

Stimulant and Related Medications: Use in Pediatric Patients



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

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

- Identify the FDA-approved indications for the use of stimulant and related medications in pediatric patients;
- Identify the available treatment guidelines for the management of attention-deficit/hyperactivity disorder (ADHD) in pediatric patients; and
- Summarize the adverse reactions and risks of using stimulant and related medications in pediatric patients.

Defining Pediatric Patients

For the purpose of this document, the term "pediatric patients" collectively includes infants, children, and adolescents younger than 18 years old. Infants are further defined to be any patient younger than 1 year old.

The literature on stimulant and related medications does not have well-defined age ranges for pediatric patients. Some studies define children as patients 1 to 12 years old and adolescents as patients 13 to 17 years old. Other studies define children as patients 1 to 17 years old. The ages of the patients were also inconsistent in the clinical trials conducted for medication approval. This inconsistency is reflected in the age ranges in Figure 1 and in the dosing table in the document "Stimulant and Related Medications: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Pediatric Patients."



FDA-Approved Indications for Stimulant and Related Medications in Pediatric Patients

Stimulant and related medications are FDA approved for the treatment of ADHD, narcolepsy, and exogenous obesity (a body mass index [BMI] at or above the 95th percentile for children of the same age and sex[1]) in pediatric patients. However, not all of the medications in this drug class are approved for each indication. Stimulant and related medications are most often used for the treatment of ADHD. The FDA-approved indications and age ranges for the use of stimulant and related medications in pediatric patients are provided in Figure 1.

Figure 1. FDA-Approved Pediatric Age Ranges and Indications for Stimulant and Related Medications

	Age Range (Years)														
	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
amphetamine/dextroamphetamine mixed salts[2]															
amphetamine/dextroamphetamine mixed salts ER[3]															
atomoxetine[4]															
benzphetamine[5, 6]															
clonidine ER[7]															
dexmethylphenidate[8]															
dextroamphetamine[9]															
dextroamphetamine SR[10]															*
guanfacine ER[11]															
lisdexamfetamine[12]															
methamphetamine[13]															
methylphenidate [14, 15, 16, 17, 18, 19, 20, 21, 22]															

■ ADHD ■ narcolepsy ■ exogenous obesity

ER = extended-release SR = sustained-release

* Dextroamphetamine extended-release (Dexedrine® Spansule®) is not approved for the treatment of ADHD in patients older than 16 years old.

Diagnosing Attention-Deficit/Hyperactivity Disorder

It is important that a diagnosis for ADHD be established prior to starting medication therapy. The criteria for the diagnosis of ADHD are defined in the “Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).” The American Academy of Pediatrics (AAP) states that information about the patient’s behavior should be obtained from family members, teachers, coaches, and other caregivers.[23]

The criteria for the diagnosis of ADHD can be found at <http://www.cdc.gov/ncbddd/adhd/diagnosis.html> on the Centers for Disease Control and Prevention (CDC) website. Symptoms of inattention, hyperactivity, or impulsivity must have been present by age 12 to diagnose ADHD. According to the DSM-5 criteria, a proper diagnosis also requires that symptoms be present in two or more settings: work, home, school, or social environments.[24] Providers should be aware that the 2015 updates to most ADHD drug labels still reference DSM-4 criteria, and they should consider the updated DSM-5 criteria the current standard.

Medications for the Treatment of Attention-Deficit/Hyperactivity Disorder in Pediatric Patients

Stimulant medications have been the mainstay of treatment for ADHD since the late 1930s.[25] Other nonstimulant medications, such as atomoxetine, extended-release clonidine, and extended-release guanfacine, are also FDA approved for the treatment of ADHD in pediatric patients. The FDA-approved indications and dosages for stimulant and related medications are provided in the document “Stimulant and Related Medications: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Pediatric Patients” available at <https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/stimulant-education.html> on the CMS website.

Stimulant Medications

The exact mechanism by which stimulant medications exert their effects in ADHD is unknown. They are thought to work by increasing the neurotransmission of dopamine and norepinephrine.[26, 27] Stimulant medications come in multiple dosage forms and strengths and are equally effective in the treatment of ADHD; however, individual response may vary.[28]

Treatment in older children and adolescents may be initiated with either a short-acting or long-acting stimulant medication. Short-acting stimulant medications may be easily titrated to dosages that produce symptom relief with manageable adverse reactions. They are often used as the initial treatment for children weighing less than 16 kg.

