NIH Public Access
Author Manuscript
Res Autism Spectr Disord. Author manuscript; available in PMC 2013 October 01.

Published in final edited form as:
Res Autism Spectr Disord. 2012 October 1; 6(4): 1311–1320. doi:10.1016/j.rasd.2012.05.007.

TARGETED TREATMENTS IN AUTISM AND FRAGILE X SYNDROME

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Abstract

Autism is a neurodevelopmental disorder consisting of a constellation of symptoms that sometimes occur as part of a complex disorder characterized by impairments in social interaction, communication and behavioral domains. It is a highly disabling disorder and there is a need for treatment targeting the core symptoms. Although autism is accepted as highly heritable, there is no genetic cure at this time. Autism is shown to be linked to several genes and is a feature of some complex genetic disorders, including fragile X syndrome (FXS), fragile X premutation involvement, tuberous sclerosis and Rett syndrome. The term autism spectrum disorders (ASDs) covers autism, Asperger syndrome and pervasive developmental disorders (PDD-NOS) and the etiologies are heterogeneous. In recent years, targeted treatments have been developed for several disorders that have a known specific genetic cause leading to autism. Since there are significant molecular and neurobiological overlaps among disorders, targeted treatments developed for a specific disorder may be helpful in ASD of unknown etiology. Examples of this are two drug classes developed to treat FXS, Arbaclofen, a $GABA_B$ agonist, and mGluR5 antagonists, and both may be helpful in autism without FXS. The mGluR5 antagonists are also likely to have a benefit in the aging problems of fragile X premutation carriers, the fragile X –associated tremor ataxia syndrome (FXTAS) and the Parkinsonism that can occur in aging patients with fragile X syndrome. Targeted treatments in FXS which has a well known genetic etiology may lead to new targeted treatments in autism.

Keywords

Fragile X Syndrome; Autism; mGluR; GABA; treatment

1. Introduction

Autism spectrum disorders (ASDs) are common and occur in about 1% of the general population (Baron-Cohen et al., 2009). Although behavioral interventions at a young age are

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Disclosure Statement: Randi Hagerman has received grant support from Novartis, Roche, Seaside Therapeutics, Curemark, Forest and HRSA for treatment studies in fragile X syndrome and autism treatment.

significantly helpful in children with ASD (Dawson et al., 2010), there are no pharmacological cures for these very impairing conditions that affect social interaction, communication, and behavioral domains. The etiology of autism is heterogeneous and may include genetic, environmental, and autoimmune etiologies (Levy, Mandell & Schultz, 2009).

2. Neurobiology of Autism

Autism is a highly genetic disorder and heritability is reported to be moderate to high (Hallmayer et al., 2011; Ronald & Hoekstra, 2011) and shared environmental factor are also important (Hallmayer et al., 2011). Research tells us that the genetics of autism is complex and caused by many different genetic mechanisms (Lo-Castro, Benvenuto, Galasso, Porfirio & Curatolo, 2010). Some of the linkage and association studies have found candidate genes that contribute small effects on the autism phenotype (Veenstra-Vanderweele, Christian & Cook, 2004). However, replication is not consistent across studies. On the other hand, recent studies suggest that rare genomic variation may explain a significant proportion of the genetic basis of ASD. One of the largest genome-wide association studies found a variant in the intergenic region between CDH 9 and CDH 10 (encoding cadherins 9 and 10) associated with ASDs in families (Wang et al., 2009). The finding of this study is important because its results implicate alterations in neuronal adhesion molecules in the pathogenesis of ASD, which could contribute to abnormal neuronal connectivity. Fassio et al. (2011) demonstrated that a mutation in the gene SYN1 (encoding the synaptic vesicle protein Synapsin 1) which predisposes to ASD and suggested that disturbances of synaptic homeostasis may underlies the pathogenesis of ASDs. Other studies have shown that mutations in synaptic proteins including neuroligins (Glessner et al., 2009; Jamain et al., 2003) and neurexins (Arking et al., 2008; Kim et al., 2008) are associated with autism. One of the well replicated finding about neurexins is association of CNTNAP2 (a gene named contactin associated proteinlike-2 which encodes Caspr2) and autism. This association was documented in several studies in various populations (Alarcón et al., 2008; Bakkaloglu et al., 2008; Li et al., 2010]. Copy-number variations (CNVs) are consistently found associated with autism in the large family studies (Levy, Mandell & Schultz, 2009). Although new strategies to identify common genetic risk variants are being applied currently, there is no single model that explains all of the phenotypic variation in cases with autism (Buxbaum, 2009). In fact, genetic heterogeneity data strongly suggest that there is not any common genetic risk variant. In a recent study, a large number of investigators presented a new approach called homozygous haplotype mapping, which aims to detect homozygous segments of identical haplotype structure that are shared at significantly higher frequency among individuals with ASD compared to parental controls. Using this strategy authors are able to identify many new ASD candidate genes and replicate some older ones (Casey et al., 2012), and they suggested this approach as a promising development to evaluate genome wide association data.

