

Antidepressants — List of Drugs and Side Effects

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The lifetime prevalence of major depressive disorders is 12-17%. Accordingly, every practicing career clinician is highly likely to come into contact with patients suffering from symptoms of depression or taking antidepressant medications. For this reason, it is important to be able to recognize depression as well as to understand the respective medications, their limitations, adverse effects, and interactions with other medications.



Introduction

Antidepressants are a **heterogeneous group of medications used for the**

treatment of major depression. Antidepressants are also commonly used for other related conditions such as anxiety disorders, [obsessive-compulsive disorders](#), and chronic pain.

The first antidepressant was [imipramine](#), which was discovered in 1957 by [psychiatrist R. Kuhn](#). Currently, antidepressants are divided into the following main classes of drugs:

- **Tricyclic antidepressants (TCAs)**
- **Selective serotonin reuptake inhibitors (SSRIs)**
- **Norepinephrine reuptake inhibitors (NRIs)**
- **Serotonin-norepinephrine reuptake inhibitors (SNRIs)**
- **Monoamine oxidase inhibitors (MAOIs)**

Each class of drug is different from each other with regards to its chemical structure, mode of action, safety profile, efficacy, and adverse effects. Generally their action is based on re-elevating mood and activation on the psychomotor drive, leading to a subsidising of physical symptoms of depression.

Note: In healthy individuals, antidepressants do not show effects—excluding vegetative side effects and slight sedation.

Pharmacology and Biochemistry of Antidepressants

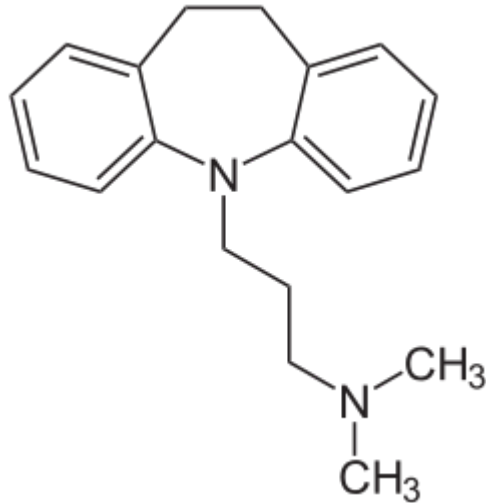
It is essential for the practicing psychiatrist to understand the mode of action of antidepressants to insure the safest and effective treatment of depressive disorders. The amine mood hypothesis postulates that the amine neurotransmitters, particularly norepinephrine and serotonin, are imbalanced in mood disorders. Generally, they are decreased in patients with depression, while they are increased in mania and psychosis.

Understandably, most antidepressants **raise the concentration of neurotransmitters norepinephrine and serotonin in the synaptic gap** by either inhibiting their reuptake into neurons or inhibiting their enzymatic breakdown.

Tricyclic antidepressants (TCAs)

The name tricyclic antidepressants (TCAs) is based on their hydrophobic, three-membered ring system. TCAs do not show any direct binding affinity to any particular neurochemical transmitter system, but rather exert their activities on the norepinephrine and serotonin levels indirectly.

TCAs also bind to peripheral acetylcholine, histamine, and adrenergic receptors. These binding activities are believed to explain some of their adverse effects.



[Image](#): "2D structure of TCA imipramine (Tofranil)" by Harbin - Own work. License: [Public Domain](#)

Like neuroleptics, TCAs show two distinctive effects.

1. First, the immediate sedative effect that is characterized by sedation, sleepiness, and reduction of mental and physical activity. This effect is also observed in the healthy individuals.
2. Second, the antidepressant effect, that solely occurs after long-time use, is only detected in patients with depression and mood disorders.

Drugs: [Amitriptyline](#), [Doxepin](#), [Imipramine](#), [Nortriptyline](#), [Desipramine](#), [Trazodone](#)

Note: Nortriptyline and Desipramine are the natural metabolites of Amitriptyline and Imipramine, respectively.

Selective serotonin reuptake inhibitors (SSRIs)

As the name implies, the selective serotonin reuptake inhibitors (SSRIs) inhibit the reuptake of serotonin into the presynaptic neurons from the synaptic gap by blocking the serotonin transporters.

