

Monoamine Oxidase Inhibitors



Eldepryl (selegiline)
Emsam (selegiline skin patch)
Marplan (isocarboxazid)
Nardil (phenelzine)
Parnate (tranylcypromine)

The **monoamine oxidase inhibitors** (MAOIs) represent a group of older antidepressants that have limited, but selective, use for treatment of depression. These agents have been replaced by newer and safer agents such as **selective serotonin reuptake inhibitors** (SSRIs) as well as other non-SSRIs such as Wellbutrin (bupropion), Effexor (venlafaxine), and Remeron (mirtazapine) for treating depression. The MAOIs include Marplan (isocarboxazid), Nardil (phenelzine), Parnate (tranylcypromine), and Eldepryl (selegiline), which was developed for treatment of Parkinson's disease rather than depression.

Neurotransmission is the process by which brain cells (neurons) communicate with each other. It starts with an electrical impulse that travels down the nerve cell, causing release of a *neurotransmitter*, such as serotonin, norepinephrine, or dopamine, from the neuron into the space between that neuron and the next neuron, thus allowing the electrical stimulus to continue into the neighboring neuron. The actions of neurotransmitters are terminated primarily by 1) reuptake of neurotransmitters back into neurons and 2) breakdown of neurotransmitters by enzymes prior to reuptake back into the neuron. A type of enzyme that breaks down neurotransmitters is **monoamine oxidase** (MAO), a complex enzyme system widely distributed throughout the body and found in the brain. MAOIs work differently from SSRIs and other antidepressants. They block MAO from breaking down neurotransmitters, resulting in an increase in the neurotransmitter concentration in the space between neurons. The older MAOIs Nardil, Parnate, and Marplan inhibit MAO enzymes nonselectively and irreversibly, whereas Eldepryl is relatively more selective for a specific type of MAO enzyme, and its inhibition is terminated more rapidly once the patient stops taking the medication.

Depression and other mental disorders may be caused by abnormally low levels of certain neurotransmitters in the brain. This abnormality may in turn produce changes in affected areas of the brain, resulting in psychiatric symptoms such as depression or anxiety. When neurotransmission is altered by the antidepressant, the affected brain areas may be restored to normal functioning, decreasing or eliminating the symptoms of the illness.

With many safe and effective antidepressants currently available, the use of MAOIs has been limited to treating refractory and severe forms of depression. Physicians usually prescribe MAOIs when trials with other antidepressants fail. MAOIs may also be used outside their indication for depression. The use of a medication for its approved indications is called its *labeled use*. In clinical practice, however, physicians often prescribe medications for *unlabeled* ("off-label") uses when published clinical studies, case reports, or their own clinical experiences support the efficacy and safety of those treatments. MAOIs, for example, may be prescribed to treat panic disorder, generalized anxiety disorder, specific phobias, posttraumatic stress disorder, and migraine headaches resistant to other therapies. Eldepryl oral tablets are not approved for treatment of depression but

are approved by the U.S. Food and Drug Administration (FDA) for treatment of Parkinson's disease, a progressive neurological disease affecting movement and mobility. A selegiline skin patch (Emsam) was recently developed and subsequently was approved for treating depression.

Dosing Information

Nardil and Parnate are the most commonly prescribed MAOIs. The recommended starting dosage for Nardil is 15 mg two or three times a day, with the dosage increasing by 15 mg weekly as needed to a therapeutic range of 45–60 mg/day. The recommended starting dosage of Parnate is 10 mg two or three times a day, with the dosage increasing by 10 mg weekly as needed to a therapeutic range of 40–60 mg/day. Marplan is usually started at a dosage of 20 mg/day, taken in two doses of 10 mg each, and the dosage is increased by 10 mg every 2–4 days to achieve a therapeutic range of 30–60 mg/day.

Common Side Effects

The MAOIs are associated with numerous side effects that often limit their usefulness and tolerability. Potential side effects may be reduced by increasing the dosage slowly or by reducing the dosage. Common side effects associated with MAOIs are daytime sedation, dizziness, dry mouth, altered taste, nervousness, muscle aches, insomnia, weight gain, sexual dysfunction, and urinary difficulty. Sexual side effects induced by MAOIs include anorgasmia (inability to achieve orgasm) and impotency, which are apparently more frequent with Nardil than Parnate. Some patients may be bothered by paresthesia (pricking or tingling sensation). This may be from the MAOI's interference with pyridoxine (vitamin B₆) metabolism. Taking a daily dose of 100 mg of vitamin B₆ may reduce or eliminate these symptoms.