Although available data suggest that a large proportion of ASD cannot be explained by single-gene models, these models represent a means of understanding the underlying neurobiology of autism (Abrahams & Geschwind, 2008) and they include fragile X syndrome (FXS) (Hatton et al., 2006), Tuberous Sclerosis (Wiznitzer, 2004), Rett syndrome (Young et al., 2008) and some other less known chromosomal abnormalities (Lo-Castro, Benvenuto, Galasso, Porfirio & Curatolo, 2010). Functions of *FMR1, MECP2* and some of the neural adhesion molecules such as neuroligins/neurexins suggest synaptic dysfunction in autism pathogenesis. Overall, genetic and neurobiological evidence demonstrate that there are similarities across disorders that are associated with autism including GABA and glutamate imbalances (Belmonte & Bourgeron, 2006), synaptic maturation and plasticity

deficits (De Rubeis & Bagni, 2011; Levy, Mandell & Schultz, 2009) and mitochondrial malfunction (Giulivi et al., 2010).

Neurotransmitters including GABA, glutamate and serotonin are important in functions of synaptic interactions and in cortical development (Manent & Represa, 2007; Pardo & Eberhart, 2007). Specific GABA and glutamate receptors have a role in neuronal migration, inhibition and synaptic plasticity including long term depression (LTD) and long term potentiation (LTP). Plasma levels of glutamate and glutamine were found to be high in high-functioning children with autism (Shimmura et al., 2011). The authors suggested that the plasma levels of glutamate and glutamine could be early markers of glutamatergic dysfunction leading to an autism pathogenesis. In animal models it was shown that GABAergic dysfunction in early development lead to excitatory/inhibitory imbalances in neural circuits and may account for some of the behavioral symptoms of ASDs (Pizzarelli & Cherubini, 2011).

The role of serotonin in autism is also widely explored and abnormalities documented in PET/SPECT studies and genetic studies found a relationship with serotonin related genes (Pardo & Eberhart, 2007). Serotonin levels were found to be low in the frontal region of the brain in children with autism under age 5 with alpha [11C] methyl-L-tryptophan and PET scans (Chugani et al., 1999). Although some studies have demonstrated an improvement in autism features following treatment with an SSRI (DeLong, Ritch & Burch, 2002; Soorya, Kiarashi & Hollander, 2008), other studies have not including a large multicenter controlled trial (King et al., 2009). In a recent review, although the data were unsuitable for a meta-analysis, the authors concluded that there is no evidence of a benefit from SSRI treatment in children with autism and little evidence of effectiveness in adults with autism (Williams, Wheeler, Silove & Hazell, 2010). This does not eliminate the possibility that there may be a critical developmental period during which an SSRI may help with autism symptoms (Chugani, 2005). Controlled trials are currently taking place with buspirone in young children 2 to 6 with autism [ClinicalTrials.gov Identifier: NCT00873509] and with sertraline in young children 2 to 6 years old with FXS [ClinicalTrials.gov Identifier: NCT01474746].

