Antidepressant Medications: Use in Adults

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 adults.

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

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

FDA-Approved Indications for Antidepressant Medications in Adults

According to the Centers for Disease Control and Prevention (CDC), approximately 1 in 10 adults in the United States is affected by depression.[1] A survey by the CDC and the National Center for Health Statistics (CDC/NCHS) showed that antidepressant medications were the prescription medications most frequently used by adults 20 to 59 years old.[2]

Antidepressants are used in adults to treat depression, major depressive disorder (MDD), obsessive-compulsive disorder (OCD), bulimia nervosa, panic disorder, social anxiety disorder, generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), diabetic peripheral neuropathy, fibromyalgia, chronic musculoskeletal pain, and seasonal affective disorder (SAD). They are also used for smoking cessation, insomnia, and as adjunct therapies for bipolar I disorder and Parkinson's disease.

There are several different classes of antidepressants: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). There are also other antidepressants that do not fall into one of these drug classes.

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Please refer to the dosing table in the document "Antidepressant Medications: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Adults" for more information. FDA-approved indications vary by medication; therefore, a summary of indications and the antidepressant(s) approved to treat each indication are provided in Table 1 below.

Table 1. FDA-Approved Indications for the Use of Antidepressant Medications in Adults

Indication	Medications
bipolar I disorder	fluoxetine[3]
bulimia nervosa	fluoxetine
chronic musculoskeletal pain	duloxetine[4]
depression	amitriptyline,[5] amoxapine,[6] citalopram,[7] desipramine,[8] doxepin,[9] imipramine,[10] isocarboxazid,[11] maprotiline,[12] nefazodone,[13] nortriptyline,[14] phenelzine,[15] protriptyline,[16] trazodone,[17] trimipramine[18]
diabetic peripheral neuropathy	duloxetine
fibromyalgia	duloxetine, milnacipran[19]
GAD	duloxetine, escitalopram,[20] paroxetine,[21] venlafaxine ER[22]
insomnia	doxepin[23]
MDD	bupropion,[24] bupropion SR,[25] bupropion ER,[26] desvenlafaxine,[27] duloxetine, escitalopram, fluoxetine, fluoxetine DR,[28] mirtazapine,[29] paroxetine, paroxetine CR,[30] selegiline,[31] sertraline,[32] tranylcypromine,[33] trazadone ER,[34] venlafaxine,[35] venlafaxine ER, vilazodone[36]
OCD	clomipramine,[37] fluoxetine, fluvoxamine,[38] fluvoxamine ER,[39] paroxetine, sertraline
panic disorder	fluoxetine, paroxetine, paroxetine CR, sertraline, venlafaxine ER
Parkinson's disease	rasagiline,[40] selegiline
PMDD	paroxetine CR, sertraline
PTSD	paroxetine, sertraline
SAD	bupropion ER
smoking cessation	bupropion SR[41]
social anxiety disorder	paroxetine, paroxetine CR, sertraline, venlafaxine ER

CR=controlled-release DR=delayed-release ER=extended-release SR=sustained-release

Treatment Guidelines for the Use of Antidepressant Medications in Adults

Information on some of the treatment guidelines for the use of antidepressants in adults 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 adults are provided in Table 2.

Table 2. Treatment Guidelines for the Use of Antidepressant Medications in Adults

Sponsoring Organization	Title of Guideline	Link to Guideline
American Psychiatric Association	Practice guideline for the treatment of patients with obsessive-compulsive disorder.	http://www.guideline.gov/content.aspx?id=11078
Department of Veteran Affairs, Department of Defense	VA/DoD clinical practice guideline for management of major depressive disorder (MDD).	http://www.guideline.gov/content.aspx?id=15675
Department of Veteran Affairs, Department of Defense: Management of Post-Traumatic Stress Working Group	VA/DoD clinical practice guideline for management of post-traumatic stress.	http://www.guideline.gov/content.aspx?id=25628
National Collaborating Centre for Mental Health	Depression. The treatment and management of depression in adults.	http://www.guideline.gov/content.aspx?id=15521
U.S. Preventive Services Task Force	Screening for depression in adults.	http://www.guideline.gov/content.aspx?id=15275

