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REVIEW ARTICLE

An update on pharmacotherapy of autism spectrum disorder in children and adolescents

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ABSTRACT

To date, no medication is proven to be effective in treating core symptoms of autism spectrum disorder (ASD). Psychotropic medications are widely used to target emotional and behavioural symptoms in ASD. This article reviewed evidence for pharmacotherapy, novel therapeutic agents, and Complementary and Alternative Medicine (CAM) in children and adolescents with ASD. Currently, only risperidone and aripiprazole have been approved by the US Food and Drug Administration (FDA) for treatment of irritability associated with ASD in children and adolescents. However, associated metabolic side-effects are concerning. Evidence supports use of methylphenidate and atomoxetine for attention deficit hyperactivity disorder (ADHD) symptoms and clonidine and guanfacine ER appear to be helpful. SSRIs are poorly tolerated and lack evidence in reducing restricted repetitive behaviours (RRB), anxiety, and depression. Buspirone shows promise in the treatment of RRB. The evidence is inconsistent for the effectiveness of anti-epileptic medications. Recent studies of glutamatergic, Gamma-aminobutyric acid (GABA)ergic, and cholinergic agents and oxytocin show inconsistent results. Despite wide use of CAM agents, the evidence is inconclusive. Melatonin can be helpful in reducing sleep problems. Overall, the evidence is limited for pharmacotherapy in children with ASD, and side-effects with long-term use can be burdensome.

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Introduction

Autism spectrum disorder (ASD) is a multifactorial neurodevelopmental condition characterized by deficits in social communication and restricted, repetitive behaviours, interests, or activities (RRB) (APA, 2013, DSM-5). ASD is a lifelong disorder that begins in early childhood. Approximately one in 160 children suffer from ASD worldwide, according to averages from several epidemiological studies (WHO, 2017). The prevalence of ASD has been increasing globally for 50 years. The disorder often negatively impacts on the social, emotional, and financial wellbeing of individuals with ASD and their families.

There is no cure for ASD. However, there is extensive evidence supporting the benefits of psychosocial treatment approaches, such as specific behaviour therapies and educational interventions, in improving social communication and RRB symptoms in children and adolescents with ASD. However, these treatments have limited accessibility, due to their high cost and the intense labour involved (Reichow, 2012; Virues-Ortega, Julio, & Pastor-Barriuso, 2013).

Pharmacological treatments are commonly used in individuals with ASD to improve associated ASD symptoms such as irritability and agitation. Medications are also frequently used to treat co-occurring psychiatric conditions such as ADHD, anxiety, depression, bipolar disorder, and other disorders. The current evidence also suggests an increase in the use of complementary and alternative medicine (CAM) agents in ASD (Höfer, Hoffmann, & Bachmann, 2016). However, medications have not been effective in improving core symptoms of ASD. Pharmacological treatments can be limited by concerns about side-effects, and difficulty in access to medication management services due to the scarcity of trained child and adolescent psychiatrists, particularly in remote areas.

In this article, we review pharmacological treatment options for children and adolescents with ASD, with emphasis on recently published studies since our previous published update (Ji & Findling, 2015). We focus on randomized double-blind placebo controlled (RDBPC) trials, with at least 10 subjects. We also

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discuss CAM treatment options used in children with ASD.

Pharmacotherapy of ASD

Despite a lack of pharmacological treatment options for ASD core symptoms, the prevalence of psychopharmacotherapy and polypharmacy in ASD patients is considerable, which is probably due to the treatment of non-core ASD symptoms and psychiatric comorbidities.

Anti-psychotics

The anti-psychotic medications have the largest body of evidence for efficacy in the treatment of irritability, and are used most widely among children and adolescents with ASD. The US Food and Drug Administration (FDA) has approved two anti-psychotic medications, risperidone and aripiprazole, for the treatment of irritability in children with ASD aged 5–16 years and 6–17 years, respectively. Multiple large RDBPC trials have shown results supporting that both medications are superior to placebo in alleviating irritability (agitation, anger outbursts, and self-injurious behaviour), stereotypy, and hyperactivity (Ichikawa et al., 2016; Kent et al., 2013; Marcus et al., 2009; McCracken et al., 2002; McDougle et al., 2005; Owen et al., 2009; Pandina, Bossie, Youssef, Zhu, & Dunbar, 2007; Shea et al., 2004).

The efficacy and tolerability of risperidone in children with ASD and co-occurring irritability were established by two large RDBPC studies prior to the FDA approval, conducted by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network (McCracken et al., 2002) and Shea et al. (2004). Both of these clinical trials showed that risperidone significantly decreased disruptive behaviours compared to placebo over the course of 8 weeks, as measured by a reduction in the Aberrant Behaviour Checklist–Irritability sub-scale (ABC-I) and improved global functioning, as measured by the Clinical Global Impressions–Improvement (CGI-I) scale. This was followed by an open-label trial discontinuation phase, which showed that the effects of risperidone were maintained in a large proportion of subjects after 4 months, and risperidone prolonged the time to relapse compared to placebo during the discontinuation phase of 8 weeks (RUPP, 2005a). Further, the RUPP trial showed that the combination of manualized parent training plus risperidone led to greater improvements in the ABC-I and CGI scores compared to risperidone alone (Aman et al., 2009). Another RDBPC trial showed that, compared to placebo, high doses of risperidone (1.25 or 1.75 mg/day) improved irritability and global functioning, but low doses (0.25 or 0.75 mg/day) did not have similar effects (Kent et al., 2013). The majority of RDBPC trials reported various side-effects of risperidone, including somnolence, drowsiness, increased appetite, and weight gain (see Table 1). Elevated prolactin levels were also reported in the risperidone treatment group (Anderson et al., 2007).

