Resources Advancing Mental Health in Pediatrics

RAMP

Psychopharmacology in Children with Autism Spectrum Disorder in Primary Care

Objectives

- List symptom areas in children with Autism Spectrum Disorder (ASD) which are amenable to pharmacologic treatment.
- Describe the evidence base for pharmacologic treatment of each symptom area in children with ASD.
- Outline benefits and risks of atypical antipsychotic medications in the treatment of aggression, irritability, and self-injurious behaviors in children with ASD, and appropriate monitoring for side effects.

Preliminary considerations

- Children with ASD develop the same mental health disorders as do other children, including anxiety disorders, depression, and bipolar disorder.
- You must rule out treatable causes of distress (pain, constipation, sensory triggers, boredom, bullying) before considering medication treatment of behaviors.
- Any medication treatment should be accompanied by thoughtfully designed behavioral strategies to maximize reward for prosocial behaviors and minimize reinforcement of problematic behaviors.
- There is no medication that specifically treats the constellation of symptoms that define ASD.
- Attempts have been made target specific symptoms of ASD or symptoms that commonly occur in children with ASD with psychopharmacologic agents.
- Repetitive behaviors and impaired social relatedness are core symptoms of ASD. Sleep disturbance, hyperactivity and impulsivity, and irritability, aggression and self-injury are all common among children with ASD but are not definitive of the disorder.
- The table below ranks symptom clusters by their response, to date, to pharmacologic intervention. It also ranks pharmacologic classes by the evidence for their efficacy in alleviating target symptoms.

Symptom Targets for Pharmacotherapy in ASD

Irritability, aggression and self-injury	**Strong Evidence**	Antipsychotics
Hyperactivity, impulsivity	⇑	Alpha-agonists
Sleep disturbance		Stimulants
Repetitive behavior		Melatonin
Impaired Social Relatedness	**Weak Evidence**	Antidepressants
		Mood Stabilizers

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Target: Social relatedness

Pharmacologic strategies to improve social relatedness in ASD have generally been unsuccessful. Studies have been of poor quality and no significant improvement has been observed. Trials have included naltrexone, lamotrigine, amantadine and d-cycloserine.

Oxytocin showed initial promise in randomized controlled trials measuring social relatedness but negative studies followed, and *a recent meta-analysis showed no difference from placebo* (Hollander, 2007; Guastella 2007, 2010; Weng 2017; Bernaerts 2020).

No pharmacologic interventions have been effective in improving social relatedness in children and adolescents with ASD.

Target: Repetitive Behaviors

Because repetitive behaviors appear phenomenologically similar to obsessive compulsive disorder, most trials targeting repetitive behaviors in ASD have involved tricyclic antidepressants such as clomipramine or the selective serotonin reuptake inhibitors. *Randomized controlled trials in children and adolescents have shown only modest improvement.* Behavioral activation with SSRIs was a concern in 2 of the studies.

Medication	Study	Benefits	Limitations
Clomipramine (McDougle 1992; Gordon 1993)	Several very small studies (n=5 or 7)	Better than placebo in children and young adults with ASD	Concerns: requires ECG prior to tx, drug level monitoring, lowers seizure threshold
Fluvoxamine (McDougle 1996)	N=30 adults DB, PC trial Dose: 300mg/d	Adults showed improvement	Increased behavioral activation, insomnia
Fluoxetine (Hollander et al. 2005) Hollander et al., 2012	N=39 children w autism 8 wk PC crossover trial N=37 adult w autism 12 wk DB, PC trial	FLX Slightly better than PBO at low doses at reducing repetitive behaviors (10% vs. 4%), small effect size 50% vs 8% responders	Tolerated with slow upward titration
Citalopram (STAART consortium 2009)	N= 149 (age 5-17) Design: 12 wk DB PC trial	No improvement vs. Placebo (on CGI-I or CY-BOCS-PDD)	Generally tolerated. Concern for behavioral activation

Trials of SSRIs and clomipramine have shown modest or no improvement in repetitive behaviors in children and adolescents with ASD.

Target: Sleep disturbance

In terms of pharmacotherapy, melatonin is the only well-studied pharmacologic treatment for sleep disturbance in children and adolescents with ASD. Immediate-release melatonin is safe and effective in improving sleep latency, and to a lesser extent, total sleep time (Gringas 2012, Malow 2012). Doses in trials were 1-3 mg nightly.