Unlike TCAs, these drugs do not block histamine, muscarinic, or adrenergic receptors. Hence, they have less adverse effects and are often used as the first-line drugs in the treatment of major depression.

Drugs: [Fluoxetine](#) (prototype), [Paroxetine](#), [Sertraline](#), [Citalopram](#), [Escitalopram](#)

Norepinephrine reuptake inhibitors (NRIs)

Similar to the mechanism of action for SSRIs, the norepinephrine reuptake inhibitors (NRIs) prevent the reuptake of norepinephrine into the presynaptic neuron. They are indicated for the treatment of mild depression.

Drugs: [Reboxetine](#)

Serotonin-norepinephrine reuptake inhibitors

(SNRIs)

The SNRIs inhibit both serotonin and norepinephrine reuptake into the presynaptic neurons.

Drugs: [Venlafaxine](#), [Duloxetine](#), [Mianserin](#), [Levomilnacipran](#)

Venlafaxine inhibits the reuptake of serotonin, norepinephrine, as well as of dopamine. At lower doses, there is mainly a serotonin reuptake inhibition activity followed by an additional norepinephrine reuptake inhibition in higher doses. Hence, venlafaxine is suitable for treatment of depression in combination with anxiety disorders.

Duloxetine has taken a special position among SNRIs. Duloxetine is specifically indicated for use in treating urinary incontinence in depressive women. Duloxetine works on the Onuf's nucleus located in the sacral region of the spinal cord, which is the origin of the pudendal nerve motor neurons.

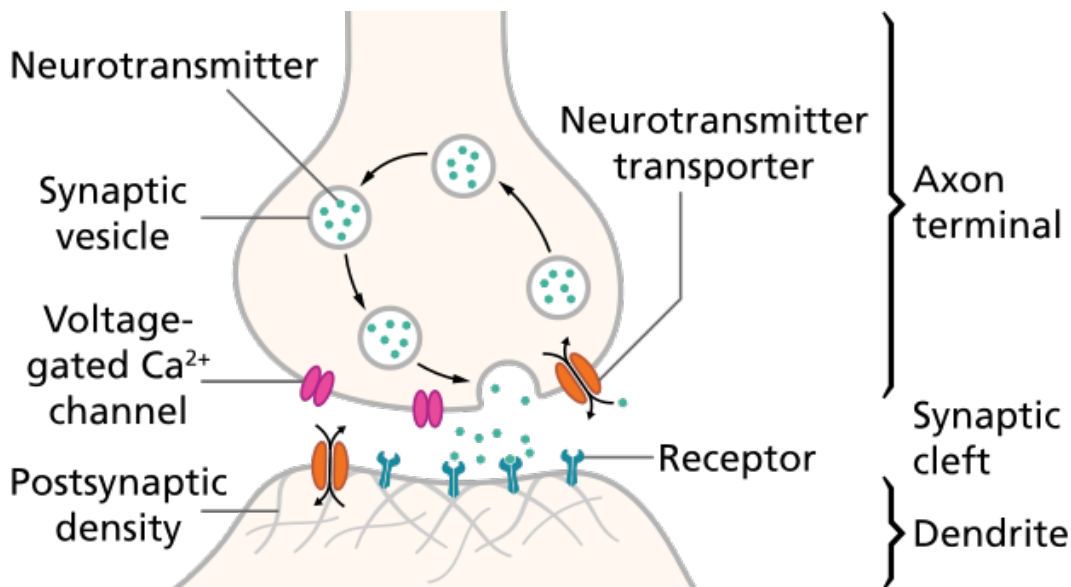


Image: "Inhibiting the reuptake transport protein results in increased concentrations of serotonin and norepinephrine in the synaptic clefts, leading to improvement of depression symptoms." by Thomas Spletstoesser (www.scistyle.com) - Own work. License: [CC BY-SA 4.0](#)

Monoamine oxidase inhibitors (MAOIs)

Monoamine oxidase enzyme catalyzes the breakdown of neuro-active and vasoactive amines. The MAO-A (monoamine oxidase type A) metabolizes norepinephrine, serotonin, dopamine, and tyramine, while MAO-B (monoamine oxidase type B), metabolizes dopamine. The monoamine oxidase inhibitors (MAOIs) block these enzymes, thus causing an increase the levels of these neurotransmitters in the synaptic cleft.