Aripiprazole was approved by the FDA for treatment of irritability in children with ASD following two large RDBPC trials that demonstrated its efficacy in the reduction of irritability, hyperactivity, and stereotypy (Marcus et al., 2009; Owen et al., 2009). The effects of aripiprazole were maintained long-term in one of the clinical trials (Findling et al., 2014). Similarly, another recent large RDBPC trial found that aripiprazole improved irritability, hyperactivity, and global functioning, and was well tolerated in a paediatric ASD population in Japan (Ichikawa et al., 2016). This study also found that aripiprazole decreased prolactin levels compared to placebo, possibly due to its dopamine D2 receptor partial agonist action. Common side-effects across trials of aripiprazole were sedation, somnolence, weight gain, increased appetite, vomiting, and extrapyramidal symptoms (EPS) (see Table 1). Significant lowering of high-density lipoprotein was reported, but only a small increase in total cholesterol, low-density lipoprotein, triglycerides, and blood glucose were observed (Marcus et al., 2011). No significant differences were observed in the improvement of irritability measures in a head-to-head trial of risperidone and aripiprazole (Ghanizadeh, Sahraeizadeh, & Berk, 2014).

There are limited RDBPC trials of other atypical anti-psychotic medications in children and adolescents with ASD. Olanzapine was found to improve measures of global functioning in a small RDBPC trial (Hollander et al., 2006b). Weight gain with olanzapine was significantly greater than with risperidone and aripiprazole (Malone, Cater, Sheikh, Choudhury, & Delaney, 2001). Lurasidone was not efficacious in improving irritability, but improved CGI-I scores with 20 mg/day dose compared to placebo in a large RDBPC trial (Loebel et al., 2016). However, higher doses of lurasidone (60 mg/day) did not improve CGI-I scores. Vomiting and somnolence were among the most common side-effects of lurasidone. RDBPC trials are lacking for quetiapine, ziprasidone, and other atypical anti-psychotic agents. Minimal improvement in irritability was observed in children

and adolescents with ASD with quetiapine, and adverse events of sedation, weight gain and aggression were reported in small open-label studies (Findling et al., 2004; Martin, Koenig, Scahill, & Bregman, 1999). Ziprasidone may improve irritability in children with ASD with less weight gain and metabolic side-effects as compared to other atypical anti-psychotic medications, but data supporting this has been limited to small open-label trials (Duggal, 2007; Malone, Delaney, Hyman, & Cater, 2007). Most anti-psychotic medications have been associated with significant side-effects; hence, these medications should be used judiciously by clinicians and as part of a broader biopsychosocial treatment approach.

There are long-standing published studies examining the effects of conventional anti-psychotics in children and adolescents with ASD. Haloperidol, a dopamine receptor D2 blocker, is the most frequently studied of these drugs in RDBPC trials. Haloperidol was found to significantly improve social withdrawal and stereotypy symptoms, as measured by the Children's Psychiatric Rating Scale (CPRS) in an RDBPC of children with ASD (Campbell et al., 1978). Dose-related sedation and acute dystonic reaction were common side-effects. Another RDBPC trial replicated these findings with haloperidol and reported significant improvement in CPRS and CGI scores in children with ASD (Anderson et al., 1984). Positive effects on learning were also reported in this study. Further studies found similar results of behaviour improvement, but also reported a high frequency of dyskinesias (Campbell et al., 1997).

In summary, haloperidol is efficacious for improving behaviour symptoms in children with ASD. The evidence is limited for the efficacy of other conventional anti-psychotics in children with ASD. Haloperidol treatment frequently resulted in adverse effects of acute dystonic reactions and dyskinesia. The high risk of EPS with haloperidol has limited the use of this medication.

Stimulants and non-stimulants

ADHD is a frequent co-occurring condition in children with ASD, with data showing that 37% (Gadow, DeVincent, & Pomeroy, 2006) to 85% (Lee & Ousley, 2006) of children with ASD have an ADHD diagnosis. RDBPC trials have investigated the efficacy of methylphenidate, atomoxetine, clonidine and guanfacine on ADHD symptoms in this population.

The RUPP Autism Network conducted an RDBPC trial for 4 weeks, followed by 8 weeks of an open-label trial to investigate the effects of methylphenidate in children with ASD and co-occurring ADHD, and observed significant improvements in hyperactivity that were maintained during the open-label trial (RUPP, 2005b). Although no serious adverse events were reported, irritability, social withdrawal, and emotional outbursts were the most common side-effects. About one-fifth of children stopped the treatment due to intolerable side-effects, including irritability (Jahromi et al., 2009). Methylphenidate extended release also led to improvement in hyperactivity and impulsivity in a small RDBPC trial over 4 weeks (Pearson et al., 2013).

RDBPC trials have examined the effects of atomoxetine in the treatment of ADHD in this population. Atomoxetine improved hyperactivity but not global functioning compared to placebo in an RDBPC trial of children with ASD, with further improvement during the open-label extension over 28 weeks (Harfterkamp et al., 2012, 2013). Nausea, decreased appetite, fatigue, and early morning awakenings were reported side-effects, but these improved with long-term use. Another large RDBPC trial investigated the efficacy of atomoxetine with and without parent training on ADHD symptoms in this population (Handen et al., 2015). The combination of atomoxetine with parent training improved ADHD symptoms the most, followed by atomoxetine alone compared to placebo and parent training alone. These effects were maintained during the open-label phase of 24 weeks (Smith et al., 2016).

In an RDBPC study of children with ASD, clonidine demonstrated significantly better ratings on measures of irritability and hyperactivity compared to placebo from parents and teachers, but not from clinicians (Jaselskis, Cook, Fletcher, & Leventhal, 1992). Another small RDBPC study in children with ASD showed that clonidine was significantly more efficacious than placebo in improving hyperarousal behaviours and social relationships (Fankhauser, Karumanchi, German, Yates, & Karumanchi, 1992). Clonidine was generally well-tolerated except for the side-effects of sedation, fatigue, and hypotension in a few children.