Adverse Reactions and Risks of Antidepressant Medications

The adverse reactions of antidepressant medications vary with each drug class. SSRIs and SNRIs are the most frequently used antidepressants because they tend to have less bothersome adverse reactions than most of the other antidepressants. The most common adverse reactions of SSRIs and SNRIs are headache, nausea, sedation, agitation, and sexual problems. Hyponatremia has been reported with SSRIs and SNRIs, which may be secondary to drug-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH). Symptoms of SIADH are confusion, weakness, difficulty concentrating, and memory impairment. Patients who develop hyponatremia should have appropriate medical intervention, and discontinuation of the SSRI or SNRI should be considered.[42]

TCAs have anticholinergic properties that cause many troublesome adverse reactions, such as dry mouth, constipation, urinary retention, and blurred vision. Drowsiness is the most common side effect and usually subsides as therapy continues. TCAs should be used with caution in patients with a heart condition. A TCA overdose may be lethal.[43]

The use of MAOIs is limited because they have several contraindications which include:

- Presence of a cerebrovascular defect;
- Presence of a cardiovascular disorder;
- Presence of a pheochromocytoma;
- Consumption of tyramine-containing foods; and
- Potential for serious drug interactions with some medications.[44]

MAOIs also have a warning that they may cause hypertensive crisis (that may be fatal) when tyramine-containing foods are consumed.[45] Information on tyramine-containing foods can be found at http://clinicalcenter.nih.gov/ccc/patient_education/drug_nutrient/maoi1.pdf on the National Institutes of Health (NIH) website.

More detailed information on adverse reactions, drug interactions, warnings, contraindications, and precautions can be found in the prescribing information for each medication. Links are available by searching for the individual medication at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm on the FDA website.

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
DoD	Department of Defense
FDA	U.S. Food and Drug Administration
GAD	generalized anxiety disorder
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MIG	Medicaid Integrity Group
NCHS	National Center for Health Statistics
NIH	National Institutes of Health
OCD	obsessive-compulsive disorder
OTC	over the counter
PMDD	premenstrual dysphoric disorder
PTSD	posttraumatic stress disorder
SAD	seasonal affective disorder
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
VA	Department of Veterans Affairs

Risk of Suicidality

Antidepressant medications have been shown to increase the risk of suicidal thinking and behavior. In pooled analyses 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.[46]

The boxed warning for all antidepressant medications states:[47]

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 and caregivers to the risk of suicidal thinking and behavior. It also includes information on precautions that may be taken.[48] The risks associated with antidepressant use must be weighed against the potential benefits.

Risk of Hypertension

Venlafaxine and desvenlafaxine have been shown to cause sustained hypertension. The increase in blood pressure appears to be dose related. Patients with preexisting hypertension should have their blood pressure controlled prior to initiation of therapy with venlafaxine or desvenlafaxine, and should be routinely monitored throughout treatment. If a patient experiences an increase in blood pressure, the dose should be decreased or the medication should be discontinued.[49, 50]

Risk of Serotonin Syndrome

Patients taking SSRIs or SNRIs 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 should also be made aware of the risk of serotonin syndrome and its signs and symptoms.[51, 52]

Risk of Hepatotoxicity

There have been reports of hepatotoxicity in patients taking duloxetine. Cases of liver failure have also been reported. Duloxetine should be discontinued if jaundice develops or if there are other indications of liver dysfunction. Patients with evidence of liver disease or who consume significant amounts of alcohol should not be prescribed duloxetine.[53]

Life-threatening liver failure has been reported with nefazodone. A boxed warning has been added to alert patients and providers to this risk.

