

Antidepressants 2

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TRICYCLIC ANTIDEPRESSANTS

The TCAs inhibit norepinephrine and serotonin reuptake into the presynaptic neuron and, thus, if discovered today, might have been referred to as SNRIs, except for their differences in adverse effects relative to this newer class of antidepressants. The TCAs include the tertiary amines *imipramine* (the prototype drug), *amitriptyline*, *clomipramine*, *doxepin*, and *trimipramine*, and the secondary amines *desipramine* and *nortriptyline* (the *N*-demethylated metabolites of *imipramine* and *amitriptyline*, respectively) and *protriptyline*. *Maprotiline* and *amoxapine* are related “tetracyclic” antidepressant agents and are commonly included in the general class of TCAs.

Mechanism of action

1. Inhibition of neurotransmitter reuptake: TCAs and *amoxapine* are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals. *Maprotiline* and *desipramine* are relatively selective inhibitors of norepinephrine reuptake.
2. Blocking of receptors: TCAs also block serotonergic, α -adrenergic, histaminic, and muscarinic receptors. It is not known if any of these actions produce the therapeutic benefit of the TCAs. However, actions at these receptors are likely responsible for many of their adverse effects. *Amoxapine* also blocks 5-HT₂ and dopamine D₂ receptors.

Therapeutic uses

The TCAs are effective in treating moderate to severe depression. Some patients with panic disorder also respond to TCAs. *Imipramine* is used as an alternative to *desmopressin* or nonpharmacologic therapies (enuresis alarms) in the treatment of bedwetting in children. The TCAs, particularly *amitriptyline*, have been used to help prevent migraine headache and treat chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of pain is unclear. Low doses of TCAs, especially *doxepin*, can be used to treat insomnia.

Pharmacokinetics

TCAs are well absorbed upon oral administration. As a result of their variable first-pass metabolism in the liver, TCAs have low and inconsistent bioavailability. These drugs are metabolized by the hepatic microsomal system (and, thus, may be sensitive to agents that induce or inhibit the CYP450 isoenzymes) and conjugated with glucuronic acid. Ultimately, the TCAs are excreted as inactive metabolites via the kidney. These drugs are highly lipid soluble and have a relatively long half-life

Adverse effects

Blockade of muscarinic receptors leads to blurred vision, xerostomia, urinary retention, sinus tachycardia, constipation, and aggravation of angle-closure glaucoma. These agents affect cardiac conduction similar to typical of class IA antiarrhythmics (*quinidine*) and may precipitate life-threatening arrhythmias in an overdose situation. They thus contribute toward the narrow therapeutic index of tricyclic antidepressants. This property is a major pharmacological distinction between the older tricyclic compounds and the newer generation compounds. The TCAs also block α -adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia. Sedation is related to the ability of these drugs to block histamine H₁ receptors. Weight gain is a common adverse effect of the TCAs. Sexual dysfunction occurs in a minority of patients, and the incidence is lower than that associated with the SSRIs. All antidepressants, including TCAs, should be used with caution in patients with bipolar disorder, even during their depressed state, because antidepressants may cause a switch to manic behavior. The TCAs have a narrow therapeutic index (for example, five- to sixfold the maximal daily dose of *imipramine* can be lethal). Depressed patients who are suicidal should be given only limited quantities of these drugs and be monitored closely. The TCAs may exacerbate certain medical conditions, such as benign prostatic hyperplasia, epilepsy, and pre-existing arrhythmias.

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver. In the neuron, MAO functions as a “safety valve” to oxidatively deaminate and inactivate any excess neurotransmitters (for example, norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest. The MAOIs may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitters to escape degradation and, therefore, to accumulate within the presynaptic neuron and leak into the synaptic space. The four MAOIs currently available for the treatment of depression include *phenelzine*, *tranylcypromine*, *isocarboxazid*, and *selegiline*. [Note: *Selegiline* is also used for the treatment of Parkinson’s disease. It is the only antidepressant available in a transdermal delivery system.] Use of MAOIs is limited due to the complicated dietary restrictions required while taking these agents.

Mechanism of action

Most MAOIs, such as *phenelzine*, form stable complexes with the enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent diffusion of excess neurotransmitter into the synaptic space. These drugs inhibit not only MAO in the brain but also MAO in the liver and gut that catalyzes oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods. The MAOIs, therefore, show a high incidence of drug–drug and drug–food interactions. *Selegiline* administered as the transdermal patch may produce less inhibition of gut and hepatic MAO at low doses because it avoids first-pass metabolism.

Therapeutic uses

Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs, SNRIs, and TCAs, is delayed several weeks. *Selegiline* and *tranylcypromine* have an amphetamine-like stimulant effect that may produce agitation or insomnia. The MAOIs are indicated for depressed patients who are unresponsive or intolerant of other antidepressants. Because of their risk for drug–drug and drug–food interactions, the MAOIs are considered last-line agents in many treatment settings.