MOA enzymes also metabolize the amino acid tyramine. It is important to clear tyramine. Ingestion of tyramine-containing foods while taking MAOIs can lead to excessive accumulation of tyramine leading to headaches, fevers, muscle twitching, hypertensive crisis, sweating, nausea, and hallucinations. Foods rich in tyramine that should be avoided include chocolate, red wine, bananas, and ripened cheese.

Drugs: [Tranylcypromine](#) (obsolete), [Moclobemide](#).

Selegiline, the MAO type B inhibitor, is used in the treatment of [parkinsonism](#).

Practical Application

Antidepressants are used in everyday clinical practice due to their drive-enhancing or sedating effect. Their efficacy has been proven in well-controlled studies. Therefore, **combining psychotherapeutic and psychopharmacological treatment** is recommended for major depression. Further indications are anxiety disorders, obsessive-compulsive disorders, chronic pain, and [eating disorders](#) such as bulimia.

Antidepressants are **started at lower doses and are slowly increased over time**. Antidepressant onset begins after two-to-three weeks. In principle, only one antidepressant should be prescribed. The antidepressant drug should be selected after consideration of the patient's health, age, comorbid conditions, and side effects. If no improvement is observed after several weeks of treatment with adequate dosage, therapy can be changed to another antidepressant.

In suicidal patients, there is an increased frequency of suicide attempts in the first three weeks and should be closely supervised. In most cases, tranquilizers like benzodiazepines or neuroleptics are co-prescribed to reduce the risk of suicide in the first few weeks.

Treatment duration has to be considered individually. For a single depressive episode, a six-month therapy with a focus on remission followed by gradual tapering is the goal. Abrupt withdrawal must be avoided since suicidal ideation is known to occur. This is called rebound.

For multiple depressive episodes, a 5-year-long therapy with antidepressants is the strategic plan of medical action. Longer periods are possible if there are no major complications. For [bipolar disorder](#), lithium can be used as a mood stabilizer.

TRD is commonly defined as a failure of treatment to produce response or remission for patients after two or more treatment attempts of adequate dose and duration. In such cases, **electroconvulsive therapy has proven effective** because of the higher plasma levels and better compliance.



Image: "An illustration depicting electroconvulsive therapy." by BruceBlaus - Own work. License: [CC BY-SA 4.0](#)

Adverse Effects and Contraindications

SSRIs are the first-choice drugs due to better safety profile and less adverse effects. Self-limiting nausea, and vomiting, as well as inner restlessness, may occur at the beginning of therapy. SSRI-caused sexual dysfunction is one of the main reasons for the lack of compliance and a premature termination of treatment. Symptoms are reduced libido, anorgasmia, and genital numbness.

Tricyclic antidepressants exert anticholinergic adverse effects including **orthostatic hypotension, constipation, dry mouth, and tachycardia**. The TCAs also cause urinary retention in elderly men, ECG abnormalities, and life-threatening arrhythmias.

Note: At the beginning, driving motor vehicles and using machines is not recommended.

It is important to differentiate adverse benefits from symptoms of a major depressive disorder. Adverse events typically occur in the first days of therapy. Hence it is advisable to begin dosing cautiously, slowly increasing dose. Major adverse effects of each antidepressant class are summarized in the following table.

Class	Adverse effects
TCAs	Voiding disorders, accommodation disorders, tremor, xerostomia, dizziness, cardiac conduction disorders, unrest, weight gain, loss of libido, erectile dysfunction, edemas, exanthema
SSRIs	Nausea, unrest, sexual dysfunction, headache, tremor
NRIs	Unrest, urinary retention, tachycardia
Venlafaxine	Nausea, hypertension, withdrawal symptoms
Mirtazapine	Fatigue increased appetite, edema, arthralgia
MAOIs	Unrest, sleep disturbance; Serotonin syndrome

Regular medical examinations are necessary during antidepressant therapy to check for blood counts, kidney and liver functions. Furthermore, blood pressure, ECG and EEG checks are recommended.

Contraindications

TCAs are contraindicated in angle closure glaucoma, pyloric stenosis, prostatic hypertrophy, and status post-acute myocardial infarction.

Selective serotonin reuptake inhibitors must not be prescribed along with MAOIs, L-tryptophan, and triptans to avoid serotonin hyperfunction syndrome.

References

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