Journal of Autism and Developmental Disorders (2021) 51:4370–4394
https://doi.org/10.1007/s10803-021-05237-9

COMMENTARY

Decades of Progress in the Psychopharmacology of Autism Spectrum Disorder

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Accepted: 7 August 2021 / Published online: 7 September 2021

Abstract

Recent decades have been marked by a wave drug treatment research in autism spectrum disorder (ASD). This work has resulted in improved ability to treat commonly occurring behavioral challenges associated with ASD including most prominently irritability marked by aggression, self-injurious behavior, and severe tantrums. While treatment of interfering behavior has progressed in our field, there remain several areas of unmet medical need including most prominently a lack of any approved drug therapies for the core, defining symptoms of autism. We outline the progress to date in the field of autism drug treatment while taking a future look forward into how decades of work can inform better future steps in this field.

Keywords Psychopharmacology · Drug treatment · Autism · Autism spectrum disorder · Anti-psychotic · Irritability

Introduction

Since the formalization of autism spectrum disorder (ASD) as a diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, decades of research has focused on medication management of both neuropsychiatric symptoms commonly occurring in persons with ASD and the potential to treat core defining features of autism with drug therapy. Significant gains have been made in the psychopharmacology of behaviors contributing to impairment and psychiatric illness in the context of ASD, particularly in the treatment of irritability (aggression, self-injurious behavior (SIB) and severe tantrums). There remains no approved drug treatments for the core, defining symptom domains of ASD. Symptom heterogeneity and reliable outcome measurement has been a challenge in drug development across all symptom domains.

Approximately half of youth with ASD in North America and Europe receive medication treatment of co-occurring neuropsychiatric conditions and symptoms including irritability (physical aggression, SIB, and severe tantrums), hyperactivity, anxiety, sleep problems and mood disturbance (Jobski et al., 2017). There are two medications, risperidone and aripiprazole, FDA approved in the United States for treating ASD-associated irritability. Other pharmacotherapies are often used "off-label". Antipsychotics, ADHD medications, and antidepressants are among the most commonly used medications in children and young adults with ASD (Jobski et al., 2017). Given the varying targets of drug treatment in the context of ASD, polypharmacy is common in children with ASD. A U.S. population surveillance sample of Medicaid-eligible children with ASD noted that 60% of children diagnosed with ASD were prescribed medication for any clinical indications, and 41% of this sample was prescribed more than one psychotropic medication (Logan et al., 2012, 2015). Despite the frequency of psychotropic medication use in autism, studies of pharmacotherapy in children with ASD are often limited by small sample sizes, heterogeneous populations, and at times open-label design. While recent research has expanded past traditional psychotropic medications, work targeting core features of autism has to date failed to result in approved drug treatment due to a number of factors, most prominently the challenges associated with population heterogeneity and quantitative measure of potential treatment response.

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Traditional Psychotropic Medications

Much of the research that has been done in ASD has focused on traditional psychotropic medications like those listed above. It is important to note several limitations here—first, many studies are heavily skewed towards white and male participants, and commonly exclude those with moderate to severe ID and/or severe self-injurious behavior (SIB) or aggression. Additionally, the choice of outcome measures can vary widely between studies, and there is sometimes question about whether or not a particular outcome measure is valid for measuring change in symptoms, or adequately captures the symptoms being targeted. See Persico et al. (2021) for additional review of these medications.

Treatment of Irritability and Aggression

Antipsychotic Medications

Antipsychotics are widely prescribed to individuals with ASD, usually targeting irritability defined by the US FDA as aggression, SIB, and severe tantrums. Risperidone was FDA approved in 2006 for the treatment of ASD-related irritability in youth starting at age 5 years, with dosing in most studies ranging from 0.5 to 3.5 mg total per day. A seminal study from the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network (2002) involving an 8 week, double-blind RCT of risperidone versus placebo in 101 youth with ASD noted significant risperidone-associated improvement over placebo in both the irritability subscale of the Aberrant Behavior Checklist (ABC) and Clinical Global Impressions, Improvement subscale (CGI-I) ($p < 0.001$) (McCracken et al., 2002). Following 24-weeks of open-label risperidone treatment, a placebo-controlled discontinuation study in 24 youth with autism demonstrated a relapse rate of 67% for those randomized from open label risperidone to placebo versus a 25% relapse rate for those continuing risperidone (Troost et al., 2005). Additional studies, both placebo-controlled and open-label, have extended these results with consistent finding of risperidone-associated reductions in irritability in youth and adults on the spectrum (McDougle et al., 1998; Nagaraj et al., 2006; Shea et al., 2004) as well as durability of response (up to 3 years) (Sharma & Shaw, 2012).

Aripiprazole was FDA approved in 2009 for the treatment of irritability associated with ASD in youth aged 6 to 17 years. Pivotal studies leading to aripiprazole approval showed efficacy in the dose range of 5 to 15 mg per day (Marcus et al., 2009, 2011; Owen et al., 2009). A 2016 Cochrane meta-analysis (including two RCTs and one placebo-discontinuation study) of aripiprazole use in ASD found mean improvement of − 6.17 points on the ABC Irritability subscale (95% CI − 9.07 to − 3.26), − 7.93 points on the ABC Hyperactivity subscale (95% CI − 10.98 to − 4.88), and − 2.66 points on the ABC Stereotypy subscale (95% CI − 3.55 to − 1.77), indicating potential improvement in irritability as well as other symptoms (Ching & Pringsheim, 2012). The Cochrane analysis also noted, however, that in the placebo-discontinuation study, there was no difference in relapse rates for those on placebo versus those continued on aripiprazole, in contrast to findings from a similar study design involving risperidone. A randomized, double-blinded, placebo-controlled trial (RDBPCT, $n = 316$) in youth with ASD also found improvement over placebo in pediatric quality of life inventory scores, in both the overall combined score as well as the emotional and cognitive functioning subscales (Varni et al., 2012).

There are few studies of other second-generation antipsychotics (SGAs) such as quetiapine, olanzapine, ziprasidone, lurasidone and paliperidone, although these are still commonly used in the treatment of irritability and aggressive behavior in children with ASD (Park et al., 2016). Outside of risperidone and aripiprazole, olanzapine is the only other SGA with a placebo-controlled trial, though this was quite small: in a double-blind placebo-controlled pilot study with 11 children with ASD or other pervasive developmental disorders, olanzapine was associated with improvement as measured by the CGI-I (Hollander et al., 2006). Olanzapine was also associated with significant weight gain. In a larger ($n = 40$) 13-week open label report on olanzapine use in youth with ASD, olanzapine was associated with reductions across all ABC subscales, and 30% of participants showed global improvement as measured by reduction in CGI Severity (CGI-S) subscale scores improved based on CGI-S scores (Fido & Al-Saad, 2008). Significant weight gain often limits the chronic use of olanzapine for interfering behavior in persons with ASD (Maayan & Correll, 2011; Yoon et al., 2016). Quetiapine has been the subject of limited published study in ASD with several small open label or retrospective chart review reports available to support quetiapine's use targeting irritability (Corson et al., 2004; Findling et al., 2004; Golubchik et al., 2011; Hardan et al., 2005; Martin et al., 1999). Ziprasidone has also shown benefit for irritability in several small open-label trials, and is associated with significantly reduced risk of weight gain compared to other SGAs (citation). A naturalistic retrospective study of 42 youth with ASD noted a 40% response rate (defined as CGI-I score of 1 or 2) in patients who had previously failed or not tolerated first line SGA therapy (aripiprazole or risperidone) (Dominick et al., 2015). Paliperidone, the active ingredient of risperidone dosed in an osmotic controlled release system (OROS) formulation, was well-tolerated and effective in improving irritability (84% responders, as measured by > 25% reduction in ABC-I scores and CGI-I scores of 1 or

2) in an open-label study (n = 25) of adolescents and young adults with ASD (Stigler et al., 2012). In contrast to other SGAs, lurasidone was not effective in a 6-week, fixed-dose RDBPCT for the treatment of moderate-to-severe irritability in youth with ASD (Loebel et al., 2016). A meta-analysis of SGA treatment response in patients with ASD and somewhat higher cognitive functioning (studies where ≥ 25% of participants had IQ ≥ 71), found that SGAs do provide improvement in behavioral symptoms, but the analysis leaned heavily on studies using risperidone (Sochocky & Milin, 2013).

Weight gain is one of the most common side effects of treatment with SGAs (at times in combination with other metabolic effects including hyperlipidemia and insulin resistance) and is one of the most common reasons given for discontinuation in ASD (Scahill et al., 2016; Wink, et al., 2014a, 2014b; Yoon et al., 2016). Additional potential side effects include somnolence, anxiety, drooling and extrapyramidal symptoms (McCracken et al., 2002; Sharma & Shaw, 2012; Troost et al., 2005) (Ching & Pringsheim, 2012; Marcus et al., 2011; Varni et al., 2012). There is also the risk for hyperprolactinemia, which can rarely lead to subsequent endocrine dysfunction, including amenorrhea, sexual side effects, galactorrhea, gynecomastia, and increased risk of osteoporosis, (Ngamsamut et al., 2016; Roke et al., 2012), highest for risperidone and paliperidone.

