



Antipsychotic Medication Use in Children & Adolescent

OBJECTIVE

To provide evidence-based recommendations for the use of antipsychotic medication in children and adolescents.

INTRODUCTION

Antipsychotic prescribing for children has increased rapidly in recent decades, driven by new prescriptions and by longer duration of use. The frequency of prescribing antipsychotics among youth increased almost fivefold from 1996–2002, from 8.6 per 1,000 children to 39.4 per 1,000. Atypical antipsychotics doubled their share of all psychotropic medication prescriptions among privately insured youth between 1997 and 2000, from 2.4 percent of all psychotropic prescriptions to 5.1 percent. A national study of Medicaid-enrolled children found that prescribing of atypical antipsychotics increased 62 percent from 2002–2007.¹

Atypical antipsychotic agents (AAAs), which are sometimes referred to as second generation antipsychotics (SGAs), are currently marketed in the United States for use in adults, adolescents and children for specific indications but are often prescribed “off-label” to treat other conditions in children and adolescents. These AAAs include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, and asenapine. Safety issues surrounding the use of AAAs in youth include:¹

- Weight changes, diabetes, and hyperlipidemia
- Cardiovascular
- Agranulocytosis and neutropenia
- Hepatic dysfunction
- Prolactin
- Seizures
- Extrapyramidal symptoms (EPS), tardive dyskinesia and withdrawal dyskinesias
- Neuroleptic malignant syndrome (NMS)
- Cataracts

Recent data from adult and child/adolescent studies and meta-analyses and reviews suggest that AAAs are not necessarily more effective than older antipsychotic agents. While supporting the use of some AAAs as adjunct treatment for refractory major depressive disorder (MDD), a FDA advisory panel opposed approval as stand-alone treatment for MDD and generalized anxiety disorders in adults due to cardiac, metabolic and other safety risks. While many AAAs can be sedative, there is minimal data supporting their use as hypnotics alone. No data is available for children or adolescents on asenapine, the newest AAA approved for use in adults with acute or ongoing schizophrenia or acute mania alone or with lithium. Evidence is strongest in supporting use of AAAs for children and adolescents with schizophrenia and bipolar I disorder, while evidence for use with disruptive behavior disorders is much less robust except in youth with autism. Only one study supports the use of AAAs in long-term treatment for disruptive behavior. Despite increasing evidence of these agents efficacy, a long-term safety profile has yet to be evaluated and characterized.¹

The American Academy of Child and Adolescent Psychiatry (AACAP) discusses the current state of research based on what is currently known regarding the six AAAs that have been marketed in the United States and have pediatric data; AAAs are presented in order of marketing release. Paliperidone and asenapine were recently approved but have no data available pertaining to their use in children and adolescents; these were not considered in the AACAP parameter.¹

- **Clozapine** is indicated for use by adults for the treatment refractory schizophrenia. Due to the associated risk of agranulocytosis, clozapine is not considered a first-line medication. Among children and adolescents, the strongest empirical evidence supports the use of clozapine for patients suffering from treatment refractory schizophrenia and for those youths who require antipsychotic treatment but who have experienced severe EPS with other agents.
- **Risperidone.** Risperidone has the most substantive amount of methodologically stringent evidence about its use in children and adolescents. Studies have found that risperidone resulted in significant improvement in serious behavioral problems in children with autism ages 5-17. In youths with disruptive behavior disorders, a study examined the impact of long-term risperidone treatment in those ages 5-17 who initially responded to a 12 week trial of medication; significant differences in relapse rates indicated that prolonged treatment with risperidone was beneficial. Prospective studies have reported the effectiveness of risperidone in the treatment of youths with schizophrenia, disruptive behaviors in autism and other PDDs, disruptive behaviors in children with sub-average intelligence, and impulsive aggression in conduct disorder/disruptive behavior disorders. The use of risperidone in the reduction of tics in Tourette's syndrome is supported by one double-blind placebo controlled trial in adolescents and several other less rigorous studies. Additional studies show risperidone has a clinical benefit for patients with bipolar illness. The Texas Children's Medication Algorithm project recommends the addition of an AAA for the treatment of comorbid ADHD and aggression not responsive to behavioral intervention and psychostimulants. In adults, there are case reports of adjunctive use of risperidone in refractory patients with OCD. However in the child and adolescent literature, reports of worsening or new onset OCD symptoms in youths treated with risperidone have been published.
- **Olanzapine:** Of the AAAs, olanzapine's receptor binding profile most closely matches that of clozapine. One study reported the short-term efficacy of olanzapine in the treatment of adolescents with schizophrenia. Another reported the short-term efficacy of olanzapine in the treatment of adolescents with bipolar illness suffering from a manic or mixed episode. A third study compared olanzapine, risperidone and haloperidol use in psychotic youths; the study found olanzapine's effectiveness to be comparable to both haloperidol and risperidone. A final study of olanzapine, risperidone, and molindone noted that both AAAs did not have superiority to molindone in treating early onset schizophrenia spectrum disorders. That study also found that olanzapine showed the greatest amount of weight gain. Olanzapine may provide benefit to patients suffering from PDDs, based on the results of open-label trials and 1 small RCT. Olanzapine may be an effective intervention for patients with anorexia and other eating disorders. Case reports and small open-label trials indicate that olanzapine may be effective in reducing tic severity in youths with Tourette's syndrome. Although olanzapine is also available as an intramuscular preparation, limited data exists about its use in youths. While the AACAP recognizes the recent double-blind studies and data about short-term efficacy and tolerability of olanzapine in the treatment of youths with mania or schizophrenia, there is a paucity of published long-term safety data. This is particularly important based on the propensity of olanzapine to cause weight gain of a substantive magnitude.
- **Quetiapine:** One double-blind study found that in adolescents with mania, treatment with quetiapine plus divalproex sodium was associated with greater symptom reduction than treatment with quetiapine plus placebo. In an acute, double-blind, placebo-controlled study, efficacy of quetiapine has been reported in children and adolescents with bipolar mania. Another placebo-controlled study has found that quetiapine has efficacy in adolescent schizophrenia. Open-label trials have noted potential benefit for aggression in conduct disorder, psychosis, mania, and tic disorders. Two reports in patients with PDD suggested sub-optimal effectiveness but another report suggested more positive findings in this patient population. A case report of improvement of OCD symptoms with quetiapine has been reported. Long-term studies of quetiapine in youths found that it was reasonably safe and associated with satisfactory clinical outcomes.¹

