

An Update on Pharmacotherapy for Autism Spectrum Disorder in Children and Adolescents



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Abstract and Introduction

Abstract

Purpose of review Although there is no known efficacious pharmacotherapy for core symptoms of autism spectrum disorder (ASD), psychotropic medications are commonly prescribed for behavioral/emotional symptoms associated with ASD. We reviewed current evidence-based pharmacotherapy options and updates from recent noteworthy studies.

Recent findings Atypical antipsychotics, particularly risperidone and aripiprazole, are effective in reducing irritability, stereotypy and hyperactivity. Metabolic adverse events, including weight gain and dyslipidemia, are common. Methylphenidate is effective in reducing attention-deficit hyperactivity disorder (ADHD) symptoms. Atomoxetine and alpha-2 agonists appear effective in reducing ADHD symptoms. Selective serotonin reuptake inhibitors are not effective in improving repetitive behaviors in children with ASD, and frequently cause activating adverse events. Efficacy of antiepileptic drugs is inconclusive. Overall, efficacy and tolerability of pharmacotherapy in children with ASD are less favorable than data seen in typically developing children with similar symptoms. Newer agents, including glutamatergic agents and oxytocin, appear promising albeit with mixed results.

Summary Current evidence-based pharmacotherapy options in children with ASD are very limited, and many have substantial adverse events. Clinicians should use pharmacotherapy as a part of comprehensive treatment, and judiciously weigh risks and benefits. New pharmacotherapy options for core symptoms as well as co-occurring symptoms of ASD are in urgent need.

Introduction

Autism spectrum disorder (ASD) is a developmental disorder characterized by persistent impairment in reciprocal social communication and restricted, repetitive patterns of behavior (RRB). Reported frequencies have approached 1% of the population, and a recent surveillance report showed a prevalence of one in 68 children in the United States.^[1,2]

In addition to the core symptoms, many patients with ASD experience co-occurring psychiatric and behavioral problems, such as aggression, self-injury, impulsivity, hyperactivity, anxiety and mood symptoms. These conditions often impede treatment, and place a heavy burden on both patients and their caregivers.^[3] Psychotropic medications are frequently prescribed to alleviate these symptoms, and recent studies showed 27–40% of youth with ASD received psychotropic medications.^[4,5] Nevertheless, children with ASD tend to respond less favorably to psychotropic medications and experience adverse effects more often and severe than their peers without ASD.^[6,7]

Therefore, it is important for the clinicians to understand current evidence-based pharmacotherapy, risks and benefits, as well as pertinent updates from recent studies, to guide patients and caregivers to make well informed decisions.

We also reviewed noteworthy novel agents that have been the focus of recent research and clinical trials. Some of these agents aim at biologically targeted pharmacotherapy, which may lead to successful individualized treatment options. This type of approach is important and needed because of the wide phenotypic and genotypic heterogeneity of ASD.

Current Evidence and Pertinent Updates

We focused primarily on recently published randomized, double-blind, placebo-controlled (RDBPC) trials. Please refer to [6–33–48] for a safety and efficacy summary for selected trials.

Table 1. Selected randomized, placebo controlled trials (RPCT) of pharmacologic interventions in ASD in pediatric populations