A retrospective, naturalistic study of weight gain in patients with ASD treated with risperidone, aripiprazole, quetiapine, ziprasidone, or olanzapine found significant increases in BMI z-score in all SGAs excepting ziprasidone or quetiapine, although the study had several limitations including differences in mean age, and no ability to control for dosing or duration (Yoon et al., 2016). Olanzapine was associated with the greatest increase in BMI z-score. In two additional retrospective, observational studies of weight gain in the use risperidone versus aripiprazole for treatment for ASD-associated irritability in children, both SGAs were independently associated with increased weight gain from baseline, but there was no difference in associated weight gain between aripiprazole and risperidone (Schoemakers et al., 2019; Wink, et al., 2014a, 2014b).

Addressing Weight Gain Associated with Antipsychotic Treatment

Several studies have shown that metformin is well tolerated and effective in weight reduction or plateauing weight gain in children and adolescents with ASD with SGA-associated weight gain (Anagnostou et al., 2016; Handen et al., 2017; Wink et al., 2017). A 16-week double-blind, placebo-controlled randomized trial of metformin in 60 youth with ASD demonstrated efficacy of metformin in reduction of BMI z-scores (metformin vs placebo difference, − 0.10 [95% CI − 0.16 to − 0.04]; ES, 0.82; p = 0.003), although for most participants, the reduction in BMI was no greater than 5% (Anagnostou et al., 2016). A naturalistic sample of 53 youth with ASD on SGAs found that treatment with metformin stabilized BMI z-score over an almost 2 year mean treatment period (Wink et al., 2017). The recent IMPACT study (Improving Metabolic Parameters in Antipsychotic Child Treatment) was a prospective, 24-week open label trial that compared adding metformin, switching antipsychotic (to aripiprazole or an FGA), and no intervention, for weight gain secondary to SGAs in children and adolescents with severe mental illness (26% with ASD) (Reeves et al., 2013). Interestingly, they found that both addition of metformin, and switch to a different antipsychotic, both resulted in significant reduction in BMI z-score (− 0.09 ± 0.03, p = 0.002, and − 0.11 ± 0.04, p = 0.003, respectively).

Studies of other potential adjunctive treatments such as topiramate have not shown significant benefit in reducing SGA-associated weight gain and are associated with significant side effects (Canitano, 2005; Rezaei et al., 2010). Metabolic monitoring, including measurement of weight, height, waist circumference, blood pressure, fasting glucose, and lipids is recommended for all patients on antipsychotics regardless of age or psychiatric diagnosis ("Consensus development conference on antipsychotic drugs and obesity and diabetes," 2004). Given that the most significant weight gain with SGAs appears to occur within the first 4–12 weeks of treatment initiation (van der Esch et al., 2020), future studies examining initiation of metformin or other interventions in conjunction with, or shortly after, starting an SGA is warranted.

First-Generation Antipsychotics

While SGAs are the most often used drug class targeting irritability in autism, first-generation antipsychotics such as haloperidol or chlorpromazine continue to play a role in the management of treatment resistant irritability in ASD (Adler et al., 2015). Haloperidol has the most evidence for use treating interfering behaviors in ASD including several controlled studies conducted prior to the availability of SGAs (reviewed in Lamy & Erickson, 2018; Lamy et al., 2020). The higher rates of abnormal movements associated with haloperidol has limited this drug's use compared to SGAs in the context of autism. In head-to-head comparison with haloperidol, risperidone use demonstrated enhanced reduction in ABC-I scores and greater global improvement as measured by the CGI-I in persons with autism (Gencer et al., 2008; Miral et al., 2008). In an open-label study (n = 12) of olanzapine versus haloperidol in children with ASD, the drugs were associated with similar general clinical improvement as rated by the CGI-I (Malone et al., 2001).

Clozapine

Though generally not used first-line due to the potential for significant adverse events including agranulocytosis and myocarditis, clozapine has been used in treatment-refractory patients with ASD who exhibit significant disruptive behaviors. In two sets of retrospective analyses (n = 6, n = 12) of institutionalized patients with ASD, authors noted a significant decrease in the proportion of days with overall aggression, decrease in total number of psychotropic drugs used, and a decrease in antipsychotic drug dose, although the latter two were found not to be statistically significant in the second study (Beherec et al., 2011; Rothärmel et al., 2018). They specifically noted reductions in property destruction, physical aggression and SIB (Rothärmel et al., 2018). A recent case study of five youth with developmental disability and treatment refractory irritability suggested that rapid titration of clozapine was effective and tolerated in an inpatient setting (Wink, et al., 2016a, 2016b). Common clozapine-associated side effects including weight gain, constipation, metabolic syndrome, and somnolence were noted in open-label study in persons with neurodevelopmental disability (Beherec et al., 2011; Kumar, et al., 2012; Rothärmel et al., 2018; Wink, et al., 2016a, 2016b). Required complete blood count (CBC) monitoring to evaluate for rare agranulocytosis risk may present a significant barrier to clozapine use in persons with ASD. Further research on the use of clozapine for drug-refractory irritability in ASD is warranted, as the literature has shown specific benefit of clozapine in reducing aggression more than other antipsychotics in schizophrenia, and small studies suggest this may also be true for other mental disorders (Frogley et al., 2012).

Long Acting Injectable Antipsychotics

Children with severe intellectual and behavioral disabilities often struggle with pill swallowing and compliance with daily medication administration, which may be worsened in the context of irritability. Long-acting injectable antipsychotics (LAIAs) may provide an ideal solution to this problem. A recent observational study of LAIAs (specifically: aripiprazole, risperidone, and paliperidone) in hospitalized adolescents with mental illness suggest that LAIAs are well tolerated and associated with improvements in the Children's Global Assessment Scale (CGAS) (Fortea et al., 2018). While there are no studies looking at LAIAs in youth with ASD specifically, outside of a single case report (Kowalski et al., 2011), work in other psychiatric disorders such as schizophrenia suggest that they are safe and well tolerated, with similar side effect profiles to oral medications. In addition, use of LAIAs is associated with improved adherence and lower overall treatment costs (Ceylan et al., 2017; Lytle et al., 2017). Future description of LAIA use in the context of ASD is needed to inform prescribing practice for patients where oral formulations may be refused or contraindicated.

Antidepressants—Treatment of Mood, Anxiety and Repetitive Behaviors

Selective serotonin reuptake inhibitors (SSRIs) are considered first-line in the treatment of many mood and anxiety disorders in persons with typical development, but there is little to no systematic controlled data specifically supporting use agents for mood and anxiety concerns in persons with ASD (Vasa et al., 2014). In addition, the evidence does not support the use of SSRIs for treatment of core ASD symptoms in childhood and early adolescence, including for repetitive behaviors (King et al., 2009). Additionally, patients with ASD may be more likely to experience adverse events with SSRIs, including GI effects and behavioral activation which may worsen irritability and aggression (King et al., 2009; Vasa et al., 2014). Fluoxetine has shown potential efficacy in reducing repetitive behaviors in two a small-scale placebo-controlled trials in patients with ASD (one with adults, the other with adolescents) (Hollander et al., 2005, 2012). However, a larger study of youth with ASD later demonstrated no improvement in repetitive behaviors with fluoxetine compared to placebo (Herscu et al., 2020). A large-scale placebo-controlled trial in youth with ASD also found that citalopram was ineffective in reducing repetitive behavior, and there was a high incidence of behavioral activation symptoms and GI side effects (King et al., 2009). In a small (n = 30), 12-week, placebo-controlled trial, treatment with fluvoxamine in adults with ASD resulted in improvement in repetitive thoughts, maladaptive behavior, and aggressions (53% of those in treatment arm found to be responders, while none in the placebo arm were) (McDougle et al., 1996). However, an open-label study of fluvoxamine in 18 children with pervasive developmental disorders found no significant overall benefit (Martin et al., 2003). These results together indicate potential developmental differences in the tolerability and potentially the effectiveness of SSRI use in autism with older individuals potentially having more benefit from treatment with this drug class.

Mirtazapine, a tetracyclic antidepressant, also has some limited studies in the ASD population. In an open label study of children and young adults with a pervasive developmental disorder, including autism, 36% of participants were responders to mirtazapine (defined as CGI-I score of much improved or very much improved) (Posey et al., 2001). There is also some evidence that mirtazapine may be helpful in reducing inappropriate sexual behaviors in individuals with ASD (Coskun et al., 2009).