- **Ziprasidone:** A double-blind, placebo-controlled trial reported that low doses (20-40mg per day) of ziprasidone was superior to placebo in the treatment of 28 patients ages 7-17 years with Tourette's syndrome. Another double-blind, placebo-controlled study reported efficacy for ziprasidone in the treatment of manic or mixed episodes in youths suffering from bipolar I disorder. However, an industry-sponsored trial of ziprasidone for early-onset schizophrenia was stopped due to concerns over lack of efficacy. Case series have reported improvement associated with ziprasidone therapy for youths with a variety of neuropsychiatric conditions, including schizophrenia, autism/PDD, major depression with psychosis, bipolar disorder, and psychosis. Case reports of a small number of youths treated with intramuscular ziprasidone have also described positive clinical outcomes without significant side effects.¹ Ziprasidone does not have FDA approval in children and adolescents.
- **Aripiprazole:** Preliminary studies suggest that patients with mania, conduct disorder with aggression, and PDD/autism might benefit from treatment with aripiprazole. Studies describe efficacy for aripiprazole in both youths ages 10-17 suffering from manic or mixed states, adolescents ages 13-17 suffering from schizophrenia, and children with irritability associated with autistic disorder.¹

PROFESSIONAL ORGANIZATIONS

The American Academy of Child and Adolescent Psychiatry (AACAP) *Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents* recommends that “dosing of AAAs [atypical antipsychotic agents] should follow the ‘start low and go slow’ approach and seek to find the lowest effective dose.” The AACAP *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Schizophrenia* calls for “adequate dosages” of antipsychotic medications and states that “instituting large dosages during the early part of treatment generally does not hasten recovery ... the medication dosage should be periodically reassessed to ensure that the lowest effective dose is being used.”¹ The AACAP outlined the following recommendations for best assessment and treatment practices (stated in accordance with the strength of the underlying empirical and/or clinical support):¹

Recommendation 1. Prior to the initiation of and during treatment with atypical antipsychotic agents (AAA), the general guidelines that pertain to the prescription of psychotropic medications should be followed.[#]

NOTE: While there are certain considerations that apply specifically to the use of AAAs in youths, the AACAP *Practice Parameter on the Use of Psychotropic Medication in Children and Adolescents* presents a series of principles to guide the clinician when using psychotropic medications in children and adolescents.² The *Practice Parameter* outlines the following principles: careful diagnostic assessment, attention to comorbid medical conditions, a review of other drugs the patient is being prescribed, the creation of a multi-disciplinary plan, including education and psychotherapeutic interventions for the treatment and monitoring of improvement, and a thorough discussion of the risks and benefits of psychotropic treatment with both the youth and their guardians. For the *Practice Parameter on the Use of Psychotropic Medication in Children and Adolescents*, visit [http://www.jaacap.com/article/S0890-8567\(09\)60156-8/pdf](http://www.jaacap.com/article/S0890-8567(09)60156-8/pdf).