Medication	Publication	Study Design Duration	N	Age (yr)	Dose	Comments	Noteworthy Adverse Events (AEs)
Antipsychotics							
Risperidone	RUPP 2002 [8]	RPCT, 8 weeks	101	5–17	0.5–3.5mg/d q.d. or divided b.i.d. Mean 1.8 mg/d	Separation from placebo in improving irritability (temper outburst, aggression and self-injurious behavior), stereotypy, and hyperactivity but not social functioning	Weight gain, increased appetite, fatigue, drowsiness, dizziness, drooling, tremor, constipation
	McDougle <i>et al.</i> 2005 [9]	RPCT, 8 weeks; Open-label, 16 weeks	101 63	5–17	0.5–3.5mg/d 0.5–4.5mg/d	Separation from placebo in improving restricted, repetitive, and stereotypical behavior but not in deficit in social interaction and communication The pattern on treatment response was maintained for 6 months	Weight gain, increased appetite, fatigue, drowsiness, drooling, dizziness
	RUPP 2005 [10]	Open-label, 16 weeks; RPCT D/C, 8 weeks	63 32	5–17	0.5–4.5mg/d Mean: 1.96 mg/d	Separation from placebo in improving irritability, hyperactivity, stereotypic behavior, and lethargy/social withdrawal Separation from placebo in time to relapse	Increased appetite, tiredness, drowsiness, abnormal movements
	Kent <i>et al.</i> 2013 [11]	RPCT 3 arms, 6 weeks	96	5–17	0.125 or 0.175 mg/d versus 1.25 or 1.75mg/d versus Placebo	Separation from placebo in improving irritability and global functioning in the high-dose group but not in the low-dose group	Somnolence, sedation and increased appetite occurred more frequently high-dose versus low-dose groups

Aripiprazole	Marcus <i>et al.</i> 2009 [12]	RPCT, 8 weeks	218	6–17	5, 10, or 15mg/d Fixed doses	Separation from placebo in improving irritability, agitation, self-injurious behavior, hyperactivity and stereotypic behavior	Sedation, drooling, EPS, weight gain
	Owen <i>et al.</i> 2009 [13]	RPCT, 8 weeks	98	6–17	2, 5, 10, 15 mg/d Flexible doses	Separation from placebo in improving irritability (tantrums, aggression, and self injurious behavior), hyperactivity, stereotypy, inappropriate speech	Fatigue, somnolence, weight gain, EPS
	Findling <i>et al.</i> 2014 [14]	Stabilization 13–26 weeks; RPCT D/C, 8 weeks	157 85	6–17	2, 5, 10, 15 mg/d Flexible doses	No separation from placebo in time to relapse (35% for aripiprazole and 52% for placebo. Hazard ratio of 0.57 and number needed to treat of 6)	Weight gain, somnolence, vomiting, EPS
Olanzapine	Hollander <i>et al.</i> 2006 [15]	RPCT, 8 weeks	11	6–14	7.5–12.5mg/d	Separation from placebo in improving global functioning	Weight gain, increased appetite, sedation
Haloperidol	Anderson <i>et al.</i> 1989 [16]	RPCT crossover, 12 weeks	45	2–7	0.25–4mg/d	Separation from placebo in improving behavioral symptoms but not in discrimination learning	None noteworthy

Medications for ADHD symptoms

Methylphenidate	RUPP 2005 [6]	RPCT crossover, 4 weeks; Open-label, 8 weeks	72 34	5–14	7.5–50mg/d Divided t.i.d.	Separation from placebo in improving hyperactivity The response was maintained for 8 weeks in the majority of responders	Irritability, decreased appetite, sleep difficulty, emotional outbursts Adverse effects were more frequent
	Jahromi <i>et al.</i> 2009 [17]	Titration; RPCT crossover, 2 weeks	33	5–13	0.125, 0.25, and 0.50mg/kg b.i.d.	Separation from placebo in children's use of joint attention initiations, response to bids for joint attention, self-regulation, and regulated affective state	18% of the participants had to stop treatment because of intolerable side-effects
Methylphenidate	Pearson <i>et al.</i>	RPCT		7–	ER10–40mg qam p	Separation from placebo in	Loss of appetite,

