Published in final edited form as:
Expert Opin Emerg Drugs. 2010 September ; 15(3): 481–494. doi:10.1517/14728214.2010.487860.

Emerging Drugs for the Treatment of Symptoms Associated with Autism Spectrum Disorders

Logan K. Wink, M.D., **Martin H. Plawecki, M.D. Ph.D.**, **Craig A. Erickson, M.D.**, **Kimberly A. Stigler, M.D.**, and **Christopher J. McDougle, M.D.**
Christian Sarkine Autism Treatment Center, James Whitcomb Riley Hospital for Children and Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA

Abstract

Importance of the Field—Autism spectrum disorders, or pervasive developmental disorders (PDDs), are neurodevelopmental disorders defined by qualitative impairment in social interaction, impaired communication, and stereotyped patterns of behavior. The most common forms of PDD are autstic disorder (autism), Asperger's disorder, and pervasive developmental disorder not otherwise specified (PDD NOS). Recent surveillance studies reveal an increase in the prevalence of autism and related PDDs. The use of pharmacologic agents in the treatment of these disorders can reduce the impact of interfering symptoms, providing relief for affected individuals and their families.

Areas Covered in this Review—This review examines results from neurobiologic research in an attempt to both elucidate the pathophysiology of autism and guide the development of pharmacologic agents for the treatment of associated symptoms. The safety and efficacy data of drugs currently in clinical use for the treatment of these symptoms, as well as pharmaceuticals currently under development, are discussed.

What the Reader will Gain—This comprehensive review will deepen the reader's current understanding of the research guiding the pharmacologic treatment of symptoms associated with autism and related PDDs. Areas of focus for future research are also discussed. The need for large-scale investigation of some commonly used pharmacologic agents, in addition to the development of drugs with improved efficacy and safety profiles, is made evident.

Take Home Message—Despite progress in the development of pharmacologic treatments for a number of interfering symptom domains associated with autism and other PDDs, a great deal of work remains.

Keywords

aripiprazole; autism; autistic disorder; methylphenidate; PDDs; risperidone; treatment

1. Background

Autism spectrum disorders, or pervasive developmental disorders (PDDs), are neurodevelopmental disorders which present in early childhood and persist throughout the lifespan. Since the original description of autistic disorder (autism) by Kanner in 1943,

Correspondence: Craig A. Erickson, M.D., Department of Psychiatry, Indiana University School of Medicine, Riley Hospital Child & Adolescent Psychiatry Clinic, 702 Barnhill Drive, Room 4300, Indianapolis, IN 46202, Phone: +1 317-274-8162, Fax: +1 317-278-4241, crericks@iupui.edu.

Declaration of interest: L Wink has no disclosures.

autism and related PDDs, specifically Asperger's disorder and pervasive developmental disorder not otherwise specified (PDD NOS), have grown in public awareness and garnered heightened research interest. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Addition (DSM-IV) defines three core features of autism; qualitative impairment in social interaction, impaired communication, and stereotyped patterns of behavior [1]. Asperger's disorder, like autism, is defined by qualitative impairment in social interaction and stereotyped patterns of behavior, however does not require the presence of language delay [1]. Diagnosis of PDD NOS requires pervasive impairment of social behavior accompanied by either communication delay or stereotyped behavior, however symptoms do not meet full criteria for either autism or Asperger's disorder [1].

Pharmacologic research has targeted interfering symptom domains associated with autism and related PDDs, which in part overlap with the core diagnostic features. These symptom domains include repetitive and stereotypic behavior, hyperactivity and inattention, irritability [including aggression, self-injurious behavior (SIB) and severe tantrums], and core social impairment. This review will follow suit by directing attention to existing treatments, current research goals, and potential developments in pharmacologic management of these four interfering symptom domains associated with autism and related PDDs.

2. Medical Need and Existing Treatment

The core and related symptom domains of autism and related PDDs have the potential to limit the quality of life of people with these disorders, as well as the lives of their families and caregivers. Early diagnosis and behavioral therapy interventions often lead to an improvement in outcomes [2]. Pharmacologic management of symptoms, though not a “cure,” is able to provide some relief, and allow this population to benefit more optimally from educational, vocational, and community-based programs.

2.1 Repetitive and Stereotypic Behavior

Repetitive, restrictive, and stereotyped behavior is both a core diagnostic characteristic and, at times, an interfering symptom domain common to autism and related PDDs. Preoccupation with restrictive patterns of interest, inflexible adherence to routines, and stereotyped motor mannerisms often interfere with daily functioning. Symptom similarity exists between these phenomena in autism and those experienced by patients with obsessive-compulsive disorder (OCD). This phenomenologic overlap combined with evidence of serotonin system dysregulation in individuals with autism, prompted pharmacologic research investigating the use of serotonin reuptake inhibitors (SRIs) in adults and children with autism and related PDDs. At this time, there are no U.S. Food and Drug Administration (FDA)-approved medications for repetitive behaviors associated with autism.

2.2 Hyperactivity and Inattention

Hyperactivity and inattention can also be interfering symptoms, especially in school-aged children with autism and related PDDs. In the DSM-IV, the symptoms of hyperactivity and inattention are not part of the diagnostic criteria for autistic disorder; however, the criteria for attention-deficit/hyperactivity disorder (ADHD) specifically preclude this diagnosis if symptoms occur within the context of a PDD [1]. Several classes of medications are employed in the clinical setting for the treatment of this symptom domain; however, psychostimulants have been the most extensively researched. Despite the growing body of evidence in this area, no medications have been FDA approved for this indication.