3. Aging with Autism

Although it was reported that general symptomatic improvements occur as individuals with autism get older, social interaction and communication problems continue into adolescence and adulthood (Levy & Perry, 2011). There is evidence that adults with ASDs are at high risk for psychopathology (Hofvander et al., 2009). In a prospective study assessing the autism symptoms and maladaptive behaviors in adolescents and adults with ASDs, it was reported that many of the individuals' symptoms remained stable (Shattuck et al., 2007). Although overall a greater proportion of the participants' symptoms decreased, individuals with intellectual disability (ID) had more autism symptoms and maladaptive behaviors with age. As the children with autism grow up with their behavior problems, their mothers' reactions also change. In a seven year follow up study Baker et al. (2011) reported that mothers' criticisms continue and tend to increase during transitions. The behavior problems of the child with autism were positively correlated with the level of criticism they received from their mothers. Externalizing behavior problems in young children with autism were reported to be associated with paternal stress (Davis & Carter, 2008). On the other hand, there is an impact of behavior problems in children with autism on both parent and teacher stress (Lecavalier, Leone & Wiltz, 2006). In a study, Barker et al. showed that fluctuations in emotional well-being of the mothers were associated with behavioral problems in children with autism across a 10-year period (Barker, Hartley, Seltzer, Floyd, Greenberg & Orsmond 2011). It was also shown that, living a child with autism has an impact on emotional well being of other sibling (Orsmond & Seltzer, 2009).

With age there are abnormal changes in the brain structure in individuals with autism. In an MRI study, Wallace et al. (2010) reported an age-diagnosis interaction; individuals with ASDs had thinner cortex with increasing age compared to normals. The authors suggested a second period of abnormal cortical development (greater thinning) besides early cortical overgrowth. In an another MRI study, Raznahan et al. (2010) suggest that cortical dysmaturation in ASD extends beyond childhood and affects brain regions involved with social cognition and language. They examined 127 males, aged 10–60 years, (76 with ASDs and 51 healthy controls) and identified significant age-by-group interactions in both cortical volume (CV) and cortical thickness (CT) (but not cortical surface area) in the temporal lobes and within these the fusiform and middle temporal gyri. Vertex based analyses replicated these findings and identified additional age-by-group interactions for CT within superior temporal, inferior and medial frontal, and inferior parietal cortices. They detected that CV and CT were significantly negatively correlated with age in controls but not in ASDs subjects; and smaller in ASDs than controls in childhood but vice versa in adulthood. They speculated that these changes may be primarily related to cortical plasticity problems or exacerbated by the disturbed interactions of individuals with ASD.

Targeted treatments may help to improve autism symptoms and maladaptive behaviors that are persistent as the individuals get older, possibly slowing down neurobiological changes through specific molecular mechanisms. Such mechanisms will be discussed further in detail in the example of FXS.

4. Fragile X Syndrome

FXS is the most common single-gene cause of the autism and approximately 30% have full autism but when PDD NOS, which occurs in an additional 30%, is also included the total percentage with an ASD is 60% (Harris et al., 2008). FXS is caused by a full mutation (>200 CGG repeats) in the 5′untranslated region of the fragile X mental retardation 1 gene (*FMR1*) which is near the distal arm of the long end of the X chromosome. This mutation causes hypermethylation at the *FMR1* promoter region and transcriptional silencing, which in turn lead to a deficit of the FMR1 protein (FMRP). The overlap between autism and FXS relates to the many functions of FMRP that is absent or deficient in FXS. FMRP binds, stabilizes and transports to the synapse hundreds of mRNAs important for synaptic plasticity (Bassell & Warren, 2008; De Rubeis & Bagni, 2010). In addition FMRP regulates, typically through inhibition, the translation of these mRNAs into their respective proteins, such that in the absence of FMRP there is significant over-expression of, many of these proteins, and under-expression of others particularly in the hippocampus in FXS (Qin, Kang, Burlin, Jiang & Smith, 2005). Many of the messages that are regulated by FMRP are associated with autism including those encoding neuroligins, neurexins, Arc, SAPAP4, SHANK3, PSD95, CYFIP and others (Darnell et al., 2011). FMRP regulates both basal and activity-dependent local protein synthesis at the synapse (De Rubeis & Bagni, 2011; Napoli et al., 2008). The mGluR5 system is up-regulated in the absence of FMRP and so is matrix metalloproteinase 9 (MMP9), whereas the GABA system is down-regulated (D'Hulst et al., 2006).

