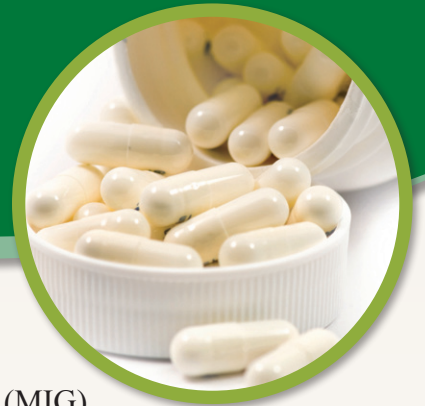


# Atypical Antipsychotic Medications: Use in Pediatric Patients



The Centers for Medicare & Medicaid Services (CMS), Medicaid Integrity Group (MIG) has identified issues with the utilization of the atypical antipsychotic drug therapy class. The U.S. Food and Drug Administration (FDA) approves product labeling for prescription drugs. The MIG has identified that some providers may have prescribed atypical antipsychotics outside of FDA-approved product labeling for indication, age, dosage, or duration of therapy. Therefore, CMS's goal is to improve quality of care and enhance patient safety by educating providers on the proper use of atypical antipsychotics in pediatric patients.

This fact sheet summarizes for providers the current FDA-approved product labeling for the use of atypical antipsychotic medications in pediatric patients. After reading this fact sheet, providers should be able to accurately:

- Describe the FDA-approved product labeling for the appropriate use of atypical antipsychotics in pediatric patients;
- Formulate treatment regimens that comply with FDA-approved product labeling; and
- Describe the adverse reactions and risks associated with atypical antipsychotic therapy in pediatric patients.

## FDA-Approved Indications for Atypical Antipsychotic Medications in Pediatric Patients

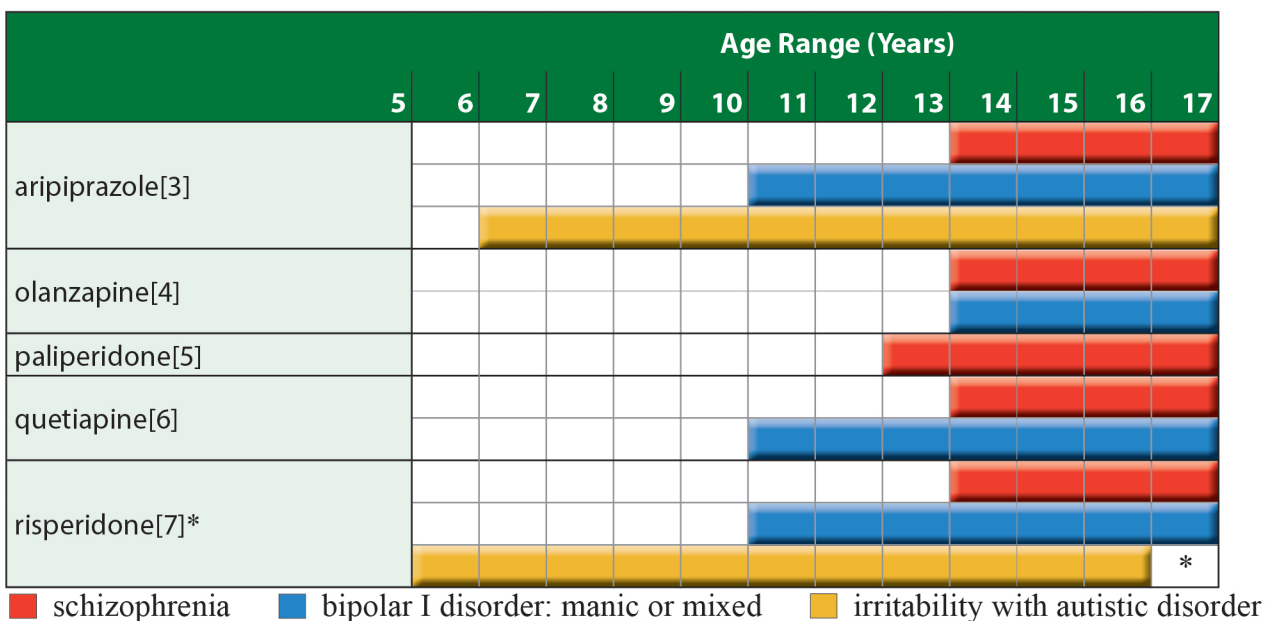
According to study results reported in an Agency for Healthcare Research and Quality (AHRQ) report, "The use of antipsychotic drugs for very young children with behavior problems approximately doubled between 1999-2001 and 2007." [2] Despite the widespread use, atypical antipsychotics are not FDA approved for children younger than five years old. Five atypical antipsychotics currently have FDA-approved indications for use in children and adolescents: aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone. The FDA-approved indications for atypical antipsychotics in pediatric patients are provided in Figure 1.