ER	2013 [18]	crossover, 4 weeks	24	12	Immediate release 2.5–10mg qpm	improving hyperactivity and impulsivity	sleeping problems
Atomoxetine (ATX)	Harfterkamp et al. 2012 [19]; 2013 [20]	RPCT, 8 weeks; Open-label, 20 weeks	97 88	6– 17	1.2 mg/kg/d	Separation from placebo in improving hyperactivity No separation in improving global functioning Up to 28 weeks treatment further improved ADHD symptoms	Nausea, decreased appetite, fatigue, and early-morning awakening AEs subsided during the open-label phase
	Handen 2014 [21]	RPCT 4 arms, 10 weeks	128	5– 14	Starting at 0.3 mg/kg/d Ceiling 1.8 mg/kg/d	ATX alone and ATX+parent training were superior to parent training+placebo and placebo only in decreasing ADHD symptoms. ATX+parent training was most effective followed by ATX alone, parent training+placebo and placebo only in improving global functioning (AACAP 2014)	Fatigue, appetite decreased, mood lability
Clonidine	Fankhauser <i>et</i> <i>al.</i> 1992 [22]	RPCT crossover, 4 weeks	9	5– 33	0.16–0.48 mg/d	Separation from placebo in improving impulsivity, hyperarousal, and self stimulating behavior	Sedation, hypertension, fatigue, decreased activity
Guanfacine ER	Scahill 2014 [23]	RPCT, 8 weeks	62	5– 14	1–4mg/d Mode 3mg/d	Separation from placebo in improving hyperactivity and global functioning (AACAP 2014)	Drowsiness, decreased energy, sleep disturbance
Antidepressants							
Fluoxetine	Hollander <i>et</i> <i>al.</i> 2005 [24] SOFIA 2009 [25]	RPCT crossover, 8 weeks RPCT, 14 weeks	45 158	5– 16 5– 17	2.4– 20mg/d 2, 9, or 18 mg/d	Separation from placebo in improving repetitive behavior No separation from placebo in improving repetitive behavior (Autism Speaks press release)	None noteworthy Unpublished

Citalopram	King <i>et al.</i> 2009 [7]	RPCT, 12 weeks	149	5–17	2.6–20mg/d Mean 16.5mg/d	No separation from placebo in improving repetitive behavior	Increased energy, impulsiveness, decreased concentration, hyperactivity, stereotypy, insomnia
Clomipramine	Remington <i>et al.</i> 2001 [26]	RPCT crossover, 7 weeks	36	10–36	100–150 mg/d Mean 16.5mg/d	No separation from placebo in improving stereotypy, irritability, or hyperactivity	Lethargy, tremors, tachycardia, insomnia, diaphoresis, nausea

Antiepileptic drugs

Valproate	Hellings <i>et al.</i> 2005 [27]	RPCT, 8 weeks	30	6–20	20 mg/kg/d level 70–100mg/ml	No separation from placebo in improving irritability and aggression	Increased appetite, skin rash, increased serum ammonia level
	Hollander <i>et al.</i> 2006 [28]	RPCT, 8 weeks	13	5–17	500–1500mg/d level 50–100mg/ml	Separation from placebo in improving repetitive behavior	Irritability, weight gain, aggression
	Hollander <i>et al.</i> 2010 [29]	RPCT, 12 weeks	27	5–17	Dosed to a mean level of 89.8mg/ml	Separation from placebo in improving irritability	Skin rash, irritability
Lamotrigine	Belsito <i>et al.</i> 2001 [30]	RPCT, 18 weeks	28	3–11	Mean 5 mg/kg/d Divided b.i.d.	No separation from placebo in improving aberrant behavior or other measures	Insomnia, increased stereotypes, aggression, echolalia
Levetiracetam	Wasserman <i>et al.</i> 2006 [31]	RPCT, 10 weeks	20	5–17	20–30 mg/kg/d	No separation from placebo in improving global functioning or irritability	Aggression, agitation

Glutamatergic and GABAergic agents

N-acetylcysteine	Hardan <i>et al.</i> 2013 [32]	RPCT, 12 weeks	33	3–10	900 mg/d–900mg t.i.d.	Separation from placebo in improving irritability	Agitation, irritability
Amantadine	King <i>et al.</i> 2001 [33]	RPCT, 4 weeks	39	5–19	2.5–5.0 mg/kg/d	No separation from placebo in improving hyperactivity or irritability	Insomnia