Recommendation 2. When selecting any AAA for use in a child or adolescent, the clinician should follow the most current available evidence in the scientific literature.[#]

Recommendation 3. Due to the specific risks associated with the use of AAAs, additional factors to address, prior to the initiation of treatment with the AAAs, include obtaining a personal and family history of diabetes and hyperlipidemia, seizures and cardiac abnormalities, as well as any family history of previous response or adverse events associated with AAAs.[#]

Recommendation 4. Dosing of the AAAs should follow the “start low and go slow” approach and seek to find the lowest effective dose, recognizing that dosing may differ based on the targeted symptoms and patient diagnosis.[^]

Recommendation 5. Target dosing should be supported by current literature; will vary depending on condition being treated.[^]

Recommendation 6. If side effects do occur, a trial at a lower dose should be considered; however, certain side effects may preclude further treatment with the specific AAA.[^]

Recommendation 7. The use of multiple psychotropic medications in refractory patients may, at times, be necessary but has not been studied rigorously and clinicians should proceed with caution.[%]

Recommendation 8. The simultaneous use of multiple AAAs has not been studied rigorously and generally should be avoided.[!]

Recommendation 9. After the failure of one AAA the selection of an alternative medication may include consideration of another AAA and/or a medication from a different class of drugs.[!]

Recommendation 10. The acute and long-term safety of these medications in children and adolescents has not been fully evaluated and therefore careful and frequent monitoring of side effects should be performed.[^]

Recommendation 11. BMI should be obtained at baseline and monitored at regular intervals throughout treatment with an AAA.[#]

Recommendation 12. Careful attention should be given to the increased risk of developing diabetes with the use of AAA, and blood glucose levels and other parameters should be obtained at baseline and monitored at regular intervals.[#]

Recommendation 13. In those patients with significant weight changes and/or a family history indicating high risk, lipid profiles should be obtained at baseline and monitored at regular intervals.[^]

Recommendation 14. Measurements of movement disorders utilizing structured measures, such as the Abnormal Involuntary Movement Scale, should be done at baseline and at regular intervals during treatment and during tapering of the AAA.[#]

Recommendation 15. Due to limited data surrounding the impact of AAAs on the cardiovascular system, regular monitoring of heart rate, blood pressure and EKG changes should be performed.[^]

Recommendation 16. Although there is a relationship between AAA use and elevations of prolactin, the current state of evidence does not support the need for routine monitoring of prolactin levels in asymptomatic youths.[%]

Recommendation 17. Due to drug-specific risks, additional monitoring should be considered for specific AAAs.[^]

Recommendation 18. The limited long-term safety and efficacy data warrants careful consideration, before the initiation of medication, of the planned duration of the medication trial.[^]

Recommendation 19. Abrupt discontinuation of a medication is not recommended.[#]

[#] Clinical Standard, [^] Clinical Guideline, [%] Option, [!] Not Endorsed

The full AACAP Practice Parameter is available at

https://www.aacap.org/App_Themes/AACAP/docs/practice_parameters/Atypical_Antipsychotic_Medications_Web.pdf.

SPECIAL CONSIDERATIONS

Although some evidence supports the efficacy of antipsychotics in youth for certain narrowly defined conditions, less is known about the safety and effectiveness of antipsychotic prescribing patterns in community use (e.g., combinations of medications, off-label prescribing, dosing outside of recommended ranges). Children and adolescents prescribed antipsychotics are more at risk for serious health concerns, including weight gain, extrapyramidal side effects, hyperprolactinemia and some metabolic effects.³ In general, the field lacks high-quality research on outcomes and side effects associated with the use of higher-than-recommended doses of antipsychotics. Worrisome adverse effects of

atypical antipsychotics have been documented even at low doses, including excessive weight gain, resulting in obesity, large increases in prolactin and higher risk of extrapyramidal side effects, including tardive dyskinesia. Girls treated with certain antipsychotics may also be at increased risk for gynecological problems⁴ and osteoporosis⁵. Studies of atypical antipsychotics in youth have demonstrated equal or worsening response when higher doses are compared with lower doses.^{6,7,8} Research has demonstrated that the pharmacokinetics of antipsychotics may vary by developmental stage.³ This finding suggests that higher-than-recommended dosing of antipsychotics may pose differing risks for children and adolescents, compared with adults.