2.3 Irritability

Irritability [including aggression, SIB, and severe tantrums] is a particularly disruptive symptom domain often present in this population. Destructive behavior has the potential to limit access to school settings and community programming and cause family distress. Currently, the most common medications used clinically to target these symptoms are atypical antipsychotics. The only pharmacologic agents FDA approved to treat maladaptive behaviors associated with autism target this symptom domain.

2.4 Core Social Impairment

Impaired social functioning is both a core diagnostic feature and an interfering symptom domain of autism and related PDDs. Core social impairment includes limited reciprocal social interaction, difficulty with non-verbal communication (e.g., eye contact, gestures, body posture), and impaired pragmatic language usage. Development of pharmacologic agents to treat this symptom domain has been challenging, as many of the medications with efficacy for other symptoms do not improve socialization and communication. Other challenges include limited understanding of the neurobiology of autism, the heterogeneity of the disorders, and their relatively uncommon occurrence [3]. Unfortunately, the development of pharmacologic approaches to this symptom domain has been slower than in other areas, and consequently, no medications are currently FDA approved for treatment of social impairment associated with autism.

3. Market Review

A surveillance study released by the Centers for Disease Control and Prevention in December 2009 estimates the prevalence of autism and related PDDs to be 9 cases per 1,000 8-year-olds in the United States [4]. Approximately 1% of children living in sites participating in the Autism and Developmental Disabilities Monitoring Network during the 2006 surveillance year met criteria for autism or a related PDD. This is an increase of 57% from data collected in the same manner in 2002. The investigators note that this large change is likely in part accounted for by improved ascertainment; however, they do not rule out the possibility of increased risk of children developing autism or related PDDs [4].

The global market for pharmacologic treatment of autism-related symptoms is currently estimated to be $2.2 to $3.5 billion annually, with selective SRIs (SSRIs) accounting for the largest portion of the market share [5]. Special education, medical care, and assisted living facilities currently are estimated to cost the United States $35 billion for treatment and management of patients with autism spectrum disorders [6]. With the growing prevalence of these disorders and the large estimated market, more research investment targeting the wide array of interfering symptoms is indicated and may prove profitable for the pharmaceutical industry.

4. Current Research Goals

Clinically, many pharmacologic agents from several classes are utilized to ameliorate the symptoms of autism and related PDDs. However, many of the treatments are of low to moderate efficacy and many have significant side effects. These limitations of current pharmacologic agents reveal the need for further development of safe and effective treatments for autism spectrum disorders.

4.1 Repetitive and Stereotypic Behaviors

Trials investigating SRIs for the treatment of stereotypic behaviors in autism have generally demonstrated disappointing to mixed results [5, 7-9], and investigation of other agents will be

necessary. Interestingly, studies of atypical antipsychotics targeting irritability in children and adolescents with autism also have shown improvement of stereotypic behavior [10-12]. These results indicate the need for further research into the treatment of repetitive and stereotypic behavior using these and other pharmacologic agents.

4.2 Hyperactivity and Inattention

The moderate response rate and high probability of side effects with psychostimulants in the treatment of hyperactivity and inattention in patients with autism and related PDDs has limited their use in this population. This prompted investigation of the role of non-stimulant medications, including the selective norepinephrine reuptake inhibitor, atomoxetine, and alpha-2 adrenergic agonists, such as clonidine and guanfacine, in the treatment of these symptoms.

4.3 Irritability

Despite a significant amount of research in the area of irritability in autism and related PDDs, primary efficacy has been demonstrated only with the use of antipsychotics. As demonstrated in the trials prompting FDA approval of risperidone and aripiprazole for the treatment of irritability, these medications have a high risk of significant side effects, including weight gain and sedation [10-12]. Furthermore, the known association between the use of antipsychotics and the development of longer term sequelae, including tardive dyskinesia, further complicates the usage of these agents in children. The severity of these potential side effects demonstrates the great need for the development of novel pharmacologic agents for the treatment of irritability in autism.

4.4 Core Social Impairment

Investigation of the role of the glutamate system in the treatment of core social impairment in autism and related PDDs has demonstrated promising though mixed results [13-16]. The desire to expand treatment options in this area of impairment has recently broadened research directions to include the study of the neuropeptides oxytocin and secretin.

5. Scientific Rationale

Despite significant effort in the search for the etiology of autism over the past fifty years, the cause of these disorders remains largely unknown. While research effort has been aimed at determining the genetic underpinnings of the PDDs [17], much research to date has focused on neurochemicals thought to contribute to the pathophysiology of autism, primarily monoamines, glutamate and gamma-aminobutyric acid (GABA), and neuropeptides [18]. Other research has focused on inflammatory and immune processes that may be associated with the pathogenesis of autism and related PDDs [19-20]. These areas of research have contributed to the development of a number of medications currently in use for interfering symptoms, and may guide the future development of novel agents.

5.1 Monoamines

Monoamines thought to contribute to the pathophysiology of autism and related disorders include serotonin, dopamine, and norepinephrine. Serotonin is distributed throughout the central nervous system and is known to play a role as a growth factor in the developing human brain [21]. Several investigations have identified elevated levels of whole blood serotonin in younger autistic subjects than those found in normal age-matched controls [22-24]. Behavioral/neuroendocrine challenge studies focusing on serotonin precursors have shown behavioral and/or biological responses in autistic subjects that differ from those of normal controls [25-29]. Investigation of genes involved in the serotonin system also has shown variation in autistic subjects [30-34]. Finally, neuroimaging studies have demonstrated

asymmetries of serotonin synthesis in the frontal cortex, thalamus, and cerebellum of some subjects with autism [35-36].