Riluzole	NCT00251303 2013 [34]	RPCT, 12 weeks	60	7– 17	100–120 mg/d	No separation from placebo in improving global functioning or repetitive and restricted behaviors (ClinicalTrials.gov)	Unpublished
Memantine	Hardan 2014 [35]	Open-Label, 12 weeks; RPCT D/C, 12 weeks	471	6– 12	D/C phase:full therapeutic dose, 50% of the dose or placebo	No separation from placebo in time to loss of therapeutic response (APA 2014)	Unpublished
Arbaclofen (STX209)	Veenstra- Vander Weele <i>et al.</i> 2013 [36]	RPCT, 12 weeks	150	5– 21	10 or 15mg t.i.d.	No separation from placebo in improving lethargy and social withdrawal symptoms but showed separation in improving global functioning (INSAR 2013)	Somnolence
Bumetanide	Lemonnier <i>et al.</i> 2012 [37]	RPCT, 12 weeks	60	3– 11	0.5mg b.i.d.	Separation from placebo in improving autistic behaviors and global functioning	Mild hypokalemia
Cholinergic agents							
Donepezil	Chez <i>et al.</i> 2003 [38]	RPCT, 6 weeks; Open-label, 6 weeks	43	2– 10	2.5 mg/d	Separation from placebo in improving expressive and receptive language as well as overall autistic features	Diarrhea, stomach cramping, increased Irritability
	Handen <i>et al.</i> 2011 [39]	RPCT, 10 weeks	34	8– 17	5–10 mg/d	No separation from placebo in improving executive functioning deficits	Diarrhea, headache, fatigue
Other agents							
Oxytocin	Guastella <i>et al.</i> 2010 [40]	RPCT, 45 min before task	16	12– 19	18 or 24 IU/d Intranasal	Separation from placebo in improvement in emotion cognition	None noteworthy
	Dadds <i>et al.</i> 2014 [41]	RPCT, 5 days live-in	38	7– 15	12 or 24 IU/d Intranasal	No separation from placebo in improving emotion recognition, social interaction skills, or general behavioral adjustment	None noteworthy
		RPCT				Separation from placebo in	

	Gordon <i>et al.</i> 2013 [42]	crossover, 45 min before fMRI	17	8–16	12 or 24 IU Intranasal	enhancing activity in the brain for social stimuli and attenuating its response to nonsocial stimuli	None noteworthy
						Salivary oxytocin level was associated with brain function	
	Guastella <i>et al.</i> 2014 [43]	RPCT, 8 weeks	50	12–18	18 or 24 IU Intranasal b.i.d.	No separation from placebo in improving social behaviors	None noteworthy
Naltrexone	Campbell <i>et al.</i> 1993 [44]	RPCT, 3 weeks	41	2–7	0.5–1mg/kg/d	Separation from placebo in improving hyperactivity	None noteworthy
	Feldman <i>et al.</i> 1999 [45]	RPCT, 2 weeks	24	3–8	1 mg/kg/d	No separation from placebo in improving communication	Transient sedation
Melatonin CR	Cortesi <i>et al.</i> 2012 [46]	RPCT 4 arms, 12 weeks	160	4–10	3 mg/d Controlled release	Melatonin plus CBT was the most effective in improving insomnia, followed by melatonin alone and then CBT alone compared with placebo	None reported
Omega-3 fatty acids	Bent <i>et al.</i> 2011 [47]	RPCT, 12 weeks	27	3–8	1.3 g	No separation from placebo in improving hyperactivity	Rashes
	Bent <i>et al.</i> 2014 [48]	RPCT, 6 weeks	57	5–8	1.3 g	No separation from placebo in improving hyperactivity	None noteworthy

AACAP, American Academy of Child and Adolescent Psychiatry annual meeting; ADHD, attention deficit hyperactivity disorder; APA, American Psychiatric Association annual meeting; ASD, autism spectrum disorder; CBT, cognitive behavioral therapy; CR, controlled release; D/C, discontinuation; EPS, extrapyramidal symptoms; ER, extended release; GABA, gamma-aminobutyric acid; INSAR, International Society of Autism Research annual meeting; qam, in the morning; qpm, in the afternoon; RUPP, Research Units on Pediatric Psychopharmacology Autism Network; SOFIA, Study of Fluoxetine in Autism.