Mood Stabilizers

Mood stabilizing medications such as anticonvulsants and lithium may be prescribed to patients with ASD to treat behavioral dysregulation, comorbid bipolar disorder, or other interfering behavior. As EEG abnormalities are common in children with ASD, symptom reduction after treatment with anticonvulsants may result from treatment of abnormal brain discharges (Yasuhara, 2010). Divalproex is one of the mood stabilizers most frequently used, although the evidence for its use in ASD is mixed. One small, retrospective, open label study found majority of individuals to have improvement on CGI-I scale for core ASD symptoms (Hollander et al., 2001). In a small (n = 27) placebo-controlled study of valproic acid (VPA) in youth with ASD, over sixty percent of those receiving VPA were deemed treatment responders compared to less than ten percent of those receiving placebo with an overall VPA-associated effect size on ABC-I score reductions of 0.44. In contrast, Hellings et al. (2005) found that VPA use was not associated with significant improvement compared to placebo as rated by the CGI-I or ABC-I in 30 youth with pervasive developmental disorder and aggression (Hellings et al., 2005). Most common adverse effects with divalproex included increased appetite, weight gain, skin rash, and GI side effects. Lithium, a non-antiepileptic mood stabilizer approved for the treatment of mania associated with bipolar disorder, was the subject of a retrospective report in thirty youth with ASD hospitalized in specialty autism behavioral care units (Siegel et al., 2014). In this report, 44% of individuals were described as having lithium-associated clinical improved based on CGI-I scores of 1 "very much" or 2 "much improved", with improvement being significantly associated with presence of pre-treatment manic/euphoric symptoms (Siegel et al., 2014). Another retrospective chart review of lithium in individuals with ASD (n = 19) found a 73.7% response rate, again based on CGI-I score of 1 or 2, and this report noted that co-occurring ADHD was significantly associated with improvement (Mintz & Hollenberg, 2019). Lastly, several cases describing individuals with ASD and SHANK3 genetic mutations have noted improvement in clinical regression and catatonic symptoms with lithium use (Serret et al., 2015). Challenges to lithium use in ASD include need for therapeutic drug level monitoring, risks of thyroid dysfunction, polyuria/polydipsia, and renal issues among other adverse effects.

Treatment of Hyperactivity and Inattention

ADHD is commonly co-occurring with ASD, and symptoms of hyperactivity and impulsivity can be significantly impairing (Mayes et al., 2020). Several studies on methylphenidate showed reduction in these symptom areas in children and adolescents with autism and related disorders (RUPP), 2005; Handen et al., 2000; Posey et al., 2007). The initial RUPP RDBPCT of methylphenidate in youth with autism and related disorders (n = 72), demonstrated a methylphenidate clinical response rate of 49% (as defined by ≥ 25% reduction in ABC-Hyperactivity subscale) with 18% dropout rate due to adverse effects, most commonly irritability (RUPP), 2005). While methylphenidate use was associated with significant clinical improvement compared to placebo, the response rate and drug tolerability profile of methylphenidate use in youth with autism was not as favorable as similar reports in youth with ADHD without autism. A later meta-analysis of four double-blind, randomized, placebo-controlled trials of methylphenidate to treat ADHD symptoms in youth with ASD noted a pooled methylphenidate-associated clinically significant effect size of 0.67 (Reichow et al., 2013). Studies have not shown methylphenidate to have any benefit for other behaviors including stereotypy, repetitive behaviors and oppositional behaviors in the context of autism (RUPP), 2005; Handen et al., 2000; Ji & Findling, 2015; Reichow et al., 2013). Adverse effects with methylphenidate use in autism are common, including decreased appetite, insomnia, and irritability, and some studies, including the RUPP study, suggest these adverse events are more prevalent in those with ASD and ADHD than individuals with ADHD alone (RUPP), 2005; Handen et al., 2000; Ji & Findling, 2015; Reichow et al., 2013).

Overall, methylphenidate shows positive treatment response compared to placebo in youth with ASD and hyperactivity symptoms, but several meta-analyses note that overall response rates and tolerability are less robust in patients with both ASD and ADHD (effect size 0.67) (Reichow et al., 2013) as compared to youth with ADHD alone (effect size 1.03) (Reichow et al., 2013; Schachter et al., 2001). Research on the use of stimulants in adults with ASD and ADHD is quite limited, however, one large retrospective chart review (which included treatment with methylphenidate, dexamphetamine, atomoxetine, and bupropion) found that both the ADHD and the ASD + ADHD groups experienced similar levels of treatment efficacy and adverse effects (Muit et al., 2020).

Atomoxetine, a norepinephrine reuptake inhibitor approved for the treatment of ADHD, has demonstrated mixed clinical results in persons with ASD (L. E. Arnold et al., 2006; Harfterkamp et al., 2012). A 2019 meta-analysis of atomoxetine in youth with ASD and ADHD found that parent ratings of hyperactivity (SMD − 0.73, 95% CI − 1.15 to − 0.34) and inattention (SMD − 0.53; 95% CI − 0.93 to − 0.12) improved, but clinician and teacher ratings did not (Patra et al., 2019). Alpha 2A receptor agonist medications, including clonidine and guanfacine have also been shown to decrease hyperactivity in patients with ASD. Two studies on guanfacine, one open label, and one RDBPCT, noted improvement in hyperactivity and inattention,

and guanfacine was generally well tolerated (Scahill et al., 2006, 2015). In the RDBPCT (n = 62), guanfacine use was associated with a 43% reduction in the ABC-Hyperactivity subscale compared to 13.2% reduction with placebo, with response rate (as measured by CGI-I ≤ 2) of 50% with guanfacine vs 9.4% for placebo (Scahill et al., 2015). Two smaller studies of clonidine (n = 8 and 9 respectively) have reported improvements in hyperactivity in patients with ASD. However, its short half-life and side effect of sedation can limit its clinical usefulness for daytime hyperactivity symptoms (Fankhauser et al., 1992; Jaselskis et al., 1992).

Pharmacotherapy of Sleep Disturbance in Youth with ASD

Sleep disturbances affect up to 80% of youth with ASD (2–3 times greater than in youth without autism) (Blackmer & Feinstein, 2016). These sleep challenges include shorter overall sleep time, increased delay in sleep onset (increased sleep latency), and increased night-time awakenings with associated decreased sleep efficiency (Souders et al., 2017). Studies into the etiology of sleep deficits in ASD have noted that children with ASD have lower nighttime concentrations of melatonin or melatonin metabolites than neurotypical controls, and there is also some evidence of delayed melatonin rhythm in this population (Blackmer & Feinstein, 2016; Braam et al., 2018; Rossignol & Frye, 2011; Tordjman et al., 2005). RDBPCTs of short-term treatment with exogenous, instant release melatonin have noted melatonin-associated (dose range 0.5–15 mg; most common dose range 2–6 mg) benefit in increased overall sleep duration (average increase of 29 min) and decreased sleep latency (average decrease of 27 min), but with less evidence supporting reduction in number of nighttime awakenings (Appleton et al., 2012; Gringras et al., 2012; Rossignol & Frye, 2011). Other reports in youth with ASD have supported the use of prolonged release melatonin (Cortesi et al., 2012; De Leersnyder et al., 2011; Gringras et al., 2017). A RDBPCT of prolonged release melatonin (n = 125 youth with ASD) found an average of 32 min greater total sleep duration associated with melatonin, and mean decreased latency of 25 min, without causing an earlier wakeup time (a problem at times noted in previous studies of instant release melatonin), and decrease in overall sleep disturbance as measured by Composite Sleep Disturbance Index (Gringras et al., 2017). Subsequent reports have found long-term melatonin use in youth with ASD to be well tolerated and effective following up to 2 years of ongoing use (Malow et al., 2021; Maras et al., 2018). A recent meta-synthesis of studies of sleep in pediatric ASD found that melatonin, behavioral interventions, and parent education were the most effective interventions to improve sleep compared to other pharmacologic treatments and alternative therapies (Cuomo et al., 2017).

While clonidine is often used clinically to improve sleep in individuals with ASD, the evidence based for this is limited. In an open-label study in youth with ASD (n = 17) clonidine use was associated with reduced sleep latency and decreased nighttime awakening, although benefits appeared to attenuate over time, requiring increases in dosing (Ming et al., 2008). While there are currently no specific studies supporting the use of trazodone for insomnia in youth with ASD, it is also a commonly prescribed agent in children and adolescents with sleep disorders (Owens et al., 2010).

Drug Development and Emerging Treatments

Numerous additional pharmaceutical agents beyond traditional psychotropic medications have been and are still actively being investigated for treatment or reduction of impairing symptoms of autism (see Tables 1 and 2; please note these are not exhaustive lists). Once again, the demographics of these studies skew heavily white and male, and often exclude those with moderate to severe ID or epilepsy. Notably, oxytocin and sulforaphane studies have little to no female participation. Limitations regarding the variation in outcome measures between studies, and the validity of outcome measures to target specific symptoms as well as measure change over time are again notable. There is also increasing discussion regarding the lack of inclusion of stake-holders in autism research, including in identifying targets for treatment (Bottema-Beutel et al., 2021), and this can result in failure to adequately differentiate between target symptoms (e.g. repetitive behaviors), which are nominally similar but are quite different in terms of how impairing or non-impairing they are. Table 3 contains a list of active and ongoing studies per the clinicaltrials.gov database, again note this is not an exhaustive list.

Glutamatergic and γ-Aminobutyric Acid (GABA) Modulating Agents

Numerous studies have suggested that an imbalance between excitatory and inhibitory signaling may contribute to the pathogenesis of ASD, and that it may be driving some of the core symptoms seen in autism (Naaijen et al., 2015; Purkayastha et al., 2015). Based on this theory, several pharmacological agents that modulate the glutamatergic (excitatory) and GABAergic (inhibitory) systems have been studied as potential treatments for the core symptoms of ASD and ASD-associated behavioral disturbances.