Adverse Reactions and Precautions

The combination of other medications that boost serotonin, such as SSRIs and tricyclic antidepressants, with MAOIs may precipitate a potentially hazardous condition called **serotonin syndrome**, a reaction caused by excessive serotonin stimulation in the brain. The early signs of serotonin syndrome are restlessness, confusion, tremors, flushing, excessive sweating, and involuntary muscle jerks. If the medications are not stopped, the individual may develop more life-threatening complications resulting in severe muscle contractions, high fever, respiratory problems, clotting problems, destruction of red blood cells (that may lead to acute renal failure), coma, and death. Patients taking MAOIs should be alerted to the possible signs of serotonin syndrome, which require immediate medical attention and discontinuation of the serotonin-boosting medications. They should be cautious of any other medications they may take with MAOIs, including over-the-counter medications and herbal supplements.

Dizziness may be caused by MAOIs' effect in momentarily dropping blood pressure. MAOIs block the body's compensatory response to maintain a stable blood pressure when a person moves from lying down to a sitting position or from sitting to standing. This reaction is known in medical terms as **orthostatic hypotension**. Seniors and those taking other medications to lower blood pressure may be particularly susceptible to orthostatic hypotension from MAOIs. Patients should be cautious when rising to their feet suddenly. When lying down, they should get up gradually to a sitting position before standing. If feeling lightheaded or dizzy, they should sit and wait for a minute or two before standing up, to allow the blood pressure to adjust.

Other important precautions for patients taking MAOIs are to avoid foods high in **tyramine** and to restrict certain medications (especially cold and allergy preparations containing decongestants) that may produce dan-

gerously elevated blood pressure and perhaps cause a stroke. Tyramine is a naturally occurring substance derived from the aging process of foods and alcohol. In the intestines, tyramine is metabolized by MAO enzymes before any significant amount is absorbed and distributed in the body. In the presence of MAOIs, tyramine is not broken down and large amounts may get absorbed. High levels of tyramine can suddenly and dangerously elevate blood pressure. Certain medications (and illicit drugs) may interact with MAOIs and elevate blood pressure. When blood pressure becomes dangerously elevated and goes untreated, a *hypertensive crisis* ensues. Food and medication restrictions for patients taking MAOIs are listed in the table below.

Foods that must be avoided	Foods that may be consumed in small amounts, but large amounts may be unsafe	Medications that must be avoided
Aged cheese (cottage and cream cheese are allowed)	Yogurt Chocolate	Cold and allergy medications containing decongestants
Liver (from any animal source), liverwurst	Caffeinated beverages Ripe fruits (e.g., bananas, avocado)	Nasal decongestants and sinus medications
Aged foods, smoked meats (e.g., salami, sausage, salami, pepperoni, and corned beef), smoked fish		Inhalants for bronchial dilatation (e.g., Atrovent) Epinephrine (e.g., bee-sting kits)
Beer and red wine		Demerol (meperidine)
Fava or broad bean pods		Stimulants (e.g., appetite suppressants, Ritalin, amphetamine, cocaine)
Meat extracts or yeast extracts (baked goods containing yeasts are safe)		
Soy sauce, tofu, fermented bean curd (found in soybean paste and miso soup)		Levodopa and dopamine medications used to treat Parkinson's disease

Use in Pregnancy and Breastfeeding: Pregnancy Category C

The safety of MAOIs during pregnancy has not been established. However, because of the risk of hypertensive crisis, MAOIs are not recommended during pregnancy. Moreover, when a pregnant woman is taking an MAOI, the potential of drug interactions may preclude use of certain medications or may complicate use of anesthesia during an emergency. Women who are taking an MAOI should always consult their physician if contemplating pregnancy or if they become pregnant. Some women may experience a recurrence of depression when they stop their antidepressant. In these circumstances, the physician will discuss the treatment options with the patient, including continuing to take the MAOI under close surveillance, if necessary.

Women taking MAOIs should not breastfeed, because small amounts will pass into breast milk and be ingested by the baby. If stopping the MAOI is not an alternative, breastfeeding should not be started or should be discontinued.

Possible Drug Interactions

There are numerous possible drug interactions with MAOIs. The interactions of greatest concern are with those drugs that may precipitate a hypertensive crisis or serotonin syndrome when combined with MAOIs; these are listed in the table on the next page.

