

Antidepressants 1

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BCPS

The symptoms of depression are feelings of sadness and hopelessness, as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts. Mania is characterized by the opposite behavior: enthusiasm, anger, rapid thought and speech patterns, extreme self-confidence, and impaired judgment.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)
<i>Fluoxetine</i> <i>Paroxetine</i> <i>Citalopram</i> <i>Escitalopram</i> <i>Fluvoxamine</i> <i>Sertraline</i>
SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)
<i>Duloxetine</i> <i>Venlafaxine</i> <i>Desvenlafaxine</i> <i>Levomilnacipran</i>
ATYPICAL ANTIDEPRESSANTS
<i>Bupropion</i> <i>Mirtazapine</i> <i>Nefazodone</i> <i>Trazodone</i> <i>Vilazodone</i> <i>Vortioxetine</i>

TRICYCLIC ANTIDEPRESSANTS (TCAs)
<i>Amitriptyline</i> <i>Nortriptyline</i> <i>Protriptyline</i> <i>Doxepin</i> <i>Amoxapine</i> <i>Imipramine</i> <i>Desipramine</i> <i>Clomipramine</i> <i>Trimipramine</i> <i>Maprotiline</i>
MONOAMINE OXIDASE INHIBITORS (MAOIs)
<i>Isocarboxazid</i> <i>Phenelzine</i> <i>Selegiline</i> <i>Tranylcypromine</i>

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The selective serotonin reuptake inhibitors (SSRIs) are a group of antidepressant drugs that specifically inhibit serotonin reuptake, having 300-to 3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter. This contrasts with the tricyclic antidepressants (TCAs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) that non selectively inhibit the reuptake of norepinephrine and serotonin. Moreover, the SSRIs have little blocking activity at muscarinic, α -adrenergic, and histaminic H₁ receptors. Because they have different adverse effects and are relatively safe in overdose, the SSRIs have largely replaced TCAs and monoamine oxidase inhibitors (MAOIs) as the drugs of choice in treating depression. The SSRIs include *fluoxetine* (the prototypic drug), *citalopram*, *escitalopram*, *fluvoxamine*, *paroxetine*, and *sertraline*. *Escitalopram* is the pure S-enantiomer of *citalopram*.

DRUG AND CLASSIFICATION	UPTAKE INHIBITORS	UPTAKE INHIBITION
	Norepinephrine	Serotonin

Selective serotonin reuptake inhibitors:

<i>Fluoxetine</i>	0/+	+++
<i>Paroxetine</i>	0	+++
<i>Sertraline</i>	0	+++
<i>Citalopram</i>	0	+++
<i>Escitalopram</i>	0	+++
<i>Fluvaxamine</i>	0	+++

PHARMACOLOGIC PROPERTY/ RECEPTOR SUBTYPE	ADVERSE CLINICAL CONSEQUENCES
Blockade of serotonin uptake at nerve endings	Gastrointestinal disturbances—nausea Increase or decrease in anxiety (dose-dependent) Drowsiness Sexual dysfunction Extrapyrarnidal side effects Drug interactions with L-tryptophan, monoamine oxidase inhibitors, and fenfluramine

Actions

The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft. Antidepressants, including SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more. A patient must be treated with an adequate dosage for at least 6 weeks before considering changing the treatment, although adverse effects due to their synaptic effects occur soon after taking the drug. However, with long-term administration of the drug, adaptive changes may occur. These changes can result in an adjustment to certain adverse effects, the development of new adverse effects, and the onset of therapeutic effects.

Therapeutic uses

The primary indication for SSRIs is depression. A number of other psychiatric disorders also respond favorably to SSRIs, including obsessive–compulsive disorder, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder, and bulimia nervosa (only *fluoxetine* is approved for bulimia).

Pharmacokinetics

All of the SSRIs are well absorbed after oral administration. Peak levels are seen in approximately 2 to 8 hours on average. Food has little effect on absorption (except with *sertraline*, for which food increases its absorption). The majority of SSRIs have plasma half-lives that range between 16 and 36 hours. Metabolism by cytochrome P450 (CYP450)–dependent enzymes and glucuronide or sulfate conjugation occurs extensively. *Fluoxetine* has the longest half-life (50 hours), and the half-life of its active metabolite *S*-norfluoxetine is quite long, averaging 10 days. ***Fluoxetine* and *paroxetine* are potent inhibitors** of a CYP450 isoenzyme (CYP2D6). Other CYP450 isoenzymes (CYP2C9/19, CYP3A4, CYP1A2) are involved with SSRI metabolism and may also be inhibited to various degrees by the SSRIs.