Our understanding of the many neurobiological consequences of the loss of FMRP has lead to development of targeted treatments for FXS (Berry-Kravis, Knox & Hervey, 2011; Wang, Berry-Kravis & Hagerman, 2010). One example is the significant up-regulation of downstream proteins in the metabotropic glutamate receptor 5 pathways (mGluR5) in the hippocampus leading to long term depression (LTD) or weakening of synaptic connections (Huber, Roder & Bear, 2001). This is considered a major cause of the intellectual disability (ID) in patients with FXS so that mGluR5 antagonists have been studied as targeted treatments for FXS. In animal models of FXS including the knock out (KO) mouse, mGluR5 antagonists can reverse the dendritic spine abnormalities, audiogenic seizures, accelerated

body growth, hyperactivity and deficits in prepulse inhibition (de Vrij et al., 2008; Gross, Berry-Kravis & Bassell, 2012; Levenga, de Vrij, Oostra & Willemsen, 2010). Therefore phase II clinical trials have taken place and fenobam which has been around for many years and recently discovered to be an mGluR5 antagonist was tried in a single dose open label study and found to not have significant side effects and also improve the deficits in prepulse inhibition in 12 adults with FXS (Berry-Kravis et al., 2009). A controlled trial of AFQ056, another mGluR5 antagonist, was also carried out in Europe and lead to significant improvements in behavior in adults with FXS who had a full mutation that was fully methylated (Jacquemont et al., 2011). This study was conducted on 30 male patients with FXS and the group as a whole did not show significant improvement on the primary outcome measure on day 20 of treatment, only those that were fully methylated showed a significant benefit. Currently there are multiple sites carrying out controlled trials of two different mGluR5 antagonists, AFQ056 (Novartis, Basel, Switzerland) and RO4917523 (Hoffmann-La Roche, Basel, Switzerland). The trials in FXS of another mGluR5 antagonist, STX107 (Seaside Therapeutics) have not been initiated in FXS yet, although they are planned for the future.

A recent report of two mouse models of autism, the fragile X KO mouse model and the tuberous sclerosis mouse model demonstrated opposite effects to an mGluR5 antagonist. The tuberous sclerosis mouse had rescue of behavior when an mGluR5 agonist was used and the KO mouse model of FXS did best with an mGluR5 antagonist (Auerbach, Osterweil & Bear, 2011). These authors then crossed a fragile X KO mouse with a tuberous sclerosis mouse and demonstrated rescue of the phenotypes of both behaviorally (Auerbach, Osterweil & Bear, 2011).

Another dysfunctional neurotransmitter system in FXS is the GABA system and 8 out of 18 known GABA subunits are significantly reduced in the cortex of the KO mice (D'Hulst et al., 2006). GABA is the major inhibitory neurotransmitter in the brain, and its proper regulation is essential for learning and memory, mood, and sleep. Dysregulation of GABAergic circuits can result in seizures, anxiety, depression, insomnia, and cognitive impairments (Sadock & Sadock, 2008). Neuroanatomical and behavioral phenotypes can be rescued with the use of GABAergic compounds in the Drosophila model of fragile X (Chang et al., 2008). GABAergic mechanisms can also down-regulate glutamate release and modulate mGluR overactivity. A $GABA_B$ agonist which is the R-isomer of baclofen, specifically Arbaclofen, has been studied in children and adults with FXS with good results in those patients with FXS who have autism or significant social deficits [Poster in 9th Annual International Meeting for Autism Research, Philadelphia 2010]. Currently controlled trials of Arbaclofen in FXS are taking place at multiple centers in the US [ClinicalTrials.gov Identifier: NCT01282268].

Use of a $GABA_A$ agonist, ganaxolone, a neurosteroid, has been in clinical trials for infantile spasms with a good safety record and is now undergoing trials in children with FXS since it specifically targets the $GABA_A\delta$ pathway which is particularly low in FXS (D'Hulst et al., 2009). Further information for this controlled crossover trial for children ages 6 to 17yo can be found at www.ClinicalTrials.gov [ClinicalTrials.gov Identifier:NCT00441896].

