

Antidepressant Medications: Use in Pediatric Patients



The Centers for Medicare & Medicaid Services (CMS), Medicaid Integrity Group (MIG) has identified issues with the utilization of the antidepressant 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 antidepressant 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 antidepressants in pediatric patients.

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

- Identify the FDA-approved indications for the use of antidepressant medications in pediatric patients;
- Identify the available treatment guidelines for use of antidepressant medications in pediatric patients; and
- Summarize the adverse reactions and risks of antidepressant medications.

FDA-Approved Indications for Antidepressant Medications in Pediatric Patients

Antidepressants are FDA approved to treat pediatric patients diagnosed with major depressive disorder (MDD), obsessive-compulsive disorder (OCD), or childhood enuresis. The results of a survey conducted by the Centers for Disease Control and Prevention and the National Center for Health Statistics (CDC/NCHS) showed that 4.8 percent of adolescents take an antidepressant medication.[1] Four of the selective serotonin reuptake inhibitors (SSRIs) have FDA-approved indications in pediatric patients: escitalopram, fluoxetine, fluvoxamine, and sertraline. Two of the tricyclic antidepressants (TCAs) have FDA-approved indications in pediatric patients: clomipramine and imipramine.

Defining Pediatric Patients

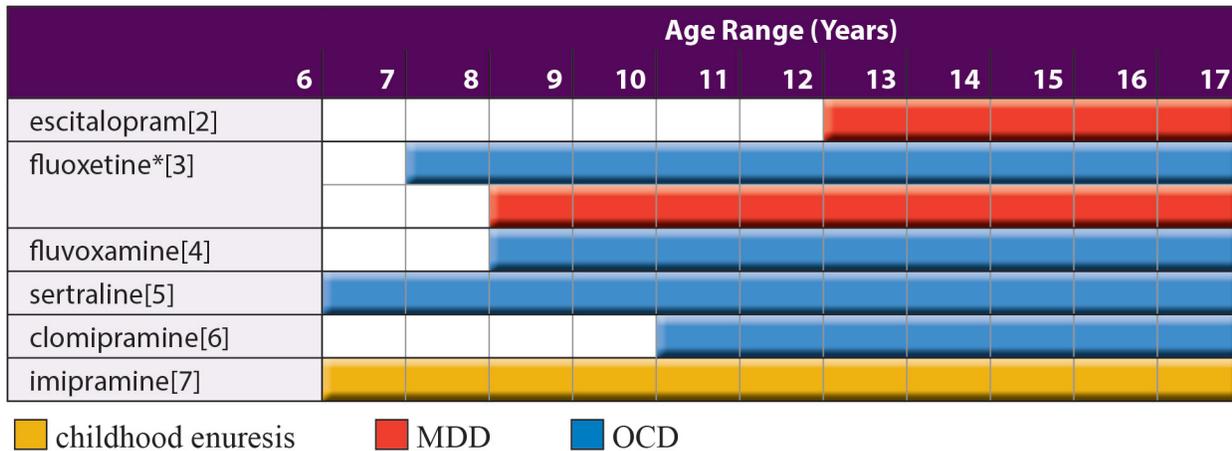
For the purpose of this document, the term “pediatric patients” collectively includes infants, children, and adolescents younger than 18 years old. Infants are further defined to be any patient younger than one year old.

The literature on antidepressant 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 patient ages 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 “Antidepressant Medications: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Pediatric Patients.”



FDA-approved indications vary by medication; therefore, a summary of the pediatric age ranges, indications, and the antidepressants approved to treat each indication are provided in Figure 1 below. The FDA-approved pediatric antidepressant indications and dosages are provided in the document “Antidepressant Medications: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Pediatric Patients.”

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



*Fluoxetine is FDA approved for the treatment of MDD in pediatric patients up to 18 years old.

Treatment Guidelines for the Use of Antidepressant Medications in Pediatric Patients

Information on some of the treatment guidelines for the use of antidepressants in pediatric patients is available in the National Guideline Clearinghouse database at <http://www.guideline.gov> on the Agency for Healthcare Research and Quality (AHRQ) website. The AHRQ is a branch of the U.S. Department of Health and Human Services. Links to some of the treatment guidelines for the use of antidepressants in pediatric patients are provided in Table 1 below.