Antipsychotics

Antipsychotics, particularly risperidone and aripiprazole, have been investigated extensively and have been shown to have efficacy for the treatment of irritability (aggression, self-injury, and severe tantrums) in children with ASD. Risperidone and aripiprazole are the only two medications that have been approved for patients with ASD by the US Food and Drug Administration (FDA). It should be noted that this regulatory approval is limited to those patients with problematic irritability. Both medications have also shown to be efficacious in improving stereotypy and hyperactivity. [8,9,12,13] However, their use needs to be reserved for patients with severe problem behavior and/or safety concerns given the high burden for metabolic adverse events, such as weight gain, dyslipidemia and hyperglycemia.

Risperidone improved irritability, stereotypy and hyperactivity with large effect sizes and high response rate, but did not

improve communication or social impairments.^[8,9] The effect was maintained in long-term treatment, and risperidone delayed time to relapse during a placebo-controlled discontinuation phase.^[9,10] A recent trial showed that combining risperidone and parent training was more efficacious than medication alone in improving problem behavior and adaptive functioning.^[49] A recent study with three arms (low-dose risperidone, high-dose risperidone and placebo) showed that low-dose risperidone (0.125 or 0.175 mg/d) was not efficacious in improving problem behavior, whereas high-dose (1.25 or 1.75 mg/d) was.^[11] Common adverse events were weight gain, increased appetite, fatigue, drowsiness, dizziness and drooling.

Aripiprazole has shown efficacy in reducing irritability, hyperactivity and stereotypy in two large short-term studies,^[12,13] and the effect was maintained long term.^[14,50] A relapse-prevention study of aripiprazole failed to show a separation from placebo in time to relapse, but suggested there might have been positive signals.^[14] More recent studies focused on long-term adverse events, and noted that increased dyslipidemia, aggression and weight gain were common.^[50,51] Antipsychotic-naïve subjects and younger subjects with a higher baseline weight were more vulnerable to weight gain.^[52]

In a small head-to-head comparison study of risperidone and aripiprazole in children with ASD, efficacy in decreasing problem behavior and frequencies of adverse events were shown to be comparable across the two treatment groups.^[53] A review of longitudinal clinical data showed comparable BMI Z-score changes between these two agents,^[54] suggesting aripiprazole may not have a more favorable metabolic adverse event profile in children with ASD, unlike data seen in other disorders.^[55]

Olanzapine was effective in improving behavioral measures in an RDBPC study, but with significantly more weight gain than placebo.^[15] Haloperidol treatment improved behavioral symptoms,^[16] but its use is limited because of the risk of extrapyramidal symptoms, particularly because risperidone may improve a broader range of problem behavior than haloperidol.^[56]

No RDBPC studies were found for quetiapine, ziprasidone or newer agents, including paliperidone, iloperidone, acenapine and lurasidone. Quetiapine was poorly tolerated and minimally effective in two small open-label studies.^[57,58] Ziprasidone and paliperidone appeared promising in open-label studies.^[59,60] A large RDBPC study of lurasidone is currently underway (NCT01911442).^[34] Ziprasidone and the newer agents may have less metabolic adverse events, and more controlled studies are needed.