Dopamine plays a role in motor and cognitive functioning, as well as hormone release. The role of dopamine in autism has been postulated primarily due to the efficacy of dopamine D2-receptor antagonists (typical and atypical antipsychotics) in the treatment of irritability associated with autism [21]. The majority of research has focused on measurement of a metabolite of dopamine, homovanillic acid (HVA), in plasma, urine, and cerebral spinal fluid (CSF) samples. Studies of plasma and urine dopamine levels have shown mixed results, with some studies demonstrating no significant difference from controls and others suggesting a defect in maturation of monoaminergic systems in subjects with autism [37-39]. Studies of CSF levels of dopamine function also show mixed results, with some showing elevated levels of HVA in subjects with autism and others demonstrating no difference when compared to controls [40-44]. Genetic studies of dopamine involvement in autism have suggested possible involvement of the A1 allele of the dopamine D2 receptor gene [45]. Other research has investigated the dopamine D1 and D5 receptor genes and the dopamine beta-hydroxylase genes as candidates for involvement in the development of autism [46]. An imaging study investigating dopamine involvement in autism using positron emission tomography (PET) demonstrated reduced accumulation of flourodopa in the anterior medial prefrontal cortex of subjects with autism [47]. Further, a recent PET study measured serotonin and dopamine transporter binding in 20 individuals with autistic disorder and age- and intelligence quotient-matched controls [48]. Serotonin binding was reduced globally in the individuals with autism. Serotonin abnormalities in the anterior and posterior cingulate cortices were shown to be associated with social symptoms, while thalamic serotonin abnormalities were correlated with repetitive symptoms. Increased dopamine binding was found in the orbitofrontal cortex and interestingly, was inversely correlated with serotonin binding.

Norepinephrine is a neurotransmitter which modulates autonomic activity and is involved in arousal, memory, and anxiety [18]. Investigation of the involvement of norepinephrine in the pathophysiology of autism has included research on blood levels of norepinephrine and its metabolites. Studies again have shown mixed results, with some demonstrating elevated levels of blood norepinephrine and others showing no significant differences between subjects with autism and controls [49-51]. Studies of CSF levels of norepinephrine metabolites have shown no significant differences from controls [40, 52].

5.2 Glutamate and GABA

Glutamate and GABA are essential amino acid neurotransmitters in the brain. Glutamate functions as the primary excitatory neurotransmitter and GABA as the primary inhibitory neurotransmitter. Both have been postulated to play a role in the pathophysiology of autism [18]. Despite the relative importance of these neurotransmitters, research has shown mixed results in their role in the pathophysiology of autism and related PDDs. Studies investigating peripheral amino acids in these disorders have shown evidence of both elevated and decreased levels [53-56]. Further, genetic studies have shown disequilibrium in the glutamate receptor ionotropic kainite 2 (GRIK2) and glutamate receptor 6 (GluR6) genes in autism [57], and the location of the GRIK2 gene has been determined to be a potential autism-susceptibility region [58]. Other genetic research investigating GABA receptors has shown conflicting results [59-63]. Postmortem studies have also investigated genes and proteins involved with glutamate and GABA, with resulting evidence suggesting abnormalities in people with autism [64-66].

5.3 Neuropetides

Several neuropeptides including oxytocin, vasopressin, opioids, cortisol/adrenocorticotropic hormone (ACTH), melatonin, and secretin have been investigated in autism and related PDDs [18]. Oxytocin and vasopressin are of particular interest as these peptides, which exist only in mammals, are thought to play a role in social behavior [67]. In animal models, disruption of these peptide systems leads to a decrease in social bonding behaviors [68]. Recently autism has been linked to oxytocin receptor gene polymorphisms in at least two distinct populations [69-70]. Despite these preliminary results, definitive association between social impairment in autism and related PDDs and alterations in these peptides has yet to be clearly linked [18, 71].

Infant animals often display elevated pain thresholds, hyperactivity, and decreased social behavior when administered opioids [18]. As these symptoms mimic those of autism, investigation into the role of endogenous opioids in these disorders has been pursued. Once again, the evidence has been contradictory, with evaluations of β-endorphin levels in blood, urine, and CSF showing conflicting results [18]. Study of cortisol and ACTH levels in patients with autism has also been conflictual, though it is clear that an excess or deficit of these hormones is not present in the majority of patients with PDDs [72-73]. Melatonin has been hypothesized to negatively impact the hypothalamic-pituitary-adrenal axis when produced in excess, possibly leading to development of autistic symptoms. However, little research has investigated melatonin in autism and related PDDs, and no evidence to date indicates a primary melatonin dysfunction in these disorders [18]. Recent animal research investigating the neuroactive properties of secretin has determined the presence of this hormone in many areas of the cerebral cortex and cerebellum [74-76]. As will be discussed in detail later, while the potential contribution of secretin to the development of autism and related PDDs remains unknown [18], its role in the treatment of autism and related PDDs appears limited.