Adverse effects

The most adverse effects of antidepressants can be explained by their synaptic effects. Although the SSRIs are considered to have fewer and less severe adverse effects than the TCAs and MAOIs, the SSRIs are not without adverse effects, such as headache, sweating, anxiety and agitation, hyponatremia, transient gastrointestinal (GI) effects (nausea, vomiting, diarrhea), weakness and fatigue, sexual dysfunction, changes in weight (weight loss followed by weight gain in some patients, especially with *paroxetine*), sleep disturbances (insomnia and somnolence), and the above-mentioned potential for drug–drug interactions.

1. Sleep disturbances: *Paroxetine* and *fluvoxamine* are generally more sedating than activating, and they may be useful in patients who have difficulty in sleeping. Conversely, patients who are fatigued or complaining of excessive somnolence may benefit from one of the more activating SSRIs, such as *fluoxetine* or *sertraline*.

2. Sexual dysfunction: Sexual dysfunction, which may include loss of libido, delayed ejaculation, and anorgasmia, is common with the SSRIs.

3. Use in children and teenagers: Antidepressants should be used cautiously in children and teenagers, because of reports of suicidal ideation as a result of SSRI treatment. Pediatric patients should be observed for worsening depression and suicidal thinking with initiation or dosage change of any antidepressant.

Fluoxetine, *sertraline*, and *fluvoxamine* are approved for use in children to treat obsessive–compulsive disorder, and *fluoxetine* and *escitalopram* are approved to treat childhood depression.

4. Overdose and toxicity: Overdose with SSRIs does not usually cause cardiac arrhythmias, with the exception of *citalopram*, which may cause QT prolongation. Seizures are a possibility because all antidepressants may lower the seizure threshold. SSRIs have the potential to cause serotonin syndrome, especially when used in the presence of an MAOI or other highly serotonergic drug. Serotonin syndrome may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs. SSRIs including all other antidepressants may increase suicidal ideation; therefore, they have a black box warning especially for children, adolescents, and young adults

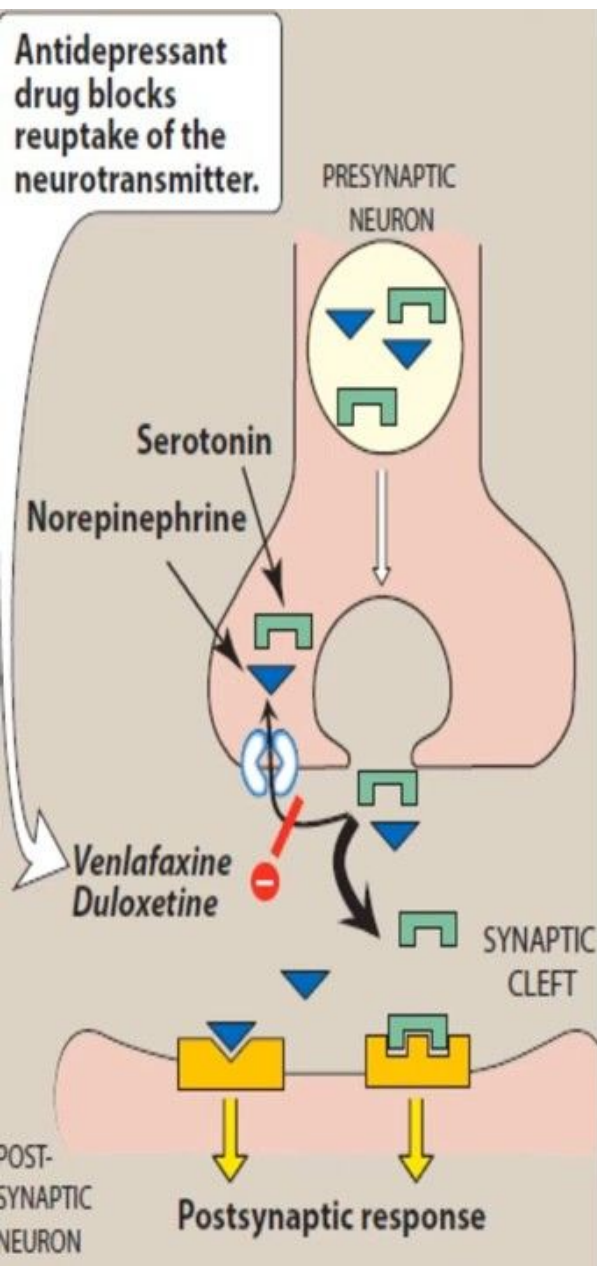
5. Discontinuation syndrome: SSRIs have the potential to cause a discontinuation syndrome after their abrupt withdrawal, particularly the agents with shorter half-lives and inactive metabolites. *Fluoxetine* has the lowest risk of causing an SSRI discontinuation syndrome due to its longer half-life and active metabolite.