A recent RDBPC study of children and adolescents with ASD treated with guanfacine extended release showed an improvement in ADHD symptoms and global functioning (Scahill et al., 2015). No serious adverse events except for drowsiness, fatigue, and decreased appetite were reported.

Antidepressants

The findings from RDBPC trials of selective serotonin reuptake inhibitors (SSRI) in children with ASD have

been inconsistent for efficacy in improving RRB, even though RDBPC studies in adults with ASD have shown more consistent efficacy in improving RRB (Hollander et al., 2012; McDougle et al., 1996). In an RDBPC trial of children with ASD, fluoxetine resulted in greater improvement than placebo in reducing repetitive behaviours, as measured by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Hollander et al., 2005). In contrast, Autism Speaks released findings from an unpublished industry-sponsored large RDBPC study of fluoxetine in children and adolescents with ASD (SOFIA), indicating no improvement in RRB (Autism Speaks Press release, 2009). Results from a large RDBPC trial of citalopram in children with ASD also did not demonstrate efficacy in improving repetitive behaviours or global functioning. Side-effects of increased energy, impulsiveness, hyperactivity, stereotypy, and insomnia were frequently reported (King et al., 2009).

An RDBPC crossover trial of the tricyclic antidepressant, clomipramine, compared to haloperidol and placebo failed to show efficacy of clomipramine in improving stereotypy. Clomipramine was also poorly tolerated with a high discontinuation rate (72.5%) (Remington, Sloman, Konstantareas, Parker, & Gow, 2001). Haloperidol, however, improved irritability and hyperactivity compared to baseline and placebo.

Buspirone, a partial serotonin receptor agonist, was also not superior to placebo in improving symptoms of ASD in young children with ASD, as measured by the Autism Diagnostic Observation Schedule (ADOS) Composite Total Score, but improved RRB significantly with low dose (2.5 mg BID) in a large RDBPC trial (Chugani et al., 2016). Further studies are needed for this potential treatment for RRB in children with ASD. RDBPC trials are lacking for other antidepressants such as mirtazapine or venlafaxine in children with ASD. Also, there are no RDBPC trials of SSRI for anxiety and depression in this population.

Anti-epileptics

The data for mood stabilizing anti-epileptic medications for irritability and aggression in children with ASD has been inconsistent. Valproate did not improve irritability in children and adolescents with ASD in a small RDBPC study (Hellings et al., 2005). In contrast, two subsequent small RDBPC trials of valproate reported improvement in irritability in this population (Hollander et al., 2006a, 2010). Side-effects included weight gain, rash, irritability, sedation, and increased serum ammonia (Table 1). Findings from RDBPC trials of lamotrigine and levetiracetam monotherapies did not show efficacy in improving irritability or global functioning in children with ASD (Belsito, Law, Landa, & Zimmerman, 2001; Wasserman et al., 2006). No RDBPC trials have been conducted for lithium, oxcarbazepine, or topiramate.

Glutamatergic and gamma-aminobutyric acid(GABA)ergic agents

Neurobiological models of ASD hypothesize an imbalance between the excitatory neurotransmitter, glutamate, and inhibitory neurotransmitter, GABA, in the pathophysiology of ASD (Fatemi et al., 2012; Moreno-Fuenmayor, Borjas, Arrieta, Valera, & Socorro-Candanoza, 1996; Purcell, Jeon, Zimmerman, Blue, & Pevsner, 2001). Hence, there is a growing interest in agents that act on glutamate receptors, mainly the N-methyl-D-aspartate (NMDA) and GABA receptors, to treat both core and associated symptoms of ASD.

N-acetylcysteine (NAC), an NMDA modulator with anti-oxidant properties, has been studied in children with ASD. Although one small RDBPC trial showed that NAC significantly improved irritability compared to placebo in children with ASD (Hardan et al., 2012), more recent and larger RDBPC trials showed that it was not superior to placebo in improving social deficits, RRB, and global functioning in this population (Dean et al., 2016; Wink et al., 2016). D-cycloserine, a partial NMDA agonist, also did not improve social functioning compared to placebo, as measured by the Social Responsiveness Scale (SRS) in an RDBPC trial of children with ASD receiving social skills training (Minshawi et al., 2016).

Memantine is an NMDA receptor antagonist that has been FDA approved for use in moderate-to-severe Alzheimer's disease. A recent large RDBPC trial in children with ASD found memantine extended release to be safe, but not superior to placebo in improving social responsiveness (Aman et al., 2017). A small RDBPC of another NMDA receptor antagonist, amantadine, also did not show significant improvement in irritability compared to placebo in children and adolescents with ASD. However, significant improvements in measures of hyperactivity and inappropriate speech were noted compared to placebo (King et al., 2001).

Interestingly, evidence showed that, in combination with risperidone, memantine, riluzole (a glutamate antagonist), NAC and amantadine improve irritability when compared to risperidone and placebo in individual RDBPC trials (Ghaleiha et al., 2013a, 2013b; Ghanizadeh & Moghimi-Sarani, 2013; Mohammadi

Table 1. Selected randomized, double-blind, placebo-controlled trials (RDBPCT) of psychotropic medications in paediatric ASD populations.