5.4 Inflammatory and Immune Processes

Etiologic research has also investigated the role of the immune system in the pathogenesis of autism and related PDDs. Areas of investigation have included infectious, autoimmune, and cytokine-related etiologies [19]. Association between development of autism and infection has been made in some cases, however several pathogens have been identified and studies have yielded discrepant results [19]. Immune studies have also been inconsistent, however evidence points to immune activation in at least a subset of individuals with autism [19-20]. Development of immune modulating therapies are currently fostering research interest [77-78], and will be of more interest if alterations in immune functions are indeed found to play a role in the pathogenesis of autism and related PDDs [19].

6. Competitive Environment

Emerging pharmacologic agents targeting the core and associated symptom domains of autism and related PDDs include a broad range of medications at various levels of development. The following sections review the pharmacologic literature, including the studies leading to FDA approval of risperidone and aripiprazole, trials currently in Phase II and III of development, and current animal research.

6.1 Repetitive and Stereotypic Behavior

Past research in the pharmacologic treatment of repetitive and stereotypic behavior has focused primarily on SRIs with mixed results. More recent research has shown the efficacy of atypical antipsychotics for these symptoms. The newest area of investigation has focused on modulation of glutamate in treatment of this symptom domain.

A double-blind, placebo-controlled 12-week study of fluvoxamine in 30 adults with autism showed that fluvoxamine is more effective than placebo in reducing repetitive thoughts and behavior [7]. Eight of the patients receiving fluvoxamine versus none of the patients receiving placebo demonstrated improvement on the Clinical Global Impression-Improvement (CGI-I) Scale. Reduction in repetitive thoughts and behavior, maladaptive behavior, and aggression were noted. Fluvoxamine was also shown to be well tolerated, with side effects of mild sedation and nausea being most prevalent.

A placebo-controlled crossover trial of liquid fluoxetine (8 weeks on drug, 8 weeks on placebo) targeting repetitive behavior in 45 children and adolescents with autism and other PDDs revealed that the drug was significantly more effective than placebo [8]. The primary outcome measure targeting repetitive behavior was the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS). Reportedly, side effects of fluoxetine did not differ significantly from placebo in frequency or severity.

More recently a large trial of fluoxetine for the treatment of repetitive behavior in children and adolescents with autism was undertaken by the Autism Clinical Trials Network [9]. This randomized, placebo-controlled trial enrolled 158 patients between the ages of 5 and 17 years with autism. Final results of this study have not yet been published; however, preliminary results report that fluoxetine was no more effective than placebo in reducing repetitive behavior in this population. Fluoxetine was reportedly well tolerated, with no serious adverse events noted.

Citalopram has been shown to lack efficacy in treating repetitive behavior in children with autism and related PDDs [5]. The National Institutes of Health (NIH)-sponsored Studies to Advance Autism Research and Treatment (STAART) Network undertook a 12-week multi-site double-blind, placebo-controlled trial of citalopram for the treatment of repetitive behaviors. In this trial, 149 children with autism and other PDDs ages 5 to 17 years were randomized to receive citalopram (n=73) or placebo (n=76). The primary outcome measures used in this study included the CGI-I scale and the CY-BOCS modified for PDDs (CY-BOCS-PDD). In this trial, there was no significant drug-placebo difference on the CGI-I or the CY-BOCS-PDD. Citalopram was noted to be significantly more likely to cause adverse events such as increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypic behavior, diarrhea, insomnia, and dry skin.

The Research Units on Pediatric Psychopharmaocology (RUPP) Autism Network risperidone trial (discussed in detail below) demonstrated a statistically significant decrease in stereotypy in the risperidone group compared to those receiving placebo [10]. Along this same line, two recent controlled trials of aripiprazole for irritability symptoms demonstrated improvement in stereotypic behavior as a secondary outcome [11-12].

Riluzole, an FDA-approved medication for the treatment of amyotrophic lateral sclerosis in adults, is generating research interest for the treatment of repetitive behavior. Riluzole is believed to inhibit glutamate release and interfere with intracellular events that occur after neurotransmitter binding at excitatory amino acid receptors [79]. Dysregulated glutamate neurotransmission has been hypothesized to play a role in the pathophysiology of autism, thus creating interest in riluzole for treatment of repetitive behavior [18]. Furthermore, a small open-label trial of this medication in treatment-resistant children with OCD showed potential benefit for reducing repetitive behavior [80]. A Phase II NIH-sponsored clinical trial is currently recruiting participants to evaluate the effectiveness of riluzole in the treatment of repetitive behavior in children and adolescents with autism [81].

Repetitive self-grooming behavior in a mouse model of autism has recently been shown to be reduced by treatment with methyl-6-phenylethynyl-pyridine (MPEP), an antagonist of the

mGluR5 metabotropic glutamate receptor [82]. This study used an inbred mouse strain which demonstrates behavioral phenotypes consistent with diagnostic criteria for autism. Treatment of these "autistic" mice with the glutamate receptor antagonist greatly reduced repetitive grooming behavior without causing sedation. This promising study incorporating a mouse model of autism and targeting glutamate as a possible contributor to the pathophysiology of autism, furthers the importance of investigation of glutamate modulators in the treatment of these disorders.

6.2 Hyperactivity and Inattention

Primary research in this symptom domain has focused on psychostimulants; however, the prominence of side effects with these medications has recently prompted investigation of non-stimulant medications, including atomoxetine and guanfacine.

