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Decision Making and Antipsychotic Medication Treatment for Youth With Autism Spectrum Disorders: Applying Guidelines in the Real World

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Autism spectrum disorder (ASD) is a diagnosis that is characterized by varying degrees of (1) impairment in social reciprocity, (2) impairment in social communication, and (3) repetitive, restrictive, stereotyped patterns of interests, activities, and behaviors.[1] While ASD prevalence varies across regions, recent prevalence rates range from 1:88 children in the United States[2] to 1:160 children worldwide.[3]

Currently, only 2 atypical antipsychotics, risperidone (in 5- to 16-year-olds) and aripiprazole (in 6- to 17-year-olds), are approved by the US Food and Drug Administration (FDA) for treatment of significant irritability (aggression toward others, deliberate self-injuriousness, temper tantrums, and labile moods) associated with ASD. In a recent report on 2,843 children and adolescents (collectively referred to here as *youth*) with ASD, 4% of 3- to 5-year-olds, 14% of 6- to 11-year-olds, and 23% of 12- to 17-year-olds were treated with atypical antipsychotics.[4] The frequent use of atypical antipsychotics in youth with ASD necessitates careful evaluation of the indication, benefits, and risks of these agents. This is especially important since youth with ASD may be at greater risk for atypical antipsychotic–related significant weight gain (≥ 7% of pretreatment weight in short-term studies) compared to youth with schizophrenia or bipolar disorder[5] (although this result may be due to reduced prior atypical antipsychotic exposure in youth with ASD[6]). In this article, we review treatment strategies for youth with ASD, focusing on the adaptation of monitoring and management guidelines for atypical antipsychotic–related adverse effects.

EVALUATION AND MANAGEMENT OF ASD

The gold-standard ASD diagnosis is made by a team of specialists using standardized diagnostic tools (Autism Diagnostic Observation Schedule,[7] Autism Diagnostic Interview-Revised[8]) in combination with clinical judgment.[9] Assessment challenges include determining functional abilities in cognitive, language, and social domains; contribution of genetic/metabolic etiologies; and presence of comorbid medical/neurologic disorders (eg, epilepsy) and comorbid psychiatric symptoms/disorders requiring clinical intervention (eg, irritability, inattention, impulsivity, anxiety, depression, sleep disruption).[9] Primary treatment for core ASD symptoms centers on evidence-based educational and behavioral interventions.[10]

While pharmacologic agents do not treat core ASD symptoms, certain agents are useful in reducing comorbid symptoms that impair functioning and interfere with therapeutic and scholastic progress.[11] A small number of well-powered randomized controlled trials (RCTs) in youth with ASD demonstrated the efficacy of (1) risperidone and aripiprazole in treating significant irritability (with additional positive effects on hyperactivity and stereotypy)[12–15]; (2) haloperidol (typical antipsychotic) in reducing symptoms of negativism (angry/labile affect),[16] although adverse effects (dystonias, withdrawal dyskinesias) limit its use[17]; and (3) methylphenidate in treating hyperactivity and impulsiveness, although effect sizes may be lower and adverse effects higher in youth with ASD compared to youth with primary attention-deficit/hyperactivity disorder.[18] Conversely, 2 large RCTs[19,20] failed to demonstrate the efficacy of the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and citalopram in reducing repetitive behaviors in ASD. No RCT has yet examined the effect of SSRIs on mood and anxiety symptoms in ASD; therefore, evidence of efficacy for these indications is currently lacking.

MONITORING AND MANAGEMENT OF ADVERSE EFFECTS IN ATYPICAL ANTIPSYCHOTIC–TREATED YOUTH AND ADAPTATION TO ASD

Youth treated with atypical antipsychotics are at increased risk of developing extrapyramidal symptoms (EPS; parkinsonism and dystonia), withdrawal dyskinesias, prolactin-related adverse effects, dyslipidemia, and weight gain compared to adults.[5,21,22] Below, we summarize guidelines for adverse effect monitoring and management in atypical antipsychotic–treated youth[23–25] and provide recommendations for overcoming clinical challenges to applying these guidelines to youth with ASD.

Monitoring During Atypical Antipsychotic Use in Youth (adapted from references 22–24)

- **Baseline and annually:** Assess personal/family history (cardiovascular/metabolic illness, seizures/other neurologic disorder, past treatment response/adverse effects, lifestyle factors [diet/exercise]) and current treatments/potential interaction effects with atypical antipsychotics (eg, fluoxetine and paroxetine may inhibit hepatic metabolism of aripiprazole and risperidone, resulting in increased blood levels of atypical antipsychotic).
- **Every visit:** Monitor (1) treatment efficacy, (2) basic clinical measures (height, weight, body mass index [BMI] percentile [assessing overweight or obese status], BMI *z*-score [tracking sex- and age-adjusted body weight trends over time], blood pressure), (3) lifestyle factors, (4) somnolence/sedation, (5) prolactin-related adverse effects (eg, galactorrhea, gynecomastia, oligorrhea/amenorrhea; measure blood prolactin levels if adverse effects are present), and (6) new medications and interaction effects with atypical antipsychotics.
- **Baseline, 3 and 6 months on treatment, and every 6 months thereafter:** Perform blood work to monitor liver function, fasting glucose, glycosylated hemoglobin, and lipids. Use clinical judgment to assess whether less-frequent monitoring (ie, baseline, 6 months, annually) is appropriate in patients with low adverse effect risk or when significant barriers to more-frequent blood draws are present.
- **Baseline, during titration, and every 3 months thereafter:** Monitor for movement disorders with objective rating scales (eg, Abnormal Involuntary Movement Scale,[26] Simpson-Angus Rating Scale[27]).