Atypical antipsychotics have the greatest mean prescription cost (\$132) of any psychotropic medication⁹ and are the most costly drug class within the Medicaid program.¹⁰ A review of 55 studies found no evidence that higher doses of antipsychotics were associated with better response¹¹; therefore, using higher than recommended doses of antipsychotics poses an increase in the cost of treatment without evidence that it is more effective for the patient. Additionally, there are substantial long-term costs of treating the health impact associated with antipsychotic medications, including treatment of obesity, diabetes and dyslipidemias. There is some evidence that these health conditions, such as new onset diabetes, do not resolve after discontinuation of the antipsychotic.¹² Although this is an understudied area, it is reasonable to assume that unresolved health impact of antipsychotics would be associated with long-term increases in health costs established for obesity and diabetes due to other causes.

PRESCRIBING GUIDANCE

American Psychiatric Association (APA)

The APA created a workgroup consisting of members from the Council on Research and Quality Care (CRQC). The following highlights were published to accompany the APA's recommendations noted above:¹³

- 1. Don't prescribe antipsychotic medications to patients for any indication without appropriate initial evaluation and appropriate ongoing monitoring.** Metabolic, neuromuscular and cardiovascular side effects are common in patients receiving antipsychotic medications for any indication, so thorough initial evaluation to ensure that their use is clinically warranted, and ongoing monitoring to ensure that side effects are identified, are essential. Components of an initial evaluation include:
 - A thorough assessment of possible underlying causes of target symptoms including general medical, psychiatric, environmental or psychosocial problems;
 - Consideration of general medical conditions; and
 - Assessment of family history of general medical conditions, especially of metabolic and cardiovascular disorders.

Ongoing monitoring includes re-evaluation and documentation of dose, efficacy and adverse effects; and targeted assessment, including assessment of movement disorder or neurological symptoms; weight, waist circumference and/or BMI; blood pressure; heart rate; blood glucose level; and lipid profile at periodic intervals.
- 2. Don't routinely prescribe two or more antipsychotic medications concurrently.** Research shows that use of two or more antipsychotic medications occurs in 4 to 35% of outpatients and 30 to 50% of inpatients. However, evidence for the efficacy and safety of using multiple antipsychotic medications is limited, and risk for drug interactions, noncompliance and medication errors is increased. Generally, the use of two or more antipsychotic medications concurrently should be avoided except in cases of three failed trials of monotherapy, which included one failed trial of Clozapine where possible, or where a second antipsychotic medication is added with a plan to cross-taper to monotherapy.
- 3. Don't routinely prescribe antipsychotic medications as a first-line intervention for children and adolescents for any diagnosis other than psychotic disorders.** There are both on and off label clinical indications for antipsychotic use in children and adolescents. FDA approved and/or evidence supported indications for antipsychotic medications in children and adolescents include psychotic disorders, bipolar disorder, tic disorders, and severe irritability in children with autism spectrum disorders; there is increasing evidence that antipsychotic medication may be useful for some disruptive behavior disorders. Children and adolescents should

be prescribed antipsychotic medications only after having had a careful diagnostic assessment with attention to comorbid medical conditions and a review of the patient's prior treatments. Efforts should be made to combine both evidence-based pharmacological and psychosocial interventions and support. Limited availability of evidence based psychosocial interventions may make it difficult for every child to receive this ideal combination. Discussion of potential risks and benefits of medication treatment with the child and their guardian is critical. A short and long term treatment and monitoring plan to assess outcome, side effects, metabolic status and discontinuation, if appropriate, is also critical. The evidence base for use of atypical antipsychotics in preschool and younger children is limited and therefore further caution is warranted in prescribing in this population.

Florida Medicaid Drug Therapy Management Program for Behavioral Health at the University of South Florida (USF) ¹⁴

In collaboration with the Agency for Health Care Administration (AHCA), USF developed the *Florida Psychotherapeutic Medication Guidelines for Children and Adolescents*.

Children Under 6 Years Old

The guidelines note that the use of antipsychotic medications in preschoolers (children under six years old) which is generally "off-label", is not recommended and should only be considered under the most extraordinary circumstances. Disruptive aggression in autism is one such circumstance. Adequately powered studies have not been conducted in preschoolers. Before considering pharmacological treatment for preschoolers the following guidelines are strongly recommended:

- Perform a developmentally-appropriate, comprehensive psychiatric assessment with diagnoses, impairments, treatment target and treatment plans clearly identified and documented.
- Comprehensive assessment must include evaluation of parental psychopathology and treatment needs, as well as family functioning.
- Psychosocial treatments should precede the use of psychotropic medications and should continue if medications are prescribed.

Antipsychotic Dosing Information for Children under Age 6* * Should only be used under rare circumstances.