Medications for Attention Deficit Hyperactivity Disorder Symptoms

Methylphenidate (MPH) has shown to be effective in improving attention deficit hyperactivity disorder (ADHD) symptoms in children with ASD. However, response rates are lower and discontinuation rates owing to adverse events are higher than data seen in typically developing children with ADHD.^[6,17] Further analyses among the subjects who had genotype data suggested that multiple monoaminergic gene variants may help explain individual differences in efficacy and tolerability of MPH.^[61] MPH was better tolerated in children with higher cognitive functioning, and when concomitant medications were allowed.^[18] Common adverse events were decreased appetite, insomnia and emotional outbursts. There are no RDBPC studies of dextroamphetamine, or mixed amphetamine salts, in this population.

Atomoxetine has shown efficacy in treating ADHD symptoms in children with ASD.^[19,21] In a recent study with four arms, combining atomoxetine and parent training (ATX + parent training) yielded a higher response rate and a lower mean dose needed compared to atomoxetine alone.^[21] Both atomoxetine alone and ATX + parent training groups were superior to parent training plus placebo and placebo alone groups in improving ADHD symptoms. Atomoxetine was well tolerated, and fatigue, nausea and appetite decrease were common adverse events. Continued treatment with atomoxetine showed further improvement in ADHD symptoms, suggesting it may take up to a half year for atomoxetine to achieve maximum effect.^[20]

An RDBPC trial of clonidine showed benefits in reducing ADHD symptoms in children with ASD.^[22] A recent RDBPC study of guanfacine extended release showed efficacy in improving hyperactivity in children with ASD.^[23] Larger trials

are warranted before more definitive conclusions can be reached.

Antidepressants

A large, high-quality study showed citalopram was not superior to placebo in reducing RRB in children with ASD and caused more adverse events, particularly increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypy and insomnia.^[7] Another large, unpublished study showed fluoxetine did not separate from placebo in reducing RRB in children with ASD.^[25] No RDBPC trials for sertraline, paroxetine or escitalopram were found. A recent Cochrane review of selective serotonin reuptake inhibitor (SSRI) trials, therefore, concluded that there is no evidence of efficacy of SSRIs in children with ASD, and emerging evidence of harm.^[62] The risk/benefit ratio of SSRIs may vary by age as tolerability was better in adults, and use for reducing coexisting anxiety and/or depressive symptoms may be helpful in older youth; however, there are no RDBPC studies that evaluated this issue specifically. Tricyclics such as clomipramine were not well tolerated and have insufficient evidence to be recommended for children with ASD.^[26,63]

Antiepileptic Drugs

Valproate may be efficacious in the treatment of irritability and RRB in children with ASD.^[28,29] But the results were inconsistent with those from an earlier study, which failed to show efficacy in improving irritability in children with ASD.^[27] Individual RDBPC trials of lamotrigine and levetiracetam did not show efficacy in improving behavioral measures.^[30,31] An RDBPC study showed that topiramate in combination with risperidone may be beneficial in improving problem behavior in children with ASD.^[64] Further RDBPC studies are needed to define the efficacy of antiepileptic drug (AED) as monotherapy or in combination with antipsychotics.

Novel Approaches and Challenges

To date, there is no medication shown to be effective in treating the core symptoms of ASD. There have been increasing efforts to find novel pharmacotherapy targets based upon molecular and cellular biomarkers, which are reflected in a number of recent trials of newer agents described below.

Unfortunately, many novel agents with promising findings from animal models and open-label studies often fail to show efficacy during RDBPC clinical trials. High placebo response rates, heterogeneity of the ASD population and imprecise diagnostic and outcome measures frequently contribute to the difficulty in capturing medication benefits.

Glutamatergic and Gamma-aminobutyric Acidergic Agents

Alterations/imbalance of glutamatergic (excitatory) and glutamatergic and gamma-aminobutyric acid (GABA)ergic (inhibitory) neurotransmission (abnormally high excitatory/inhibitory ratios) have been implicated in pathophysiology of ASD and other neurodevelopmental disorders, including fragile X syndrome (FXS).^[65] A number of N-methyl-D-aspartate (NMDA) receptor (an ionotropic glutamate receptor) and GABA receptor modulators have been investigated for improving ASD core symptoms as well as associated problem behavior. The results from clinical trials have been inconsistent, however.