Arbaclofen (active enantiomer in racemic baclofen) is a selective GABA receptor type B ($GABA_B$) agonist which additionally may block the release of glutamate

Table 1 Study design and drug dosing

Drug	Citation	Study design	n	Age	Dose
Arbaclofen	2012 Berry-Kravis	DBRPCT in FXS; Crossover trial, Two 4-week treatment phases with interim 1–2 week washout	63 (ASD 37)	6–11 year: 24 12–17 year: 22 18–40 year: 17	Flex dosing; 1 mg BID to 10 mg TID (10 mg BID max for < 12 year)
	2014 Erickson	Open label, 8 weeks	32	6–11 year: 12 12–17 year: 20	Flex dosing; 1 mg BID to 10 mg TID (10 mg BID max for < 12 year)
	2017 Veenstra-VanderWeele	DBRPCT, 8 weeks	150	5–11 year: 76 12–21 year: 74	10 mg TID max < 12y 15 mg TID max ≥ 12 year
	2017 Berry-Kravis	Adol/Adult—DBRPCT in FXS 8 weeks	125 (ASD 91)	12–50 years	Flex dosing; 5 mg BID to max 15 mg TID
		Children—DBRPCT in FXS 8 weeks	172 (ASD 136)	5–11 year: 76 12–21 year: 74	5 mg BID 10 mg BID 10 mg TID
Bumetanide	2012 Lemonnier	RDBPCT, 3 months followed by 1 month washout	60	3–11 years	0.5 mg BID
	2015 Hadjikhani	Open label, 10 months	7	14–28 years	1 mg BID
	2017 Lemonnier	RDBPCT, 3 months 3 tx groups and 1 placebo group	88	2–17 years	0.5 mg BID, 1 mg BID, or 2 mg BID
	2018 Hadjikhani	Open label, 10 months	9	14–28 years	1 mg BID
	2020 Sprengers	RDBPCT, 91 days followed by 28 day washout	92	7–15 years	< 30 kg: max 0.030 mg/kg/day ≥ 30 kg: max 1.0 mg BID
	2020 Zhang	RDBPCT, 3 months	83	3–6 years	0.5 mg BID
Pregnenolone	2014 Fung	Open label, 12 week	12	18–35 years	Flex dosing 50 mg BID → max 250 mg BID
Acamprosate	2011 Erickson	Open label, 10–30 weeks	6	6–12 years	Flex dosing 333 mg/day→ max 1332 mg/day
	2013 Erickson	Open label in FXS, 10 week	12 (ASD 10)	6–17 years	< 50 kg max 1332 mg/day ≥ 50 kg max 1998 mg/day
	2014 Erickson	Open label FXS and idiopathic ASD	FXS-ASD: 9 IDP-ASD: 6	6–15 years	
	2014 Erickson	Single-blind, placebo lead-in trial 12 weeks	12	5–15 years	Flex dosing 666–1998 mg/day
Riluzole	2018 Wink	RDBPCT, Crossover 12–5 weeks each arm, with interim 2 week washout	8	13–18 years	200 mg/day
Memantine	2006 Owley	Open label in PDD, 8 weeks	14	3–12 years	5–20 mg/day
	2007 Chez	Open label, naturalistic/add-on; ratings at 4–8 weeks	151 (105 ASD)	2–26 years	2.5–30 mg/day
	2007 Erickson	Retrospective open label Mean 19.3 weeks (range 1.5–56 weeks)	18	6–19 years	2.5–20 mg/day
	2016 Joshi	Open label, 12 weeks	19	18–47 years	5–40 mg/day

Table 1 (continued)

Drug	Citation	Study design	n	Age	Dose
	2017 Aman	RDBPCT, 12 weeks	121	6–12 years	First 8 weeks: Target 3–15 mg/day (≥ 60 kg–15 mg; 40–59 kg–9 mg; 20–39 kg–6 mg; < 20 kg–3 mg)
		Open label extension, 42 weeks	102	6–12 years	Doses maintained from first phase
	2019 Hardan	Open label used to identify memantine responders (MEM-MD-91)	906	6–12 years	≥ 60 kg–15 mg; 40–59 kg–9 mg; 20–39 kg–6 mg; < 20 kg–3 mg)
		DB withdrawal trial—Responders randomized to placebo, reduced dose, or full dose memantine	479	6–12 years	Reduced dose tx arm reduced by ≥ 50%
Amantadine	2001 King	RDBPCT	39	5–15 years	5 mg/kg
	2015 Ellul	Case report of 27yM with ASD and catatonia			
	2020 Hutchinson	Case report of 15yM with ASD and catatonia			
Ketamine	2021 Wink	RDBPCT—crossover; Two doses of escalating dose ketamine given 1 week apart; Two week washout; two doses of placebo given 1 week apart	21	14–29 years	30 mg → 50 mg
Minocycline	2013 Pardo	Open label trial; children with ASD and regression	11	3–12 years	1.4 mg/kg/day (Given with adjunct Vitamin B6 0.6 mg/kg BID)
NAC	2012 Hardan	RDBPCT, 12 week	33	3–10 years	900 mg/day × 4 weeks → 900 mg BID × 4 weeks ⟶ 900 mg TID × 4 weeks
	2016 Wink	RDBPCT, 12 week	31	4–12 years	33.6–64.3 mg/kg
	2017 Dean	RDBPCT, 6 months	98	3–9 years	500 mg/day
	2020 Pesko	Case series of 4 adolescents with ASD augmented with NAC			1200 mg BID (target dose)
Sulforaphane	2014 Singh	RDBPCT, 18 weeks (followed by 4 week washout)	44	13–27 years	< 101 lb–50 µmol/day 101–199 lb–100 µmol/day > 199 lb–150 µmol/day
	Zimmerman 2011*	RDBPCT, 22 weeks (2:1 drug:placebo)	45	13–30 years	< 101 lb–50 µmol/day 101–199 lb–100 µmol/day > 199 lb–150 µmol/day
	Zimmerman 2015*	Phase 1, RDBPCT (15 weeks), Phase 2, Open label (15 weeks), Phase 3 wash out 6 weeks	50	3–12 years	2.2 µmol/kg
RG7713	2017 Umbricht	RDBPCT, Single dose crossover	19	Mean 23 years	20 mg (IV infusion over 2 h)
Balovaptan (RG7314)	2019 Bolognani	RDBPCT, Parallel, 12 weeks	223	Median 22–26 years	1.5 mg, 4 mg, and 10 mg
	Phase II Trial NCT02901431	RDBPCT, 24 weeks (Terminated early due to lack of benefit)	339	5–17 years	

Table 1 (continued)

Drug	Citation	Study design	n	Age	Dose
	NCT03504917 NCT04049578	Phase III trials, terminated early due to lack of benefit			
Intranasal vasopressin	2019 Parker	RDBPCT, Parallel, 4 weeks	30	6–12 years	24 IU/day (6–9.5 years) 32 IU/day (≥9.6 years)
Cannabidiol	2019 Barchel	Prospective cohort (30–588 days; mean 66 days)	53	4–22 (11)	
	2019 Schleider	Prospective cohort—6 months	188	<5–18 (12.9)	
	2019 Pretzsch (multiple papers)	RDBPCT—single dose crossover (Neurotypical and ASD groups, placebo vs. drug; crossover visits separated by 13 days minimum)	34 (17 ASD)	Mean 28–31 years	
	2020 Fusar-Poli	Systematic Review—Including review of case reports, case series, and cohort studies			
Oxytocin	2003 Hollander	RDBPCT, within subject comparison, - Single dose IV, placebo or drug; administration of other agent after interim 2–3 weeks	15	19–56 years	10 u/mL diluted in 1.0 L saline infused over 4 h
	2010 Andari	RDBPCT—single dose intranasal, Within subject comparison plus comparison to NT controls, single dose intranasal, placebo/drug visits separated by 1 week	13 ASD 13 NT	17–39 years	24 IU/day (Intranasal)
	2012 Anagnoustou	RDBPCT—parallel design; 6 weeks	19	Mean 33.2 years	24 IU BID (Intranasal)
	2014 Dadds	RDBPCT—5 day 'live-in' intervention	54	7–16 years	≥40 kg–24 IU/day <40 kg–12 IU/day (Intranasal)
	2014 Watanabe 2015 Aoki	RDBPCT—Single dose, within-subject crossover; 1 week interim between visits	40	Mean 28.5 years	24 IU (Intranasal)
	2016 Yatawara	RDBPCT—Crossover; 5 weeks each treatment arm, with interim 4 week washout	39	3–8 years	12 IU BID (Intranasal)
	2016 Kosaka	RDBPCT, Parallel × 12 weeks → Open label × 12 weeks → 8 week follow up	60	15–39 years	Low dose—16 IU/day High dose—32 IU/day (Intranasal)
	2017 Parker	RDBPCT—Parallel design; 4 weeks	32	6–12 years	24 IU BID (Intranasal)
	2018 Yamasue 2019 Owada (post-hoc)	RDBPCT—Parallel; 6 weeks	106	18–48 years	48 IU/day (Intranasal)

Table 1 (continued)

Drug	Citation	Study design	n	Age	Dose
	2019 Kruppa	RDBPCT—Crossover, Single Dose; 2 sessions on 2 consecutive days	35 NT; 25 ASD	NT mean 22 years ASD mean 21 years	20 IU—Single dose (Intranasal)
	2020 Bernaerts	RDBPCT—Parallel; 4 weeks, Additional follow up at 4 weeks and 1 year	40	18–35	24 IU/day (Intranasal)