Medication	Publication	Study design Duration	*n*	Age (years)	Dose	Results	Noteworthy adverse events (AEs)
Anti-psychotics							
Risperidone	McCracken et al. (2002)	RDBPCT 8 weeks	101	5–17	0.5–3.5 mg/d QD or divided BID Mean 1.8 mg/day	Superior to placebo in improving irritability (temper outburst, aggression and self-injurious behaviour), stereotypy, and hyperactivity, but not social functioning	Weight gain, increased appetite, fatigue, drowsiness, dizziness, drooling, tremor, constipation
	Shea et al. (2004)	RDBPCT 8 weeks	79	5–12	0.01–0.06 mg/kg/day	Superior to placebo group in improving irritability, hyperactivity/non-compliance, inappropriate speech, lethargy/social withdrawal, stereotypic behaviour, conduct problems, hyperactive, insecure/anxious, and overly sensitive behaviours	Somnolence, weight gain, increased pulse rate and systolic blood pressure. (elevated systolic pressure was not clinically significant)
	McDougle et al. (2005)	RDBPCT 8 weeks; OL, 16 weeks	101 63	5–17	0.5–3.5 mg/day 0.5–4.5 mg/day	Superior to placebo in improving RRB but not social communication deficits The pattern on treatment response was maintained for 24 weeks	Weight gain, increased appetite, fatigue, drowsiness, drooling, dizziness
	RUPP (2005a)	OL, 16 weeks; RDBPCT D/C 8 weeks	63 32	5–17	0.5–4.5 mg/day Mean: 1.96 mg/day	Superior to placebo in improving irritability, hyperactivity, stereotypic behaviour, and lethargy/social withdrawal Superior to placebo in time to relapse	Increased appetite, tiredness, drowsiness, abnormal movements
	Pandina et al. (2007)	RDBPCT 8 weeks	55	5–12	0.5–4.2 mg/day	Superior to placebo in improving irritability	Somnolence
	Kent et al. (2013)	RDBPCT 3 arms 6 weeks	96	5–17	0.125 or 0.175 mg/day vs 1.25 or 1.75 mg/day vs Placebo	Superior to 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 vs low dose groups
Aripiprazole	Marcus et al. (2009)	RDBPCT 8 weeks	218	6–17	5, 10, or 15 mg/day Fixed doses	Superior to placebo in improving irritability, agitation, self-injurious behaviour, hyperactivity, and stereotypic behaviour	Sedation, drooling, EPS, weight gain
	Owen et al. (2009)	RDBPCT 8 weeks	98	6–17	2, 5, 10, 15 mg/day Flexible doses	Superior to placebo in improving irritability (tantrums, aggression, and self-injurious behaviour), hyperactivity, stereotypy, inappropriate speech	Fatigue, somnolence, weight gain, EPS
	Findling et al. (2014)	Stabilization 13–26 weeks; RDBPCT D/C 8 weeks	157 85	6–17	2, 5, 10, 15 mg/day Flexible doses	Not superior to 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
	Ichikawa et al. (2016)	RDBPCT 8 weeks	92	6–17	1–15 mg/day	Superior to placebo in improving irritability, hyperactivity, and global functioning Superior to placebo in decreasing prolactin	Somnolence, weight gain, increasing BMI, EPS

(*continued*)

Table 1. Continued

Medication	Publication	Study design Duration	*n*	Age (years)	Dose	Results	Noteworthy adverse events (AEs)
Olanzapine	Hollander et al. (2006b)	RDBPCT 8 weeks	11	6–14	7.5–12.5 mg/day	Superior to placebo in improving global functioning	Weight gain, increased appetite, sedation
Haloperidol	Anderson et al. (1989)	RDBPCT crossover 12 weeks	45	2–7	0.25–4 mg/day	Superior to placebo in improving behavioural symptoms but not in discrimination learning	None noteworthy
Lurasidone	Loebel et al. (2016)	RDBPCT 3 arms 6 weeks	150	6–17	20 mg/d vs 60 mg/d vs Placebo	Not superior to placebo group in improving irritability Superior to placebo in improving global functioning, only for lurasidone 20 mg/day	Vomiting, somnolence Modest changes in weight and selected metabolic parameters only with lurasidone 60 mg/day
Medications for ADHD symptoms							
Methylphenidate	RUPP (2005b)	RDBPCT crossover 4 weeks; OL, 8 weeks	72 34	5–14	7.5–50 mg/day Divided TID	Superior to placebo in improving hyperactivity The response was maintained for 8 weeks in the majority of responders	Irritability, social withdrawal, decreased appetite, sleep difficulty, emotional outbursts Adverse effects were more frequent
	Jahromi et al. (2009)	Titration; RDBPCT crossover 2 weeks	33	5–13	0.125, 0.25, and 0.50 mg/kg BID	Superior to 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, including irritability
Methylphenidate ER	Pearson et al. (2013)	RDBPCT crossover 4 weeks	24	7–12	ER10–40 mg qam + IR 2.5–10 mg qpm	Superior to placebo in improving hyperactivity and impulsivity	Loss of appetite, sleeping problems
Atomoxetine (ATX)	Harfterkamp et al. (2012, 2013)	RDBPCT 8 weeks; OL, 20 weeks	97 88	6–17	1.2 mg/kg/day	Superior to placebo in improving hyperactivity Not superior to placebo 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 OL phase
	Handen et al. (2015) Smith et al. (2016)	RDBPCT 4 arms 10 weeks; Extension with combination of DB and OL 24 weeks	128 117	5–14	Starting at 0.3 mg/kg/day Ceiling 1.8 mg/kg/day	ATX alone and ATX + PT were superior to PT + placebo and placebo only in decreasing ADHD symptoms. ATX + PT was the most effective followed by ATX alone, PT + placebo and placebo only in improving global functioning Most ATX responders maintained their responses during the extension	Decreased appetite
Clonidine	Fankhauser et al. (1992)	RDBPCT crossover 4 weeks	8	5–33	0.16–0.48 mg/day	Superior to placebo in improving impulsivity, hyperarousal, and self-stimulating behaviour	Sedation, hypertension, fatigue, decreased activity
Guanfacine ER	Scahill et al. (2015)	RDBPCT 16 weeks	62	5–14	1–4 mg/day	Superior to placebo in improving inattention, hyperactivity, impulsivity, and global functioning	Drowsiness, fatigue, and decreased appetite
Antidepressants and anti-anxiety medications							
Fluoxetine	Hollander et al. (2005)	RDBPCT crossover 8 weeks	45	5–16	2.4–20 mg/day	Superior to placebo in improving repetitive behaviour	None noteworthy
	Autism Speaks Press release, SOFIA (2009)	RDBPCT 14 weeks	158	5–17	2, 9, or 18 mg/day	Not superior to placebo in improving repetitive behaviour (Autism Speaks press release)	Unpublished

