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Second-Generation Antipsychotic Use in Children and Adolescents

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In children and adolescents, second-generation antipsychotics have been studied for a variety of conditions including autism, schizophrenia/first-episode psychosis, and bipolar I disorder. Drugs with Food and Drug Administration (FDA) approval in children or adolescents are listed in **Table 1**. However, antipsychotics are often prescribed off-label for other conditions or age groups despite the lack of evidence and potential safety concerns. The goal of this newsletter is to review the evidence for antipsychotic use in children, describe appropriate place in therapy and guideline monitoring recommendations, and provide resources for alternative first-line therapies in young children.

Table 1. Current FDA approved indications and ages of second-generation antipsychotics in children and adolescents

Drug	Schizophrenia	Bipolar I disorder	Irritability associated with Autism	Tourette's Disorder
aripiprazole[1]	≥13 yrs	≥10 yrs	≥6 yrs	≥6 yrs
asenapine[2]		≥10 yrs		
lurasidone[3]	≥13 yrs	≥10 yrs		
olanzapine[4]	≥13 yrs	≥13 yrs		
paliperidone[5]	≥12 yrs			
quetiapine[6]	≥13 yrs	≥10 yrs		
risperidone[7]	≥13 yrs	≥10 yrs	≥5 yrs	

Efficacy of Antipsychotics

A recent systematic review from the Drug Effectiveness Review Project (DERP) evaluated effectiveness and harms of antipsychotic use in children and adolescents up to 17 years of age.[8] The review identified randomized controlled trials (RCTs) in the following 4 different conditions: schizophrenia, bipolar disorder, autusm spectrum disorders, and disruptive behavior/ impulse control/conduct disorders (e.g. oppositional defiant disorder).[8] The primary outcome for most studies was symptom improvement (based on a variety of rating scales; **Table 2**). Very few of these scales have well defined or commonly accepted minimum clinically important differences. For all conditions, there was a lack of data for outcomes such as progression through school, reduction in hospitalizations, efficacy for acute symptoms, or improved engagement in social settings.

Schizophrenia and First Episode Psychosis

The DERP review identified 8 placebo-controlled RCTs and 8 head-to-head studies evaluating antipsychotics in patients with schizophrenia or first episode psychosis.[8] Average age at study enrollment was 15 years and trials ranged from 6 to 52 weeks. Most studies required participants to have moderate to severe symptoms at baseline (Positive and Negative Symptom Scale [PANSS] score ≥20 and Clinical Global Impressions-Improvement [CGI-I] ≥3).[8] In general, antipsychotics demonstrated symptom improvement compared to placebo, but most studies directly comparing drug treatment demonstrated no difference between drug therapies.[8] Quality of evidence ranged from very low to moderate depending on the specific comparison. Data was limited by small sample sizes, high attrition rates, and in most cases, only one study was available to support each comparison.[8]

Table 2. Common assessment scales for symptom severity[8]

Scale	Description
Aberrant Behavior Checklist-Irritability subscale (ABC-I)	15 items each rated on a 0 to 3 Likert scale (range 0-45)*
Clinical Global Impressions-Improvement (CGI-I)	7-point Likert scale (range of very much improved to very much worse)
Children's Depression Rating Scale (CDRS)	17 items assessing depressive symptoms (range 17-113)*
Nisonger Child Behavior Rating Form (NCBRF) - conduct problems subscale	16 items rated on a 0-3 Likert scale (range 0-48)*
Positive and Negative Symptom Scale (PANSS)	30 items (total range 30-210; usual range 60-150)*
Young Mania Rating Scale (YMRS)	11 items assessing mania over the prior 48 hours (range of 0-60)*

* higher scores indicate more severe disease

Bipolar Disorder

In patients with bipolar disorder, 9 RCTs evaluated efficacy of antipsychotics in children compared to placebo.[8] Only 2 drugs (aripiprazole and quetiapine) were supported by more than a single RCT, and outcomes were graded as very low to low quality evidence due to short treatment periods, a high placebo response, high attrition, and small sample sizes.[8] Only one small head-to-head RCT of risperidone versus quetiapine was identified (n=22). Average age at study enrollment was 13-14 years, and study duration ranged from 3 to 72 weeks.[8] Most studies required participants to have moderate to severe symptoms at baseline (Young Mania Rating Scale [YMRS] total score ≥20 and CGI-I ≥4). Use of olanzapine, risperidone and aripiprazole resulted in a mean improvement in mania symptoms of 6 to 9 points on the YMRS compared to placebo.[8] The most commonly cited minimum clinically important difference for the YMRS is a change of 6 points.[9] There was no change in YMRS with quetiapine vs. placebo (one RCT; n=316).[8] In general, assessments of depressive symptoms based on the revised Children's Depression Rating Scale (CDRS-R) did not show consistent improvement compared to placebo for quetiapine, asenapine, or aripiprazole.[8] CDRS-R was improved in one