The RUPP Autism Network undertook a 5-site double-blind, placebo-controlled, crossover trial of methylphenidate in 72 children with PDDs and hyperactivity ages 5 to 14 years [83]. The primary outcome measure was the teacher-rated Hyperactivity subscale of the Aberrant Behavior Checklist (ABC). Methylphenidate was shown to be superior to placebo in treating hyperactivity associated with PDDs, as 35 of the 72 patients (49%) showed statistically significant improvement on the primary outcome measure. Unfortunately, 13 of the 72 patients (18%) discontinued the trial due to adverse events, primarily increased levels of irritability. The response rate of this population to methylphenidate was less than that of typically developing children with ADHD, and the rate of adverse events was higher.

A retrospective assessment of atomoxetine, a selective norepinephrine transporter inhibitor approved for the treatment of ADHD in children, adolescents, and adults, suggested potential use for the treatment of these symptoms in children and adolescents with PDDs [84]. Atomoxetine has also been examined in a placebo-controlled crossover pilot trial that demonstrated that it can be effective in treating hyperactivity in some children with autism and related PDDs [44]. The effect size in this small trial was similar to that shown in the larger methylphenidate trial, and fewer side effects were demonstrated. Atomoxetine has also been evaluated in an open-label trial in high-functioning (nonverbal IQ ≥ 70) children with PDDs. This study demonstrated significant improvement in ADHD symptoms, and the medication was generally well tolerated [85]. The results of these trials indicate the need for larger placebo-controlled trials to determine the efficacy and safety of atomoxetine for ADHD symptoms in PDDs.

Guanfacine, an alpha-2 adrenergic agonist FDA-approved for the treatment of hypertension in adolescents and adults, has been investigated for the treatment of ADHD symptoms in autism and related PDDs. A retrospective analysis of 80 cases of autism and PDDs treated with guanfacine demonstrated the agent to be well tolerated and showed symptom improvement in hyperactivity, inattention, insomnia, and tics [86]. A prospective open-label trial of guanfacine in children with PDDs, who did not respond to or tolerate methylphenidate, demonstrated improvement in hyperactivity symptoms in a significant number of participants [87]. In this trial, guanfacine was again well tolerated, although irritability occurred in 3 of the 25 participants, leading to discontinuation of the medication. A recent double-blind, placebo-controlled crossover trial of guanfacine in children with intellectual disability and/or autism or PDDs and symptoms of hyperactivity demonstrated that 45% of trial participants had a reduction of at least 50% on the ABC Hyperactivity subscale [88]. In this study, several side effects, including drowsiness and irritability, were noted. These promising results again indicate the need for larger placebo-controlled trials of guanfacine in the treatment of hyperactivity and inattention in autism and PDDs.

6.3 Irritability

The irritability symptom domain has been the most extensively studied area for treatment within autism, and solid evidence demonstrating the efficacy of atypical antipsychotics in treating severe behavioral disturbance is available. Despite FDA approval of medications targeting this symptom area, the significant side effects associated with the atypical antipsychotics necessitates the need for alternative agents. Research looking at a novel atypical antipsychotic and a GABA receptor antagonist is currently underway.

The RUPP Autism Network evaluated risperidone in the treatment of children with autism and serious behavioral problems [10]. This study was a multisite, randomized, double-blind, placebo-controlled trial of risperidone for the treatment of severe tantrums, aggression, and SIB in 101 children ages 5 to 17 years with autism. The primary outcome measures were the Irritability subscale of the ABC and the CGI-I scale. Thirty-four of 49 children treated with risperidone (69%) were determined to be treatment responders after 8 weeks. In two-thirds of the children showing improvement at 8 weeks, the benefit continued after 6 months of treatment. Unfortunately, adverse events were common in the risperidone group. At 8 weeks, risperidone was associated with a weight gain of 2.7+/-2.9 kg, as well as increased appetite, fatigue, drowsiness, dizziness, and drooling. The short length of the trial also limits inference with respect to the likelihood of development of tardive dyskinesia in this population [10].

An 8-week placebo-controlled, fixed-dose study of aripiprazole in the treatment of children and adolescents with autism and irritability was recently published [11]. This trial evaluated 218 children ages 6 to 17 years with autistic disorder and tantrums, aggression, and SIB. The children were randomized to placebo, 5, 10, or 15 mg/day of aripiprazole. The primary outcome measure was the caregiver-rated ABC Irritability subscale. The clinician-rated CGI-I scale was also administered. At the end of the trial, all doses of aripiprazole demonstrated statistically significant improvement on the primary outcome measure and the CGI-I compared with placebo.

Another aripiprazole study employing flexible dosing demonstrated efficacy in treating irritability in children and adolescents with autism [12]. In this 8-week randomized, double-blind, placebo-controlled study, 98 children ages 6 to17 years with autism and tantrums, aggression, and SIB received either placebo or flexibly-dosed aripiprazole. The majority of patients received either 5 mg/day or 10 mg/day at the end of the study. The primary outcome measures employed were the ABC Irritability subscale and the CGI-I. Improvement was noted from week 1 through week 8 on both measures in the aripiprazole group. Side effects noted in both aripiprazole trials included sedation, drooling, and tremor. All aripiprazole treatment groups also showed a greater increase in weight when compared to placebo [11-12].

Given the prior success of atypical antipsychotics in obtaining FDA approval for treatment of irritability associated with autism, investigations of related medications are ongoing. A Phase III clinical trial investigating the atypical antipsychotic paliperidone extended-release in adolescents and young adults with autistic disorder is currently underway [89]. The primary outcome measures include the ABC Irritability subscale and the CGI-I. As in prior research of medications in the antipsychotic class, secondary measures include assessment of repetitive behaviors, hyperactivity, social responsiveness and improved language usage [89].

