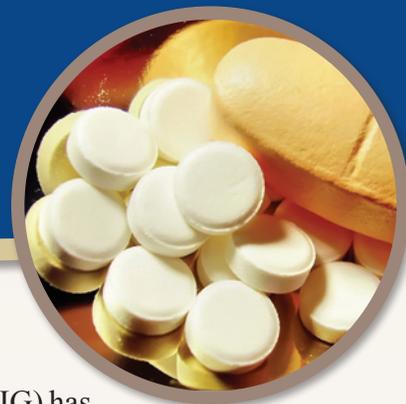


Stimulant and Related Medications: Use in Adults



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's goal is to improve quality of care and enhance patient safety by educating providers on the proper use of stimulant and related medications in adults.

This fact sheet summarizes for providers the current FDA-approved product labeling for the use of stimulant and related medications in adults. 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 adults;
- Identify the available treatment options for attention-deficit/hyperactivity disorder (ADHD) and narcolepsy in adults; and
- Summarize the adverse reactions and risks of stimulant and related medications.

FDA-Approved Indications for Stimulant and Related Medications in Adults

Stimulant and related medications are FDA approved for the treatment of ADHD, narcolepsy, exogenous obesity (a body mass index [BMI] of 30 or higher[1]), and as adjunct therapy for obstructive sleep apnea. However, not all of these medications are FDA approved for each indication. They are most often used by adults for the treatment of ADHD or narcolepsy.

Diagnosing Attention-Deficit/Hyperactivity Disorder in Adults

The diagnosis of ADHD in adults is difficult to make, since the diagnostic criteria in the “Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)” are specific to children.[2] 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.



ACRONYMS

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
DRESS	drug rash with eosinophilia and systemic symptoms
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
FDA	U.S. Food and Drug Administration
MIG	Medicaid Integrity Group
OTC	over the counter

Symptoms of diagnosed or undiagnosed ADHD can continue from childhood to adulthood.[3] Thus, adults presenting with suspected ADHD need to be evaluated for the presence of symptoms since childhood. Symptoms of inattention, hyperactivity, or impulsivity must have been present before seven years of age to diagnose ADHD. According to the DSM-IV criteria, a proper diagnosis also requires that impairment be present in at least two settings: work, home, school, or social environments.[4]

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

Stimulant medications have been the mainstay of treatment for ADHD since the late 1930s.[5] Atomoxetine is a nonstimulant medication that is FDA approved for the treatment of ADHD.

FDA-Approved Indications and Dosages

Several dosage formulations of stimulant medications are not FDA approved for use in adults. There are also some medications only approved for use in children, such as extended-release guanfacine and extended-release clonidine. As a result, FDA-approved treatment options are more limited for adults diagnosed with ADHD.

The FDA-approved dosages and indications for the use of stimulant and related medications in adults are provided in the document “Stimulant and Related Medications: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Adults.”

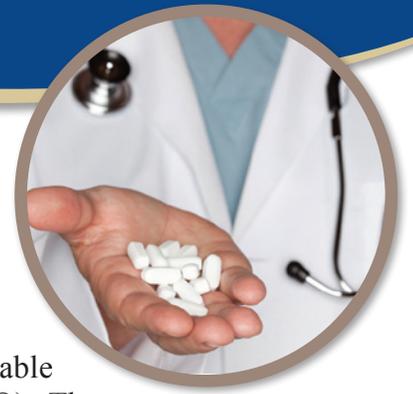
Stimulant Medications

The exact mechanism by which stimulant medications exert their effects in ADHD is unknown. Stimulant medications are thought to work by increasing the neurotransmission of dopamine and norepinephrine.[6, 7] Stimulant medications come in multiple dosage forms and strengths that are equally effective in the treatment of ADHD; however, individual patient response may vary.[8]

Treatment may be initiated with either a short-acting or long-acting stimulant medication. The short-acting stimulant medications may be easily titrated to dosages that produce symptom relief with manageable adverse reactions. However, adherence to treatment plans may improve with the use of a long-acting stimulant medication.

