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Chapter · February 2019

DOI: 10.1017/9781108297769.008

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MNU 1481878 / 50377317

Title: Autism and Pervasive Developmental Disorders
ArticleTitle: Psychopharmacology of Autism Spectrum Disorder.
ArticleAuthor: Mooney L, Fosdick C, Erickson CA.
Date: 2019 Pages: 158-75

Chapter 7

Psychopharmacology of Autism Spectrum Disorders

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Introduction

While no drug treatments have proven to be effective in targeting the core social and communicative impairments of autism spectrum disorders (ASD), many drug treatment strategies may be effective in targeting the interfering symptoms and behaviors that often co-occur in the disorder. Primary drug targets of treatment in ASD include irritability marked by aggression, self-injury, and severe tantrums, co-morbid attention deficit hyperactivity disorder (ADHD) symptoms, interfering repetitive behavior, and anxiety among other concerns. Despite a growing body of literature informing psychotropic drug prescribing in ASD, the majority of prescribing in ASD remains off-label and subject to a limited evidence base. Following review of psychotropic drug use organized by target symptoms of treatment, we review several compounds undergoing clinical study targeting the core social impairment of the disorder.

Irritability

Irritability marked by physical aggression, self-injurious behavior (SIB), and severe tantrums is a common target of drug treatment in ASD (Posey et al., 2008). The behaviors that comprise irritability can become a greater concern to families compared to the core features of the disorder (Hastings et al., 2005; Lecavalier et al., 2006). Irritability often becomes a target of psychotropic drug treatment when the behaviors become refractory to non-drug environmental management and behavioral therapy approaches and present a risk to the individual or others around them and/or when such behavior significantly impedes participation in activities and therapies (Stigler & McDougle, 2008). Reduction of interfering irritability in persons with ASD is an evidence-based treatment approach designed to enhance individual and family safety while working to improve overall stakeholder quality of life.

Second-Generation Antipsychotics

Over the last 20 years, atypical or second-generation antipsychotics (SGAs) have become the most commonly prescribed drug class targeting irritability in ASD (Politte & McDougle, 2014). SGAs have significantly reduced rates of extra pyramidal symptoms compared to first-generation agents. Specifically among SGAs, risperidone and aripiprazole are United States Food and Drug Administration (FDA) approved for the treatment of irritability in youth with ASD.

Risperidone: The short-term efficacy of risperidone targeting irritability in youth with ASD has been established in two large double-blind, placebo-controlled trials

(McCracken et al., 2002; Shea et al., 2004). In an 8-week, multisite, randomized, double-blind, placebo-controlled flexible dosing 8-week trial in 101 children aged 5–17 years, risperidone use was associated with a significant reduction in irritability as measured by the caregiver report Aberrant Behavior Checklist – Irritability subscale (ABC-I (M.G. Aman et al., 1985)) compared to placebo (56.9% reduction with risperidone versus 14.1% with placebo) (McCracken et al., 2002). In this report, significantly higher clinical response rates were noted in the risperidone treated group (56.9%) compared to the placebo response rate (12%). Risperidone use was associated with significant weight gain (mean 2.7 kg compared to 0.8 kg mean gain with placebo) as well as increased appetite, tiredness, and drooling compared to placebo. In a 6-month, open-label extension trial phase, two-thirds of those responders initially receiving risperidone continued to show positive response at 6 months (23 of 34 subjects remaining responders). In further follow-up, original participants from the double-blind, short-term trial were continually followed for an average of 21 months (Aman et al., 2015). In this long-term, open-label group, risperidone use continued to remain effective targeting irritability and concerns including weight gain, increased appetite, and enuresis were associated with long-term risperidone use (Aman et al., 2015).

Consistent with the first Research Units on Pediatric Psychopharmacology (RUPP) autism units double-blind, placebo-controlled risperidone trial, in an 8-week, double-blind, placebo-controlled study in 5- to 12-year olds with pervasive developmental disorder (PDD; diagnoses inclusive of autistic disorder, PDD-NOS, and Aspergers). Shea et al. (2004) reported a 64% risperidone-associated reduction in the ABC-I which was significantly higher than the 31% reduction noted with placebo use. In this report, risperidone use was associated with frequent somnolence (72.5%) and weight gain (2.7 kg gained versus 1 kg with placebo).

A single, double-blind, placebo-controlled trial of risperidone in adults with ASD preceded the two youth trials that led to FDA approval of risperidone in pediatric autism. McDougle et al. (1998) conducted a 12-week, double-blind, placebo-controlled, parallel groups trial of risperidone in 31 adults (mean age = 28.1 years) with autistic disorder or pervasive developmental disorder not otherwise specified (PDD-NOS) (McDougle et al., 1998). In this report, 8 of 14 persons receiving risperidone compared to none of 16 receiving placebo were judged treatment responders and significant risperidone-associated improvement was noted in anxiety, irritability, aggression, repetitive behavior, and depression. Overall, risperidone was well tolerated with only transient mild sedation noted.