Due to the research implicating a role for GABA in the pathophysiology of autism, the effects of arbaclofen, a GABA B receptor antagonist, are being investigated for the treatment of irritability in a Phase II clinical trial with the ABC Irritability subscale as the primary outcome measure [90].

6.4 Core Social Impairment

Recent studies investigating the core social impairment domain of autism have focused their attention on glutamate modulation. Trials of D-cycloserine [13], lamotrigine [14], amantadine [15], and memantine [16] have shown mixed results. Further work related to the neurochemistry of these disorders has focused on oxytocin [68, 71] and secretin [91-98], also with mixed results.

The overlap between negative symptoms of schizophrenia and the social impairment in autism led to investigation of D-cycloserine in autism. D-cycloserine, an FDA-approved antibiotic used to treat tuberculosis, acts as a partial agonist at the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor. Action at this receptor has been shown to be of benefit in the treatment of the negative symptoms of schizophrenia [99]. A single-blind study of D-cycloserine in 12 subjects with autism showed promising results [13]. Following a 2-week single-blind, placebo lead-in phase, subjects were given ascending doses of D-cycloserine (30, 50, 85 mg/day) during three 2-week phases. The primary outcome measures included the CGI-I and ABC Social Withdrawal subscale. Statistically significant improvement on both scales was noted for the 10 subjects finishing the trial. Two subjects withdrew from the study during the placebo phase due to noncompliance and worsening stereotypic behavior, respectively.

Lamotrigine is an anticonvulsant medication which modulates glutamate release. This medication has been investigated in the treatment of autism with less promising results [14]. In a double-bind, placebo-controlled, parallel group study in 28 children ages 3 to 11 years with autism, no statistically significant improvement was shown on any outcome measure, including the Autism Behavior Checklist, the Autism Diagnostic Observation Schedule, the ABC, and the Childhood Autism Rating Scale.

Amantadine, a non-competitive antagonist at the NMDA subtype of glutamate receptor, has also been investigated in autism and related PDDs. A double-blind, placebo-controlled trial in 39 children and adolescents (ages 5 to 19 years) with autism showed mixed results [15]. In this trial, parent ratings of hyperactivity and irritability did not demonstrate statistically significant improvement in the amantadine group versus placebo. However, clinician ratings demonstrated statistically significant improvement in hyperactivity and inappropriate speech. A trend toward improvement was also noted on the CGI-I, however the results on this scale were not statistically significant. Amantadine was well tolerated with mild insomnia being the most prevalent side effect, occurring in 21% of the amantadine group.

Memantine, a glutamatergic antagonist FDA approved for the treatment of Alzheimer's disease, has been investigated as a possible treatment for the core social impairment of autism. A retrospective study in children and adolescents with PDDs demonstrated clinical improvement in social withdrawal after treatment with memantine [16]. This small study, in part, laid the ground work for a subsequent large-scale investigation of memantine as a possible treatment of this core diagnostic feature of autism.

Oxytocin has recently been investigated for treatment of core social impairment in this population [67]. A study investigating the effects of intravenous oxytocin infusion on retention of social information in adults with autism demonstrated improvement in affective speech comprehension versus placebo [68]. Further, a recent study investigating the effects of intranasal oxytocin administration in 13 adults with Asperger's disorder or high-functioning autism (average to above-average intelligence and verbal abilities) showed improved social interactions such as nonverbal communication, as well as subjective report of improved social relatedness [71]. These studies suggest that oxytocin may play a role in social information processing, and indicate the need for further research into oxytocin as a treatment for the core social impairment in autism and related PDDs.

Secretin, a peptide hormone associated with digestion, has been the subject of interest since an anecdotal report of improvement in social behavior in 3 children with autism after an upper gastrointestinal endoscopy [100]. Since that time, multiple comparative and randomized control trials have investigated the role of this peptide under a variety of conditions [91-94]. Subsequent summaries of this data, including systematic review and meta-analysis, have consistently shown this intervention to be ineffective [95-98]. The last clinical trial investigating secretin appears to have closed in 2005 [101].

7. Potential Development Issues

The development of pharmacologic agents effective in treating the interfering symptom domains of autism and related PDDs has encountered many challenges. Limited understanding of the precise etiology of these disorders is a major barrier to drug development. Despite research into the genetics and pathophysiology of these disorders, there remains a lack of reproducible neurobiologic findings. Research has discovered abnormalities in a wide range of monoamines and neuropeptides, numerous possible genetic susceptibility loci, and intriguing immunologic findings. However, attempts to replicate these findings have often been met with contradictory results. This lack of replicable research results has hindered translational research efforts [3].

The broad range of disorders and symptom severity encompassed by the autism spectrum also contributes to difficulties encountered in pharmacologic treatment development. Within the diagnostic criteria for these disorders there is wide variability in level of impairment. This variability impacts both neurobiologic research and pharmacologic investigation, as the heterogeneity in the pathophysiology of these disorders is likely related to the inconsistent treatment responses to various medications. Furthermore, the interfering symptoms associated with these disorders often change across an individual's lifespan. As demonstrated by the opposing outcomes in trials investigating the use of SSRIs in the treatment of repetitive behavior in adults versus children [5, 7], variability in developmental neurobiology may be another contributing factor.