ACRONYMS

AACAP	American Academy of Child and Adolescent Psychiatry
AAP	American Academy of Pediatrics
ADHD	attention-deficit/hyperactivity disorder
AHRQ	Agency for Healthcare Research and Quality
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CMS	Centers for Medicare & Medicaid Services
DSM-4	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FDA	U.S. Food and Drug Administration
MIG	Medicaid Integrity Group
MPIE	Medicaid Program Integrity Education over the counter
OTC	

Atomoxetine

Atomoxetine was the first nonstimulant approved by the FDA for the treatment of ADHD[29] and is an option for patients who cannot take a stimulant medication. It inhibits presynaptic norepinephrine transport, which is thought to be the mechanism responsible for the therapeutic effects in ADHD, and studies have shown it is superior to placebo in the treatment of ADHD. Atomoxetine is not a controlled substance so it has a lower potential for substance abuse. It also has a long duration of action, which allows for once-a-day dosing.[30]

Clonidine and Guanfacine

Two nonstimulant drugs, clonidine and guanfacine, are indicated for monotherapy or adjunctive treatment with a stimulant drug for ADHD. Only the extended-release formulations of the respective drugs are approved to treat ADHD. Clonidine is a centrally acting alpha₂-adrenergic agonist. Guanfacine is a central alpha_{2A}-adrenergic receptor agonist. The immediate-release formulations of these drugs are used to treat hypertension, but they cannot be substituted for the extended release formulations to treat ADHD. Because of the cardiovascular use, however, both drugs also have related warnings about use in patients at risk for hypotension, heart block, bradycardia, syncope, other vascular diseases (including of the heart and brain), cardiac conduction abnormalities, and chronic renal failure. Establish a baseline for heart rate and blood pressure and monitor periodically, especially after initiation and dose increases.

Both drugs also have warnings about somnolence and sedation, especially when used with a central nervous system depressant. [31, 32]

Treatment Guidelines for Attention-Deficit/Hyperactivity Disorder

The standard of care for the treatment of ADHD is determined by guidelines. One of the treatment guidelines most often used in clinical practice was developed by the AAP. Other organizations and health care systems have also developed guidelines focused on the treatment of ADHD in children and adolescents. Search “ADHD” in the National Guideline Clearinghouse database at <https://www.guideline.gov> for information on some of the ADHD guidelines. The database is hosted by the Agency for Healthcare Research and Quality (AHRQ), a branch of the United States Department of Health and Human Services. Some of the treatment guidelines for the use of stimulant and related medications in pediatric patients are provided in Table 1.

Table 1. Treatment Guidelines for the Use of Stimulant and Related Medications in Pediatric Patients

Sponsoring Organization	Title of Guideline	Link to Guideline
National Institute for Health and Clinical Excellence	Attention deficit hyperactivity disorder. Diagnosis and management of ADHD in children, young people and adults. [2013]	https://www.guideline.gov/content.aspx?id=14325
American Academy of Pediatrics	ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. [2011]	https://www.guideline.gov/content.aspx?id=36881

Adverse Reactions and Risks of the Use of Stimulant and Related Medications in Pediatric Patients

Stimulant and related medications are generally well tolerated. The most common adverse reactions to stimulant and related medications are loss of appetite, upset stomach, insomnia, and headache. Other less common adverse effects include rebound irritability, dysphoria, agitation, tics, and growth impairment.[33, 34, 35] Because of the warnings associated with stimulant and related medications, the risks must be weighed against the potential benefits before they are prescribed to pediatric patients.

Patients may experience increases in heart rate and blood pressure as a result of the sympathomimetic properties of stimulant medications. These cardiovascular effects have also been reported with atomoxetine.[36]

Cardiovascular Risks with Stimulant Medications and with Atomoxetine

Sudden death, stroke, and myocardial infarction have been reported with stimulant medications and with atomoxetine. Patients should have a medical history and physical exam conducted prior to the initiation of therapy to assess cardiac disease, including family history of sudden cardiac death, family history of ventricular arrhythmia, or structural cardiac abnormalities. Patients with preexisting cardiac conditions should avoid the use of stimulant medications and the use of atomoxetine. The manufacturers of stimulant and related medications recommend a cardiac evaluation for any patient who presents with cardiac symptoms.[37, 38]

The FDA and AHRQ sponsored a study on the cardiovascular risks associated with ADHD medications in children and young adults (2 to 24 years old). More than 1.2 million patient records were evaluated. Results showed no association between the use of stimulant medications and adverse cardiovascular events. However, the FDA encourages periodic monitoring of heart rate and blood pressure and encourages avoiding the use of stimulant medications in patients with serious heart problems.[39]

In 2007, the FDA instructed the manufacturers of medications approved for the treatment of ADHD to develop Medication Guides to be dispensed with every new or refilled prescription. The Medication Guides inform patients, parents, and caregivers about the possible cardiovascular risks and precautions that they may take to minimize the risks. The Medication Guides were recently updated to include information regarding circulatory problems.[40]

Peripheral Vasculopathy, Including Raynaud's Phenomenon

In June 2013, the FDA published MedWatch drug safety labeling changes as a result of postmarketing reports of circulatory problems in fingers and toes associated with stimulant medications and atomoxetine. The FDA recommends instructing patients who are beginning treatment with these medications about the risks of peripheral vasculopathy, including Raynaud's phenomenon and the associated signs and symptoms. The Medication Guides have been revised to include this drug safety information as well.[41]

Risk of Priapism with Methylphenidate Products

In December 2013, the FDA published a Drug Safety Communication to warn that methylphenidate-containing products may cause priapism in pediatric and adult patients. Events occurred most frequently in patients on established drug therapy undergoing dose escalation, but were also reported during withdrawal periods (drug holidays or discontinuation). The FDA cautions individuals who experience abnormally sustained or frequent and painful erections lasting more than four hours to seek immediate medical attention.[42]