Since the seminal placebo-controlled trials which form the foundation for risperidone prescribing in ASD today, many additional systematic risperidone treatment papers have confirmed the original findings and continued to note consistent adverse effect risks including prolactin elevation, sedation, and weight gain among other adverse effects (Fitzpatrick et al., 2016).

Aripiprazole: Aripiprazole is FDA-approved for treatment of irritability in youth with ASD based on the finding of two large double-blind, placebo-controlled trials in this population. Ninety-eight youth aged 6–17 years with autistic disorder enrolled in an 8-week, double-blind, placebo-controlled, parallel groups trial of flexibly dosed aripiprazole (5, 10, or 15 mg daily) versus placebo (Owen et al., 2009). In this report, aripiprazole use was associated with significant overall clinical improvement and significant reductions in irritability as measured by the ABC-I as compared to placebo. Regarding tolerability, aripiprazole use was associated with significant weight gain (2.0 kg versus 0.8 kg) and

higher rates extrapyramidal symptoms (EPS; 14.9% versus 8% EPS rate on placebo). No serious aripiprazole-associated adverse effects were noted.

A larger ($n = 218$) fixed dose (5 mg, 10 mg, 15 mg, or placebo) 8-week, short-term, efficacy study of aripiprazole in youth with autistic disorder targeting irritability noted significant drug-associated reductions in irritability as measured by the ABC-I at each dose evaluated (Marcus et al., 2009). The most common adverse effect leading to aripiprazole discontinuation was sedation and significant weight gain compared to placebo, which were noted at each dose evaluated. In contract to findings from risperidone studies in ASD, no prolactin elevations were noted with either placebo-controlled aripiprazole registration trials in youth with ASD. In fact, significant reductions in prolactin compared to placebo were noted in both reports.

In a 52-week, open-label, long-term, follow-up of the fixed-dosing aripiprazole study ($n = 199$, youth with ASD aged 6–17 years), reductions in irritability, as measured by average ABC-I scores, were unchanged throughout long-term follow-up (Marcus et al., 2011). Over long-term use, aripiprazole was generally well-tolerated, though weight gain, dyslipidemia, and extrapyramidal symptoms were significant concerns with long-term use (Marcus et al., 2011).

In a comparison trial of aripiprazole (mean dose = 5.5 mg/day) and risperidone (mean dose = 1.12 mg/day), 59 youth (aged 4–18 years) with ASD showed similar drug-associated improvement in irritability as measured by the ABC-I and similar adverse effect rates overall (Ghanizadeh et al., 2014). Most commonly reported adverse effects include drowsiness, drooling, and weight gain. Wink et al. (2014) compared change in age- and gender-adjusted body mass index Z-scores in 142 persons with ASD aged 2–20 years receiving long-term aripiprazole (mean 1.47 years of treatment; mean dose 11.9 mg/day) or risperidone (mean 2.37 years of treatment; mean dose 2.23 mg/day) monoantipsychotic therapy (Wink et al., 2014). No difference in BMI Z-score change was noted between the treatment groups. Available evidence does not aid in delineating a differential response rate or differing overall tolerability profile between risperidone and aripiprazole use targeting irritability in persons with ASD.

Paliperidone: Paliperidone is the active metabolite of risperidone administered in an extended release Oros formulation. Despite the drug's relationship to risperidone, paliperidone has not been subject to placebo-controlled testing in persons with ASD. The drug did show promise in a prospective 8-week, open-label study where 21 of 25 persons with autistic disorder (84%) showed significant clinical improvement in symptoms of irritability with treatment (Stigler et al. 2012). Clinical response was defined by a combination of a score of "much" or "very much improved" on the CGI-I and improvement on the ABC-I. Weight gain and prolactin elevation were noted with treatment comparable to reports of risperidone use in this population. Paliperidone is available in a sustained-release injectable version paliperidone palmitate. A single case report described administration of 39 mg of paliperidone palmitate monthly in a 5-year-old child with severe aggression and refusal to take medications by mouth (Kowalski et al., 2011). In this case, significant behavioral improvement was noted across domains including irritability, stereotypy, and hyperactivity. Significant weight gain was noted with treatment (Kowalski et al., 2011).

Quetiapine: Quetiapine has been the subject of several open-label reports, however, no placebo-controlled data supporting the drug's use are available. Over 12-weeks of open-label treatment, 2 of 9 boys (22%) with autism aged 10–17 years were judged clinical responders (Findling et al., 2004). Over 8-weeks of treatment in 11 subjects (13–17 year olds) with ASD, quetiapine use was reportedly well tolerated and associated with reductions in aggressive behavior and sleep disturbances (Golubchik et al., 2011). Corson et al. (2004) described quetiapine treatment (mean dose 248.7 mg/day) over a mean 59.8 weeks of treatment in 20 youth and young adults with pervasive developmental disorder (Corson et al., 2004). Eight subjects (40%) were judged treatment responders and 10 (50%) experienced adverse drug effects leading to drug discontinuation in 3 (15%) participants.