RDBPCT randomized double-blind placebo-controlled trial, *FXS* Fragile X Syndrome, *BID* twice a day, *TID* three times a day, *IU* International units, *ASD* Autism Spectrum Disorder, *NT* neurotypical, *NAC N*-acetylcysteine

*Unpublished data

presynaptically. Arbaclofen has been extensively studied in fragile X syndrome (FXS), the most common single gene cause of ASD. In FXS, an initial report of potential arbaclofen-associated improvement in the ABC Social Avoidance subscale (ABC FXS factor structure) (Berry-Kravis et al., 2012; Sansone et al., 2012) was not replicated in two subsequent large-scale Phase III studies in FXS (Berry-Kravis et al., 2017). In idiopathic ASD, an 8-week arbaclofen open-label study (n = 32) in youth demonstrated broad clinical improvement across several domains (Erickson et al., 2014). However, a subsequent randomized controlled trial (n = 150, age range 5-21y) found no arbaclofen-associated benefits across subscales of the ABC (Veenstra-VanderWeele et al., 2017). Arbaclofen was generally well tolerated across studies in FXS and ASD, with the most common adverse events noted being somnolence and affect lability, without serious adverse events attributable to arbaclofen noted (Berry-Kravis et al., 2017; Brondino et al., 2016; Erickson et al., 2014; Frye, 2014; Veenstra-VanderWeele et al., 2017). Further investigation of arbaclofen in ASD is ongoing; as of this writing, there are two RDBPCTs actively recruiting (NCT03682978 and NCT03887676).

Bumetanide, a sodium–potassium–calcium (Na–K–Ca) Cotransporter-1 (NKCC1) chloride-importer inhibitor, potentiates GABAergic inhibition. Target engagement study has noted that bumetanide treatment in persons with autism improved emotion recognition and increased activation in brain regions related to social and emotional perception during the viewing of emotional faces (Hadjikhani et al., 2015, 2018). A 2012 double-blind placebo-controlled study of short-term bumetanide use in youth with ASD (n = 60, age range 3–11 years) noted significant reduction in Childhood Autism Rating Scale (CARS) scores from baseline compared to placebo (Lemonnier et al., 2012). A subsequent RDBPCT of bumetanide in eighty-eight 2–18 year-olds with ASD also noted bumetanide-associated improvement in CARS scores across four dosing groups divided by participant age (Lemonnier et al., 2017). Two recent RCTs of bumetanide offer different results with positive treatment response on social behavior noted in a report involving eighty-three 3–6 year-olds (dose 0.5 mg BID [twice a day]) (Zhang et al., 2020), but no treatment response noted in ninety-one 7–15 year-olds receiving 1 mg BID or placebo. (Sprengers et al., 2020). Overall, across studies bumetanide has been well tolerated with common, but not severe, adverse effects including hypokalemia, enuresis, decreased appetite, and dehydration. Two phase III studies of bumetanide in ASD are active but not recruiting (Crutel et al., 2020), another randomized double-blind, placebo-controlled trial is active and recruiting (NCT04766177).

Memantine, an antagonist of the NMDA glutamate receptor, has been extensively studied in ASD targeting core social impairment. An initial open-label study of memantine on a large cohort (n = 151) of individuals (2–26 years) with idiopathic ASD showed significant improvement on CGI-I, with 70% of participants receiving CGI-I scores of 1 or 2 at 4–8 weeks following start of medication; language function and social behavior were noted to have particularly improved. Participants continued for a total of 21 months with no serious adverse events noted (Chez et al., 2007). A smaller (n = 18) retrospective review of youth with ASD also found a similar responder rate of 61% based on CGI-I scores of 1 or 2 (Erickson et al., 2007) and an additional small open-label study (n = 18) of adults with high-functioning ASD showed significant reduction on the informant rated Social Responsiveness Scale-Adults (SRS-A, -28 ± 25; $p < 0.001$) (Joshi et al., 2016). Another small, open-label trial of memantine with children with ASD found significant improvement from baseline on the Children's Memory Scale Dot Learning Substest, but not on measures of expressive or receptive language or non-verbal IQ (Owley et al., 2006). A large (n = 121) phase II RDBPCT trial found no benefit of memantine ER on the scores of the Social Responsiveness Scale, or any of the secondary endpoints at either 12 weeks or in a 48-week open-label extension (Aman et al., 2017). A

Table 2 Study outcome measures and results

Drug	Citation	Primary outcome	Secondary/exploratory outcomes	Adverse effects
Arbaclofen	2012 Berry-Kravis	ABC-I, no benefit	CGI-I, no benefit	Headache (8%), Sedation (8%), Fatigue (6%), Increased appetite (6%), Vomiting (6%)
	2014 Erickson	ABC-I—10pt reduction	Reduction in ABC-L/SW, H, IS, and S scores/ SRS—Improvement CY-BOCS-PDD—Improvement	Agitation, Irritability, Fatigue, Psychomotor hyperactivity, Diarrhea, Insomnia, Aggression, Disturbance in attention, Headache,
	2017 Veenstra-VanderWeele	ABC—L/SW—no benefit	CGI-S—greater reduction vs. placebo (− 0.6 vs − 0.2) CGI-I, VABS—no difference;	Affect lability, Somnolence
	2017 Berry-Kravis	ABC-CFX—SA—no benefit	CGI-S, CGI-I, VAS, VABS—no benefit	Headache, nausea, vomiting, anorexia, irritability, anxiety, agitation
		ABC-CFX—SA—no benefit	ABC-CFX—I—improvement in highest dose group; CGI-S—no improvement, VABS—No improvement	Vomiting, aggression, URI, headache, rhinorrhea, nasal congestion, anxiety, insomnia, ear infection, and gastroenteritis
Bumetanide	2012 Lemonnier	CARS—reduction of score > placebo at 90d	CGI-I—improvement > placebo / ADOS—No SS improvement	Hypokalemia
	2015 Hadjikhani	> Improved accuracy and response time of face emotion matching task (with no improvement seen in object matching) > Increased activation was observed for emotional (vs. neutral) faces in early visual and face-processing areas	> Increased activation was seen in cortical and subcortical areas involved in emotional, social, and attentional processing, including the nucleus accumbens and the amygdala	
	2017 Lemonnier	CARS scores- found greater improvement in tx groups over placebo; in completers' subgroup, improvement was dose-dependent, with highest dose showing greatest improvement (− 5.35 ± 3.88)	SRS score -Reduction all tx groups > 10 points, greatest difference seen in highest dose group (− 21.8 ± 19.8 vs − 1.55 ± 20.38 in placebo); CGI-I—greater improvement over placebo;	Hypokalemia, enuresis, polyuria, Loss of appetite, Dehydration, asthenia, weight loss, vomiting, diarrhea, fatigue, abdominal pain, hyperuricemia, thirst/polydipsia
	2018 Hadjikhani	> Significant decrease in amygdala activation compared with the baseline (pre-treatment) during constrained eye gaze following bumetanide treatment according to a nonparametric Wilcoxon signed ranks test (z = − 2.100, p = 0.036, 2-tailed)	> The Wilcoxon signed ranks tests revealed a significant increase in time looking in the eye AOI after treatment compared with baseline (z = 2.521, p = 0.012, 2-tailed)	
	2020 Sprengers	SRS-2 scores—no difference	RBS-R—no difference ABC-I no difference	Hypokalemia, dehydration, Vomiting, Nausea, Abdominal pain, orthostatic hypotension, common cold, myalgia, diuresis, dizziness
Bumetanide (Con't)	2020 Zhang	CARS—Improvement over placebo in total score and in # items scored ≥ 3 CGI-I—Improvement over placebo CGI-EI—Improvement over placebo	GABA and Glu concentrations within a VOI (Volume of interest) as measured by MRS—GABA/Glu ratio in both the insular and visual cortex decreased more in the bumetanide group; decrease in insular cortex was associated with a reduction in symptom severity (based on CARS score)	Polyuria, hypokalemia, loss of appetite, fatigue, hyperuricemia
Pregnenolone	2014 Fung	ABC-I: Improvement—from 17.4 ± 7.4 at baseline to 11.2 ± 7.0 at 12 weeks (p = 0.028)	ABC-SW—Improvement Other subscales no SS improvement No change seen after 4 week washout period	Fatigue, diarrhea, depressive affect
Acamprosate	2011 Erickson	5 of 6 subjects were responders as defined by CGI-I score of 1 or 2	Improvement seen in ABC-SW, ABC-H, CGI-S, and SRS	Nausea, Reduced appetite
	2013 Erickson	9 of 12 subjects were responders (CGI-I of 1 or 2)	ABC-SW, ABC-H, ABC-SA– Improved SRS, VABS—Communication, CGI-S—Improved Increase in BDNF plasma level	Irritability, Increased repetitive behavior

Table 2 (continued)