Minocycline, which is FDA-approved as a broad-spectrum antibiotic with good CNS penetration, is also being tested as a targeted treatment for FXS because it lowers MMP9 levels which are high in FXS. The KO mouse studies have shown that minocycline treatment for one month after birth normalized the dendritic spine defects and improved behavior and cognition in these fragile X mice (Bilousova et al., 2009). Subsequently a survey of patients with FXS who were treated with minocycline clinically demonstrated improvements in approximately 70% (Utari, Chonchaiya et al., 2010) and an open trial of

minocycline in adolescents and young adults with FXS demonstrated improvements in behavior (Paribello et al., 2010). Minocycline also slows down translation so it is thought to lower other elevated protein levels in addition to MMP9. MMP9 is one of a family of proteins important for synaptic plasticity. Currently a controlled trial of minocycline in children and adolescents has preliminary positive results [Leigh et al, SSBP abstract, Brisbane, 2011] and this trial will be completed in 2012.

Lithium is also a targeted treatment in FXS because it can down-regulate mGluR5 signaling by inhibiting inositol phosphate turnover thereby attenuating phospholipase C activity and inhibiting glycogen synthase kinase 3β (GSK3β) (Berry-Kravis et al., 2008). An open trial of lithium was effective for behavioral improvements in FXS but a randomized double blind controlled trial is needed (Berry-Kravis et al., 2008). Other potential treatments of FXS are currently undergoing preclinical (animal) studies including PAK inhibitors, GSK3 antagonists and antioxidants and, if promising, approval will be sought for human trials (Berry-Kravis, Knox, & Hervey, 2011). The summary of targeted treatments in FXS is shown in Table 1:

Targeted treatments for FXS are likely to also help the aging problems and in a study of 62 patients with FXS over age 40 years (range 40–71yo; mean 49.2) 38.7% had neurological problems and 20% of those older than age 55 had Parkinson's disease (PD) (Utari, Adams et al., 2010). The high rate of PD may be related to the importance of FMRP in the functioning of the dopamine system (Wang et al., 2008). FMRP is needed for adult neurogenesis (Luo et al., 2010) so the lack of FMRP and problems with adult neurogenesis may be related to the occasional patient with FXS seen with cognitive decline in aging (Utari, Adams et al., 2010). Preliminary studies have shown that one mGluR5 antagonist, AFQ056, is helpful in the dyskinesias in Parkinson's disease so it may be helpful for the parkinsonian symptoms seen in aging in some patients with FXS (Utari, Adams et al., 2010). The most severe problems with aging are seen in patients with the FMR1 premutation (55 to 200 CGG repeats) and approximately 40% of males and up to 16.5% of females with the premutation develop the fragile X-associated tremor ataxia syndrome (FXTAS). This is characterized by intention tremor, ataxia, cognitive decline, autonomic dysfunction, neuropathy and psychiatric problems (Hagerman & Hagerman, 2004). The cause of FXTAS is excessive *FMR1* mRNA levels (RNA toxicity) that dysregulate cellular function because of sequestration of critical proteins (Garcia-Arocena et al., 2010; Sellier et al., 2010). Inclusions occur in neurons and astrocytes and in the peripheral nervous system and tissues (Hunsaker et al., 2011). Brain atrophy with significant white matter disease is characteristic of FXTAS (Adams et al., 2007). In childhood a subgroup of premutation carriers particularly boys have ADHD and ASD, the latter in 10% or higher if they present as probands (Farzin et al., 2006). The presence of ASD in carriers is related to RNA toxicity in addition to mild deficits of FMRP. Recently the affect of a mild deficit of FMRP in carriers was the most important molecular factor associated with lowered levels of amygdala activation in adult carriers (Hessl et al., 2011). The presence of seizures in children with the premutation can exacerbate autism symptoms so seizures should be treated vigorously in these patients (Chonchaiya et al., 2012). The premutation neurons dies more easily in culture (Chen et al., 2010) and they appear to be more vulnerable to environmental toxicity (Paul et al., 2010) so the premutation is a model for the combination of genetic and environmental factors leading to autism.

5. Targeted Treatment Studies in Autism

Although there are many studies on treating secondary behavioral problems in autism, treatments targeting the core symptoms of autism are relatively few. In a recent review, Mc Pheeters et al. (2011) reported that risperidone and aripiprazole are effective in aggressive,

self injurious, hyperactive and repetitive behavior in children with ASDs, although they have some adverse effects. Perhaps the most significant side effect is weight gain that can lead to metabolic problems including type II diabetes (Newcomer, 2005). They concluded that there is insufficient evidence for benefits of other drugs, including SSRIs and stimulants. On the other hand, in recent years, there are some preliminary results that targeted treatments may be beneficial in children with autism. These agents include mGluR5 antagonists, tetrahydrobiopterin, D-cycloserine, arbaclofen and memantine and evidence related to their use in autism is discussed below.