Olanzapine: Limited data is available describing systematic use of olanzapine targeting irritability in persons with ASD. In a small ($n = 11$) double-blind, placebo-controlled, parallel groups with 8-week trial, 50% of those receiving olanzapine versus 20% of those receiving placebo were considered treatment responders (Hollander et al., 2006). Olanzapine was associated with significant weight gain compared to placebo (mean gain of 7.5 pounds versus 1.5 pounds on placebo). In a small comparative effectiveness trial of olanzapine versus haloperidol in 12 youth (mean age = 7.8 years) with autism, 5 of 6 youth receiving olanzapine versus 3 of 6 youth receiving haloperidol were judged to be clinical responders (Malone et al., 2001). Olanzapine was associated with significantly more weight gain than other second-generation antipsychotics commonly prescribed targeting irritability in a sample of 202 persons with ASD (Yoon et al., 2016). Weight gain remains a limiting factor in olanzapine use in ASD.

Ziprasidone: Ziprasidone use has been the subject of open-label and chart review reports in ASD. The clear benefit of ziprasidone compared to other SGAs is weight neutrality. In a 6-week, open-label, pilot study, 9 out of 12 (75%) adolescents with ASD showed clinical improvement on the CGI-I (Malone et al., 2007). Ziprasidone-associated adverse effects included sedation, dystonic reaction, and QTc prolongation (mean increase of 14.7 ms). Dominick et al. (2015) reviewed systematic treatment with ziprasidone (mean dose 98.7 mg) in 42 youth (mean age 11.8 years) with ASD (Dominick et al., 2015). Seventeen participants (40%) were deemed clinical responders based on CGI-I scores of "much" or "very much improved." No changes in BMI, QTc interval, or other vital signs were noted. The treatment primarily represented patients who had failed FDA-approved SGAs due to lack of clinical response or because of adverse effects with other agents, primarily excessive weight gain.

Clozapine: While clozapine likely holds promise as a drug treatment of severe, treatment-resistant irritability in persons with ASD, usage of the drug is limited by the agent's risk profile. The requirement of regular blood draws to monitor for potentially life-threatening agranulocytosis at times limits the feasibility of clozapine use in this population. Prescribing and dispensing clozapine must be done through the FDA-mandated Clozapine Risk Evaluation and Mitigation Strategy (Clozapine REMS) due to this monitoring need. The published evidence supporting clozapine use in persons with ASD is limited to case reports, chart reviews, and case series (Beherec et al., 2011; Chen et al., 2001; Gobbi & Pulvirenti, 2001; Lambrey et al., 2010; Wink et al., 2016). In a review of inpatient treatment of severe drug-refractory irritability in 5 youth with ASD (mean age 13.1 years), clozapine use (mean dose 380 mg) was associated with clinical improvement in each youth. Long-term safety data describing clozapine use in ASD is not available. Clozapine remains a potential effective treatment of severe irritability in ASD, though safety concerns and the requirement of chronic lab monitoring during treatment limit the use of this drug.

Lurasidone: Lurasidone use is not rooted in evidence for use in ASD. Lurasidone was not associated with significant clinical improvement compared to placebo in a 6-week, 150-subject controlled trial targeting irritability in youth with ASD (Loebel et al., 2016).

Lurasidone use in ASD remains limited given the negative trial results in a field with more evidence-based effective agents are available (McClellan et al., 2017).

First-Generation Antipsychotics

Haloperidol: The efficacy of haloperidol in youth with ASD targeting irritability has been demonstrated in multiple placebo-controlled studies conducted in the 1970s and 1980s (Anderson et al., 1984, 1989; Campbell et al., 1978, 1979). In 40 young children (aged 2.3–6.9 years) with autistic disorder, a placebo-controlled study of haloperidol use (dose range 0.5–3.0 mg/day) was associated with significant clinical improvement as measured by the CGI-I when paired with language training compared to language training alone (Anderson et al., 1984). Sedation, acute dystonic reactions, extrapyramidal symptoms, and withdrawal dyskinesias were the most frequent adverse effects noted across short-term studies in ASD (Anderson et al., 1984, 1989; Campbell et al., 1978). While haloperidol is an evidence-based treatment for interfering behavior in persons with ASD, given concern over higher rates of extrapyramidal symptoms, haloperidol is generally considered a second line treatment following failures with evidence-based SGAs.