Atomoxetine

Atomoxetine was the first and remains the only nonstimulant approved by the FDA for the treatment of ADHD in adults[9] 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.[10]



Treatment Guidelines for the Use of Stimulant and Related Medications in Adults

The National Guideline Clearinghouse at <http://www.guideline.gov> is a searchable database hosted by the Agency for Healthcare Research and Quality (AHRQ). The AHRQ is a branch of the U.S. Department of Health and Human Services. Some of the treatment guidelines that direct the use of stimulant and related medications in adults are provided in Table 1 below.

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

Sponsoring Organization	Title of Guideline	Link to Guideline
European Federation of Neurological Societies	Management of narcolepsy in adults.	http://www.guideline.gov/content.aspx?id=34901
National Institute for Health and Clinical Excellence	Attention deficit hyperactivity disorder. Diagnosis and management of ADHD in children, young people and adults.	http://www.guideline.gov/content.aspx?id=14325

Adverse Reactions and Risks of the Use of Stimulant and Related Medications in Adults

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.[11, 12, 13] Increases in heart rate and blood pressure have also been seen as a result of the sympathomimetic properties of stimulant medications. Atomoxetine has been reported to cause a mild increase in blood pressure, which usually persists during treatment and resolves with discontinuation.

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 for 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.[14, 15]

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 recommends periodic monitoring of heart rate and blood pressure and avoiding use in patients with serious heart problems. Two more studies in adults are being reviewed to evaluate the risk of cardiovascular events with stimulant medications.[16]



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, families, and caregivers about the possible cardiovascular risks and the precautions that may be taken to minimize the cardiovascular risks.[17]

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, families, and caregivers about the risks of adverse psychiatric symptoms associated with stimulant and related medications.[18]

Abuse and Misuse of Stimulant Medications

Stimulant medications have significant abuse potential. Prescribing information warns about 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.[19]

A boxed warning has been added to stimulant medications due to their high potential for dependence and abuse.

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.

Hepatotoxicity with Atomoxetine

Atomoxetine has been shown to cause severe liver injury manifested by significantly elevated bilirubin concentrations and hepatic enzymes. Product information states, “**STRATTERA should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted.**”[22] This bolded warning was added after reports that two patients developed severe liver injury which resolved after the medication was discontinued.[23]

The boxed warning for amphetamine and amphetamine derivatives states:[20]

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NONTHERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

The boxed warning for one of the methylphenidate medications, which is very similar to the warnings for other methylphenidate medications, states:[21]

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.

Suicidality with Atomoxetine

An increased risk of suicidality (suicidal thinking) in children and adolescents has been identified through an analysis of placebo-controlled trials including more than 2,200 patients. There was an increased risk of suicidal thinking in patients treated with atomoxetine. As a result of this analysis, a boxed warning was added to the product information for atomoxetine. A similar analysis in adult patients found no increased risk of suicidal ideation or behavior with atomoxetine.[24]

The boxed warning for atomoxetine states:[25]

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 a Medication Guide be dispensed with every new or refilled prescription for atomoxetine. The Medication Guide informs patients, families, and caregivers about the increased risk of suicidal thinking and behavior with atomoxetine.[26]

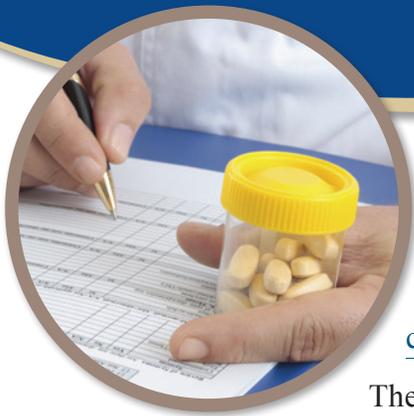
Risk of Serious Rash with Armodafinil and Modafinil

A serious rash has been reported with modafinil and armodafinil. The severity of the rash has required hospitalization and discontinuation of therapy. Stevens Johnson Syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported. A bolded warning has been added to the product information for armodafinil and modafinil to alert prescribers, patients, families, and caregivers of this rare but serious reaction.[27, 28]

Resources

Please 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 adults (20 years old and older) can be found at http://www.cdc.gov/healthyweight/assessing/bmi/adult_BMI/english_bmi_calculator/bmi_calculator.html 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.

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