Drug	Citation	Primary outcome	Secondary/exploratory outcomes	Adverse effects
	2014 Erickson	Acamprosate treatment reduces overall sAPP levels in both FXS-associated ASD and idiopathic ASD, Possible greater redirection toward the α-secretase processing pathway in FXS-associated than in idiopathic ASD		
	2014 Erickson	6 of 9 were responders based on CGI-I of 1 or 2 and ≥ 25% improvement on ABC-SW	ABC-SW, ABC-H—Improvement CGI-S, SRS—Improvement	Loose stools, headache, insomnia, irritability, fatigue
Riluzole	2018 Wink	ABC-I and CGI-I—No improvement		Physical aggression
Memantine	2006 Owley	Improvement on Children's Memory Scale Dot Learning Substest	No improvement on measures of receptive or expressive language	Hyperactivity
	2007 Chez	CGI-I—Language -70% of subjects were responders based on CGI-I of 1 or 2 CGI-I—Behavior—70.7% were responders based on CGI-I of 1 or 2		Worsened behavior (22)
	2007 Erickson	11 responders (CGI-I 1 or 2) CGI-S change 4.2 ± 0.8 to 3.6 ± 0.9		Irritability, increased seizures, emesis, sedation
	2016 Joshi	83% of subjects had CGI-I of 1 or 2 33% of subjects had 30% or greater reduction in SRS-A scores		Headache, dizziness, sedation
	2017 Aman	No difference in SRS score improvement (placebo and drug had ~ 10 point improvement)	Open label extension: Further improvement in SRS scores	No adverse effects clearly separated from placebo
	2019 Hardan	Phase 1 open label: 517 participants (59.6%) deemed responders based on ≥ 10 pt reduction in SRS	Phase 2: Double-blind withdrawal trial: No difference seen between treatment arms in LTR (loss of treatment response, defined as ≥ 10 point increase in SRS score)	
Amantadine	2001 King	No change in parent rated ABC-CV, but clinician rated ABC-CV showed reduction in hyperactivity and inappropriate speech		No SAEs, Insomnia
	2015 Ellul	BFCRS improvement from 46 to 4		
	2020 Hutchinson	BFCRS improvement and allowed large reduction in lorazepam dose requirements		
Ketamine	2021 Wink	ABC-SW—No difference	CGI-I—No difference	Emesis, bad taste, dizziness, fatigue, headache, nausea, throat irritation; transient tachycardia, bradycardia, and hypertension
Minocycline	2013 Pardo	No difference in CGI-I or CGI-S	No changes in cytokine or chemokine levels in serum or CSF Changes in BDNF isoforms were found—unclear significance	Headache, hematuria, weight gain, appetite increase
NAC	2012 Hardan	ABC-I—Improved with NAC	ABC-S—No change RBS-Stereotypies—Improvement with NAC SRS—No change in overall score, but improvement seen on Social Cognition and Autism Mannerisms subscales	Constipation, nausea/vomiting, diarrhea, increased appetite, akathisia

Table 2 (continued)

Drug	Citation	Primary outcome	Secondary/exploratory outcomes	Adverse effects
	2016 Wink	CGI-I (Anchored to core social impairment)—No difference vs placebo	CGI-S, ABC, SRS—No difference VABS II—No difference GSH levels—Increased in NAC group vs. placebo; but otherwise no difference in oxidative stress markers	Headache, stomachache, fever
	2017 Dean	SRS—No difference CCC-2—No difference RBS-R—No difference	No difference in CGI-I or CGI-S	No difference in adverse events vs. placebo
	2020 Pesko	Reduction in symptoms of irritability and/or antipsychotic dose		
Sulforaphane	2014 Singh	SRS—Greater reduction in total score in sulforaphane group (− 20.4 vs − 2.0 in placebo) ABC- Greater reduction in irritability and lethargy subscales	Significantly higher numbers of responders in CGI-I categories for social interaction, aberrant behavior, and verbal communication (CGI-I scores of 1 or 2)	Weight gain
	Zimmerman 2011*	Preliminary—Improvement in OACIS-S score		
	Zimmerman 2015*	Preliminary—38% improvement at 15 weeks on the OACIS-I		
RG7713	2017 Umbricht	Eye-tracking—increased orientation to biological motion No significant difference overall in ability to detect emotion in tasks	No difference in RMET or CGI-I	Dizziness, attention problems, rash, and anxiety
Balovaptan (RG7314)	2019 Bolognani	SRS-2—No difference from placebo	VABS—Improvement (primarily in socialization and communication scores) over placebo in 4 mg and 10 mg groups ABC subscales—No difference RBS-R, CGI-I—No difference	
	Phase II Trial NCT02901431	VABS—No difference from placebo	CGI-I—No difference from placebo	
Intranasal vasopressin	2019 Parker	SRS-2—Greater reduction in scores compared to placebo	CGI-I (Focused to social communication)—Improvement over placebo RMET and FERT- Improved > placebo SCAS—Scores reduced > placebo RBS-R—No difference	No difference in adverse events from placebo
Cannabidiol	2019 Barchel	Parent report on 4 areas Hyperactivity—68% had improvement Self-injury—67.6% had improvement Sleep problems—71.4% had improvement Anxiety—47.1 had improvement		Somnolence, appetite decrease, appetite increase
	2019 Schleider	30.1%—significant improvement 53.7%—moderate improvement 6.4%—no improvement 8.6%—no change		Restlessness, sleepiness, psychoactive effect, increased appetite, digestion problems, dry mouth, and lack of appetite
	2019 Pretzsch (multiple papers)	A) MRS—Upregulation of GABA in the dorsomedial prefrontal cortex was significantly greater in those with ASD compared to neurotypical controls	B) fMRI—Differences in functional connectivity response in the ASD-cannabidiol group, specifically in the cerebellar vermis	None

Table 2 (continued)

Drug	Citation	Primary outcome	Secondary/exploratory outcomes	Adverse effects
Oxytocin	2003 Hollander	Greater reduction in repetitive behavior over time oxytocin group compared to reduction in placebo, but otherwise no differences observed		Drowsiness, anxiety, depression, headache, tingling, trembling, restlessness, stomach cramps, enuresis
	2010 Andari	Social Ball Tossing Game—in ASD pts, increased social reciprocity towards "good" player compared to baseline with oxytocin; also reported increased feelings of trust and stronger preference for "good" player (over bad player)	Facial scanning—Significantly longer period spent looking directly at face, specifically eyes, after oxytocin, compared to baseline, although still overall less time spent compared to NT controls	
	2012 Anagnoustou	RBS-R—No difference CGI-I—No difference DANVA-2—No difference	RMET—Greater improvement compared to placebo WHOQOL—Greater improvement	Increased tics, increased irritability, fatigue, headache, staring spells
	2014 Dadds	Video observation of repetitive behaviors and social interaction skills, and facial emotion recognition task—no difference vs. placebo	CARS—No difference vs placebo SRS—No difference	No major adverse effects
	2014 Watanabe 2015 Aoki	Behavioral task (Identifying non-verbal vs. verbal social cues): -Significantly increased number of non-verbal judgements in OXT group vs placebo -OXT group had shortened processing time when presented with incongruent verbal and non-verbal stimuli	fMRI: OXT group had changes in activation of medial PFC regions while processing non-verbal stimuli, and improved functional connectivity between dmPFC and ACC H-MRS—OXT induced increased markers for neuronal energy demand in the vmPFC, which were tied to improvements in reading nonverbal cues	None reported
Oxytocin (Con't)	2016 Yatawara	SRS-P—Greater improvement over time between subjects when comparing drug to placebo; greater mean improvement at post-test RBS-R-P—No difference	ADOS—No difference vs placebo CGI-I—No difference vs. placebo	Increased thirst, polyuria, constipation; 3 SAEs—increased hyperactivity and aggression
	2016 Kosaka	CGI-I—No difference between any groups in ITT population; in male-only subgroup greater improvement in high dose group vs. placebo Interaction Rating Scale Advanced—No difference in ITT or male subgroup	ABC—no difference in any of the subscales OXTR gene polymorphisms not predictive of treatment response	No SAEs, no hormone-related abnormalities observed in non-pregnant females
	2017 Parker	SRS—Greater improvement vs. placebo Plasma OXT as biomarker—Addition of pre-tx OXT levels to analysis significantly improved explanatory power of the model	RBS-R—No difference Spence Children's Anxiety Scale—No difference	No difference in adverse events vs. placebo
	2018 Yamasue 2019 Owada	ADOS—social reciprocity—No difference vs. placebo	ADOS—repetitive behavior—Reduced vs. placebo Increased duration of gaze fixation on socially relevant regions in OXT	Transient gynecomastia; otherwise no significant difference in adverse events vs. placebo
	2019 Kruppa	Probabilistic social reinforcement learning task with fMRI—oxytocin enhanced learning in response to social targets and feedback, which correlated with changes seen in the nucleus accumbens on functional MRI in the oxytocin treatment group (not seen in placebo)		None reported

Table 2 (continued)

Drug	Citation	Primary outcome	Secondary/exploratory outcomes	Adverse effects
	2020 Bernaerts	SRS-A-No difference vs. placebo in self- or informant-rated scales	RBS-R—Improvement seen in score reduction over placebo State Adult Attachment Measure—Improvement vs. placebo > Improvements persistent a 1 year follow up WHO-QOL—No difference vs. placebo	None reported