Autism and related PDDs present in early childhood, therefore often making children with interfering symptoms the initial recipients of pharmacologic agents. Pharmacologic investigation is particularly difficult with children due to the need for increased safety concerns. Medications indicated for treatment of the most disruptive behaviors associated with autism and related PDDs are fraught with potentially significant side effects, including metabolic syndromes and movement disorders. These considerations present challenges in the design of large-scale trials of novel pharmacologic agents in children.

Despite the relative increase in prevalence of autism and related PDDs, as demonstrated by the most recent Centers for Disease Control investigation, they remain relatively uncommon [4]. This limitation further compounds the difficulties inherent in recruiting large cohorts of research subjects for pharmacologic trials.

8. Conclusion

Autism and related PDDs encompass a large spectrum of disorders defined diagnostically by impairments in communication, social relatedness, and behavioral flexibility. FDA-approved treatments for interfering symptoms associated with these disorders remain limited. The need for more effective pharmacologic agents is driven by the growing prevalence of these disorders. Neurobiologic research has met with difficulty elucidating the various etiologies of these disorders. The majority of studies have been unable to demonstrate reproducible evidence of involvement of specific monoamines and neuropeptides, immune functions, or genetic factors, though a number of possibilities have been discovered.

Current pharmacologic research has focused on treatment of interfering symptom domains, including stereotypic behavior, hyperactivity, irritability, and social impairment. Pharmacologic management of repetitive behavior has focused on SRIs, though recent research has failed to find a separation of SRIs from placebo, particularly in children and adolescents. Hyperactivity has been shown to be manageable in some cases with psychostimulants, though the occurrence of interfering side effects has prompted investigation of non-stimulant medications. Large-scale investigations of the atypical antipsychotics risperidone and aripiprazole have demonstrated their efficacy in the management of irritability, though the presence of significant side effects may limit their usefulness over time. Core social impairment has proven a most difficult symptom domain to treat pharmacologically, though glutamate modulators have revealed some promising results. Further research both into the neurobiology of autism and related PDDs and pharmacologic agents for treatment of interfering symptoms associated with these disorders is needed.

9. Expert Opinion

Despite progress in the development of pharmacologic treatments for a number of interfering symptom domains associated with autism and other PDDs, a great deal of work remains. The repetitive and stereotypic behavior characteristic of autism is both a core diagnostic feature and, at times, an interfering symptom type. In large part, however, repetitive behavior is performed by the individual in an effort to reduce anxiety and agitation. In this case, attempts to eliminate or reduce it with a drug or non-drug treatment may be contraindicated. While SSRIs have been shown to be the most effective drug monotherapy for treating symptoms of OCD, not all things that are repetitive in nature can be equated with obsessions and compulsions. Although it was a logical starting point, it may have been naïve to believe that SSRIs would be particularly effective for treating the repetitive and stereotypic behavior of autism. The two drugs FDA-approved for the treatment of irritability in children and adolescents with autism, risperidone and aripiprazole, were each shown to be more effective than placebo for reducing stereotypic behavior. Due to their significant potential side effects, however, it will be important to continue to search for alternative treatment approaches with a more favorable safety profile, for this symptom domain. Studies of combined treatment with drugs and behavior therapy may also prove beneficial.

As with the SSRIs, a similar lesson may have been learned with regard to the pharmacologic treatment of motor hyperactivity and inattention associated with autism. Individuals with autism can be extremely hyperactive, impulsive and distractible. Again, however, these symptoms are associated with a number of neuropsychiatric disorders. To assume that psychostimulants would be as effective across these varied conditions, including autism, as they are in ADHD, may have been too much to ask. That the efficacy and tolerability of psychostimulants in autism are vastly different from what is seen in ADHD should therefore not be that surprising. In order to move treatment of this constellation of symptoms forward, the field needs a better understanding of the neural dysfunction underlying what we currently refer to as “inattention” and “hyperactivity” in autism. Utilizing functional imaging approaches to differentiate these symptoms between those with autism and ADHD may be useful in this regard.

Among the drug treatments of interfering symptom domains discussed in this review, the most robust response is that of irritability to antipsychotics, particularly those with prominent affects at the dopamine D2 receptor. Continued pursuit of drugs within this class may result in incremental advances, particularly in identifying drugs with fewer side effects. Significant steps forward, however, will likely not occur until novel compounds with effects

on other neurochemical or biological systems emerge, possibly from studies in related disorders with a known etiology, like fragile X syndrome or from genetic research or animal models.

Some may argue that it is impossible that a drug or class of drugs will emerge as a consistently effective treatment for the core social and communicative impairment of autism. Certainly that is true to date. On the other hand, it is clear that drugs can improve the social dysfunction associated with a number of neuropsychiatric conditions, such as social anxiety disorder. Antidepressants clearly alter the reduced social interest/function associated with major depressive disorder. And, at least to some extent, the second generation antipsychotics can lead to a decrease in the so-called negative symptoms of schizophrenia. Whether a pro-social neurohormone like oxytocin or a drug with prominent effects at particular sites within glutamate systems will prove useful for this purpose remains to be determined. Combining drugs with social skills training approaches should also be considered.

There are other interfering symptoms associated with autism and other PDDs that have yet to be addressed from a pharmacotherapeutic perspective. These include sleep disorders, “anxiety” and depression, among others. Clinicians currently use a number of different drugs to treat disturbed sleep in autism. It will be important to begin to conduct randomized controlled trials of drugs that hold some clinical promise for sleep disorders in autism. Objectifying changes in sleep architecture, with polysomnograms for example, will require careful consideration for this patient population. Most clinicians would agree that “anxiety” occurs commonly in autism. Efforts to better characterize this “anxiety” are needed; determining if/how it relates to currently defined disorders (i.e., social anxiety disorder, OCD, generalized anxiety disorder) will be challenging but necessary. A number of “higher-functioning” individuals with autism, Asperger's disorder or PDD NOS appear to become depressed during late elementary school and beyond. Will this “depression” respond to antidepressants as it does in children and adolescents with primary mood disorders? This important question has yet to be addressed in a systematic manner.