Pharmacokinetics

These drugs are well absorbed after oral administration. Enzyme regeneration, when irreversibly inactivated, varies, but it usually occurs several weeks after termination of the drug. Thus, when switching antidepressant agents, a minimum of 2 weeks of delay must be allowed after termination of MAOI therapy and the initiation of another antidepressant from any other class. MAOIs are hepatically metabolized and excreted rapidly in urine.

Adverse effects

Severe and often unpredictable side effects, due to drug–food and drug–drug interactions, limit the widespread use of MAOIs. For example, tyramine, which is contained in foods, such as aged cheeses and meats, liver, pickled or smoked fish, and red wines, is normally inactivated by MAO in the gut. Individuals receiving an MAOI are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in a hypertensive crisis, with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and, possibly, stroke. Patients must, therefore, be educated to avoid tyramine-containing foods. Other possible adverse effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation. SSRIs should not be coadministered with MAOIs due to the risk of serotonin syndrome. Both SSRIs and MAOIs require a washout period of at least 2 weeks before the other type is administered, with the exception of *fluoxetine*, which should be discontinued at least 6 weeks before an MAOI is initiated. In addition, the MAOIs have many other critical drug interactions, and caution is required when administering these agents concurrently with other drugs.

ATYPICAL ANTIDEPRESSANTS

The atypical antidepressants are a mixed group of agents that have actions at several different sites. This group includes ***bupropion, mirtazapine, nefazodone, trazodone, vilazodone, and vortioxetine.***

Bupropion

Bupropion is a weak dopamine and norepinephrine reuptake inhibitor that is used to alleviate the symptoms of depression. *Bupropion* is also useful for decreasing cravings and attenuating withdrawal symptoms of nicotine in patients trying to quit smoking. Side effects may include dry mouth, sweating, nervousness, tremor, and a dose-dependent increased risk for seizures. It has a very low incidence of sexual dysfunction. *Bupropion* is metabolized by the CYP2B6 pathway and has a relatively low risk for drug–drug interactions, given the few agents that inhibit/induce this enzyme. Use of *bupropion* should be avoided in patients at risk for seizures or those who have eating disorders such as bulimia.

Mirtazapine

Mirtazapine enhances serotonin and norepinephrine neurotransmission by serving as an antagonist at central presynaptic α_2 receptors. Additionally, some of the antidepressant activity may be related to antagonism at 5-HT₂ receptors. It is sedating because of its potent antihistaminic activity, but it does not cause the antimuscarinic side effects of the TCAs, or interfere with sexual function like the SSRIs. Sedation, increased appetite, and weight gain frequently occur.

Nefazodone and trazodone

These drugs are weak inhibitors of serotonin reuptake and are also antagonists at the postsynaptic 5-HT_{2a} receptor. Both agents are highly sedating, probably because of their potent histamine H₁-blocking activity. *Trazodone* is commonly used off-label for the management of insomnia. These drugs cause gastrointestinal disturbances. Sexual effects are limited except that *trazodone* has been associated with priapism in men. *Nefazodone* has been associated with a rare risk for hepatotoxicity. Both agents also have mild-to-moderate α_1 receptor antagonism, contributing to orthostasis and dizziness.

Vilazodone

Vilazodone is a serotonin reuptake inhibitor and a 5-HT_{1a} receptor partial agonist. Although the extent to which the 5-HT_{1a} receptor activity contributes to its therapeutic effects is unknown, this possible mechanism of action renders it unique from that of the SSRIs. The adverse effect profile of *vilazodone* is similar to the SSRIs, including a risk for discontinuation syndrome if abruptly stopped.

Vortioxetine

Vortioxetine utilizes a combination of serotonin reuptake inhibition, 5-HT_{1a} agonism, and 5-HT₃ and 5-HT₇ antagonism as its suggested mechanisms of action to treat depression. It is unclear to what extent the activities other than inhibition of serotonin reuptake influence the overall effects of *vortioxetine*. The common adverse effects include nausea, constipation, and sexual dysfunction, which may be expected due to its serotonergic mechanisms.

SEROTONIN-DOPAMINE ANTAGONISTS

While 60% to 80% of patients respond favorably to antidepressants, 20% to 40% experience a partial or poor response to monotherapy. The serotonin-dopamine antagonists (SDAs), or atypical antipsychotics, are occasionally used as adjunctive treatments to antidepressants in partial responders. *Aripiprazole*, *brexpiprazole*, *quetiapine*, and the combination of *fluoxetine* and *olanzapine* are approved for use as adjuncts in major depressive disorder (MDD).