Non-antipsychotic Medications

Clonidine: Clonidine is an alpha-two agonist developed for the treatment of hypertension and now additionally FDA-approved in a long-acting formulation for the treatment of ADHD. Clonidine use has been described to target broad interfering symptoms in a small number of youth with ASD. Eight youth (aged 5–10 years) with ASD participated in a short-term, placebo-controlled trial of clonidine (Jaselskis et al., 1992). In this report clonidine use was associated with improvement on teacher, but not clinician, reported ratings across behaviors including hyperactivity, irritability, and stereotypy. In a review of systematic treatment in 19 youth with ASD receiving immediate release of clonidine, some clinical improvement was generally noted in aggression, insomnia, and hyperactivity (Ming et al., 2008). Daytime clonidine presents a risk for sedation. Use of this drug targeting irritability remains limited compared to antipsychotic use.

Lithium: Lithium is not a first line treatment for ASD-associated irritability (Accordino et al., 2016), but there is some evidence to support its use in cases of irritability in the context of significant co-morbid mood symptoms. Siegel et al. (2014) conducted a systematic review of lithium treatment in 30 inpatients with ASD treated with lithium (Siegel et al., 2014). Overall, only 13 of the 30 patients (43%) studied showed significant clinical improvement. The response rate was much higher (71%) for children with significant mood disorder symptoms prior to treatment, especially those with symptoms concerning co-morbid bipolar disorder. Mean serum lithium levels reported were 0.70 mEq/L. Almost half of those receiving lithium (47%) reported treatment-associated adverse effects including, most commonly, emesis (13%), tremor (10%), fatigue (10%), irritability (7%), and enuresis (7%). Two adolescents with ASD associated with Phelan-McDermid Syndrome reportedly responded clinically to lithium use including improvements in behavior and catatonia-like symptoms previously unresponsive to benzodiazepines (Serret et al., 2015). While lithium may have a role for the treatment of irritability in the context of significant mood symptoms in ASD, the drug's use remains limited to second-line status given the need to monitor for therapeutic/toxic drug levels and given risks of renal impairment and thyroid dysfunction (McKnight et al., 2012).

Antiepileptics: Given the elevated risk of epilepsy in ASD, there is some thought that seizure or seizure-like activity may contribute to behavioral disturbance in some persons with autism. A meta-analysis reviewed seven double-blind, randomized, placebo-controlled studies of antiepileptic drugs (AEDs) in ASD (4 with valproic acid; 1 lamotrigine; 1 levetiracetam; 1 topiramate) targeting irritability or general interfering behavior demonstrated no difference between drug and placebo treatment (Hirota et al., 2014). The authors noted that the limited number and small size of AED studies in ASD must be considered when interpreting the results of the meta-analysis. Looking at the individual studies included in the meta-analysis, lamotrigine and levetiracetam did not separate from placebo, and valproic acid yielded mixed results. The most studied AED in ASD, valproate, was not associated with increased response compared to placebo in a short-term randomized, double-blind, placebo-controlled trial in 30 youth (aged 6–20) with ASD (Hellings et al., 2005). In a separate double-blind, placebo-controlled trial of valproate in 27 youth (mean age 9.5 $\pm$ 2.5 years) with ASD with severe irritability, valproate use was associated with significant reduction in irritability compared to placebo (Hollander et al., 2010). In this report, higher blood valproic acid levels correlated with enhanced clinical response. Given the mixed results with valproate combined with the requirement to monitor valproic acid drug levels and the risks of liver toxicity, hyperammonemia, and rare pancreatitis, use of valproate targeting interfering behavior in ASD remains second-line treatment.

N-Acetylcysteine (NAC): NAC is an antioxidant used to treat acetaminophen overdose and available as a supplement without prescription. NAC is known to support glutathione formation and impact extracellular glutamate levels. In a 12-week, double-blind, placebo-controlled evaluation of NAC (titrated up to 2,700 mg/day given in divided doses), oral NAC was well-tolerated and NAC use was associated with significant improvement on the ABC-I compared to placebo (Hardan et al., 2012). Dean et al. (2016) conducted a 6-month, double-blind, placebo-controlled trial of NAC 500 mg daily in 102 youth (aged 3.1–9.9 years; 98 subjects with available data) with ASD (Dean et al., 2016). NAC use was not associated in any positive clinical change across a number of caregiver and clinician reported outcome measures. The authors hypothesized that NAC may have been under-dosed in this evaluation. Wink et al. (2016) conducted a 12-week, double-blind, placebo-controlled trial of NAC (mean daily dose of 56.2 mg/kg) in 31 youth (age range 4–12 years) with ASD (Wink et al., 2016). In this report, NAC use was associated with significant increase in blood glutathione levels, but no clinical improvement was noted across caregiver and clinician report measures. The results of NAC testing in ASD remain mixed, marked by a solid tolerability profile and inconsistent reports describing effectiveness in reducing interfering behavior.

Naltrexone: Naltrexone is an opioid antagonist used in addictive disorders that has been studied as a potential treatment for self-injury in ASD. A systematic review of 10 heterogeneous naltrexone trials including an overall 127 subjects receiving naltrexone and 27 receiving placebo observed that generally naltrexone use was associated with reduction in irritability and hyperactivity though the strength of the evidence was limited by the trial designs (Roy et al., 2015). Across trials, there was no evidence of improvement in core features of ASD. Sedation, emesis, and weight loss were common adverse effects noted with some risk of liver toxicity noted with continued dosing. Naltrexone use remains of limited potential in targeting irritability in ASD.