Total sleep time is a big deal for parents of children with ASD who tend to sleep only until 3 or 4 am and who cannot be left unsupervised once they are awake. Gringas et al (2017) evaluated a pediatric formulation of prolonged-release melatonin (PedPRM). This formulation was designed to be shaped in a way that is relatively easy to swallow. The study enrolled 125 subjects with ASD aged 2-17 years whose sleep did not improve with behavioral intervention. They were randomized to PedPRM (2-5 mg) or placebo for 13 weeks. In the subjects who received PRM *sleep latency decreased 40 minutes as compared to a 12-minute decrease with placebo. Total sleep time increased 57.5 minutes with PedPRM versus 9.1 minutes with placebo.*

What about the long term? Many parents wonder if it is safe to use melatonin on a nightly basis for an extended period of time. The same research team (Malow et al 2021) conducted an open-label 2-year extension in 80 of the patients from the trial described above. Dosing in the continuation phase ranged from 2 to 10 mg of prolonged-release melatonin. *Improvements in sleep and caregiver satisfaction maintained for the 104-week period.* Adverse effects included fatigue (6.3%), somnolence (6.3%) and mood swings (4.2%).

Melatonin and prolonged-release melatonin are safe and effective for the long-term management of delayed sleep onset and total sleep time (prolonged-release only). No other pharmacologic treatments have been studied in children with ASD to date.

Target: Hyperactivity and Inattention

Medications used to treat ADHD in children without ASD have been evaluated in small trials in children with ASD. The only randomized controlled trial of stimulants was conducted by the Research Units in Pediatric Psychopharmacology group, or RUPP, in 2005. *Methylphenidate was less effective, and effective in a smaller percentage of patients in this trial than in trials of stimulants in neurotypical children*. Additionally, 18% of patients had increased irritability with methylphenidate. A small prospective open-label trial of atomoxetine, or Strattera, in children and adolescents with ASD resulted in significant improvement among 12 of 16 patients, with 2 out of the 16 patients worse due to irritability.

MEDICATION	STUDY	BENEFITS	TOLERABILITY
Stimulants	RUPP (2005a) N=72 (Age 5-14yr) Design: 7 d test-dose then 4 wk DB crossover trial of 3 dose levels Drug: MPH vs PBO	Outcome: 50% of patients respond (vs. nearly 80% in non-ASD) with effect size of 0.2-0.54, smaller than effect size in non-ASD	Irritability in up to 18%
Atomoxetine **Mean dose: 1.2 mg/kg/d**	Posey, 2006 N= 16 (Age 6-14) Design: Prospective open label Dose :0.8mg/kg/d x 1wk then increased to 1.4mg/kg/d by week 4	Outcome: 75 % of those who also had ADHD symptoms significant improvement on CGI	13% were much worse due to irritability

The alpha-agonists appeared effective in a few small studies of immediate-release clonidine and guanfacine. A randomized controlled trial of guanfacine extended release (ER) compared 31 children on guanfacine ER with 31 children on placebo for 8 weeks. The modal dose was 3 mg. Children on guanfacine ER showed a 44% decrease on the hyperactivity scale of the Aberrant Behavior Checklist as compared to 13% on placebo. The

most common side effects were drowsiness and fatigue. Slight blood pressure decrease in the early weeks of the study returned to normal by the end of the study.

Medication (alpha agonists)	Study	Benefits	Tolerability
Clonidine immediate release	2 small (8 & 9 patients) crossover trials in 1992	Some improvement on some scales; mixed results	sedation
Guanfacine immediate release	open-label study in 25 MPH non-responders (Scahill 2006)	39% ↓on the Aberrant Behavior Checklist hyperactivity subscale and a 48% (12 of 25) ↑ CGI-I	sedation
Guanfacine extended release	RCT in 62 subjects mean age 8.5 years GER or PBO for 8 weeks, modal dose 3 mg/day (range 1-4 mg) (Scahill 2015)	↓44% on Aberrant Behavior Checklist –hyperactivity scale with GER vs ↓13% PBO; CGI-I improvement 50% GER vs 9% PBO	Drowsiness, fatigue Blood pressure ↓ in first 4 weeks, returned to normal in 2nd 4 weeks

Overall, the evidence most strongly supports alpha-agonists in the management of hyperactivity and inattention in children with ASD. Stimulants may be effective but may increase irritability.

Target: Irritability, aggression and self-injury

Typical Antipsychotics

The first medication used to treat aggression in children with ASD was the antipsychotic haloperidol. *Use of haloperidol was limited by significant side effects including sedation, dystonia and dyskinesias.*

Haloperidol was FDA-approved for severe behavioral disturbances in children, with no specific mention of autism.

Atypical Antipsychotics: Risperidone

By the 1990s, atypical or second-generation antipsychotics were beginning to replace older antipsychotics like haloperidol in large part due to their better neurologic safety profile with less risk of dystonia and tardive dyskinesia. Of the atypical antipsychotics risperidone was the first to be systematically studied in the treatment of irritability, aggression and self-injury in children with ASD. The 2002 Research Units in Pediatric Psychopharmacology or RUPP study, and its 2005 open-label extension evaluated tantrums, aggression and self-injury in 101 youth with ASD over an 8-week period. The risperidone group improved 57% on an aggression scale vs placebo 14%. The mean dose was 1.8mg/day, dosed by weight. There was continued improvement even after there were no more increases in the dose.