The boxed warning for nefazodone states:[54]

Warning

Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone hydrochloride tablets. The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000 to 300,000 patient-years of nefazodone hydrochloride treatment. The total patient-years is a summation of each patient's duration of exposure expressed in years. For example, 1 patient-year is equal to 2 patients each treated for 6 months, 3 patients each treated for 4 months, etc. (See WARNINGS.)

Ordinarily, treatment with nefazodone hydrochloride tablets should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases. There is no evidence that pre-existing liver disease increases the likelihood of developing liver failure, however, baseline abnormalities can complicate patient monitoring.

Patients should be advised to be alert for signs and symptoms of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur.

Nefazodone hydrochloride tablets should be discontinued if clinical signs or symptoms suggest liver failure (see PRECAUTIONS, Information for Patients). Patients who develop evidence of hepatocellular injury such as increased serum AST or serum ALT levels ≥ 3 times the upper limit of NORMAL, while on nefazodone hydrochloride tablets should be withdrawn from the drug. These patients should be presumed to be at increased risk for liver injury if nefazodone hydrochloride is reintroduced. Accordingly, such patients should not be considered for re-treatment.

Risk of Seizures

Bupropion has been associated with seizures. The risk for seizures appears to be dose related, but is also related to patient factors, clinical condition, and concomitant medications. If a patient experiences a seizure while taking bupropion, the medication should be discontinued and should not be restarted.[55]

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.[56]

Maprotiline has been associated with seizures, especially in patients with a known seizure disorder. However, rapid increases in dose, concurrent administration with medications that lower the seizure threshold, and dosages that exceed the therapeutic range have also been associated with seizures. The prescribing information recommends initiating maprotiline at a low dosage, maintaining the initial dose for at least two weeks, increasing the dose in small increments, and maintaining maprotiline at the lowest effective dosage.[57]

Seizures have been associated with other antidepressant medications. SSRIs, SNRIs, TCAs, mirtazapine, nefazodone, and vilazodone warn that they should be used with care when antidepressant therapy is initiated in a patient with a known seizure disorder.

Risk of Neuropsychiatric Events with Bupropion

Bupropion has been reported to cause neuropsychiatric events when used for smoking cessation. Symptoms associated with these events include behavioral changes, agitation, depression, hostility, and suicidality. Patients and caregivers should be instructed to discontinue bupropion and to contact a healthcare provider if any of these symptoms occur. Bupropion has also been reported to worsen pre-existing psychiatric illness in patients who were taking it to stop smoking.[58]

Zyban® is the only bupropion product that is FDA-approved for smoking cessation. Although the other products do not have FDA approval for smoking cessation, they all have a boxed warning to alert providers, patients, and caregivers to the risk of neuropsychiatric events when used for smoking cessation.[59, 60, 61]

The boxed warning for bupropion states:[62]

WARNING

Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking ZYBAN for smoking cessation. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking ZYBAN who continued to smoke.

All patients being treated with ZYBAN should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking ZYBAN in the postmarketing experience. When symptoms were reported, most were during treatment with ZYBAN, but some were following discontinuation of treatment with ZYBAN. These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of ZYBAN.

Advise patients and caregivers that the patient should stop taking ZYBAN and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of ZYBAN was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of ZYBAN should be weighed against the benefits of its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking for as long as 6 months compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (See WARNINGS: Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment and PRECAUTIONS: Information for Patients.)

Risk of Cardiac Arrhythmias with Fluoxetine and Citalopram

Two recent FDA Drug Safety Communications have been published to notify patients and healthcare providers about the potential risk of abnormal heart rhythms with fluoxetine and with high doses of citalopram. Citalopram has been shown to cause prolongation of the QT interval and fluoxetine has been associated with reports of post-marketing cases. 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 and citalopram are not recommended for use in patients who are taking another medication that can prolong the QT interval. The use of citalopram is not recommended in patients who have had a recent myocardial infarction or who have uncompensated heart failure, congenital long QT syndrome, bradycardia, hypokalemia, or hypomagnesemia.[63] Fluoxetine should be used with caution in these patients. Additionally, fluoxetine should be used with caution 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.[64]

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.

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