RCT of lurasidone versus placebo (mean difference of 5.7 points), but differences were small and results of this study may have been influenced by high placebo response rates.[8]

Autism Spectrum Disorder

Aripiprazole and risperidone are the primary medications studied in autism. The DERP report identified 14 RCTs evaluating these 2 products, including 2 head-to-head studies.[8] Ten of these studies evaluated outcomes at 8 weeks, and the longest study duration was 6 months.[8] Most studies were in children 8 to 11 years of age and 2 studies evaluated therapy in patients as young as 4 or 5 years of age.[8] Commonly studied outcomes included irritability symptoms and global clinical improvement. Most patients were required to have moderate to severe agitation at baseline (Aberrant Behavior Checklist-Irritability subscale [ABC-I] scores of at least 18). Compared to placebo, symptoms of irritability improved with risperidone (change in ABC-I of -12.1 to -14.9 vs. -3.6 to -6.5 with placebo; 3 RCTs, N=331) and aripiprazole (ABC-I change of -11.4 to -14.4 vs. -5 to -8.4 with placebo; 4 RCTs, N=493).[8] A minimum clinically important difference in ABC-I has not been established. CGI-I scores showed similar trends with significant symptom improvement with risperidone or aripiprazole compared to placebo. Two RCTs directly compared effects of aripiprazole and risperidone with no difference in ABC-I or CGI-I scores between groups (N=120).[8] Only one other antipsychotic, lurasidone, has been studied for symptoms of irritability and demonstrated no improvement in ABC-I, mixed results with CGI-I, and no dose response compared to placebo (1 RCT, N=150, moderate quality evidence).[8]

Disruptive Behavior, Impulse Control or Conduct Disorder

Eight RCTs evaluating quetiapine or risperidone vs. placebo in patients with disruptive behavior or conduct disorders were included in the DERP report. Trial durations ranged from 2 to 52 weeks.[8] All trials had moderate to high risk of bias with small sample sizes and high attrition rates. Most evidence evaluated risperidone compared to placebo (4 RCTs; n=640); evidence supporting other drugs was limited.[8] Patients had a mean NCBRF-conduct problems score of 32 to 34 at baseline indicating severe symptoms.[8] Use of risperidone improved symptom severity on the NCBRF scale by an average of 15-16 points compared to 6-7 points in patients randomized to placebo.[8] In an open-label extention trial, symptom improvement was maintained over 48 weeks.[8] There is no well established minimum clinially important difference for the NCBRF conduct problems subscale.

Safety of Antipsychotics

Adverse events frequently associated with antipsychotics include metabolic effects (e.g., weight gain and diabetes), extrapyramidal symptoms (e.g., akathisia, dyskinesia and dystonia), cardiovascular effects (e.g., prolonged QT interval), and hormonal effects (e.g., increased prolactin levels).[8] A summary of the relative frequency of these adverse events by drug in the general population is available from the Mental Health Clinical Advisory Group. Current evidence in children and adolescents supports these general trends,[8] though incidence may differ between adult and pediatric patients. For example, metabolic adverse events may be more frequent in children compared to adults.[10] However, because RCTs are often of short duration, many of the long-term effects of antipsychotic use in children and adolescents remain unknown, and the specific frequency and severity of adverse effects for pediatric patients is difficult to determine.