Table 1. Treatment Guidelines for the Use of Antidepressant Medications in Pediatric Patients

Sponsoring Organization	Title of Guideline	Link to Guideline
American Psychiatric Association	Practice guideline for the treatment of patients with major depressive disorder, third edition.	http://www.guideline.gov/content.aspx?id=24158
American Psychiatric Association	Practice guideline for the treatment of patients with obsessive-compulsive disorder.	http://www.guideline.gov/content.aspx?id=11078
U.S. Preventive Services Task Force	Screening and treatment for major depressive disorder in children and adolescents: U.S. Preventive Services Task Force recommendation statement.	http://www.guideline.gov/content.aspx?id=14294

Off-Label Use of Antidepressant Medications in Pediatric Patients

Some antidepressants are FDA approved for the treatment of childhood enuresis, MDD, and OCD in children and adolescents; however, not all antidepressants are FDA approved for use in pediatric patients.

Clinical trials with the SSRIs citalopram, paroxetine, and sertraline do not support their use in the treatment of MDD.[8, 9, 10] The antidepressant venlafaxine has been studied for MDD and generalized anxiety disorder (GAD) and did not show efficacy in pediatric patients.[11] Details from the studies that do not support the use of some antidepressants unapproved for use in pediatric patients are as follows:

- Citalopram was studied in 407 pediatric patients in 2 placebo-controlled clinical trials. There was insufficient evidence to support a pediatric indication for the treatment of MDD.[12]
- Paroxetine has been studied in pediatric patients for the treatment of MDD. The results of three placebo-controlled clinical trials failed to show adequate evidence to support its use. Studies also showed an increase in the incidence of suicidal thoughts, mood fluctuations, hostility, tremor, sweating, hyperkinesia, decreased appetite, and agitation when compared to placebo.[13]
- Sertraline was studied in pediatric patients with MDD in two placebo-controlled clinical trials. There was insufficient evidence to support a pediatric indication for the treatment of MDD.[14]
- Venlafaxine extended-release has been studied in pediatric patients (6 to 17 years old) for the treatment of MDD and GAD. The data from two placebo-controlled clinical trials for each indication failed to show sufficient evidence to support the use of venlafaxine in pediatric patients. Weight loss was significantly higher in the treatment group. Height increases were also less than expected in patients taking venlafaxine.[15]

Adverse Reactions and Risks of the Use of Antidepressant Medications in Pediatric Patients

Adverse reactions vary for each antidepressant drug class. SSRIs may cause headache, nausea, insomnia or drowsiness, and agitation. Common adverse reactions of TCAs are drowsiness, dry mouth, urinary retention, blurred vision, weight gain, and dizziness.[16, 17] The adverse reactions and risks associated with TCAs tend to limit their use. TCAs should be used with caution in patients with a heart condition. A TCA overdose may be lethal.[18]

Risk of Seizures

Seizures were reported during premarket evaluation of clomipramine. The risk of seizures was related to either the dose of clomipramine or the duration of treatment, or both. Caution should be used when prescribing clomipramine to patients with a history of seizures or other factors that may predispose them to seizures.[19]

Seizures have also been associated with SSRIs; thus, SSRIs should be used with caution in patients with a known seizure disorder.

Acronyms

AHRQ	Agency for Healthcare Research and Quality
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CMS	Centers for Medicare & Medicaid Services
FDA	U.S. Food and Drug Administration
GAD	generalized anxiety disorder
MDD	major depressive disorder
MIG	Medicaid Integrity Group
NCHS	National Center for Health Statistics
OCD	obsessive-compulsive disorder
OTC	over the counter
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

Risk of Serotonin Syndrome

Patients taking SSRIs are at risk for serotonin syndrome when combined with another serotonergic medication. Other medications that are known to increase the risk for serotonin syndrome are the triptans, linezolid, and methylene blue. Symptoms of serotonin syndrome are highly variable, but can include hyperthermia, hypertension, hallucinations, confusion, weakness, dizziness, and ataxia. The risk of concomitant treatment should be weighed against the potential benefits. If it is determined that a patient needs to be treated with both medications, close monitoring is recommended. Patients, parents, and caregivers should also be made aware of the risk of serotonin syndrome and its signs and symptoms.[20, 21]