ABC Aberrant Behavior Checklist (Subscales: *I* irritability, *LSW* lethargy/social withdrawal, *H* hyperactivity, *IS* inappropriate speech, *S* stereotypy); ABC-CFX-SA Specialized version of ABC for Fragile X Syndrome Social avoidance subscale, *CGI* clinical global impressions (*CGI-I* improvement, *CGI-S* Severity), *SRS/SRS-2* Social responsiveness scale (*SRS-A* SRS for adults, *SRS-P* parent report), *CY-BOCS* Children's Yale-Brown Obsessive Compulsive Scale (*PDD* specialized version for Pervasive Developmental Disorder), *VABS* Vineland Adaptive Behavior Scale, *CARS* childhood autism rating scale, *ADOS* Autism Diagnostic Observation Schedule, *SS* statistically significant, *RBS-R* repetitive behaviors scale-revised (RBS-R-P parent report), *GABA* glu neurotransmitters GABA and glutamate, *MRS* magnetic resonance spectroscopy, *BDNF* brain-derived neurotrophic factor, *sAPP* serum amyloid precursor protein, *ABC-CV* ABC Community Version, *BFCRS* Bush-Francis Catatonia Rating Scale, *NAC* N-acetylcysteine; GSH Glutathione; CCC-2 Children's Communication Checklist; OACIS Ohio Autism Clinical Impression Scale (OACIS-S Severity, OACIS-I Improvement), *RMET* Reading the Mind's Eye Test, *FERT* Facial Expression Recognition Test, *SCAS* Spence Children's Anxiety Scale, *fMRI* functional magnetic resonance imaging, *DANVA-2* diagnostic analysis of nonverbal accuracy, *WHOQOL* World Health Organization Quality of Life measure, *OXT* oxytocin, *PFC* prefrontal cortex (dmPFC dorsomedial PFC, vmPFC ventromedial PFC), *ACC* anterior cingulate cortex, *SAE* serious adverse event, *ITT* intention to treat, *NT* neurotypical

*Unpublished data

multi-site study in Europe on memantine in ASD and OCD struggled with serious recruitment difficulty was ultimately terminated (Hage et al., 2016; "Translational Adolescent and Childhood Therapeutic Interventions in Compulsive Syndromes (TACTICS)," 2018). A series of 3 large, multi-site studies, one of which was a double-blind placebo-controlled randomized withdrawal trial, and the rest of which were open-label, had mixed results (Hardan et al., 2019). The initial study (MEM-MD-91) was open label and was used to identify memantine responders (as defined by ≥ 10 point reduction in SRS total raw score from baseline at 2 consecutive visits); 517 participants (59.6%) were deemed confirmed responders. The second study (MEM-MD-68) used a randomized withdrawal design where memantine responders from MEM-MD-91 were randomized to one of 3 treatment arms (full dose memantine, reduced dose memantine, and placebo), with the primary outcome being loss of therapeutic response (LTR, defined as ≥ 10 point increase in SRS total raw score at any double-blind visit versus SRS score at randomization). In this study, no significant difference in proportion of patients who experienced LTR between any of the treatment arms, although authors noted that LTR criteria may have not been ideal, and there may have been over-broad identification of possible responder subgroup due to placebo effects in the initial study (Hardan et al., 2019).

In contrast to memantine, ketamine is a noncompetitive agonist of the NMDA receptor, with multiple potential indications from anesthesia to treatment refractory depression. There is some evidence to suggest that individuals with ASD are more likely to have successful sedation with ketamine over more typical agents like midazolam in emergency room and pre-operative settings (Arnold et al., 2015; Bachenberg, 1998; Brown et al., 2019; Wink, et al., 2014a, 2014b). A double-blinded, randomized, placebo-controlled crossover study of 2-dose intranasal ketamine in adolescents and young adults with idiopathic ASD (n = 21) was recently published and found no significant impact on primary or secondary outcomes (ABC-SW subscale and CGI-I scores). (Wink et al., 2021).

N-acetylcysteine (NAC) is involved in the regulation of extracellular glutamate levels and acts an antioxidant in restoring intracellular glutathione. NAC has mixed evidence for use in ASD. A 2012 RDBPCT of NAC in youth with ASD (n = 33, ages 3–10 years) noted NAC-associated reduction in irritability based measured by the ABC-I with additional improvement in repetitive behavior and hyperactivity noted (Hardan et al., 2012). Two RDBPCTs of NAC in youth with ASD have not demonstrated clinical improvement including a report involving thirty one 4–12 year-olds (Wink, et al., 2016a, 2016b) and a second study involving one hundred and two 3- to 9-year-olds with ASD (Dean et al., 2017).

Table 3 Ongoing/unpublished studies

Drug	Studies
Arbaclofen	Two RDBPCTs recruiting—NCT03682978, NCT03887676
Bumetanide	Two RDBPCTs active but not recruiting—NCT03715153, NCT03715166 One RDBPCT recruiting—NCT04766177
Pregnenolone	One pilot RDBPCT recruiting—NCT02627508
AZD7325	One RDBPCT recruiting—NCT03678129 One completed, but no results posted—NCT03678129
Acamprosate	One completed but no results posted—NCT01813318
Riluzole	None
Memantine	One completed neuroimaging study, no results posted -NCT02811627
Amantadine	None
Ketamine	One RDBPCT recruiting—NCT03434366
Minocycline	One RDBPCT (crossover) completed, no results posted—NCT04031755
NAC	Two studies actively recruiting -NCT04278898, NCT03757585
Sulforaphane	One study completed but no results posted—NCT02879110 Two ongoing studies, one RDBPCT, one open label—NCT02677051, NCT04805957
Intranasal vasopressin	One RDBPCT actively recruiting—NCT03204786
Cannabidiol	Epidiolex: Open-label NCT03900923 and RDBPCT crossover NCT04517799 One RDBPCT NCT04745026 One RDBPCT—crossover study NCT04520685
Oxytocin	Ten completed studies with no results posted: NCT01945957, NCT01788072, NCT03640156, NCT03183674, NCT02414503, NCT03337035, NCT01914939, NCT02302209, NCT01093768, NCT03282162 Two neuroimaging studies with results posted: NCT03033784, NCT02940574 Two completed, but with data issues: NCT01183221, NCT01256060 Four active but not recruiting: NCT02493426, NCT02985749, NCT01931033, NCT03466671 Three actively recruiting: NCT02918864, NCT04007224, NCT03370510 Completed: NCT01308749—RDBPCT, results posted; improvement in SRS scores Completed: NCT01944046—Large RDBPCT with open label phase, results posted, appears no difference in primary or secondary outcomes (of note, SRS, ABC, VABS) Completed: NCT01908205—RDBPCT, results posted, appears no difference in primary outcome (ABC-SW)

Sulforaphane

Sulforaphane, a dietary phytochemical derived from broccoli sprouts which is postulated to protect cells from oxidative stress, has shown potential benefit in improving social deficits in children and young adults with ASD. A RDBPCT of sulforaphane versus placebo (n = 44, ages 13–27 years, all male) found significant reduction in ABC and SRS scores in the treatment group vs placebo at 18 weeks (ABC: − 21.44 ± 4.34 vs − 2.00 ± 4.59, p < 0.001; SRS: − 20.40 ± 4.54 vs. − 2.00 ± 3.46, p 0.017). Overall CGI-I scores did not differ between groups, but specific CGI-I scores for verbal communication, social interaction, and aberrant/abnormal behavior significantly improved (p 0.015, p 0.007, and p 0.014, respectively) (Singh et al., 2014).

Cannabidiol

The endocannabinoid system is thought to be involved in social interaction and emotional responses and is being investigated as a component of the underlying pathophysiology of ASD (Karhson et al., 2016; Zamberletti et al., 2017). Cannabidiol (CBD) products are thought to have neuroprotective and anti-inflammatory effects as well as the ability to modulate the endocannabinoid signaling pathways (Campbell et al., 2017). A 2020 literature review found mostly open label case series and cohort studies, which mainly found benefit in associated symptoms including sleep, hyperactivity, and behavioral disturbances/outbursts; though only one of the studies actually examined any core ASD symptoms (Barchel et al., 2018; Fusar-Poli et al., 2020). However, the authors noted some additional significant findings that in patients with comorbid epilepsy, cannabidiol significantly reduced severity and frequency of seizures (Fleury-Teixeira et al., 2019), and participants trialed on cannabidiol had

significant reduction in dose and number of other psychotropic medications (Aran et al., 2019). Recently, a series of double-blind, randomized, placebo-controlled single dose neuroimaging comparison studies between adults with ASD and non-autistic controls have also shown some interesting positive findings (n = 34, all adult males). In one study, magnetic resonance spectroscopy showed multiple changes related to GABA and glutamate across groups in the cannabidiol treatment arm, notably a decrease in GABA (measured with associated macromolecules) in the dorsomedial prefrontal cortex in ASD in contrast to an increase seen in neurotypical controls (Pretzsch, et al., 2019a, 2019b). Additionally, this group functional MRI implicated differences in functional connectivity response in the ASD-cannabidiol group, in regions generally associated with abnormalities in ASD (Pretzsch, et al., 2019a, 2019b). Cannabidiol was generally well tolerated; most common adverse effects noted were increased appetite, irritability, and somnolence, with one report of psychosis as a serious adverse event (Fusar-Poli et al., 2020). Cannabidiol remains an area of active and ongoing interest (NCT04517799, NCT04520685, NCT04745026, NCT03900923) however, purity of tested compounds remains an important concern, given that compounds containing delta-9-tetrahydrocannabidiol (THC)-like compounds may exacerbate neurologic symptoms without significant therapeutic benefit (Solimini et al., 2017).