In the majority of clinical trials, use of antipsychotics was associated with increased changes in weight compared to placebo.[8] However, many studies did not evaluate statistical differences between groups. In children with autism, studies with longer duration were associated with increased weight gain, though the exact amount of weight gain which can be correlated with antipsychotic use is difficult to poinpoint in a young, growing population.[8] In patients with schizophrenia or bipolar disorder, olanzapine was associated with more weight gain compared to other antipsychotics.[8] Risperidone was consistently associated with elevated prolactin levels for all conditions.[8] Elevated prolactin levels were also reported with paliperidone in patients with schizophrenia.[8] In contrast, aripiprazole was associated with lower prolactin levels.[8] For patients with schizophrenia, risperidone was also associated with higher rates of extrapyramidal symptoms compared to other drugs.[8] Use of aripiprazole, risperidone, asenapine, and lurasidone were all associated with akathisia.[8]

Because of these adverse effects, guidelines recommend frequent evaluation and discontinuation if therapy has not demonstrated clinically meaningful improvements in symptoms. Recommended monitoring before treatment includes weight, height, waist and hip measurements, pulse and blood pressure, blood glucose, hemoglobin A1c (A1C), lipid, and prolactin levels, assessment of any movement disorders, nutritional status, diet and level of physical activity.[11,12] During initial treatment, follow-up should occur within the first 3 to 4 weeks. Identifying treatment goals, anticipated duration of treatment and pre-specified plans for stopping therapy prior to treatment initiation can assist when evaluating benefits and risks of therapy. Once therapy is stable, reassessment for adverse events should occur at every 4 to 6 months.[12,13] If adverse events occur, management strategies may include switching to a different antipsychotic or addition of adjunctive behavioral or medication therapy to target the adverse effect (e.g., addition of metformin for metabolic effects).[10,14] However, to date, there is limited evidence to support any single approach.

Guideline recommendations

Recommendations from the National Institute for Health and Care Excellence (NICE) for use of antipsychotics in children are described in **Table 3**. First-line therapy for many psychiatric conditions in children focuses on non-pharmacological treatment. Antipsychotic use in children or adolescents is typically only recommended in conjunction with a child/adolescent psychiatrist. Specifically, consultation with a specialist is recommended upon initiation of an antipsychotic for psychosis or schizophrenia, autism, conduct disorder or oppositional defiant disorder and for any patient with bipolar disorder younger than 14 years of age.[11-13,15] In all cases, frequent reassessment is required to evaluate efficacy and monitor for adverse effects.

Table 3. NICE guidance for appropriate antipsychotic use

Condition	Appropriate Use In Patients Under 19 Years of Age
Psychosis or schizophrenia[12]	➢ Only recommended if there are sufficient symptoms to definitively diagnose psychosis or schizophrenia ➢ Use is recommended in conjunction with psychological interventions such as CBT. CBT is most effective when combined with medication.
Bipolar Disorder[15]	➢ May be considered to treat mania, hypomania, or moderate to severe depressive symptoms. ➢ Routine use for >12 weeks is not recommended.
Autism[13]	➢ Routine use is not recommended. ➢ Recommended only with severe behavior non-responsive to psychosocial therapy. ➢ Treatment discontinuation is recommended within 6 weeks if efficacy is not established.
Conduct Disorder or Oppositional Defiant Disorder[11]	➢ Routine use is not recommended. ➢ Risperidone may be considered for short-term management of severely aggressive behavior. ➢ Treatment discontinuation is recommended within 6 weeks if efficacy is not established.
ADHD, PTSD, Anxiety, Mood[16] or Sleep Disorders	➢ Use of antipsychotics is not typically recommended ➢ For psychotic, recurrent depression or depression unresponsive to treatment, augmentation of an antidepressant with an antipsychotic may be considered in combination with intensive psychological therapy

Abbreviations: ADHD = attention deficit-hyperactivity disorder; CBT = cognitive behavioral therapy; PTSD = post-traumatic stress disorder

In patients with schizophrenia, guideline recommendations focus on early and regular monitoring for both treatment benefit and adverse events (see above for monitoring parameters and frequency). Specific recommendations on use of antipsychotics in children with autism and conduct disorders focus on frequent evaluation of therapy to establish benefit and assess adverse events.[13] Before prescribing antipsychotics, providers should identify the target behavior that's challenging, decide on an appropriate measure to monitor effectiveness, review effectiveness and adverse effects after 3-4 weeks, and stop treatment if there is no indication of clinically important response at 6 weeks.[13] Measures to evaluate effectiveness should include both frequency and severity of the targeted behavior and one measure to evaluate global impact. Guidelines recommend starting with a low dose and using the minimum effective dose needed for benefit. Similarly, when transferring care into the primary care setting, the specialist should communicate the monitoring plan, selection of target behaviors, potential for minimally effective dosing, planned duration of treatment and plans for stopping treatment.[13]

Oregon Medicaid Policy

In 2021, the Oregon Pharmacy and Therapeutics Committee recommended implementation of safety edits in young children (≤ 5 years of age) on Medicaid with antipsychotic use. While use of antipsychotics in this population has steadily decreased over time, there is still a small proportion of children on Medicaid less than 6 years of age prescribed antipsychotics (66 patients in 2020 and 55 patients in 2021). This safety edit is intended to ensure appropriate antipsychotic use and monitoring for this population.

