD found that treatment with intranasal oxytocin for six weeks resulted in increased quality of life scores as well as improved scores on the RMET. CGI scores were rated as 'improved' for 30% of treatment group participants, and 11% of control group participants (Anagnostou et al., 2012). Long-term administration (six months) of intranasal oxytocin was found to be well tolerated by eight adolescent boys with ASD, and was associated with modest improvement on the social communication aspects of the ADOS (Tachibana et al., 2013). On the other hand, Dadds et al. found no difference in social interaction or emotion recognition scores in 38 male youths with ASD treated with parent-child training and intranasal oxytocin vs. placebo. Oxytocin was administered only four times during the five-day intervention, however, compared to other trials of longer duration (Dadds et al., 2013). Response to intranasal oxytocin may vary on a case-by-case basis. This is highlighted by a case report from Japan, in which dramatic improvements in ABC scores across all domains (total score decreased from 69 to seven) resulted from chronic intranasal oxytocin administration in one adolescent with ASD (Kosaka et al., 2012). Based on the above data, several large-scale trials are currently being funded to examine the role of intranasal oxytocin in autism (see Table 1).

There is a large volume of literature investigating the role of AVP with respect to social communication in animals (Albers, 2012). When administered intranasally to typically developing individuals, AVP has been observed to trigger gender specific changes in interpretation of social cues from faces (Thompson, George, Walton, Orr, & Benson, 2006). Early trials to further elucidate the effects of intranasal AVP on typically developing individuals are under way (NCT01327027, NCT01680718). In addition, RG7314 is a small molecule antagonist of AVPR1A that is in the early stages of development, with trials starting up in adult patients with ASD (NCT01793441).

Conclusions

Treatment of social communication deficits in ASD through NMDA neuroreceptor modulators, mGluR antagonists and GABA receptor agonists has shown mixed results in humans. It is plausible that alterations in excitatory and inhibitory signaling may vary in direction, or brain region affected, in different individuals with ASD. Therefore, treatment strategies may require targeting drug therapy to final common pathways.

Our survey of potential new agents reveals that the greatest number of clinical trials have been completed, or are currently under way using oxytocin as a treatment for social communication impairment in ASD, either alone, or paired with a social/behavioral intervention (see Table 1). Clinical data suggest that typically developing individuals as well as those with autism seem to respond to oxytocin administration with improved social cognition and function, although the magnitude of the response may vary on an individual basis. The data with respect to AVP are far more preliminary, however small molecule modulators of the AVPR1A are currently under investigation.

Moving forward, further consensus is required regarding the standardized measurement and meaningful interpretation of social communication scores. As well, further investigation into optimal medication administration protocols is

needed, which may pair pharmacotherapy with social skills or behaviour-based treatments. Translational approaches across genetic subtypes of ASD are necessary to make optimal use of therapeutic agents, and may permit hypothesis generation with respect to mechanism of action and etiopathogenesis.

In summary, social communication impairment is emerging as an independent symptom cluster amenable to pharmacologic intervention in ASD. This represents a paradigm shift in autism research and treatment, where traditionally behaviour-based therapies are considered first line for core symptoms. The potential clinical approval of medications to enhance social communication has broad implications for other neuropsychiatric conditions. Ideally, evidence-based treatment protocols that combine pharmacotherapy and behavioral interventions will be able to improve outcomes and facilitate greater independence for affected individuals in the future.

Acknowledgements/Conflicts of Interest

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