Risk of Cardiac Arrhythmias with Fluoxetine

In July 2013, an FDA Safety Communication was published to notify patients and healthcare providers about the potential risk of abnormal heart rhythms with fluoxetine. Post-marketing cases of QT interval prolongation and ventricular arrhythmia including Torsade de Pointes have been reported. Patients with underlying heart conditions, hypokalemia, or hypomagnesemia are at risk of developing prolongation of the QT interval, which may lead to Torsade de Pointes. Fluoxetine is not recommended for use in patients who are taking another medication that can prolong the QT interval. Fluoxetine should be used with caution in patients who have had a recent myocardial infarction or who have uncompensated heart failure, congenital long QT syndrome, bradycardia, hypokalemia, or hypomagnesemia as well as in patients with conditions which may predispose them to increased fluoxetine exposure such as overdose, hepatic impairment, CYP2D6 poor metabolizer status, and concurrent use of CYP2D6 inhibitors or other highly protein bound drugs.[22]

Risk of Suicidality

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.[23]



The boxed warning for all antidepressant medications states:[24]

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. [Insert Drug Name] is not approved for use in pediatric patients. [The previous sentence would be replaced with the sentence, below, for the following drugs: Prozac: Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). Zoloft: Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). Fluvoxamine: Fluvoxamine is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD).] (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use).

The FDA also requires that a Medication Guide be dispensed with every antidepressant prescription to alert patients to the risk of suicidal thinking and behavior. It also includes information on precautions that may be taken.[25] The risks associated with antidepressant use in pediatric patients must be weighed against the potential benefits.

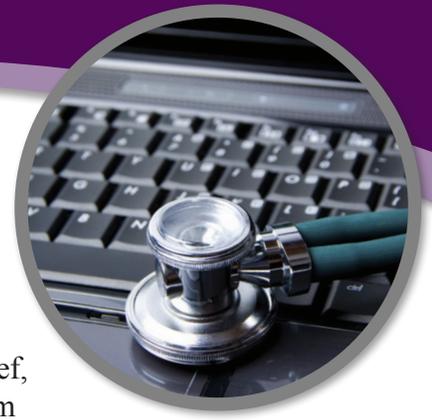
Resources

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 information to patients on serious adverse reactions and 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.

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.



References

- 1 Gu, Q., Dillon, C. F., & Burt, V. L. (2010, September). Prescription Drug Use Continues to Increase: U.S. Prescription Drug Data for 2007–2008. NCHS Data Brief, No. 42. (DHHS Publication No. [PHS] 2010-1209). Retrieved August 10, 2011, from <http://www.cdc.gov/nchs/data/databriefs/db42.pdf>
- 2 Lexapro® (escitalopram) prescribing information. (2011, May 12). Retrieved August 8, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021323s033,021365s024lbl.pdf
- 3 Prozac® (fluoxetine) prescribing information. (2013, July). Retrieved August 14, 2013, from <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=c88f33ed-6dfb-4c5e-bc01-d8e36dd97299>
- 4 Luvox® (fluvoxamine) prescribing information. (2011, March 16). Retrieved August 8, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021519s002lbl.pdf
- 5 Zoloft® (sertraline) prescribing information. (2009, January 30). Retrieved August 9, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019839s070,020990s032lbl.pdf
- 6 Anafranil® (clomipramine) prescribing information. (2007, July 13). Retrieved August 9, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/019906s34lbl.pdf
- 7 Tofranil® (imipramine) prescribing information. (2009, September). Retrieved October 24, 2012, from <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=1827a5aa-733a-49d9-89d9-48ea0367b230>
- 8 Celexa® (citalopram) prescribing information. (2009, January 30). Retrieved August 5, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020822s037,021046s015lbl.pdf
- 9 Paxil® (paroxetine) prescribing information. (2011, July 8). Retrieved August 9, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020031s058s066,020710s022s030lbl.pdf
- 10 Zoloft® (sertraline) prescribing information. (2009, January 30). Retrieved August 9, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019839s070,020990s032lbl.pdf
- 11 Effexor® (venlafaxine) prescribing information. (2010, January 6). Retrieved August 9, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020151s056s057lbl.pdf
- 12 Celexa® (citalopram) prescribing information. (2009, January 30). Retrieved August 5, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020822s037,021046s015lbl.pdf
- 13 Paxil® (paroxetine) prescribing information. (2011, July 8). Retrieved August 9, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020031s058s066,020710s022s030lbl.pdf
- 14 Zoloft® (sertraline) prescribing information. (2009, January 30). Retrieved August 9, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019839s070,020990s032lbl.pdf
- 15 Effexor® (venlafaxine) prescribing information. (2010, January 6). Retrieved August 9, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020151s056s057lbl.pdf
- 16 U.S. Department of Health and Human Services. National Institutes of Health. National Institute of Mental Health. (2011, July 27). How Is Depression Diagnosed and Treated? Retrieved August 11, 2011, from <http://www.nimh.nih.gov/health/publications/depression/how-is-depression-diagnosed-and-treated.shtml>
- 17 U.S. Department of Health and Human Services. National Institutes of Health. National Institute of Mental Health. (2008). Mental Health Medications. Retrieved August 11, 2011, from <http://www.nimh.nih.gov/health/publications/mental-health-medications/complete-index.shtml#pub5>
- 18 Anafranil® (clomipramine) prescribing information. (2007, July 13). Retrieved August 9, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/019906s34lbl.pdf
- 19 Anafranil® (clomipramine) prescribing information. (2007, July 13). Retrieved August 9, 2011, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/019906s34lbl.pdf