Adverse Effect Management During Atypical Antipsychotic Use in Youth (adapted from references 22 and 28)

Weight gain and metabolic abnormalities.

- **At treatment initiation:** Provide healthy lifestyle counseling/intervention, begin with an atypical antipsychotic with low adverse effect risk.
- **If adverse effect occurs:** Provide healthy lifestyle/weight-loss counseling/intervention, switch to lower-risk atypical antipsychotic.
- **If adverse effect progresses:** Provide healthy lifestyle or weight-loss counseling/intervention, switch to lower-risk atypical antipsychotic. Consider targeted treatment for abnormal weight, laboratory value, or blood pressure value (eg, lipid-lowering diet for dyslipidemia)[29] and specialist referral.

Neuromotor adverse effects.

- **General:** "Start low, go slow, but go" regarding atypical antipsychotic use.
- **Parkinsonism, dystonia (EPS):** Reduce dose, add anticholinergic medication, switch to lower-risk agent.
- **Akathisia:** Reduce dose, add benzodiazepine or β-blocker, switch to lower-risk agent.
- **Dyskinesia:** Review indication/consider stopping, switch to lower-risk agent.

Other adverse effects.

- **General:** "Start low, go slow, but go"; adjust dose; switch to lower-risk agent.

Adaptations for Atypical Antipsychotic Use in Youth With ASD

Complementary information for the adaptations outlined in this section can be found in 2 freely available clinical resources: the Autism Speaks Autism Treatment Network (ATN) series of tool kits on Challenging Behaviors, Visual Supports, Blood Draws, Safe and Effective Medicine Use, and Medication Decision Aid[30] (http://www.autismspeaks.org/family-services/tool-kits) and the Treatment of Maladaptive Aggression in Youth (T-MAY) Tool Kit[28,31] (http://www.thereachinstitute.org/tmay.html).

Determining whether atypical antipsychotic treatment is needed.

- Assess meaning, origin, and impact of the treatment target:
  - Assess potential medical (ie, pain), psychiatric (ie, anxiety), and situational factors/triggers (ie, sensitivity to transitions or sensory stimuli, exposure to bullying) contributing to target symptom expression.
  - Establish the function of behavior (eg, escape, avoidance, attention), evaluating ***a***ntecedents, ***b***ehaviors, and ***c***onsequences ("ABCs").
  - Compare "ABCs" across settings, using collateral information.
- Use behavioral interventions to help youth identify alternative/more rewarding ways to communicate needs (see ATN Challenging Behaviors Tool Kit[30]).
- Atypical antipsychotics are indicated for irritability in ASD; however, stereotypy, hyperactivity, tics, and sleep may also improve with atypical antipsychotic treatment.
- Clearly explain to families the benefits and risks of various treatment options. Decision aids can be used to help families improve knowledge regarding treatment options and the benefits and risks and reach choices that are consistent with their values[32] (see ATN Medication Decision Aid and Autism and Medication Tool Kit[30] and reference [33]).

Identifying and tracking target symptoms.

- Use objective measures at baseline to establish target symptom frequency, intensity, and duration across settings (home/school/community).
- Establish treatment response expectations in advance and review regularly.
- Use brief objective rating scales in the clinic to monitor symptom severity and frequency (see T-MAY Tool Kit[28,31]).
- Consider commonly occurring sensory sensitivities in youth with ASD (eg, sensitivity to taste or to swallowing pills) to improve medication adherence. Aripiprazole and risperidone are available as disintegrating oral tablets and liquid, which can be mixed with soft food (eg, applesauce). Youth can also practice pill swallowing with candies or using a pill-swallowing cup.[30]

Monitoring/managing cardiometabolic adverse effects.

- Obtaining basic clinical measures (height, weight, blood pressure) and regular bloodwork may pose unique challenges in youth with ASD. Every effort should be made to ensure that metabolic monitoring is completed with minimal distress. Simple behavior supports such as visual schedules, use of simple language (eg, "First…then…"), behavior modeling, and inclusion of families in procedures promote cooperation in the clinic (see ATN Visual Supports Tool Kit[30]).
- The ATN Blood Draw Tool Kit[30] provides strategies to parents and providers for completing successful blood draws in youth with ASD, including instructions regarding relaxation and distraction, topical anesthetics, reinforcements, and visual supports.
- Weight management may be challenging in youth with ASD due to dietary selectivity or presence of hypotonia/motor delays that interfere with physical activity. Families often benefit from consultation regarding portion size and healthy food choices with a registered dietician. Support around developing/implementing an exercise program across settings may be helpful.[30]

Monitoring movement abnormalities/disorders.

- Monitoring for movement disorders in youth with ASD can be challenging, as baseline stereotypic and repetitive behaviors can be mistaken for atypical antipsychotic–related neuromotor adverse effects.
- Comprehensively assess abnormal movements at baseline and follow-up, using objective rating scales[26,27] (individualized strategies and family member participation may be required for compliance).
- Record all repetitive and stereotyped behaviors present at baseline. If families consent, video recordings can be helpful to refer back to if motor symptoms arise during atypical antipsychotic treatment.

CONCLUSION

Youth with ASD require careful diagnostic evaluation to rule out addressable environmental causes of problem behaviors. Although the atypical antipsychotics risperidone and aripiprazole are currently the only FDA-approved treatments for youth with ASD, atypical antipsychotics target irritability, not core ASD deficits. Given the related adverse effects, atypical antipsychotics should be reserved for youth with severe symptoms not responding to nonpharmacologic interventions or lower-risk medication options. Clinicians must help families to carefully weigh risks and benefits of atypical antipsychotics prior to treatment initiation. Advanced treatment planning including ASD-specific adaptations will help facilitate successful treatment, adverse effect monitoring, and management in youth with ASD.

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