General Procedures for Monitoring Side Effects of Antipsychotic Medication in Children and Adolescents

Conduct side effect and metabolic assessments and laboratory tests that are clinically relevant, comprehensive, and based on established guidelines.

- Monitor for metabolic syndrome criteria when prescribing atypical antipsychotics, with three of five criteria met:
 - Waist circumference greater than 90% for age
 - BP if <10 years old, then >90% for blood pressure **OR** BP if > 10 years old then >130 systolic or >85 diastolic
 - Triglycerides greater than 150 or greater than 95% for age
 - HDL <40 or <5% for age
 - Fasting blood glucose >100 (If metabolic abnormalities, refer to primary care physician)
- Monitor for extrapyramidal side effects (EPS) associated with second-generation antipsychotic use utilizing at least one of the following:
 - The Abnormal Involuntary Movement Scale (AIMS)
 - The Extrapyramidal Symptom Rating Scale (ESRS)
 - Dyskinesia Identification System: Condensed User Scale (DISCUS)

NOTE: Links to measures listed above are available at <http://medicaidmentalhealth.org/resourcesLinks/diagnosticTreatmentScales.cfm>

- Provide accessible information to parents and families about identifying and managing side effects, including lifestyle and nutritional changes, monitoring labs, etc.

For additional information on levels of care for specific behavioral health conditions, consult the USF guidelines available at <http://www.medicaidmentalhealth.org> under “Child Guidelines”.

CHILDREN IN FOSTER CARE

Primary Care Providers (PCPs) play an important role and are in an excellent position to perform screenings of children for potential mental disorders. In addition, PCPs should be able to diagnose and treat relatively straightforward situations (e.g., uncomplicated ADHD, anxiety, or depression). Consideration should be given regarding the need for referral for counseling, psychotherapy, or behavioral therapy. Short courses and intensive skills oriented seminars may be beneficial in assisting PCPs in caring for children with mental disorders. Active liaisons with child psychiatrists who are available for phone consultation or referral can also be beneficial in assisting PCPs to meet the mental health needs of children.¹⁵

Multiple factors and barriers can complicate diagnosis for children in foster care. Similarly, caregivers and health providers may be faced with critical situations that require immediate decisions about the care to be delivered. Children may have:¹⁵

- Multiple needs, including those related to emotional or psychological stress.
- Experienced abusive, neglectful, serial or chaotic care taking environments.
- Limited or no birth family history.
- Presented with a fluidity of different symptoms over time reflective of past traumatic and reactive attachment difficulties that may mimic many overlapping psychiatric disorders.
- Difficulty establishing rapport with a provider.
- A lack of access due to geographic location to mental health professionals such as child psychiatrists.

Based on the reasons listed above, a need exists for treatment guidelines and parameters regarding the appropriate use of any psychotropic medications in foster children.¹⁵ Due to the complex issues involved in the lives of foster children, it is important that a comprehensive evaluation be performed before beginning treatment for a mental or behavioral disorder. Except in the case of an emergency, a child should receive a thorough health history, psychosocial assessment, mental status exam, and physical exam before the prescribing of any psychotropic medication. The role of non-pharmacological interventions should be considered before beginning any psychotropic medication, except in urgent situations such as suicidal ideation, psychosis, self-injurious behavior, physical aggression that is acutely dangerous to others, or severe impulsivity endangering the child or others; when there is marked disturbance of psychophysiological functioning (e.g., profound sleep disturbance), or when the child shows marked anxiety, isolation, or withdrawal. The FDA does not regulate physician and other health provider practice; the FDA has stated that it does “not limit the manner in which a practitioner may prescribe an approved drug.” Studies and expert clinical experience often support the use of a medication for an “off-label” use. Physicians should utilize the available evidence, expert opinion, their own clinical experience, and exercise their clinical judgment in prescribing what is best for each individual patient.¹⁵

MEASUREMENT OF COMPLIANCE

The following are measurements of compliance used by WellCare for NCQA accreditation purposes, pertaining to antipsychotic use in children:

Use of Multiple Concurrent Antipsychotics in Children and Adolescents (APC). The percentage of children and adolescents 1–17 years of age who were on two or more concurrent antipsychotic medications.

Use of First-Line Psychosocial Care for Children and Adolescents on Antipsychotics (APP). The percentage of children and adolescents 1–17 years of age who had a new prescription for an antipsychotic medication and had documentation of psychosocial care as first-line treatment.

Metabolic Monitoring for Children and Adolescents on Antipsychotics (APM). The percentage of children and adolescents 1–17 years of age who had two or more antipsychotic prescriptions and had metabolic testing.

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MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

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8/6/2015	<ul style="list-style-type: none"> • Approved by MPC. New.