- 20 U.S. Department of Health and Human Services. U.S. Food and Drug Administration. (2006, July 19). Selective Serotonin Reuptake Inhibitors (SSRIs). [FDA Safety Information]. Retrieved August 15, 2011, from <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150751.htm>
- 21 U.S. Department of Health and Human Services. U.S. Food and Drug Administration. (2011, July 26). FDA Drug Safety Communication: Serious CNS Reactions Possible when Linezolid (Zyvox) is Given to Patients Taking Certain Psychiatric Medications. [FDA Drug Safety Communication]. Retrieved August 15, 2011, from <http://www.fda.gov/Drugs/DrugSafety/ucm265305.htm>
- 22 U.S. Department of Health and Human Services. U.S. Food and Drug Administration. (2013, July). FDA Drug Safety Communication: Prozac (fluoxetine hydrochloride) Delayed Release Capsules. [FDA Drug Safety Communication]. Retrieved August 14, 2013, from <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm364458.htm>
- 23 U.S. Department of Health and Human Services. U.S. Food and Drug Administration. (2009, February 25). Labeling Change Request Letter for Antidepressant Medications. [Drug Safety and Availability Information by Drug Class]. Retrieved August 11, 2011, from <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096352.htm>
- 24 U.S. Department of Health and Human Services. U.S. Food and Drug Administration. (2007). Revisions to Product Labeling. [Drug Safety and Availability Information by Drug Class]. Retrieved August 11, 2011, from <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM173233.pdf>
- 25 U.S. Department of Health and Human Services. U.S. Food and Drug Administration. (2004, October 15). FDA Launches a Multi-Pronged Strategy to Strengthen Safeguards for Children Treated with Antidepressant Medications. [FDA News Release]. Retrieved August 15, 2011, from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108363.htm>

Disclaimer

This fact sheet was current at the time it was published or uploaded onto the web. Medicaid and Medicare policies change frequently, so links to the source documents have been provided within the document for your reference.

This fact sheet was prepared as a service to the public and is not intended to grant rights or impose obligations. This fact sheet may contain references or links to statutes, regulations, or other policy materials. The information provided is only intended to be a general summary. Use of this material is voluntary. Inclusion of a link does not constitute CMS endorsement of the material. We encourage readers to review the specific statutes, regulations, and other interpretive materials for a full and accurate statement of their contents.

August 2013

This fact sheet was prepared by the Education Medicaid Integrity Contractor for the CMS Medicaid Integrity Program (MIP). For more information on the MIP, please visit <http://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/pharmacy-ed-materials.html> on the CMS website or scan the Quick Response (QR) code on the right with your mobile device.