Oxytocin

Oxytocin (OXT) is an endogenous hormone found to play a major role in social functioning and relationship formation in both humans and animals, which has shown potential benefit in ASD core symptoms, although evidence has been mixed, possibly due to treatment only being effective in certain subgroups. A randomized crossover trial of young children with ASD (n = 31, 3–8 years) showed that intranasal oxytocin treatment led to improvement in caregiver-rated social responsiveness versus placebo (as measured by greater mean improvement in SRS scores—F = 13.8, d.f. = 1, p 0.01) (Yatawara et al., 2016). Another double-blind RCT of intranasal OXT vs. placebo in children with ASD (n = 32, 6–12 years) expanded on this finding, noting that pre-treatment plasma oxytocin levels predicted treatment response (lower levels predicting greater improvement in SRS scores), and that inclusion of endogenous pretreatment OXT measures in the statistical model improved explanatory power by 43% (Parker et al., 2017). Another double-blind crossover RCT in male adults with ASD (n = 39) found that oxytocin enhanced learning in response to social targets and feedback, which correlated with changes seen in the nucleus accumbens on functional MRI in the oxytocin treatment group (which were not seen in the placebo group) (Kruppa et al., 2019). However, other studies have shown mixed or negative results – two RDBPCTs of oxytocin in adults (n = 19; n = 40) and one in children with ASD (n = 38, ages 7–16 years, dosing over 5 days) all failed to find any benefit over placebo on the SRS and other measures of social functioning. These two adult studies also failed to find any benefit over placebo in repetitive behavior as measured by the Repetitive Behavior Scale-Revised (RBS-R) (Anagnostou et al., 2012; Bernaerts et al., 2020; Dadds et al., 2014). A large, multi-site, RDB-PCT of oxytocin in adults with ASD in Japan had mixed findings—there was no improvement over placebo in the primary outcome, Autism Diagnostic Observation Scheduled (ADOS)—social reciprocity subscale, but there was improvement noted on ADOS—repetitive behavior, as well as gaze fixation on socially relevant regions (Yamasue et al., 2020). A subsequent analysis of the same study also found that oxytocin improved emotive facial expression (Owada et al., 2019). Among the studies with negative findings, several reported a large placebo effect, which in addition to not controlling for endogenous oxytocin markers, may have masked positive findings. As of this writing, there are several active studies of oxytocin in ASD in the clinicaltrials.gov database.

Vasopressin Modulation

In the brain**,** vasopressin acts primarily on two receptors, V1b, which is involved in the HPA system, and V1a, which modulates social and aggressive behavior. Variants of the vasopressin receptor 1A (AVPR1A) gene, which encodes the V1a receptor, have been associated with ASD (Kim et al., 2002; Yang et al., 2010; Yirmiya et al., 2006). Early studies using single dose administration of RG7713, a selective V1a receptor antagonist, in adults with ASD have provided preliminary evidence that modulation of V1a receptors in individuals with ASD may provide a novel target for treatment of social deficits, although direct results from the study were mixed (Umbricht et al., 2017). Balovaptan (previously known as RG7314), a vasopressin 1a (V1a) receptor antagonist, initially showed promise – preliminary results from a phase II RCT in adult males (n = 223) reported improvement in the Vineland Adaptive Behavior Scale (Schnider et al., 2020). However, a phase II trial in children (n = 339, ages 5–17 years) did not find any similar benefit (NCT02901431). Phase III trials in both children and adults are currently listed as terminated in the clinicaltrials.gov database, some raw data is available but appears there is no analysis planned at this time (NCT03504917, NCT04049578). One RCT (n = 30) of intranasal vasopressin vs. placebo in children with ASD found improvement over placebo in several measures, including reduction in SRS-2 scores, CGI-I scores (targeted to social communication), although no difference in RBS-R scores. There is currently one actively

recruiting study looking at intranasal vasopressin in ASD (NCT03204786).

Future Directions for Drug Development in Autism

Two problems significantly complicate drug treatment development in ASD: (1) the heterogeneity of ASD and (2) limited objective measurements of target engagement beyond traditional caregiver questionnaires and clinician assessments. Heterogeneity is a multi-faceted problem. Given the sheer number of genes, environmental factors, epigenetic changes, and separate but potentially overlapping physiological processes (e.g. excitatory-inhibitory imbalance, immune dysregulation and increased oxidative stress, potential dysregulation of the gut-brain axis) implicated at times in autism, there are numerous potential treatment targets, but often insufficient evidence on how to a priori identify clinically relevant subgroups for a particular treatment. An additional complication is the nature of potential changing treatment targets across the lifespan—there may be treatment targets which show benefit in early childhood, but not in adolescence or adulthood. Attempts to focus on biologic subgroups within autism has been limited in our field with most efforts to date involving broad clinical trial inclusion/exclusion criteria such as focus on presence of absence of epilepsy or intellectual disability guiding study entry. Additionally, clinical outcome measurements such as the ABC or the CGI scale may be limited in the degree to which they support differentiation of treatment response in potential subgroups of ASD. Such traditionally employed clinical ratings are subject to significant placebo response in ASD trials, further blurring the ability of pen and paper measures to accurately and reproducibly support treatment responder subgroup analysis.

To address these concerns, the incorporation of biological markers and other objective measures into drug trials may help to address both subject heterogeneity and treatment response measurement concerns. While the study of biomarkers in ASD is not new, most of this work has been targeted toward improving diagnostic clarity, not toward understanding treatment outcomes. Numerous potential biomarkers in ASD have been identified including molecular/chemical, neuroimaging, electrophysiological, autonomic, and quantitative behavioral markers among others (Frye et al., 2019; Goldani et al., 2014). Rationally employing such markers early in drug treatment development will enable both early evaluation of target engagement while in parallel providing quantitative evidence defining specific subgroups of persons with ASD who may be displaying the most robust potential treatment response. Such an approach if utilized in early Phase Ib and IIa study will de-risk large-scale trial efforts while simultaneously limiting the large stakeholder burden associated with repeated failed large Phase III projects.

Conclusion

While significant progress has been made in the medication management of interfering behavior in persons with ASD, several areas require future study to meet unmet needs in this area. First, the two FDA approved treatments for irritability in youth with ASD are marked by significant adverse effect profiles, most commonly weight gain and obesity. The ability to predict and then effectively managed SGA-associated adverse effects in persons with autism requires more dedicated investigation by our field. In this vein, work to evaluate potential non-antipsychotic approaches to irritability treatment remains limited without significant success to date. Second, limited, if any, rigorous controlled data exists guiding the medication management of anxiety or mood symptoms in the context of ASD. This has led to potentially overuse of SSRIs in our populations resulting at times in behavioral disinhibition consistent with published work describing SSRI use in youth with ASD (King et al., 2009). This prescribing pattern likely reflects a lack of well defined, evidence-based prescribing guidelines targeting anxiety, repetitive behavior, and mood disturbance in persons with autism. Finally, our field has failed to develop target drug therapies for core symptoms of autism including social impairment, interfering repetitive behaviors, and/or communication challenges. This failure will likely require a new approach to ASD as a construct for targeted treatment development. As a broad descriptive diagnosis, autism holds within its umbrella a myriad of molecularly genetic drivers of pathophysiology that likely have at times converging and sometimes diverging aspects that result in a roughly similar pattern of behavior. Success for "core" symptom drug treatment in autism will likely be based upon evidence-based biologic subtyping efforts that match potentially small percentages of persons with autism who share common physiologic features with specific targeted drug or drug combination therapy. Such a targeted therapeutics approach will also need to rely on biomarker development in this field to demonstrate marked brain and/or performance functional change early in drug development to appropriately support and help map future large-scale trial efforts. Not taking such an approach may result in more "promising" treatments that inevitably lose traction in large-scale trials in ASD involving broad, physiologically and phenotypically diverse patient samples.

Author contribution EH and ML were responsible for reviewing the literature and writing the initial manuscript. KD and CE reviewed and edited the manuscript. All authors read and approved the final manuscript.

Funding This work was supported in part by the Division of Child and Adolescent Psychiatry, Cincinnati Children's Hospital Medical Center.

Declarations

Conflict of interest The authors declare that they have no interests that compete directly with this work, though Drs. Lamy and Erickson do receive research support from various sources for other work. Dr. Lamy's current research is supported by OVID Therapeutics and the Simon's Foundation. Dr. Erickson has received current and/or past research support from the National Institutes of Health, the United States Department of Defense, the United States Centers for Disease Control, the John Merck Fund, Autism Speaks, the Simons Foundation, Cincinnati Children's Hospital Research Foundation, the FRAXA Research Foundation, the National Fragile X Foundation, the Roche Group, Seaside Therapeutics, Novartis, Stalicla, Scioto Bioscience, Janssen, Neuren, Alcobra, and Indiana University School of Medicine. He is a current consultant to Impel, Forge Therapeutics, and Stalicla. He holds equity interest in and is a consultant to Confluence Pharmaceuticals. He is the inventor on intellectual property held by Cincinnati Children's Hospital Research Foundation and Indiana University describing methods for diagnosis and treatment methods in autism spectrum disorder and fragile X syndrome.

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