Alternative non-pharmacological therapies are available for common disorders in children such as autism or challenging behavior. The Oregon Health Authority (OHA) covers a wide range of non-pharmacological applied behavioral analysis-based interventions including parent training, early intensive behavioral intervention, play/interaction based interventions, and joint attention interventions. Alternative first-line options for treatment of irritability or challenging behavior associated with autism include psychosocial interventions targeted to anticipate and prevent behavior that challenges and develop a care plan with the patient and caregivers which includes steps to address triggers that may provoke challenging behavior.[13] For example, care plans may include addressing and treating coexisting physical, mental health and behavioral conditions, providing support for family and caregivers, and/or making adjustments to increase structure and minimize unpredictability within the environment.[13] Additional resources available to providers in Oregon are available below.

Resources

- Safety edit for Medicaid patients ≤ 5 years of age
- Oregon Psychiatric Access Line: free, same-day (Monday through Friday) psychiatric phone consultation service for primary care providers in Oregon. Provides Care guides.
- Provider resources for alternative first-line therapies in early childhood including parent-child interaction therapy
- OHA Resources for Applied Behavior Analysis
- Programs with local supports for patients including the Early Assessment and Support Alliance for youth with psychosis

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References

1.Abilify (aripiprazole) tablets [package labeling]. Tokyo, Japan: Otsuka Pharmaceuticals, LLC; February 2020.
2.Saphris (asenapine) sublingual tablets [package labeling]. Irvine, CA: Allergan USA, Inc; February 2017.
3.Latuda (lurasidone) tablets [package labeling]. Marlborough, MA: Sunovion Pharmaceuticals, Inc; December 2019.
4.Zyprexa (olanzapine) tablets [package labeling]. Indianapolis, IN: Lilly USA, LLC; April 2020.
5.Invega (paliperidone) extended-release tablets [package labeling]. Titusville, NJ: Janssen Pharmaceuticals, Inc; February 2021.
6.Seroquel (quetiapine) tablets [package labeling]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; September 2020.
7.Risperdal (risperidone) tablets [package labeling]. Titusville, NJ: Janssen Pharmaceuticals, Inc; February 2021.
8.Lindsey W, Fahim S, Jackson C, Quin J, Grabowsky A. Second generation antipsychotics in children and adolescents. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2020.
9.Butler M US, Desai P, Sponheim SR, Popp J, Nelson VA, Thao V,, B S. Treatment for Bipolar Disorder in Adults: A Systematic Review. Comparative Effectiveness Review No. 208. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 18-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2018. Posted final reports are located on the Effective Health Care Program search page. DOI: https://doi.org/10.23970/AHRQEPCCER208.
10.McClellan J, Stock S. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia. *J Am Acad Child Adolesc Psychiatry.* 2013;52(9):976-990.
11.National Institute for Health and Care Excellence. Antisocial behaviour and conduct disorders in children and young people: recognition and management. Clinical guideline [CG158]. April 2017. https://www.nice.org.uk/guidance/cg158. Accessed October 30, 2019.
12.National Institute for Health and Care Excellence. Psychosis and schizophrenia in children and young people: recognition and management. Clinical guideline [CG155]. October 2016. https://www.nice.org.uk/guidance/cg155. Accessed October 30, 2019.
13.National Institute for Health and Care Excellence (NICE). Autism spectrum disorder in under 19s: support and management. Clinical guideline [CG170]. https://www.nice.org.uk/guidance/cg170. Updated June 14, 2021. Accessed November 8, 2021.
14.Maayan L, Correll CU. Management of antipsychotic-related weight gain. *Expert review of neurotherapeutics.* 2010;10(7):1175-1200.
15.National Institute for Health and Care Excellence. Bipolar Disorder: assessment and management. Clinical guideline [CG184]. April 2018. https://www.nice.org.uk/guidance/cg185. Accessed October 30, 2019.
16.National Institute for Health and Care Excellence. Depression in children and young people: identification and management. NICE guideline [CG134]. June 2019. https://www.nice.org.uk/guidance/ng134. Accessed October 30, 2019.