Most persons with autism and other PDDs present for a psychopharmacologic evaluation with interfering symptoms in a number of domains. There is not one drug that effectively treats interfering repetitive behavior, irritability, hyperactivity and impaired social relatedness. As a result, this often necessitates the use of more than one agent if multiple domains of symptom interference exist. Because clinicians are confronted with this situation on a daily basis, researchers will need to address this area of study in the very near future via combination drug treatment studies.

There are more adults with autism and other PDDs than children. To date, only a very limited number of controlled drug trials have been completed in adults. Because developmental differences are likely to contribute to treatment response, it seems imperative that studies including adults with autism be conducted. If reports of increased prevalence and possibly incidence of autism are accurate, this need may be even more critical.

A tremendous degree of clinical heterogeneity exists among persons with autism and other PDDs. No etiology has been identified for the majority of cases. Considering this, the development of effective pharmacologic treatments for a number of disabling symptoms associated with these disorders is commendable. In order for significant further advances to be made, however, a paradigm shift is necessary. To continue to investigate heterogeneous samples of patients with autism and other PDDs as we currently do is unlikely to result in the identification of novel, viable drug targets in the near future. Efforts are needed to better define meaningful subtypes of these disorders for research studies, in order to avoid

continued findings that are non-replicable. Whether genetic, post-mortem or neuroimaging approaches will assist in this regard remains to be seen. It may be that broader etiologic mechanisms common to disease manifestation in other areas of medicine will need to be considered for this purpose.

Acknowledgments

C A Erickson receives research grant support from Roche, Bristol-Myers Squibb and Seaside Therapeutics. C A Erickson's work is also supported in part by The Division of Disability & Rehabilitative Services, Indiana Family and Social Services Administration; National Institute of Health grant K12 UL1 RR025761 Indiana University Clinical and Translational Sciences Institute Career Development Award. M Plawecki is a recipient of the American Psychiatric Institute for Research and Education (APIRE)/Janssen Psychiatric Resident Scholars Fellowship. C J McDougle is a consultant, receives grand support, and serves on the Speaker's Bureau for Bristol-Meyer Squibb. C J McDougle's work is also supported in part by The Division of Disability & Rehabilitative Services, Indiana Family and Social Services Administration; NIMH grant R01 MH072964.

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Table 1

Examples of New Developments in the Treatment of Autistic Disorder[1]

Compound	Company*	Indication - Target	Stage of Development	Mechanism of Action
Fluoxetine ODT	Neuropharm	Autism - *Repetitive Behavior*	Pre-registered	Selective Serotonin Reuptake Inhibitor
Citalopram	Forest	Autism – *Repetitive Behavior*	Phase II	Selective Serotonin Reuptake Inhibitor
Riluzole	Sanofi-Aventis	Autism - *Repetitive Behavior*	Phase II	Glutamate Antagonist
MPEP	Novartis	Autism - *Repetitive Behavior*	Preclinical	Metabotropic Glutamate Antagonist
Atomoxetine	Eli Lilly & Co	Autism – *ADHD Symptoms*	Phase III	Selective Norepinephrine Reuptake Inhibitor
Methylphenidate	Novarits**	Autism – *ADHD Symptoms*	Phase II	Norepinephrine and Dopamine Reuptake Inhibitor
Guanfacine	AH Robbins**	Autism – *ADHD Symptoms*	Phase II	Alpha-2 Adrenergic Agonist
Risperidone	Johnson & Johnson**	Autism - *Irritability*	FDA-approved	Dopamine D2 Antagonist;Serotonin 2A Antagonist
Aripiprazole	Otsuka – Bristol-Myers Squibb	Autism - *Irritability*	FDA-approved	Dopamine D2 Partial Agonist;Serotonin 2A Antagonist;Serotonin 1A Partial Agonist
Paliperidone	Johnson & Johnson	Autism - *Irritability*	Phase III	Serotonin 2A Antagonist;Dopamine D2 Antagonist
Arbaclofen	Seaside Therapeutics	Autism - *Irritability*	Phase II	GABA B Agonist
Secretin	RepliGen	Autism – *Social Impairment*	Phase III	Secretin Agonist
Memantine Hydrochloride	Forest	Autism – *Social Impairment*	Phase II	NMDA Antagonist; Glutamate Release Antagonist
D-cycloserine	Eli Lilly & Co**	Autism – *Social Impairment*	Phase III	NMDA Modulator
Lamotrigine	GlaxoSmithKline**	Autism – *Social Impairment*	Phase II	Glutamatergic Modulator
Amantadine	Endo**	Autism – *Social Impairment*	Phase II	NMDA Antagonist
AFQ-056	Novartis	Autism	Preclinical	Metabotropic Glutamate 5 Antagonist
CM-AT	CureMark	Autism – *Core symptoms*	Phase III	Digestive Supplement

* Indicates primary US manufacturer.

** Indicates that the compound is available as a generic and/or multiple formulations of the pharmaceutical are produced by several manufacturers. MPEP: methyl-6-phenylethynyl-pyridine

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