### Defining Pediatric Patients

For the purpose of this document, the term "pediatric patients" collectively includes children and adolescents. Children are further defined to be any patient younger than 12 years old and adolescents are defined to be any patient 13 to 17 years old. [1] The literature on atypical antipsychotics is fairly consistent with these age ranges as reflected in Figure 1.



**Figure 1. FDA-Approved Pediatric Age Ranges and Indications for Atypical Antipsychotics**



\*Risperidone should not be used by patients older than age 16 who have been diagnosed with irritability with autistic disorder.

## Atypical Antipsychotic Dosing in Pediatric Patients

Atypical antipsychotic dosing schedules are guided by the specific indication for use. The FDA-approved indications and dosages for atypical antipsychotics in pediatric patients are provided in the dosing table in the document “Atypical Antipsychotics: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Pediatric Patients.”

## Treatment Guidelines for the Use of Atypical Antipsychotics in Pediatric Patients

The Agency for Healthcare Research and Quality (AHRQ) hosts a database of treatment guidelines. Please search “atypical antipsychotics,” or any of the conditions for which an atypical antipsychotic is an indicated treatment, in the AHRQ’s National Guideline Clearinghouse at <http://www.guideline.gov> for information on the available treatment guidelines. The AHRQ is a branch of the U.S. Department of Health and Human Services.

## Off-Label Use of Atypical Antipsychotics in Pediatric Patients

Atypical antipsychotic use in pediatric patients has increased. More than three-fourths of youths on Medicaid are taking one of these medications for an indication that is not FDA approved. Atypical antipsychotics are being used to treat attention-deficit/hyperactivity disorder (ADHD) and aggressive behavior.[8]

An AHRQ report titled “Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics” was published in 2007.[9] In September 2011, the AHRQ released an update titled “Off-Label Use of Atypical Antipsychotics: An Update.” According to the 2011 update, children taking antipsychotic medications receive an atypical antipsychotic 90 percent of the time and in the majority of patients the use is for an off-label indication. There are few clinical trials using atypical antipsychotics for off-label indications in pediatric patients. Additional research needs to be done to show safety and efficacy in this patient population.[10] Links to the 2007 report and the 2011 update are available at <http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=778&PCem=EN> on the AHRQ website.

## Adverse Reactions and Risks of the Use of Atypical Antipsychotics in Pediatric Patients

Patients, parents, and caregivers should be made aware of the risks of taking an atypical antipsychotic prior to initiating therapy. Because atypical antipsychotic medications are associated with significant weight gain and metabolic changes, a baseline for weight should be established and the patient should be routinely monitored for weight and metabolic changes.[11] Specific recommendations for monitoring, when indicated, are provided in the prescribing information for each medication. Other common adverse reactions are:

- Sedation;
- Orthostatic hypotension;
- Tachycardia;
- Menstrual problems;
- Blurred vision;
- Skin rashes; and
- Sun sensitivity.[12]

Prescribing information for all atypical antipsychotics warns against their use in pediatric patients with a history of seizure disorders, since these medications may lower seizure threshold. Safety and efficacy in pediatric patients have not been established for asenapine, clozapine, iloperidone, lurasidone, and ziprasidone.