(*continued*)

Table 1. Continued

Medication	Publication	Study design Duration	*n*	Age (years)	Dose	Results	Noteworthy adverse events (AEs)
Citalopram	King et al. (2009)	RDBPCT 12 weeks	149	5–17	2.6–20 mg/day Mean 16.5 mg/day	Not superior to placebo in improving repetitive behaviour	Increased energy, impulsiveness, decreased concentration, hyperactivity, stereotypy, insomnia
Clomipramine	Remington et al. (2001)	RDBPCT crossover 7 weeks	36	10–36	100–150 mg/day	Not superior to placebo in improving stereotypy, irritability, or hyperactivity	Lethargy, tremors, tachycardia, insomnia, diaphoresis, nausea
Buspirone	Chugani et al. (2016)	RDBPCT 3 arms, 23 weeks OL 24 weeks	166	2–6	2.5 mg BID vs 5 mg BID vs Placebo	Not superior to placebo in improving measure of symptoms of autism: Autism Diagnostic observation Schedule (ADOS) Composite Total score Superior to placebo in improving repetitive behaviour, only at the group with 2.5 mg BID	None noteworthy
Mood stabilizers and anti-epileptic medications							
Valproate	Hellings et al. (2005)	RDBPCT 8 weeks	30	6–20	20 mg/kg/day level 70–100 mcg/ml	Not superior to placebo in improving irritability and aggression	Increased appetite, skin rash, Increased serum ammonia level
	Hollander et al. (2006a)	RDBPCT 8 weeks	13	5–17	500–1500 mg/day level 50–100 mcg/ml	Superior to placebo in improving repetitive behaviour	Irritability, weight gain, aggression
	Hollander et al. (2010)	RDBPCT 12 weeks	27	5–17	Dosed to a mean level of 89.8 mcg/ml	Superior to placebo in improving irritability	Skin rash, irritability
Lamotrigine	Belsito et al. (2001)	RDBPCT 18 weeks	28	3–11	Mean 5 mg/kg/day Divided BID	Not superior to placebo in improving aberrant behaviour or other measures	Insomnia, increased stereotypies, aggression, echolalia
Levetiracetam	Wasserman et al. (2006)	RDBPCT 10 weeks	20	5–17	20–30 mg/kg/day	Not superior to placebo in improving global functioning or irritability	Aggression, agitation

ASD: autism spectrum disorder; RUPP: Research Units on Pediatric Psychopharmacology Autism Network; D/C: discontinuation; EPS: extrapyramidal symptoms; OL: open-label; ADHD: attention deficit hyperactivity disorder; ER: extended release; IR: immediate release; PT: parent training; SOFIA: Study of Fluoxetine in Autism; APA: American Psychiatric Association annual meeting; INSAR: International Society of Autism Research annual meeting; CBT: Cognitive behavioural therapy; SCI: social communication impairment; RRB: restricted and repetitive behaviours; DB: double blind.

Table 2. Selected randomized, double-blind trials (RDBPCT) of glutamatergic, GABAergic, cholinergic, and opioid antagonist agents in paediatric ASD populations.

Medication	Publication	Study design Duration	*n*	Age (years)	Dose	Results	Noteworthy adverse events (AEs)
Glutamatergic agents							
N-Acetylcysteine	Hardan et al. (2012)	RDBPCT 12 weeks	33	3–10	900 mg/day – 900 mg TID	Superior to placebo in improving irritability	Agitation, irritability
	Dean et al. (2016)	RDBPCT 24 weeks	102	3.1–9.9	500 mg/day	Not superior to placebo in improving social deficits or RRB	None noteworthy
	Wink et al. (2016)	RDBPCT 12 weeks	31	4–12	60 mg/kg/day	Not superior to placebo in improving global functioning, social deficits, RRB, or other associated features	None noteworthy
D-Cycloserine	Minshawi et al. (2016)	RDBPCT 10 weeks	67	5–11	50 mg given before social skill training	Not superior to placebo in improving social functioning	None noteworthy
Amantadine	King et al. (2001)	RDBPCT 4 weeks	39	5–19	2.5–5.0 mg/kg/day	Not superior to placebo in improving hyperactivity or irritability	Insomnia
Memantine ER	Aman et al. (2017)	RDBPCT, 12-weeks; OL, 48 weeks	121	6–12	3–15 mg/day	Not superior to placebo in improving social interaction and communication One communication measure was significantly worse with memantine compared with placebo	No treatment emergent laboratory or ECG concerns Two serious AEs deemed unrelated to treatment (lobar peumonia and affective disorder)
GABAergic agents							
Arbaclofen	Veenstra-VanderWeele et al. (2016)	RDBPCT 12 weeks	150	5–21	10 or 15 mg TID	Not superior to placebo in improving lethargy and social withdrawal symptoms, but showed separation in improving global functioning	Affect lability, sedation
	Berry-Kravis et al. (2017)	RDBPCT 8 weeks	125 with FXS,73% with ASD	12–50 54% adolescents	flexible dose	Not superior to placebo in improving social avoidance	Headache, nausea, vomiting Anorexia, irritability, anxiety, agitation
		RDBPCT 8 weeks 4 arms	172 with FXS, 79% with ASD	5–11	5 mg BID 10 mg BID, 10 mg TID, placebo	Not superior to placebo in improving social avoidance Superior to placebo in improving irritability and parenting stress, in 10 mg TID group	Vomiting, aggression, headache, rhinorrhea, nasal congestion, anxiety, insomnia, ear infection, and gastroenteritis
Bumetanide	Lemonnier et al. (2012)	RDBPCT 12 weeks	60	3–11	0.5 mg BID	Superior to placebo in significantly improving Childhood Autism Rating Scale (CARS), CGI-I, and ADOS observation schedule values	Mild hypokalemia
	Lemonnier et al. (2017)	RDBPCT 12 weeks	88	2–18	0.5, 1.0, or 2.0 mg BID	Superior to placebo in significantly improving scores of CARS, SRS, and CGI-I	Dose dependent mild hypokalemia, increased urine elimination, loss of appetite, dehydration, and asthenia
Cholinergic agents							
Donepezil	Chez et al. (2003)	RDBPCT 6 weeks; OL, 6weeks	43	2–10	2.5 mg/day	Superior to placebo in significantly improving CARS scores and measures of expressive and receptive language	Diarrhoea, stomach cramping, increased irritability
	Handen et al. (2011)	RDBPCT 10 weeks	34	8–17	5–10 mg/day	Not superior to placebo in improving executive functioning deficits	Diarrhoea, headache, fatigue
Opioid antagonist							
Naltrexone	Campbell et al. (1993)	RDBPCT 3 weeks	41	2–7	0.5–1 mg/kg/day	Superior to placebo in improving hyperactivity	None noteworthy
	Feldman et al. (1999)	RDBPCT 2 weeks	24	3–8	1 mg/kg/day	Not superior to placebo in improving communication	Transient sedation