Attention-Deficit/Hyperactivity Disorder

ADHD symptoms commonly occur in persons with ASD, often contributing to functional impairment (Leyfer et al., 2006). While many of the same agents are used to treat co-morbid ADHD in persons with ASD as in the general population of persons with ADHD, some differences in drug response and tolerability will be highlighted below to inform ASD-specific prescribing.

Methylphenidate: Methylphenidate derivatives have undergone double-blind, placebo-controlled study targeting ADHD symptoms in youth with ASD. In placebo-controlled conditions, overall methylphenidate is associated with significant improvement in ADHD symptoms with an average estimated positive response rate of 50% (Handen et al., 2000; Quintana et al., 1995; Reichow et al., 2013; Research Units on Pediatric Psychopharmacology Autism, 2005). Adverse effects associated with stimulant use including insomnia, behavioral activation/irritability, appetite loss, and social withdrawal may occur at higher rates in ASD compared to populations of youth with neurotypical development (Handen et al., 2000; Research Units on Pediatric Psychopharmacology Autism, 2005). For example, the RUPP (2005) trial of methylphenidate in youth with ASD noted a total 18% discontinuation rate due to adverse effects including overall rates of treatment-associated irritability noted in about 1 in 10 youth (Research Units on Pediatric Psychopharmacology Autism, 2005). As a point of comparison, the RUPP trial overall positive clinical response rate of 49% is lower than the 77% positive response rate in the Multimodal Treatment Study in Children with ADHD (MTA) trial and the overall discontinuation rate of 18% due to adverse effects is higher than the 1.4% discontinuation rate in the MTA project (Greenhill et al., 2001; Research Units on Pediatric Psychopharmacology Autism, 2005). Stimulant-associated adverse effect rates may peak in the preschool age range where 50% of younger children with ASD had difficulties tolerating methylphenidate (Ghuman et al., 2009). In a large retrospective chart review, using DSM-IV-TR criteria, methylphenidate clinical response significantly increased in those more mildly impact by ASD symptomatology who were diagnosed with Asperger's disorder or Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS) compared to those with full autistic disorder (Stigler et al., 2004). While clearly methylphenidate shows promise in the treatment of ADHD symptoms in persons with ASD, given reduced clinical response rates and reduced tolerability in the ASD population, stimulant use in ASD requires a level of caution beyond that required during use in typically developing youth.

Guanfacine: Guanfacine is an alpha-2-agonist FDA approved for the treatment of hypertension that for many years has been used off-label in the treatment of ADHD in youth and now more recently an extended release guanfacine (guanfacine ER) formulation has been FDA-approved for the treatment of ADHD. Scahill et al. (2015) reported on the impact of guanfacine ER (modal dose 3 mg/day; range 2–4 mg/day) in 62 youth (mean age 8.5 years) participating in a double-blind, placebo-controlled, short-term 8-week, multi-site trial (Scahill et al., 2015). In this report, guanfacine ER use was associated with significant reductions in hyperactivity as measured by the ABC Hyperactivity subscale (ABC-H). Overall clinical response to drug was significantly greater with guanfacine ER (50% rated as "very much" or "much improved" on the CGI-I) versus a 12.5% positive clinical response rate in those receiving placebo. Overall guanfacine ER use was well tolerated with no increased rates of study discontinuation noted in those receiving guanfacine. The most common guanfacine ER associated adverse effects were drowsiness/fatigue and reduced appetite. In a smaller 11 subject double-blind, placebo-controlled crossover trial, guanfacine use in youth aged 5–9 years was associated with significant general clinical improvement and reduction in teacher-rated hyperactivity (Handen et al., 2008). Drowsiness was the most common reported adverse effect in this report. Given the tolerability and response rate is comparable if not exceeding stimulant response rates in ASD, guanfacine is often considered a first-line ADHD agent in youth with ASD.

Atomoxetine: Atomoxetine is FDA approved for the treatment of ADHD in youth. Three placebo-controlled studies have evaluated the short-term efficacy of atomoxetine targeting ADHD symptoms in youth with ASD (Arnold et al., 2006; Handen et al., 2015; Harfterkamp et al., 2012). In a double-blind, placebo-controlled, 8-week trial of atomoxetine (1.2 mg/kg/day) in 97 youth aged 6–17 years with ASD, the overall clinical response rate to atomoxetine (20.9%) was not significantly higher than response to placebo (8.7%) (Harfterkamp et al., 2012). Handen et al. (2015) conducted a 10-week, double-blind, placebo-controlled study of atomoxetine (max 1.8 mg/kg/day) combined with or without standard parent training versus placebo in 128 subjects (5–14-year-old youth) with ASD (Handen et al., 2015). In this report, atomoxetine use and parent training were associated with significant reduction in ADHD compared to placebo. Atomoxetine use was associated with reduced appetite but was otherwise well-tolerated. In a small placebo-controlled, 6-week treatment period crossover trial involving 16 youth with ASD (age range 5–15 years), atomoxetine use was associated with significant reductions in hyperactivity as measured by the ABC-H (effect size = 0.9) (Arnold et al., 2006). With conflicting results regarding the short-term efficacy of atomoxetine in ASD, this drug remains a second-line treatment of ADHD symptoms in youth with autism.