Possible signs and symptoms of SSRI discontinuation syndrome include headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern. These effects may persist up to 2 months. SSRIs should be gradually withdrawn to minimize these effects.

6. Drug interactions: SSRIs have been reported to cause though rarely but potentially fatal reaction with other drugs that increase serotonin activity called “serotonin syndrome.” *Fluoxetine* and *paroxetine* inhibit CYP2D6 isozyme potentiating the action of other drugs metabolized by this isozyme.

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS

Venlafaxine, desvenlafaxine, levomilnacipran, and duloxetine inhibit the reuptake of both serotonin and norepinephrine and, thus, are termed SNRIs. Depression is often accompanied by chronic painful symptoms, such as backache and muscle aches, against which SSRIs are also relatively ineffective. This pain is, in part, modulated by serotonin and norepinephrine pathways in the central nervous system. Both SNRIs and the TCAs, with their dual inhibition of both serotonin and norepinephrine reuptake, are sometimes effective in relieving pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, and low back pain. The SNRIs, unlike the TCAs, have little activity at α -adrenergic, muscarinic, or histamine receptors and, thus, have fewer of these receptor-mediated adverse effects than the TCAs. The SNRIs may precipitate a discontinuation syndrome if treatment is abruptly stopped.



Venlafaxine and desvenlafaxine

Venlafaxine is an inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine reuptake. *Venlafaxine* has minimal inhibition of the CYP450 isoenzymes and is a substrate of the CYP2D6 isoenzyme. *Desvenlafaxine* is the active, demethylated metabolite of *venlafaxine*. The most common side effects of *venlafaxine* are nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation. At high doses, there may be an increase in blood pressure and heart rate. The clinical activity and adverse effect profile of *desvenlafaxine* are similar to those of *venlafaxine*.

Duloxetine

Duloxetine inhibits serotonin and norepinephrine reuptake at all doses. It is extensively metabolized in the liver to inactive metabolites and should be avoided in patients with liver dysfunction. GI side effects are common with *duloxetine*, including nausea, dry mouth, and constipation. Insomnia, dizziness, somnolence, sweating, and sexual dysfunction are also seen. *Duloxetine* may increase blood pressure or heart rate. *Duloxetine* is a moderate inhibitor of CYP2D6 isoenzymes and may increase concentrations of drugs metabolized by this pathway, such as antipsychotics. *Duloxetine* may rarely cause hepatotoxicity.

Levomilnacipran

Levomilnacipran is an enantiomer of *milnacipran* (an older SNRI used for the treatment of depression in Europe and fibromyalgia in the United States). The adverse effect profile of *levomilnacipran* is similar to other SNRIs. It is primarily metabolized by CYP3A4, and, thus, activity may be altered by inducers or inhibitors of this enzyme system.

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)
<i>Duloxetine</i>
<i>Venlafaxine</i>
<i>Desvenlafaxine</i>
<i>Levomilnacipran</i>

DRUG AND CLASSIFICATION	UPTAKE INHIBITORS	UPTAKE INHIBITION
	Norepinephrine	Serotonin
Other antidepressants:		
<i>Trazodone</i>	0	++
<i>Maprotiline</i>	+++	0
<i>Buprapion</i>	0/+	0/+
<i>Venlafaxine</i>	++	+++
<i>Nefazodone</i>	0	0/+
<i>Mirtazapine</i>	0	0
<i>Duloxetine</i>	+++	+++

Symptoms & Management in Serotonin Syndrome:

Mild

Mydriasis
Shivering
Sweating
Tachycardia (mild)

Moderate

Altered Mental Status
(agitation, disorientation, excitement)
Autonomic Hyperactivity
(rigidity, tachycardia, hyperthermia of $>40^{\circ}\text{C}$)
Neuromuscular Abnormalities
(tremor, clonus, hyperreflexia)

Life Threatening

Delirium
Hypertension
Hyperthermia
Muscle rigidity
Tachycardia

Management stages:

Observe for at least 6 hrs
Benzodiazepines



Admit to hospital
Cardiac monitoring
Cyproheptadine



Intensive care unit
Esmolol or nitroprusside
Cooling measures,
Sedation, SkM paralysis, ventilation