A Janssen company trial in 2004 in 79 subjects replicated this data (Shea et al. 2004).

Adverse events were weight gain which was problematic in 25%, tremor, and drooling. There were no dyskinesias or dystonia.

In a 4-month open label extension of the study: effects were stable over 6 months and it was not necessary to increase the dose. Weight gain averaged 5.6 kg over the course of the study vs. expected weight gain of 2.4kg.

The final phase of study asked, is it possible to discontinue medication and maintain benefits? The answer was No. The study was halted because of significant relapse.

The overall study outcome: approximately 70% of autistic children show about 50% improvement from baseline in serious maladaptive behaviors on risperidone.

Irritability in Young Children with ASD

The RUPP study included children aged 5-17. What about younger children with irritability in ASD? A small unblinded placebo-controlled trial of risperidone in preschool-aged children with ASD showed a less impressive level of symptom reduction as compared to placebo, and significant side effect burden including appetite increase and weight gain, increased prolactin, drooling and sedation (Luby 2006).

Based on these studies, risperidone was approved by the FDA for treatment of aggressive behavior in children aged 5 years and up with pervasive developmental disorders in 2005.

Atypical Antipsychotics: Aripiprazole

Once risperidone was given an FDA indication, several groups sought to assess another atypical antipsychotic, aripiprazole, in the treatment of irritability and aggression in children with ASD. You can see that 3 studies published in 2009 all came to the same conclusions: aripiprazole was more effective than placebo in targeting irritability. Fatigue, extrapyramidal side effects, and modest weight gain were common adverse effects.

Aripiprazole was granted FDA approval for the treatment of irritability and aggression in patients aged 6 years and up 2009.

Authors	Study	Dose	Response	Adverse Effects
Stigler, et al. (2009)	N=25 Asp. and PDD NOS (IQ range 50-132) 14-week open label study	7.8mg/d, range 2.5-15mg/d	CGI-I much or very much improved and >25% improvement in irritability in 84% of patients on the ABC	Tiredness EPS Weight gain average of 2.3 pounds
Owen, et al. (2009)	N=98 children with autism and significant irritability 8-week DB, PC flexibly dosed trial	Dose range 2-15mg/d.	8.5mg/day was more efficacious than placebo	Fatigue and somnolence
Marcus, et al. (2009)	N=313 Two 8- week DB PC fixed dose study	5mg, 10mg or 15mg	All doses more efficacious than placebo on ABC irritability subscale	Sedation, Drooling, tremor, akathisia, EPS Weight gain

Other Atypical Antipsychotics

Other atypical antipsychotics have been evaluated for efficacy and tolerability in the treatment of irritability and aggression in children and adolescents. Large randomized controlled trials are lacking. *Current evidence is summarized below. As you can see in the notes on each medication, the response rate and adverse effect profiles for these medication does not support their use as a first-line treatment for aggression or irritability in children or adolescents with ASD.*

Clozapine: Case reports only, risks of seizure and agranulocytosis

Lurasidone: randomized controlled trial of lurasidone 20 mg (N=50), lurasidone 60 mg (N=49), placebo (N=51), aged 6-17 years, effectiveness not different at either lurasidone dose from placebo. Vomiting and somnolence occurred in about 4% in the lurasidone groups.

Olanzapine: Olanzapine versus haloperidol: 6 week open-label parallel groups in 12 children with autism; better response on olanzapine but 3 times greater weight gain.

Olanzapine: double blind placebo-controlled trial: 11 children with ASD in 8-week trial received average dose of olanzapine 10mg/day; half responded. There was 7 times more weight gain in olanzapine versus placebo.

Quetiapine: 4 open-label studies: response rate ranged 20-60%.

Ziprasidone: Case series and prospective open label study (75% response); no weight gain.

Combined Treatment: Medication and Behavior Therapy

Another RUPP study was a 24-week clinical trial that randomized 124 children aged 4-13 years with ASD and serious behavior problems to medication alone or combination of medication and parent training. Among blinded evaluators: there was 77% improvement in the med-only group vs 87% improvement in the combined group. According to parents, the combined group showed significant difference and continued gains. The final daily risperidone dose was lower in combined treatment, 1.98 mg vs. 2.26 mg in the medication-only group, indicating that combined treatment may allow for less medication exposure.

The atypical antipsychotics risperidone and aripiprazole have the best evidence for treating irritability and aggression in children and adolescents with ASD. Combining risperidone with parent training allows for better results with less risperidone.