Interfering Repetitive Behavior

Restrictive and repetitive behaviors and activities are a core feature of ASD and often are significantly interfering for individuals and their families. Limited positive data exists describing drug-associated reduction in repetitive behavior in ASD. In 18 young children (age range 4.5–7.2 years) with autistic disorder, haloperidol use was associated with significant reduction in stereotypic movements compared to placebo (Campbell et al., 1978). The impact of valproic acid in persons with ASD has yielded mixed results. In a small 13 subject, double-blind, placebo-controlled, 8-week trial of valproic acid in subjects with ASD, valproic acid was associated with significant improvement in repetitive behavior as measured by the Children's Yale Brown Obsessive Compulsive Scale (CY-BOCS) (Hollander et al., 2006). In a subsequent 12-week, double-blind, placebo-controlled trial of valproic acid targeting irritability in youth with ASD, no valproic acid-associated improvement was noted in repetitive behavior as measured by the CY-BOCS (Hollander et al., 2010). Despite a strong evidence base for use in obsessive-compulsive disorder (OCD), a disorder whose features share some overlap with interfering repetitive behavior in ASD, SSRIs have not been successful in targeting interfering repetitive behavior in autism. A recent Cochrane review evaluated 9 randomized, controlled trials of SSRIs involving a total of 320 individuals with autism (Williams et al., 2013). This evaluation involved three fluoxetine studies and two studies each involving fenfluramine, citalopram, or fluvoxamine. Four studies involved adults and five youth with ASD. Overall, the review concluded that there is no evidence of positive effect from SSRIs in youth with ASD and some emerging

evidence of SSRI-associated harm in this population including risk of behavioral agitation/disinhibition (King et al., 2009). In adults, there is limited evidence of SSRI effectiveness including specific use of fluvoxamine (McDougle et al., 1996). In summary, limited evidence supports the use of pharmacotherapy targeting repetitive behavior in youth with autism with some evidence of potential response with SSRI use targeting repetitive phenomena in adults with ASD.

Anxiety

While anxiety is a common co-morbidity in the context of ASD that can significantly impact overall functioning (Leyfer et al., 2006), the evidence base for drug treatment of anxiety in this population remains limited (Vasa et al., 2014). No placebo-controlled trials have specifically targeted anxiety in persons with ASD. Two retrospective chart reports on citalopram treatment in youth (total $n = 32$; age range 4–16 years) noted improvement as measured by the CGI-I on an average 60% of youth (Couturier & Nicolson, 2002; Namerow et al., 2003). An open-label trial of fluvoxamine targeting anxiety in 18 subjects (7–18 year olds) with ASD did not show any clinical improvement with treatment and behavioral activation which led to treatment discontinuation in 3 patients (17%) (Martin et al., 2003). In an open-label study of buspirone for anxiety or irritability in children with ASD ($N = 22$, aged 6–17), buspirone was well-tolerated and benefit was unclear – 41% had a marked response and 32% had a moderate response in the CGI, with no control (Buitelaar et al., 1998). Psychotherapy targeting anxiety at least in higher functioning persons with ASD has a stronger evidence base supporting its use compared to drug treatment (Vasa et al., 2014). A significant gap in the evidence base exists regarding potential drug treatment of anxiety in persons with ASD. While drugs may often be prescribed in this context, no solid evidence exists to support this practice, and risks including behavioral activation must be weighed against potential idiosyncratic benefit.

Sleep Disturbance

Sleep complaints commonly occur in persons with ASD in particular during the childhood and adolescent years (Goldman et al., 2012). Parent training and behavioral approaches to promoting quality sleep are often essential and may be considered first-line in treatment of sleep disorders in children with ASD (Malow et al., 2012). Despite this, such training may not be feasible in some cases or the presentation of insomnia in ASD may remain refractory to these interventions. Melatonin use has been extensively studied as an insomnia treatment in ASD. In a double-blind, placebo-controlled, crossover study in 51 youth (aged 2–18 years) extended release of melatonin (5 mg) was associated with significant improvement in sleep latency and total night-time sleep (Wasdell et al., 2008). Seventeen youth with ASD whose insomnia was refractory to supported behavior management completed a 3-month double-blind, placebo-controlled crossover trial of melatonin (flexible titrated to a 10 mg maximum) (Wright et al., 2011). In this report, melatonin use significantly improved sleep latency by an average of 47 minutes, total sleep by an average of 52 minutes, but the number of night awakenings was not reduced with melatonin use. Melatonin use was not associated with increased adverse effects compared to placebo. In a large-scale, 12-week, double-blind, placebo-controlled trial of extended release melatonin alone and in combination with cognitive behavioral therapy in 162 youth (age range 4–10 years) with ASD, consistent with other reports, melatonin use alone improved sleep and a trend existed pointing to added benefit from combining melatonin use with sleep-focused therapy (Cortesi et al., 2012). In addition to melatonin, refractory sleep issues in ASD may be treated with trazodone or clonidine, with some concern about risk of paradoxical effects from diphenhydramine and benzodiazepines potentially limiting use of these drugs (Blackmer & Feinstein, 2016).