Permanent Loss of Skin Color with Daytrana® Patch

The FDA recently issued a warning about permanent loss of skin color (chemical leukoderma) in patients who use the Daytrana methylphenidate transdermal patch for the treatment of ADHD. Affected areas have been as large as 8 inches in diameter. The condition is not physically harmful, but the discoloration of skin may cause emotional distress in patients. If this occurs, the patient should not remove the patch until discussing an alternate therapy regimen with their provider.[43]

Rhabdomyolysis with Stimulant Drugs

In April 2015, the FDA required all stimulant manufacturers to add rhabdomyolysis to the Adverse Reactions section of the respective drugs' prescribing information. Rhabdomyolysis is the breakdown of muscle tissue, which is then released into the blood stream. This can cause kidney damage. Symptoms include dark, red, or cola-colored urine, decreased urine output, general weakness, and various muscle problems, including stiffness, aching, and tenderness.[44, 45]

Risk of Psychiatric Adverse Events

An FDA review of stimulant medications showed an increase in the risk of medication-related psychiatric events, such as hearing voices or experiencing mania. The previously mentioned Medication Guides also inform patients, parents, and caregivers about the risks of adverse psychiatric symptoms associated with stimulant and related medications.[46]

Growth Suppression

Growth suppression with long-term use of stimulant medications is an area of controversy. Studies have shown mixed results. A follow-up study on methylphenidate suggests that children who are continuously treated with the medication experience a temporary decrease in growth rate without evidence of growth rebound during this period of development; however, there is inadequate data to determine whether chronic amphetamine use may cause similar suppression. The study recommends that growth should be monitored during treatment and to suspend treatment in patients who are not achieving expected growth or weight gain. [47] In two studies referenced in a Surgeon General report, there were no long-term effects of stimulant medications on height or weight.[48]

Abuse of Stimulant Medications

Stimulant medications have significant abuse potential. Prescribing information warns of the high potential for abuse and also warns that extended use may lead to drug dependence. Stimulant medications with an FDA-approved indication should only be taken by patients for whom they have been prescribed.[49] A boxed warning has been added to stimulant medications due to their high potential for dependence and abuse.

The boxed warning for amphetamine and amphetamine derivatives states:[50]

WARNING: POTENTIAL FOR ABUSE

Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence. Pay particular attention to the possibility of subjects obtaining amphetamines for nontherapeutic use or distribution to others and the drugs should be prescribed or dispensed sparingly [see DRUG ABUSE AND DEPENDENCE (9)].

Misuse of amphetamine may cause sudden death and serious cardiovascular adverse reactions.

The boxed warning for methylphenidate and methylphenidate derivatives is similar to the boxed warning for amphetamines. However, it informs providers to use caution when prescribing methylphenidate to patients with a history of drug dependence or alcoholism.

The boxed warnings for methylphenidate medications are very similar to each other. The boxed warning for one of the methylphenidate medications states:[51]

DRUG DEPENDENCE

CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Hepatotoxicity with Atomoxetine

Atomoxetine has been shown to cause severe liver injury manifested by significantly elevated bilirubin concentrations and hepatic enzymes. Prescribing information states “**STRATTERA should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted.**”[52] This bolded warning was added after reports that two patients developed severe liver injuries, which resolved after the medication was discontinued.[53]

Suicidality with Atomoxetine

An increased risk of suicidality (suicidal thinking and behavior) in children and adolescents has been identified through an analysis of placebo-controlled trials that included more than 2,200 patients. There was an increased risk of suicidal thinking in patients treated with atomoxetine. A boxed warning was added to the product information for atomoxetine.

The boxed warning for atomoxetine states:[54]

WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS

STRATTERA (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of STRATTERA in a child or adolescent must balance this risk with the clinical need. Co-morbidities occurring with ADHD may be associated with an increase in the risk of suicidal ideation and/or behavior. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. STRATTERA is approved for ADHD in pediatric and adult patients. STRATTERA is not approved for major depressive disorder.

Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of STRATTERA in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving STRATTERA compared to placebo. The average risk of suicidal ideation in patients receiving STRATTERA was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials [see Warnings and Precautions (5.1)].

The FDA also requires that a Medication Guide be dispensed with every new or refilled prescription for atomoxetine. The Medication Guide informs patients, parents, and caregivers about the increased risk of suicidal thinking and behavior with atomoxetine.[55]

Resources

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

The FDA requires that a Medication Guide be issued with some medications to provide patients with information on serious adverse effects and recommendations on how to avoid them. Links to the required Medication Guides can be found at <http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm> on the FDA website.

A BMI calculator for use with children and teens (from 2 to 19 years old) can be found at <http://nccd.cdc.gov/dnpabmi/Calculator.aspx> on the CDC website.

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 for information on the compendia.

To see the electronic version of this fact sheet and the other products included in the “Stimulants and Related Medications” Toolkit, visit the Medicaid Program Integrity Education page at <https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/pharmacy-ed-materials.html> on the CMS website.

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