

Monoamine Oxidase Inhibitors

Eldepryl (selegiline), Marplan (isocarboxazid), Nardil (phenelzine), Parnate (tranylcypromine)

Monoamine oxidase inhibitors (MAOIs) represent a group of older antidepressants that have limited, but selective, use for treatment of depression. These agents have been supplanted by newer and safer agents such as **selective serotonin reuptake inhibitors** (SSRIs) as well as other non-S SRIs 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 monoamine oxidase enzymes non-selectively 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 due to 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 these medications for these unapproved indications. 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 (selegiline) does not have a labeled indication for depression but for Parkinson's disease, which is a progressive neurological disease

affecting movement and mobility. When taken at dosages higher than those used for treating Parkinson's disease, Eldepryl may be effective 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 for 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. Dosages of 20–50 mg/day of Eldepryl have been reported to be effective for treatment of depression.

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. The common side effects associated with MAOIs are daytime sedation, dizziness, dry mouth, 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 muscle aches and 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, 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, renal failure, coma, and death. Hence, patients taking MAOIs should be alerted to 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. They should be cautious when rising to their feet suddenly. When lying down, they should get up gradually to a sitting position first before standing. If feeling lightheaded or dizzy, they should sit and wait for a minute or two to allow the blood pressure to adjust before standing up.

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 dangerously 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 presences 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 and fish (e.g., salami, smoked fish, sausage, salami, pepperoni, and corned beef)		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)		Levodopa and dopamine medications used to treat Parkinson's disease
Soy sauce, tofu, fermented bean curd (found in soybean paste and miso soup)		

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 medication may preclude use of certain medications or 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, if necessary, under close surveillance.

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 those with drugs that cause a hypertensive crisis or serotonin syndrome, such as:

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)	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.

Overdose

Early signs and symptoms of MAOI overdose include drowsiness, irritability, low blood pressure, restlessness, and breathing difficulties. The individual 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 if other medications are involved.

Any suspected overdose should be treated as an emergency. The person should be taken to the emergency department 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.

The controversial issue of suicide and antidepressants has prompted the U.S. Food and Drug Administration to ask manufacturers of some antidepressants, particularly the SSRIs, to provide warnings in their package insert that the risk of suicide may be increased in depressed individuals (especially children) during the first several weeks after beginning an antidepressant. However, 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. Depressed individuals who are at risk for suicide should be closely watched at the outset of therapy, and any signs of suicidal or violent behavior should be immediately reported to the physician or a mental health provider.

- **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 dosing. If longer, skip the missed dose and continue on your regular dosing schedule, but 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 Medic Alert bracelet to alert health care professionals that you are taking an MAOI. Inform your physician and dentist that you are receiving 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.
- Keep your medication out of reach of children.

Dietary guidelines while taking MAOI Medications

There can be a dangerous interaction between your medicine and tyramine, a substance found in some foods and beverages. For this reason, you must follow these dietary instructions from the day you start taking an MAOI medicine until 3 to 4 weeks after you stop taking it.

Tyramine is found in foods that are fermented, aged, or spoiled. Normally, an enzyme (called monoamine oxidase) in your digestive tract keeps tyramine levels within a safe range. But when you take an MAOI medicine, this enzyme can no longer work on tyramine. When tyramine levels increase, they can cause potentially serious reactions such as severe hypertension (high blood pressure), headaches, heart problems, nausea, vomiting, visual disturbances, and confusion. For this reason, you will need to avoid eating foods containing significant amounts of tyramine.

1. Do not eat any of the following (these foods contain >6 mg tyramine/serving)

- All aged and mature cheeses. (The only cheeses that are okay to eat are: cottage cheese, cream cheese, ricotta, part-skim mozzarella, and processed cheeses like American, if refrigerated for no more than 2 to 3 weeks).
- All improperly stored meats, fish, and poultry. See details below under Guidelines.
- Air-dried sausages such as pepperoni, summer “dry” sausage, salami, pastrami, and mortadella.
- Fermented soy products including soy sauce, teriyaki, soybean paste, fermented bean curd (fermented tofu), miso soup, tamari, natto, shoyu, and tempeh.
- Sauerkraut.
- All tap beers.

The following foods are rarely eaten in the U.S., so you may not be familiar with them.

Avoid: Fava or broad bean pods, banana peel, Marmite spread.

Limit to no more than two servings per day:

- wine (one serving = 4 oz)
- bottled or canned beer (including non-alcoholic) (one serving = 12 oz)
- liqueurs or distilled spirits (one serving = 1 1/2 oz).

Guidelines

- All foods that you eat must be very fresh, or properly frozen.
- Store all fresh packaged meat, fish, poultry, and dairy products in the refrigerator/freezer immediately. Eat allowed refrigerated meat products within 3 to 4 days. Eat allowed refrigerated cheeses within 2 to 3 weeks. Avoid foods if you are unsure of their storage conditions.

- Remember to stay away from combination foods that contain foods to be avoided. These include items such as cheese crackers, sub sandwiches, stir-fried dishes containing soy sauce, etc. Pizza, lasagna, and other cheese-containing dishes may be eaten only if made with “allowed” cheeses and toppings.
- There are many non-prescription and prescription medicines you must avoid. Tell your doctor, dentist, or pharmacist that you are taking an MAOI medication before taking any other medicines, either over-the-counter or prescription.
- Be especially aware of diet or weight-reducing drugs; sinus, hay fever, or cold medicines; nose sprays or drops; asthma inhalants or tablets; cough medicines; and herbal stimulants like ginseng and ma huang (ephedra).

Dietary guidelines for MAOI antidepressants

There can be a dangerous interaction between your medicine and tyramine, a substance found in some foods and beverages. For this reason, you must follow these dietary instructions from the day you start taking an MAOI medicine until 3 to 4 weeks after you stop taking it. If you are taking Emsam, this warning only applies to the 9 or 12mg dose.

Tyramine is found in foods that are fermented, aged, or spoiled. Normally, your stomach keeps tyramine levels within a safe range. MAOI medicines alter the metabolism of tyramine. High tyramine levels can cause potentially serious reactions such as severe hypertension (high blood pressure), headaches, heart problems, nausea, vomiting, visual disturbances, and confusion.

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- All aged and mature cheeses. (The only cheeses that are okay to eat are: cottage cheese, cream cheese, ricotta, part-skim mozzarella, and processed cheeses like American, if refrigerated for no more than 2 to 3 weeks).
- All improperly stored meats, fish, and poultry. See details below under *Guidelines*.
- Air-dried sausages such as pepperoni, summer “dry” sausage, salami, pastrami, and mortadella.
- Fermented soy products including soy sauce, teriyaki, soybean paste, fermented bean curd (fermented tofu), miso soup, tamari, natto, shoyu, and tempeh.
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