ASD: autism spectrum disorder; D/C: discontinuation; OL: open-label; GABA: Gamma-Aminobutyric Acid; APA: American Psychiatric Association annual meeting; SCI: social communication impairment; RRB: restricted and repetitive behaviours; CARS: childhood autism rating scale; ADOS: autism diagnostic observation schedule; SRS: social responsiveness scale.

et al., 2013). These data suggest that glutamatergic agents can be beneficial as an adjunct to risperidone treatment in children with ASD; however, more controlled trials are needed to establish their efficacy in monotherapy.

Arbaclofen, a selective GABA-B agonist, was not efficacious in improving social withdrawal/lethargy in ASD in a recent phase 2 RDBPC trial of 150 subjects, aged 5–21 years (Veenstra-VanderWeele et al., 2016). However, further secondary analysis showed significant improvement in clinician-rated global functioning compared to placebo. Additionally, two large phase 3 RDBPC trials investigated a flexible dose and fixed dose of arbaclofen in fragile X (almost 2/3 subjects with ASD) adolescents and adults, and children, respectively (Berry-Kravis et al., 2017). Arbaclofen did not show efficacy in improving social avoidance in either trial. Side-effects across trials included emotional lability, sedation, insomnia, anxiety, and gastrointestinal side-effects (see Table 2).

Bumetanide is a GABA modulator and was found to be superior to placebo in improving ASD symptoms measured by the Childhood Autism Rating Scale (CARS), SRS, and CGI-I in children and adolescents in two RDBPC phase 2 trials (Lemonnier et al., 2012, 2017). Side-effects included dose-dependent hypokalemia, increased urination, dehydration, loss of appetite, and asthenia. The authors concluded that 1 mg twice daily dosing was the best compromise between efficacy and safety. Hence, bumetanide may be beneficial in reducing core symptoms of ASD, particularly social communication and restricted interest, in children.

Cholinergic agents

Cholinergic system abnormalities have been hypothesized in individuals with ASD (Bauman & Kemper, 2005; Deutsch, Urbano, Neumann, Burket, & Katz, 2010; Karvat & Kimchi, 2014; Lee et al., 2002; Perry et al., 2001). However, the evidence for donepezil (cholinesterase inhibitor) treatment in children with ASD has been inconsistent. One small RDBPC study reported that, compared to placebo, donepezil significantly improved scores on the CARS and measures of expressive and receptive language (Chez et al., 2003). However, another more recent RDBPC trial reported that donepezil was not superior to placebo in improving executive function deficits in children with ASD (Handen, Johnson, McAuliffe-Bellin, Murray, & Hardan, 2011). A recent clinical trial investigating the efficacy of donepezil on sleep and ASD symptoms was terminated due to poor enrollment. Further large and controlled trials for donepezil in children with ASD are warranted to establish its efficacy and safety.

Opioid antagonists

Abnormalities of the opiate system have been documented in individuals with ASD, especially in relation to self-injurious behaviours (Panksepp & Sahley, 1987; Sandman & Kemp, 2011). Naltrexone is an opiate antagonist investigated in several RDBPC trials in ASD. In an RDBPC study of children with ASD, naltrexone was superior to placebo in improving hyperactivity (Campbell et al., 1993). Another RDBPC trial of children with ASD showed that it was not efficacious in improving communication (Feldman, Kolmen, & Gonzaga, 1999). In a recent systematic review, Roy, Roy, Deb, Unwin, and Roy (2014) concluded that naltrexone may have a role in improving hyperactivity, but it has not been established to improve other ASD symptoms.

Complementary and alternative medicine (CAM) agents

CAM agents are widely used to treat children with ASD (Owen-Smith et al., 2015). Despite lack of clear evidence of their efficacy, families use these therapies frequently, due to the assumption that there are fewer risks related to side-effects compared to medications. The most researched CAM treatments include omega-3 fatty acids, melatonin, and oxytocin. Vitamin B12, folinic acid, vitamin D3, and digestive enzymes have fewer published studies.

Oxytocin

Emerging evidence suggests that neuropeptides such as oxytocin may be beneficial in the treatment of core ASD symptoms. The evidence, however, is inconsistent. A recent meta-analysis found that oxytocin has no significant effect on social cognition and RRB in children with ASD (Ooi, Weng, Kossowsky, Gerger, & Sung, 2016). Findings from one unpublished RDBPC study of oxytocin in children with ASD reported during oral presentation at International Meeting for Autism Research (IMFAR) 2017, that oxytocin was not superior to placebo in improving social withdrawal, but was superior to placebo in improving social recognition (Anagnostou et al., 2017) (Table 3). In contrast, oxytocin improved social functioning as compared to placebo in children with ASD, as measured by SRS in a recent RDBPC (Parker et al., 2017). Findings from studies in healthy individuals indicate a potential for oxytocin in

Table 3. Selected randomized, double-blind, placebo-controlled trials (RDBPCT) of complementary and alternative medicine (CAM) agents in paediatric ASD populations.