A small RDBPC study of N-acetylcysteine (NAC; NMDA modulator) showed efficacy in improving irritability in children with ASD.^[32] Despite more promising preclinical data, NMDA receptor antagonists, amantadine, riluzole (NCT00251303) and memantine have failed to show efficacy in RDBPC trials.^[33–35]

Recently, small individual RDBPC trials of glutamatergic agents (amantadine, memantine, riluzole, NAC) as an adjunctive therapy to risperidone reported efficacy in improving behavioral measures compared with placebo plus risperidone group.^[66–69] Thus, these agents may be helpful in a combination with antipsychotic treatment, but the results need to be replicated in larger trials.

An RDBPC study of arbaclofen (also called STX209, GABA-B agonist) in an FXS population, ages 6–39 years (73% youths) and 59% with comorbid autism, suggested improved social function in the posthoc analyses.^[70] A large

RDBPC study in children with ASD showed no efficacy in improving social withdrawal, but showed a significant improvement in clinical global impressions.^[36] The authors suggested that there were more favorable responses in a higher functioning subgroup. An RDBPC study in children with ASD showed that bumetanide (GABA modulator) was efficacious in improving the Childhood Autism Rating Scale scores and clinical global impressions.^[37]

Cholinergic Agents

Postmortem and animal studies suggest that abnormalities in the cholinergic system may be involved in pathogenesis of ASD.^[71,72] Two RDBPC trials of donepezil, (cholinesterase inhibitor) in children with ASD so far showed mixed results. One described efficacy in improving language functioning and overall autistic features,^[38] but the other did not show efficacy in improving executive functioning.^[39]

With a hypothesis that a deficiency in cholinergically driven rapid eye movement (REM) sleep, seen in children with ASD, may contribute to an abnormal neural organization, Buckley et al.^[73] conducted a small open-label study of donepezil. The results showed that donepezil increased REM sleep in children with ASD, and an RDBPC trial to evaluate donepezil for sleep enhancement and behavioral change in children with ASD is currently underway (NCT01887132).^[34]

Oxytocin

The oxytocin system has been identified to be involved in social behavior, and preclinical data have been promising.^[74] It has generated excitement within autism research, and over a dozen clinical trials are currently recruiting.^[34]

A recent RDBPC functional MRI study in children with ASD noted that intranasal oxytocin enhanced activity in the brain for social stimuli and attenuated its response to nonsocial stimuli, and the enhancement in brain function was associated with changes in salivary oxytocin.^[42] Interestingly, two recent RDBPC trials in children with ASD failed to show efficacy in improving emotional cognition or social behavior after four days to 8 weeks of treatment.^[41,43] Gordon et al.^[42] suggested that it may be most therapeutic to use oxytocin before evidence-based behavioral treatments to enhance social learning. In fact, a large RDBPC trial of oxytocin as an adjunct to behavioral therapy for ASD is currently recruiting (NCT01914939).^[34]

Other Agents

Disturbance of the opiate system has been implicated in individuals exhibiting self-injurious behavior (SIB) and hypoalgesia, perhaps related to chronic elevation of endogenous opiates.^[75] Naltrexone has been used in children with SIB who failed to respond to other medications, even though there is not definite evidence to support this treatment. A recent systemic review of 10 RDBPCs concluded that naltrexone may improve hyperactivity and restlessness, but there was not sufficient evidence that it had an impact on core features of ASD.^[76]

A large RDBPC study with four arms found that the melatonin plus cognitive behavioral therapy (CBT) group was the most effective in reducing insomnia symptoms, followed by melatonin alone and then the CBT alone group compared with the placebo group.^[46]

Following a small RDBPC trial that showed a trend in improving hyperactivity in children with ASD,^[47] omega-3 fatty acids (O3FA) were investigated in an Internet-based, RDBPC trial.^[48] O3FA failed to show efficacy; however, the study demonstrated the feasibility of conducting Internet-based RDBPC trials in children with ASD.