Core Social Impairment

While significant efforts in the last 20 years have focused on potential drug treatments to address the core social impairment associated with ASD, no drugs have to date been successfully developed for this indication. Several molecules including the gamma hydroxybutyric acid type B (GABA(B)) agonist arbaclofen (Veenstra-VanderWeele et al., 2017), the N-methyl-D-aspartate (NMDA) glutamate receptor antagonist memantine (M. G. Aman et al., 2017), and the gastrointestinal peptide secretin (Krishnaswami et al., 2011) among other molecules have failed in large-scale, placebo-controlled study in ASD. Several drug treatments remain in development in ASD with final results remaining to be determined.

Sulforaphane, a phytochemical derived from broccoli sprouts, was the subject of a 18-week, double-blind, placebo-controlled trial in 44 males with ASD (age range 13–27 years; $n = 29$ received active drug; $n = 15$ received placebo) (Singh et al., 2014). Sulforaphane use was associated with improvement as rated by the ABC total score, Social Responsiveness Scale (SRS), and the CGI-I compared to placebo. The authors hypothesized that the antioxidant anti-inflammatory properties of this phytochemical may have been responsible for the positive response in this first autism study. These results warrant replication and further study.

We have conducted initial studies of acamprosate, a modifier of glutamate and GABA neurotransmission, FDA-approved for the treatment of alcoholism, in humans with ASD. In our initial description of clinical use of acamprosate in youth with ASD (age range 6–12.5 years) significant reduction in social withdrawal, hyperactivity, and global clinical improvement were uniformly noted during open-label treatment (Erickson et al., 2011). We then conducted a 12-week, single-blind placebo lead in study of acamprosate in 12 youth with ASD (age range 5–17 years) (Erickson et al., 2014). In this report, 6 of 9 subjects (67%) not deemed placebo responders entered active acamprosate treatment and showed significant positive response to the drug with particular improvement as measured by the ABC Social Withdrawal subscale (ABC-SW). In our initial reports on acamprosate use in youth with ASD the drug was well tolerated without drug-associated discontinuations noted. We are now completing a 36 subject, double-blind, placebo-controlled, parallel groups study of flexibly dosed acamprosate in youth aged 5–17 years with ASD (clinicaltrials.gov; NCT01813318).

The endogenous oxytocin system plays a role in social cognition and attachment and has been a target of treatment development in ASD. Thirty-one youth (age range 3–8.9 years) with ASD participated in a double-blind, placebo-controlled, crossover, intranasal oxytocin trial where significant caregiver reported improvement in social responsiveness was reported during oxytocin treatment compared to placebo (Yatawara et al., 2016). Engagement of oxytocin treatment with brain regions involved in social–emotional processing was noted in a double-blind, placebo-controlled, crossover study involving functional brain imaging in 16 youth (mean age 13 years) with ASD (Gordon et al., 2016).

Specifically, oxytocin use was associated with enhanced connectivity between the brain's reward and social–emotional processing systems in response to social versus nonsocial stimuli. Anagnostou et al. (2012) conducted a 6-week, double-blind, placebo-controlled trial of intranasal oxytocin in 19 adult males with ASD (mean age = 33.2 years) (Anagnostou et al., 2012). In this report, oxytocin use was associated with significant social improvement on primary outcome measures. On a secondary quantitative measure of social cognition, oxytocin-associated improvement was noted on the Reading-the-Mind-in-the-Eyes Test and oxytocin-associated improvement was also noted in a standardized measure of quality of life. Oxytocin use was well tolerated with no serious adverse effects reported. Study of intranasal oxytocin in ASD continues including an ongoing double-blind, placebo-controlled, parallel groups study in 290 youth with ASD aged 3–17 years (clinicaltrials.gov; NCT01944046). Likely this large-scale study will provide a more definitive evidence base for or against routine use of oxytocin in persons with ASD targeting core social impairment.