Prescribing and Monitoring Atypical Antipsychotics in Children and Adolescents with ASD

Atypical antipsychotics: dosing

	formulations	dosing range	dosing frequency
aripiprazole	2, 5, 10, 15, 20, 30 mg tablets 5 mg/ ml liquid	2-30 mg/day	daily
risperidone	0.25, 0.5, 1, 2, 3, 4 mg tablets 0.5, 1 mg ODT 1 mg/1 ml liquid	0.5-6 mg/day	bid

The above table covers the formulations, dosing range, and dosing frequency of aripiprazole and risperidone, the 2 atypical antipsychotics with the most evidence for use in treatment of irritability and aggressive behaviors in children with ASD.

Antipsychotics: side effects-metabolic/endocrine

Increased appetite, weight gain, impaired glucose metabolism, hyperlipidemia

- All may occur with atypical antipsychotics.
- Glucose and lipid changes may be related to increased appetite leading to increased food intake, or direct metabolic effects of the medication.
- Aggression around food-seeking behavior may emerge, negating some of the benefits of the medication on aggressive behavior.
- Studies have shown substantial evidence for metformin in reducing or averting antipsychotic-associated weight gain.

Hyperprolactinemia

- May be associated with gynecomastia, galactorrhea, amenorrhea, oligomenorrhea, hirsutism, erectile dysfunction, and decreased libido.
- Prolactin levels are not part of routine monitoring but routine surveillance for gynecomastia or galactorrhea in all genders is appropriate.
- Hyperprolactinemia is generally reversible with discontinuation of the drug.
- Aripiprazole, a partial D2 receptor agonist, **decreases** prolactin levels.

Neurologic symptoms

- **Dystonia** and **akathisia** often present early in treatment.
- Dystonia is a sudden stiffening or abnormal movements, often of face, neck, trunk.
    - Dystonia is rapidly reversible with oral or IM diphenhydramine.
    - Dystonia may be prevented or controlled with benztropine
- Akathisia is a sense of intense restlessness, unable to be still, acute change from baseline.
    - Akathisia may be controlled with a beta blocker, but this is not always effective.
- Consider dose reduction or change in medication if dystonia or akathisia are not controllable with adjunctive medication.
- **Tardive dyskinesia** appears after prolonged treatment with antipsychotics.
    - Common with first-generation antipsychotics, can still occur in patients taking high-potency second generation antipsychotics such as risperidone over long periods.

Cardiac conduction changes

- Antipsychotic-associated prolongation of QTc can occur.
- Unclear if antipsychotic-associated prolongation of QTc increases risk of Torsade de Pointes.
- ECGs are not routinely done prior to starting atypical antipsychotics but should be done if
    - patient has a family history of prolonged QTc or other conduction abnormalities
    - patient taking other medications that prolong QTc
    - starting ziprasidone

Adverse effect profile of commonly used atypical antipsychotic medications

	aripiprazole	lurasidone	olanzapine	quetiapine	risperidone	ziprasidone
weight gain	0/+	0/+	+++	++	++	0/+
diabetes	0/+	0/+	+++	++	+	0/+
increased lipids	0/+	0/+	+++	++	+	0/+
increased prolactin	0/+	+	+	0	+++	+
sedation	0/+	+/++	+/++	++	+	+
extra-pyramidal effects (dystonia)	+	+/++	0/+	0	++	+
akathisia	++	+/++	+	+	+	+/++

0/+ = minimal + = mild ++ = moderate +++ = severe

Adapted from C Correll in Dulcan's Textbook of Child and Adolescent Psychiatry, 2nd edition, APPI 2016

The above table summarizes some of the adverse effects of commonly prescribed atypical antipsychotics. There may be some children who respond quite differently than indicated here.

Because of concerns around metabolic changes associated with SGAs, the American Diabetes Association and the American Psychiatric Association wrote consensus guidelines on monitoring for adverse metabolic changes. The following summarizes their recommendations.

Metabolic monitoring parameters based on American Diabetes Association/American Psychiatric Association consensus guidelines

	Baseline	Week 4	Week 8	Week 12	Q 3 months thereafter	Annually

Medical history (personal and family h/o obesity, HTN, diabetes and CV disease)	X			X		X
Weight, height, BMI	X	X	X	X	X	X
Blood pressure	X			X		X
Fasting glucose/HbA1C	X			X		X
Fasting lipids	X			X		X

Outside these guidelines, but standard practice:
If signs of hyperprolactinemia (gynecomastia, galactorrhea), check prolactin level.
If rapid weight gain, consider liver function tests for fatty liver.

Atypical antipsychotics: long-term use

Risperidone and aripiprazole are effective in the treatment of aggression and irritability in children with ASD, and in one study, discontinuation of risperidone resulted in a rapid return of symptoms.

and

Long-term use is often associated with metabolic side effects which can negatively affect short- and long-term health.

Continued use requires an ongoing exploration of therapeutic and environmental strategies to reduce aggressive behavior.

Continued use requires an ongoing cost-benefit assessment made in conjunction with the patient and family.