Medication	Publication	Study design Duration	*n*	Age (years)	Dose	Results	Noteworthy adverse events (AEs)
Endocrinologic agents							
Oxytocin	Dadds et al. (2013)	RDBPCT 5 days	38	7–15	12 or 24 IU/day	Not superior to placebo in improving emotion recognition, social interaction skills, or general behavioural adjustment	None noteworthy
	Guastella et al. (2014)	RDBPCT 8 weeks	50	12–18	18 or 24 IU BID	Not superior to placebo in improving social responsiveness, RRB, global functioning, social cognition	None noteworthy
	Kosaka et al. (2016)	RDBPCT 12 weeks OL 12 weeks; follow-up phase 8 weeks	60	15–39 (mean 24.2)	16 or 32 IU/day	Not superior to placebo in improving global functioning and social interaction Superior to placebo in improving global functioning, in male subjects with higher dose	None noteworthy
	Yatawara, Einfeld, Hickie, Davenport, and Guastella (2015)	RDBPCT crossover 2 × 5 weeks separated by 4 weeks	31	3–8	12 IU BID	Superior to placebo in improving social responsiveness Not superior to placebo in improving RRB, emotional difficulties	Thirst, urination, and constipation
	Parker et al. (2017)	RDBPCT 4 weeks	32	6–12	24 IU BID	Superior to placebo in improving social responsiveness Not superior to placebo in improving RRB or anxiety	None noteworthy
	Anagnostou et al. (2017)	RDBPCT 12 weeks	60	Mean age: 12.4 ± 1.8 years	0.4 IU/kg BID	Not superior to placebo in improving social withdrawal Superior to placebo in improving social recognition	Unpublished
Melatonin	Wright et al. (2011)	RDBPCT crossover 2 × 12 weeks	17	3–16	Initial 2 mg/day flexible dose, maximum 10 mg/day	Superior to placebo in improving sleep latency and total sleep Not superior to placebo in decreasing the number of nighttime awakenings	None noteworthy
Melatonin Controlled Release	Cortesi et al. (2012)	RDBPCT 4 arms 12 weeks	160	4–10	3 mg/day	Melatonin plus CBT was the most effective in improving insomnia, followed by melatonin alone and then CBT alone compared to placebo	None noteworthy
Paediatric appropriate prolonged-release melatonin mini-tabs (PedPRM)	Gringras et al. (2017)	RDBPCT 13 weeks	125	2–17.5	2 mg/day to 5 mg/day	Superior to placebo in increasing total sleep time and decreasing sleep latency Overall sleep disturbance decreased	Somnolence
Metabolic and nutritional agents							
Omega-3 fatty acids	Bent, Bertoglio, Ashwood, Bostrom, and Hendren (2011)	RDBPCT 12 weeks	27	3–8	1.3 g/day	Not superior to placebo in improving hyperactivity	Rashes
	Voigt et al. (2014)	RDBPCT 24 weeks	48	3–10	200 mg of docosahexaenoic acid	Not superior to placebo in improving global functioning or core symptoms of autism	Headaches, restlessness, agitation
	Bent et al. (2014)	RDBPCT 6 weeks	57	5–8	1.3 g/day	Not superior to placebo in improving hyperactivity	None noteworthy

(*continued*)

Table 3. Continued

Medication	Publication	Study design Duration	*n*	Age (years)	Dose	Results	Noteworthy adverse events (AEs)
	Mankad et al. (2015)	RDBPCT 24 weeks	38	2–5	0.75–1.5 g/day	Not superior to placebo in improving core symptoms of autism, adaptive function, or language skills Omega-3 fatty acids treatment significantly worsened externalizing behaviours compared to placebo	None noteworthy
Tetrahydrobiopterin	Klaiman et al. (2013)	RDBPCT 16 weeks	46	3–7	20 mg/kg/day	Superior to placebo in improving social awareness, autism mannerisms, hyperactivity, and inappropriate speech	None noteworthy
Sulforaphane	Singh et al. (2014)	RDBPCT 22 weeks	44	13–27	50–150 μmol/day	Separation from placebo in improving irritability, aberrant behaviours, lethargy, autistic symptoms	Weight gain
Digestive Enzymes* Neo-Digestin (Papain and Pepsin)	Saad et al. (2015)	RDBPCT 12 weeks	101	3–9	15 ml/day (Papain 1.6 g + pepsin 0.8 g/100 ml)	Superior to placebo in improving emotional response, autistic behaviours, general behaviour, and GI symptoms	Skin rashes, itching, abdominal pain
Vitamin D3	Saad et al. (2016)	RDBPCT 4 weeks	120	3–10	300 IU/kg/day Max 5000 IU/day	Superior to placebo in improving autism symptoms, irritability, hyperactivity, social withdrawal, and inappropriate speech	Mild transient skin rashes, itching, diarrhoea
Methyl B12	Hendren et al. (2016)	RDBPCT 8 weeks	57	3–7	75 μg/kg subcutaneous injection every 3 days	Superior to placebo in improving clinician-rated global functioning, correlated with improvements in transmethylation metabolism and cellular methylation capacity No improvements noted in parent-rated symptoms	None noteworthy
Folinic acid	Frye et al. (2018)	RDBPCT 12 weeks	45	3–14	2 mg/kg/day Max 50 mg/day	Superior to placebo in improving verbal communication, adaptive functioning, and aberrant behaviours, particularly in those participants who were positive for folate receptor-α autoantibody	None noteworthy

ASD: autism spectrum disorder; RRB: restricted and repetitive behaviours.

improving social cognition and RRB (Bakermans-Kranenburg & Van IJzendoorn, 2013; Van IJzendoorn & Bakermans-Kranenburg, 2012).