5.1. mGluR 5 Antagonists

Based on the hypothesis that excessive metabotropic glutamatergic signaling in autism may cause some of the core symptoms, several studies tested mGluR5 antagonists in animal models of autism. In a recent study, Mehta et al. (2011) reported a reduction in repetitive behaviors and anxiety-like behaviors in mice with 2-methyl-6-phenyethyl-pyrididine (MPEP) which is an mGluR5 receptor antagonist. In another study reporting similar results the authors expressed concern that some measures of sociability may worsen, although they improve the stereotypies (Burket, Herndon, Winebarger, Jacome, & Deutsch, 2011). Silverman et al. (2010) also reported a similar result of mGluR5 antagonist on repetitive self grooming behavior and suggested mGluR5 receptors as specific targets for decreasing stereotypic behaviors in autism. As previously discussed mGluR5 antagonists are targeted treatments for FXS and human trials in autism will hopefully be tried in the future.

5.2. Tetrahydrobiopterin

Tetrahydrobiopterin is an essential cofactor of several enzymes that convert aminoacids to neurotransmitters, for example, tyrosine hydroxylase, the rate-limiting enzyme in synthesis of dopamine. The pathways of these neurotransmitters are thought to be involved in etiology of ASDs (Frye, Huffman, & Elliott, 2010). In one study, Fernell et al. (1997) reported improvement with tetrahydrobiopterin in six autistic children. A double blind placebo controlled study conducted by Danfors et al. (2005) reported general improvement in autism symptoms with tetrahydrobiopterin. In that study, daily dose of 3 mg tetrahydrobiopterin per kilogram were administered for 6 months alternating with placebo. The authors reported small non-significant changes in the total scores of CARS after the treatment. However, with a post hoc analysis, a significant improvement was observed in three core symptoms of autism, social interaction, communication and stereotyped behaviors after 6 months of active treatment.

5.3. D-cycloserine

D-cycloserine is a partial N-methyl-D-aspartate (NMDA) receptor agonist that enhances the receptor activation in presence of glutamate (Watson, Bolanowski, Baganoff, Deppeler & Lanthorn, 1990). It has been focus of interest in recent years as an accelerator of extinction learning and there is some evidence that it is effective as an adjunctive therapy to cognitive behavioral therapy for social phobia (Hofmann et al., 2006), acrophobia (Ressler et al., 2004), obsessive compulsive disorder (Kushner et al., 2007) and post traumatic stress disorder (Heresco-Levy et al., 2002).

In an animal model of ASD, Modi and Young (2011) suggested that D-cycloserine may improve social behavior especially when combined with social behavioral therapy. They alleged that glutamate transmission has a role in the formation of social bonds in animals and NMDA receptor agonist D-cycloserine accelerates the acquisition of social information. In a placebo-controlled study of D-cycloserine trial in children with autistic disorder improvement was reported in certain aspects social impairment (Posey et al., 2004).

5.4. Arbaclofen

Arbaclofen is a powerful $GABA_B$ agonist and the dextro (D) enantiomer of racemic baclofen as discussed in the FXS section. Arbaclofen is hypothesized to indirectly efficient on mGluR5 signaling by lowering the glutamate. Then glutamate mediated receptor activation at the synapse is reduced. One unpublished open label study of Arbaclofen in children with autism was carried out by Seaside Therapeutics and the results are positive for both the primary and secondary measures [Berry-Kravis et al., 9th Annual International Meeting for Autism Research, Philadelphia, 2010]. This has lead to the organization of the multisite double blind randomized controlled treatment trial for children and young adults with autism currently in progress in the US (ClinicalTrials.gov Identifier: NCT01288716).

5.5. Memantine

Memantine is a moderate affinity antagonist of the N-methyl-D-aspartic acid (NMDA) glutamate receptor and can block excessive glutamate effects (Parsons, Danysz & Quack, 1999). Hypothesizing that memantine can potentially modulate learning, and can influence neuroinflammatory activity including neuroglial activity, in an open-label long-term study, Chez et al. (2007) showed that memantine helps with language function, social behavior, and self-stimulatory behaviors in children with autism and PDD-NOS. There are other case series and case reports showing that memantine may be effective in ASDs. It helps with social withdrawal and inattention (Erickson et al., 2007), irritability (Niederhofer, 2007), and disruptive behavior (Erickson & Chambers, 2006). Currently a randomized placebo controlled trial is taking place at multiple centers in the US [ClinicalTrials.gov Identifier: NCT01078844].