D-cycloserine (DCS) is an approved antibiotic treatment of tuberculosis discovered to act as a partial agonist at NMDA glutamate receptors. DCS has been extensively studied as a treatment of the negative symptoms associated with schizophrenia, symptoms that are thought to bear some resemblance to autistic social impairment (Schade & Paulus, 2016). A first study of DCS in ASD involved 10 persons (mean age 10 years) with autism participating in an 8-week, single-blind, placebo-controlled study (Posey et al., 2004). Following a two-week placebo lead-in, DCS treatment was well tolerated and was associated with significant overall clinical improvement as rated by the CGI-I and with reductions in social withdrawal as measured by the ABC-SW. A subsequent 8-week, double-blind, placebo-controlled, parallel groups trial of daily DCS (1.7 mg/kg/day) in 80 youth aged 3–12 years with ASD noted no improvement with DCS treatment compared to placebo on any outcome measure utilized (D. Posey et al., 2007). DCS treatment was well tolerated with no increased adverse effects experienced compared to placebo. In an other human autism study, Urbano et al. have described randomized treatment with DCS 50 mg daily versus 50 mg weekly over 8 weeks of treatment in older adolescents and young adults with ASD ($n = 20$; mean age 17.6 years; range 14–25 years) (Urbano et al., 2014, 2015). Positive DCS-associated improvement in social deficits was noted with both daily and weekly dosing as measured by the caregiver reported SRS total score, ABC-SW, and objective subject testing of social perception. A weakness of this work is a lack of a placebo treatment group thus making the objective subject testing, in this case the Social Perception-Affect Naming Subset, of increasing importance. In this report, response to daily and weekly low-dose DCS could not be differentiated. A recent 10-week, placebo-controlled trial of weekly social skills training immediately following a weekly D-cycloserine dose in 67 children with ASD (mean age 8.56 years, IQ > 70 given the demands of social skills training) demonstrated no significant impact of D-cycloserine on social skills or any primary or secondary outcome measure 1 week following completion of the weekly social skills training (Minshawi et al., 2016). Post-treatment 22-week follow-up assessments did demonstrate more sustained social skills gain in the DCS-treated group in follow-up as measured by the SRS total score with a moderate to large effect size ($p = 0.003$, $d = 0.82$) (Wink et al., 2017). This is the first report of DCS-associated improved maintenance of therapy response post-treatment in persons with ASD. Future work to understand if DCS can consistently facilitate gains from social skills training or other therapies is warranted.

Discussion

Significant progress has been made in the field of autism psychopharmacology. With two FDA approved agents for the treatment of irritability marked by aggression, self-injury, and severe tantrums in youth with autism, this symptom cluster has by far the most defined drug treatment approach in the field. While significant progress in the field has defined first-line drug treatment approaches targeting irritability, more limited data is available to describe treatment of drug refractory irritability which commonly occurs within the referral base of tertiary care centers (Adler et al., 2015). Management of drug refractory aggression and self-injury often balances adverse effect profile against potential effectiveness, in particular when evaluating the appropriateness for clozapine therapy. Factors that contribute to the development of drug-refractory irritability in ASD remain poorly understood.

With changes in the DSM 5 that allow the additional diagnosis of ADHD in persons with ASD, it is likely that the treatment of ADHD symptoms in persons with ASD may gain added attention. The evidence base for methylphenidate treatment of ADHD in persons with ASD is based upon positive trial results from well-designed controlled study. Despite this data, the tolerability of stimulants and treatment response rates in ASD are diminished compared to experience in neurotypically developing youth. Guanfacine remains a supported treatment for ADHD symptoms in youth with ASD, with response rates at or above experience with stimulants in this field. Compared to methylphenidate use, guanfacine likely has reduced risk for behavioral disinhibition upon drug initiation.

Treatment of interfering repetitive behavior and anxiety in persons with ASD has limited evidence base. Neither domain has been the subject of well-established prescribing recommendations supported by well-designed, positive clinical trial results. Despite this, SSRIs continue to be widely prescribed in persons with ASD, often at risk of adverse effects including most prominently behavioral disinhibition. In our experience, non-evidence-based use of SSRI therapy in ASD in particular with persons with anxiety and agitation contributes to behavioral crises at times resulting in inpatient hospitalization. This reality is likely driven by limited effective treatment options. More research is needed to better understand the presentation of anxiety in ASD and continued exploration of novel drug treatment approaches of anxiety or repetitive behavior.

The generally off-label nature of ASD pharmacotherapy combined with potential drug tolerability challenges within this population renders this area of practice challenging. More work is needed from the field to identify potential predictors of treatment response across target symptom domains. Given the heterogeneity of the clinical presentation of ASD, it is not surprising that variable responses to drug treatment are consistently noted. Likely quantitative measures including use of molecular blood assay, electrophysiology, eye tracking, and/or computer-based testing among other modalities hold promise to quantitatively track symptom changes with drug treatment and potentially predict, prior to drug initiation, what treatment may be most effective in persons with ASD. Such approaches added to clinical trial design will become increasingly imperative to parse the heterogeneity of treatment response in ASD.

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