Melatonin

Melatonin has substantive evidence for its use in treating sleep disturbances in children with ASD. Multiple RDBPC clinical trials reported that melatonin was well tolerated, and significantly increased total sleep duration and decreased sleep latency compared to placebo in children with ASD. A combination of melatonin and cognitive behaviour therapy (CBT) was found to be most efficacious in improving sleep, followed by melatonin alone and CBT alone as compared to placebo in an RDBPC trial of children with ASD (Cortesi, Giannotti, Sebastiani, Panunzi, & Valente, 2012). A recent large RDBPC study reported that paediatric appropriate prolonged-release melatonin minitablets (PedPRM) not only improved total sleep time and sleep latency, but also improved overall sleep disturbances more than placebo in children with ASD (Gringras, Nir, Breddy, Frydman-Marom, & Findling, 2017). In addition to its effect on sleep, a few RDBPC trials have shown that melatonin can improve communication (Wright et al., 2011), rigidity (Garstang & Wallis, 2006), and anxiety (Wasdell et al., 2008) in children with ASD.

Omega 3 fatty acids

Supplementation with omega 3 fatty acids has not been effective in improving ASD symptoms in children and adolescents. Four RDBPC clinical trials (Table 3) reported no significant differences compared to placebo in improving core symptoms of ASD, e.g. social communication deficits and RRB, language, hyperactivity, global and adaptive functioning. Significant improvements were noted on measures of stereotypy and lethargy in young children with ASD compared to placebo by parents, but not teachers (Bent et al., 2014). Omega 3 fatty acids were well tolerated and minimal-to-no adverse events were reported in an RDBPC study (Voigt et al., 2014).

Other nutritional agents

There is insufficient evidence for the effectiveness of digestive enzyme supplementation in ASD. In a RDBPC trial of children with ASD, the neo-digestin (a combination of digestive enzymes) compared to placebo improved ASD behaviours, emotional responsiveness, and gastrointestinal symptoms (Saad et al., 2015).

Sulforaphane, a phytochemical with antioxidant properties, was found to be efficacious in improving irritability, lethargy, social communication, and global functioning, compared to placebo in an RDBPC trial in adolescents and adults (aged 13–27) with ASD (Singh et al., 2014).

Vitamins and minerals have a role in neurotransmitter metabolism and have been used for potential benefits in individuals with ASD (Adams et al., 2011). However, a limited number of studies have been found for each agent (Table 3). Subcutaneous use of methyl B12 was observed to improve clinician-rated CGI-I score in children with ASD over 8 weeks in a recent RDBPC study (Hendren et al., 2016). This improvement was correlated with improvement in cellular methylation ability. However, parents did not indicate improvement in CGI-I.

Vitamin D3 (Saad et al., 2016) and tetrahydrobiopterin (Klaiman, Huffman, Masaki, & Elliott, 2013) improved ASD symptoms including social awareness, hyperactivity, irritability, and inappropriate speech compared to placebo in children with ASD. Folinic acid was reported to improve communication and ASD symptoms in children with ASD and language impairment, compared to placebo, particularly in a sub-group with autoantibodies blocking folinic acid from entering brain cells (Frye et al., 2018).

Conclusion

To date, risperidone and aripiprazole are the two medications that have FDA approval for children and adolescents with ASD, and both target irritability, with additional efficacy for hyperactivity and stereotypy. However, metabolic side-effects related to atypical anti-psychotic medications are concerning. Hence, clinicians need to weigh the risks and benefits when using these medications in children with severe behaviour problems. Furthermore, it is recommended that these medications are used in combination with multidisciplinary non-pharmacological treatment modalities.

Several medications may improve ADHD symptoms in children with ASD, including methylphenidate, which has shown consistent efficacy in reducing ADHD symptoms in children with ASD. Atomoxetine, clonidine, and guanfacine extended release have also been shown to help treat ADHD symptoms in children with ASD, but more trials are needed to establish their efficacy.

In terms of serotonergic agents, SSRIs are not effective in the treatment of RRB, and there are no data on their use in anxiety and depression. These

medications can cause activating side-effects in this population. Buspirone shows promise in the treatment of RRB in children with ASD, but needs further evidence.

Studies of the newer agents, including glutamatergic and oxytocin, have mixed results in children with ASD, but have the potential to target core symptoms of ASD.

The evidence for CAM agents also remains limited and controversial. These agents are generally well tolerated without significant side-effects, and their efficacy is encouraging in reducing some core and associated symptoms of ASD, such as social responsiveness, irritability, lethargy, hyperactivity, and insomnia.

As ASD is a lifelong developmental disorder, the importance of multidisciplinary approaches including behavioural, educational and occupational support cannot be overstated. Pharmacotherapy should be prescribed in conjunction with close monitoring of side-effects, and periodic assessment of the need for continued treatment.

Challenges and future directions

Medication options to improve core symptoms of ASD are lacking. Therefore, newer agents and CAM that target the underlying molecular and cellular pathogenesis of ASD have been drawing more attention.

There are limited outcome measures that are sensitive and reliable enough to detect behavioural changes in this population. For this reason, the development of more sensitive and specific outcome measures to detect changes in social communication and RRB is needed. Another challenge is that a majority of the current clinical trials measure a short-term treatment efficacy, while observable behavioural changes might take much longer than a few weeks to months. Therefore, long-term clinical trials are needed in order to detect medication effects on a behavioural level.

In addition, ASD is a highly heterogeneous disorder with a multifactorial aetiology, and a large number of heterogeneous subjects can obscure medication effects that are present in a sub-group. Thus, clinical trials focusing on more individualized treatment approaches and more homogeneous subjects might increase the chances of accurately measuring treatment outcomes.

Even with an effective pharmacotherapy, the side-effects are often burdensome, particularly in the long-term. Therefore, clinical trials that combine behavioural therapy with pharmacotherapy are needed, as this combination approach might be able to lower the need for medication dose and polypharmacy.

Disclosure statement

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