5.6. Oxytocin

Emerging evidence indicates that the neuropeptide oxytocin may be a treatment option to improve social functioning in autism. Oxytocin is believed to facilitate human social interactions such as social learning (Insel & Young, 2001) and social memory (Ferguson, Young & Insel, 2002). In a double blind placebo controlled study, Hollander et al. (2003) showed that oxytocin infusion reduced repetitive behaviors in adults with autism and Asperger Disorder. In another study, Hall et al. (2012) demonstrated that intranasal oxytocin helps with social anxiety in children with FXS. You can see a summary of possible targeted treatment and their mechanism of actions in Table 2.

6. Conclusion

There is still continuing need for more effective treatments in autism for both core and behavioral symptoms. The lack of molecular information for many types of autism has slowed down the development of targeted treatments for this heterogeneous group of disorders. FXS has been helpful for leading the way for targeted treatment in autism because of the molecular similarities between FXS and some types of autism (Wang, Berry-Kravis, & Hagerman, 2010). As targeted treatments are developed for other known genetic ASDs, such as Tuberous Sclerosis including mTOR inhibitors (de Vries, 2010), this may guide further treatments for idiopathic autism. These targeted treatments in other disorders with a well known genetic etiology, including FXS, may be a good starting point for targeted treatments in autism. Some may argue that ASDs seen in these genetic disorders may represent different classes of ASDs; therefore their treatment may be different from idiopathic autism cases. Nevertheless, whatever the genetic etiology of the autism, the number of targeted treatment studies in autism warrant further exploration, and they may lead to identification of new pathways and mechanisms for more of the unknown cases. The development of specific molecular biomarkers for different pathways may also be helpful

for designating a specific targeted treatment for many cases. There is much more to be done to develop effective treatments for all of the cause of ASDs.

Acknowledgments

This work was supported by National Institute of Health grants HD036071, and HD02274; Neurotherapeutic Research Institute (NTRI) grants DE019583, and DA024854; National Institute on Aging grants AG032119 and AG032115; National Institute of Mental Health grant MH77554; National Center for Resources UL1 RR024146; and support from the Health and Human Services Administration of Developmental Disabilities grant 90DD05969.

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Highlights

1. There is a need for efficient treatments in ASDs which has a heterogeneous etiology.
2. Autism is caused by single-gene disorders in some cases including Fragile X Syndrome.
3. Targeted treatments in FXS may be a good starting point for targeted treatments in ASDs.

Table 1

Summary of targeted treatments in FXS

Drug	Mechanism of action	Effect
mGluR5 antagonists (RO4917523, AFQ056..)	Reduction of mGluR signaling	Reduction of downstream effectors of mGluR5 pathway and mature dendritic spines
Ganaxolone	Stimulation of $GABA_A\delta$ activity	Upregulates GABA activity and perhaps may crosstalk to glutamate pathways
Arbaclofen	GABA B agonist	Modulation of mGluR activity, decrease the glutamate level and reduce the activation of mGluR and mature spines
Minocycline	Reduction of excessive activity of proteins regulated by FMRP (e.g. MMP9)	Maturation of dendritic spines
Lithium	Reduction of activity downstream of the mGluR5 receptor	Reduction of increased intracellular signaling in the absence of FMRP (inhibits IP3, PLC, ..)

Table 2

Targeted treatments in autism

Drug	Mechanism of action	Effect
mGluR5 antagonists	Reduction of mGluR signaling	Reduction of increased intracellular signaling
D-cyclocerine	Partial NMDA agonist	Modulation of glutamate effects
Arbaclofen	GABA B agonist	Modulation of mGluR activity, decrease the glutamate level and reduce the activation of mGluR
Memantine	NMDA antagonist	Reduction of excessive glutamate effects
Oxytocin	Receptor mediated effects	Increasing neuronal proliferation and differentiation, synaptic plasticity