### Aripiprazole

The incidence of events related to extrapyramidal side effects (EPS) in adults diagnosed with schizophrenia who were being treated with aripiprazole monotherapy was 13 percent versus 12 percent for placebo. In pediatric patients (13 to 17 years old) who were treated with aripiprazole, the percentage of EPS-related events was 25 percent versus 7 percent for placebo.[13]

Aripiprazole is not indicated as monotherapy for major depressive disorder in any population. It can increase the risk of suicidal thinking in children, adolescents, and young adults (18 to 24 years old).[14]

#### ACRONYMS

<b>ADHD</b>	attention-deficit/hyperactivity disorder
<b>AHRQ</b>	Agency for Healthcare Research and Quality
<b>CDER</b>	Center for Drug Evaluation and Research
<b>CMS</b>	Centers for Medicare & Medicaid Services
<b>EPS</b>	extrapyramidal side effects
<b>FDA</b>	U.S. Food and Drug Administration
<b>MDD</b>	major depressive disorder
<b>MIG</b>	Medicaid Integrity Group
<b>OTC</b>	over the counter



### **Olanzapine**

Adolescents who take olanzapine have an increased potential for weight gain and hyperlipidemia compared with adult patients who take olanzapine. Prescribing information for olanzapine states: “Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents.”[15]

### **Paliperidone**

Metabolic changes such as weight gain have been associated with paliperidone. A baseline hemoglobin A1c (HgA1c) level, blood glucose level, and lipid panel should be obtained, and periodic monitoring of a patient’s weight is recommended.[16]

### **Quetiapine**

In clinical trials for quetiapine, an increased risk of hypertension exists for pediatric patients. Baseline blood pressure and periodic monitoring is recommended in children and adolescents.[17]

### **Risperidone**

Weight gain is a documented side effect of risperidone in adolescents diagnosed with schizophrenia. In one open-label study, 14 percent of the adolescents experienced an average weight gain of 9 kg (about 20 pounds) during 8 months of risperidone treatment, with much of the weight gain occurring during the first 6 months of treatment. When a patient is taking risperidone, monitoring weight gain and related factors against normal development patterns is recommended.[18]





## Risk of Suicidality

The atypical antipsychotics aripiprazole and quetiapine are FDA approved for the treatment of depression episodes in bipolar I disorder or as adjunctive treatment for major depressive disorder in adults. Antidepressant medications have been shown to increase the risk of suicidal thinking and behavior. In a pooled-analysis of short-term, placebo-controlled trials of nine antidepressant medications, patients taking an antidepressant had twice the risk of suicidality in the first few months of treatment than those taking placebo. The long-term risk is unknown. As a result of this analysis, a boxed warning was added to all antidepressant medications since the risk was not confined to one class of antidepressants.[19] Even though aripiprazole and quetiapine are not FDA approved for the treatment of depression episodes in bipolar I disorder or as adjunctive treatment for major depressive disorder in pediatric patients, the risk of suicidality may still be present.

The boxed warning for aripiprazole, quetiapine, and olanzapine (when used in combination with fluoxetine) states:[20]

### SUICIDALITY AND ANTIDEPRESSANT DRUGS

**Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.**

The FDA also requires that a Medication Guide be provided with each aripiprazole, olanzapine, or quetiapine prescription to alert patients to the risk of suicidal thinking and behavior. Each Medication Guide also includes information on precautions that may be taken.[21] Links to the required Medication Guides can be found at <http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm> on the FDA website.





## Resources

Please visit <http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-State/By-State.html> for links to State Medicaid program websites.

The Center for Drug Evaluation and Research (CDER) hosts a website providing health professionals with current information on over-the-counter (OTC) and prescription drugs. Visit <http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals> to access drug-related databases, information on drug recalls and alerts, current information on new and generic drug approvals, and information on drug safety and availability.

Section 1927(g)(1)(B) of the Social Security Act identifies the predetermined standards that the State's drug use review program must use to assess data on drug use. Visit [http://www.ssa.gov/OP\\_Home/ssact/title19/1927.htm](http://www.ssa.gov/OP_Home/ssact/title19/1927.htm) for information on the compendia.

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