Metabolic pathways associated with oxidative stress may be involved in ASD pathogenesis,^[77] and small RDBPC studies of sulforaphane, tetrahydrobiopterin, L-carnitine and methyl B12 showed promising results and warranted larger trials.^[78–81]

Secretin is one of the most extensively studied agents; however, a Cochrane review that included 16 RDBPC trials found no evidence that secretin is effective in improving the core symptoms of ASD.^[82]

Conclusion and Future Directions

Despite the high rates of medication usage in children with ASD, current evidence-based pharmacotherapy options are extremely limited. Antipsychotics treatment, particularly risperidone and aripiprazole, are effective in reducing irritability, stereotypy and hyperactivity, and MPH is effective in improving ADHD symptoms. Atomoxetine and alpha-2 agonists appear effective in reducing ADHD symptoms. SSRIs are not effective in improving RRB in children with ASD, and may lead to activating adverse events. Efficacy of AED is inconclusive. Even with the medications with evidence-based efficacy, their response rates and tolerability tend to be less favorable than data seen in typically developing children with similar symptoms. Therefore, clinicians should carefully weigh the risk/benefit ratio, closely monitor adverse events and periodically re-assess needs for continued pharmacotherapy for the target symptoms.

ASD is a lifelong neurodevelopmental disorder that often requires a comprehensive and multidisciplinary treatment. Nonpharmacologic options such as modifications in the setting and behavioral interventions may improve target symptoms without medications. Therefore, pharmacotherapy should be a part of comprehensive treatment.

Nevertheless, new pharmacotherapy options for severely impairing co-existing and core symptoms are in urgent need. However, developing new drugs for ASD faces a number of challenges.

First of all, largely unknown cause and wide genotypic and phenotypic heterogeneity bring an inherent challenge to treatment development for the population. Large-scale clinical trials that include highly heterogeneous subjects often fail to capture effects of treatment that may be indeed effective in a more homogeneous subgroup. Investigating ASD associated with monogenic disorders (e.g. FXS and tuberous sclerosis) may mitigate this challenge. In fact, targeted agents such as acamprosate for FXS and rapamycin for tuberous sclerosis are currently in clinical trials.^[34] Future research investigating genotypic and/or phenotypic characteristics influencing medication response and tolerability will be valuable in further individualizing pharmacotherapy.^[83]

Another substantial challenge in drug development for ASD is lack of gold standard outcome measures, particularly for the core symptoms. Future research utilizing biomarkers such as eye-tracking, electrophysiological measures and/or functional neuroimaging may aid in capturing treatment benefits more accurately.

Despite substantive challenges, autism treatment research has made considerable progress in recent years. With genetic testing and animal models rapidly increasing our understanding of ASD, the field is now at an exciting juncture, and researchers are eagerly anticipating important discoveries for targeted pharmacotherapy, which may one day be available in clinical settings in the near future.

Sidebar

Key Points

- There is no known efficacious pharmacotherapy for the core symptoms of ASD.
- Risperidone and aripiprazole are the only two FDA-approved medications for irritability (aggression, selfinjury and severe tantrums) in children with ASD.
- Atypical antipsychotics should be reserved for those patients in whom the risks of potentially serious medication-related adverse events are justified.
- For ADHD symptoms, methylphenidate has been shown to be effective, and atomoxetine and alpha-2 agonists appear to be effective.
- SSRIs are not effective in reducing repetitive behavior in children with ASD, and may lead to activating adverse events.

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* This article illustrated challenges in developing new pharmacotherapies for autism, and proposed future directions for individualized pharmacotherapy.

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