Demerol (meperidine)	The combination of MAOIs and Demerol may result in agitation, seizures, and fever, which may lead to coma and death. This reaction is possible weeks after the MAOI is stopped.
Anesthetics	MAOIs should be discontinued at least 10 days before elective surgery requiring general anesthesia. Local anesthesia with epinephrine or cocaine should also be avoided.
Antidepressants	MAOIs in combination with another antidepressant, or shortly after beginning any of these agents, may result in a serious serotonin syndrome reaction or hypertensive crisis.
Tegretol (carbamazepine) and Trileptal (oxcarbazepine)	Hypertensive crisis, seizures, and circulatory collapse may ensue with this combination.
Wellbutrin or Zyban (bupropion)	Bupropion in Wellbutrin antidepressants or Zyban (for smoking cessation) should not be combined with an MAOI. The combination may trigger a dangerous reaction.
Dextromethorphan (e.g., Robitussin)	The ingredient dextromethorphan in many cough preparations should not be combined with MAOIs. The combination may be dangerous.
Decongestants	Decongestants such as phenylpropanolamine and pseudoephedrine, commonly found in cold and allergy over-the-counter medications, should not be combined with MAOIs. The combination may precipitate a hypertensive crisis.
Bronchodilators (e.g., Ventolin, Primatene)	The combination of MAOIs and bronchodilators used for breathing should be avoided. The combination may trigger a hypertensive crisis.
Antiparkinson medications (e.g., levodopa, Sinemet)	The combination of these medications may precipitate a hypertensive crisis.
BuSpar (buspirone)	MAOIs should not be combined with BuSpar. There have been reports of elevated blood pressure when BuSpar was added to medication regimens including an MAOI.

Other medications and herbal products that can interact with MAOIs include Flexeril (cyclobenzaprine), diet pills and herbal weight-loss products, St. John's wort, and stimulants, among others.

Overdose

Early signs and symptoms of MAOI overdose include drowsiness, irritability, low blood pressure, restlessness, and breathing difficulties. The person may develop rapid breathing and rapid heart rate, movement disorders, severe headaches, and hypertensive crisis. Convulsions and coma may follow, and death may occur. The severity of symptoms depends on the amount of MAOI ingested and whether other medications are involved.

Any suspected overdose should be treated as an emergency. The person should be taken to the emergency room for observation and treatment. The prescription bottle of medication (and any other medication suspected in the overdose) should be brought as well, because the information on the prescription label can be helpful to the treating physician in determining the number of pills ingested.

Special Considerations

Most cases of major depression can be treated successfully, usually with medication, psychotherapy, or both. The combination of psychotherapy and antidepressants is very effective in treating moderate to severe depression. The medications improve mood, sleep, energy, and appetite, while therapy strengthens coping skills, deals with possible underlying issues, and improves thought patterns and behavior.

In general, antidepressants alone help about 60%–70% of those taking them. Although a few individuals may experience some improvement from antidepressants by the end of the first week, most people do not see significant benefits from their antidepressants until after 3–4 weeks, and it can sometimes take as long as 8 weeks for the medication to produce its full effects. Thus it is critical that patients continue to take their antidepressant long enough for the medication to be beneficial and that patients not get discouraged and stop their medication prematurely if they do not feel better immediately.

In short-term studies, antidepressants were found to increase the risk of suicidal thinking and behavior in children and adolescents with major depression and other psychiatric disorders. The FDA requires the prescriber to warn of this risk in children and adolescents when starting antidepressant therapy. According to the FDA findings, the risk of suicidal thoughts and behaviors associated with antidepressants is age-related. This phenomenon tends to occur in the younger population and is most likely to occur early in the course of treatment. In adults over 24 years of age, there did not appear to be an increased risk of suicidality with antidepressants compared with placebo. In patients over age 65, the findings showed that antidepressants had a “protective effect” against suicidal thoughts and behavior. Other studies have found that when more people in a community are taking antidepressants, the suicide rate is lower.

The risk of suicide is inherent in depression and may persist until the individual responds to treatment. After starting or changing antidepressant therapy, the person, especially a child or adolescent, should be closely observed for worsening signs of depression, and the family or caregiver should communicate any concerns to the physician.

- **Warning:** Always let your physician or a family member know if you have suicidal thoughts. Notify your psychiatrist or your family physician whenever your depressive symptoms worsen or whenever you feel unable to control suicidal urges or thoughts.
- Do not discontinue your MAOI abruptly. The medication should be tapered gradually before completely stopping it.
- If you miss a dose, take it as soon as possible, within 2–3 hours of the scheduled dose. If it is close to the next scheduled dose, skip the missed dose and continue on your regular dosing schedule. Do not take double doses.
- Your MAOI may be taken with or without food.
- It is recommended that you carry an identification card or wear a MedicAlert bracelet to alert health care professionals that you are taking an MAOI. Inform other physicians and your dentist that you are taking an MAOI.
- Avoid foods that are high in tyramine. If you are unsure of the food, avoid it until you check with your physician or pharmacist. Furthermore, even after stopping your MAOI, it takes about 2 weeks before it is safe to resume a regular diet or take certain medications; therefore, it is very important to maintain your dietary and medication restrictions for 2 weeks after discontinuation of your MAOI.
- Store the medication in its originally labeled, light-resistant container, away from heat and moisture. Heat and moisture may precipitate breakdown of your medication, and the medication may lose its therapeutic effects.
- Keep your medication out of reach of children.

If you have any questions about your medication, consult your physician or pharmacist.

