

Dietary Restrictions and Drug Interactions With Monoamine Oxidase Inhibitors: The State of the Art

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Antidepressant activity of monoamine oxidase inhibitors (MAOIs) was initially noted in the 1950s, and by the early 1960s, they were a mainstay of antidepressant treatment. Reports of adverse events such as acute hypertensive reactions following the ingestion of certain foods and beverages tempered clinicians' enthusiasm for MAOIs. Introduction of the tricyclic antidepressants and the selective serotonin reuptake inhibitors led to declines in the use of MAOIs. However, MAOIs have been well established as an effective intervention for people with treatment-resistant depression, and transdermal formulations may provide a valuable therapeutic option and eliminate the drug-food interaction.

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Despite their known efficacy in the treatment of major depressive disorder, the older monoamine oxidase inhibitors (MAOIs) (phenelzine, tranylcypromine, isocarboxazid, and selegiline) are an underutilized class of agents. This lack of acceptance by both physicians and patients was spurred on because of the potentially serious side effect profile of these compounds. The hypertensive or "cheese" effect associated with tyramine and MAOIs has been well documented since the early 1960s.^{1–3} Soon after the introduction of the MAOIs in the early 1960s, more than 40 cases of acute episodes of throbbing headache with marked elevations in blood pressure had been reported in people taking MAOIs. These episodes were sometimes complicated by intracerebral hemorrhage and were typically associated with

tranylcypromine.⁴ Subsequent investigations revealed that episodes predictably followed ingestion of cheese containing high concentrations of tyramine, a monoamine long recognized as a vasopressor and degradation of which usually involves MAO systems in various cell types within the body.^{5,6} Horwitz et al.⁶ produced acute hypertensive episodes in patients by administering tyramine during treatment with MAOIs and found that sensitivity to ingested tyramine increased 10-fold to 100-fold, depending on the MAOI. Stimulated by a number of similar and new adverse reports, the U.S. Food and Drug Administration considered withdrawing market approval for tranylcypromine. However, the results of a careful scientific review eventually concluded that the clinical benefits outweighed the risks for depressed patients. The FDA did require new labeling that included extensive precautions about concomitant use with foods known to contain high levels of tyramine.⁷

Since then, there have been numerous reports of hypertensive reactions associated with MAOIs following ingestion of a wide variety of foods. At one point, an international survey of diets reported that as many as 70 different types of foods were considered to be hazardous for patients taking MAOIs, but that many of the restricted items were based on case reports or a single report of adverse reactions.^{7,8} Serious hypertensive reactions between MAOIs and foods other than cheese have been confirmed, but are limited to a relatively small number of foods.⁹ Blackwell et al.¹⁰ observed a patient who developed a headache and hypertension after eating a commercial yeast extract. Hodge and colleagues¹¹ reported a hypertensive reaction involving broad beans. Boulton et al.¹² reported a case of a patient who ate spoiled beef liver and presented with a hypertensive crisis; a similar occurrence had been noted with rancid chicken livers.¹³ Generali et al.¹⁴ reported a severe but nonfatal hypertensive reaction in a patient who ingested a large amount of avocados. However, 80% of all hypertensive crises have been associated with cheese.⁴

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MECHANISM OF ACTION

Monoamine oxidases represent a family of enzymes that metabolize and subsequently inactivate monoamine and indolamine neurotransmitters, including dopamine, epinephrine, norepinephrine, serotonin, and tyramine.¹⁵ MAO is present in the nervous system, liver, gastrointestinal tract, mitochondrial membranes, and platelets and consists of 2 subtypes: MAO-A and MAO-B.¹⁶ MAO-A occurs primarily in the brain and the intestine; in the brain, the primary substrates are norepinephrine, dopamine, and serotonin. Other amines, such as tyramine—a precursor to dopamine—are also catabolized by MAO-A after being absorbed from the gastrointestinal tract or after being generated as the result of bacterial metabolic transformations. MAO-B is found in the brain, platelets, and other tissues, and its preferred substrates include β -phenylethylamine, dopamine, and tyramine. MAO-B accounts for about 80% of total MAO activity in human basal ganglia. MAO-A is present within the dopaminergic, serotonergic, and noradrenergic nerve terminals. Within the human brain, MAO-A is located in regions with a high density of catecholaminergic neurons and is colocalized with dopamine- β -hydroxylase, the enzyme that converts dopamine to norepinephrine.¹⁷ The antidepressant activity of MAOIs is thought to occur as a result of the MAO-A inhibition. However, inhibition of MAO-A also inhibits tyramine breakdown, with the resultant adverse consequences.

Normally, monoamine oxidase (primarily MAO-A) in the digestive tract keeps tyramine levels at a safe range. However, when peripheral MAO-A is inhibited by 80% or more, tyramine is not catabolized, is able to enter the circulatory system, and causes a significant release of norepinephrine from the peripheral adrenergic neurons. In an effort to lessen this effect, reversible and selective MAOIs have been developed and have undergone clinical testing. Moclobemide, which is not available in the United States, is the most widely studied MAOI and appears to have a diminished sensitivity to the pressor effects of tyramine. Another alternative is the recent development of the selegiline transdermal system, which offers an advantage over existing MAOIs because it does not inhibit MAO-A in the periphery and thus does not inhibit tyramine metabolism.¹⁸

Individual factors relating to the hypertensive reaction include the amounts of food eaten, rate of gastric emptying, type and potency of the MAOI, and dose of the MAOI.^{9,19} Another consideration is the variation in the amount of tyramine in food relative to bacterial flora, maturation time, and degree of decomposition or degradation. Because tyramine is an amino acid derived from protein degradation, any protein food that has spoiled can become a source of large amounts of tyramine. The severity of the reaction is ultimately related to the amount of tyramine absorbed into the bloodstream; however, the amount of tyramine required to induce the reaction may vary greatly among different people. Researchers have noted a rise in blood pressure from

Table 1. Relative Restrictions of Food and Beverages With MAOI Use^a

Absolute	Aged cheese; aged and cured meat; banana peel; broad bean pods; improperly stored or spoiled meats, poultry, and fish; Marmite; sauerkraut; soy sauce and other soy condiments; tap beer
Moderate	Red and white wine, bottled or canned beer
Unnecessary	Avocados; bananas; beef/chicken bouillon; chocolate; fresh and mild cheese; fresh meat, poultry, or fish; gravy (fresh); monosodium glutamate; peanuts; properly stored pickled or smoked fish; yeast extracts

^aAdapted with permission from Gardner et al.²³
Abbreviation: MAOI = monoamine oxidase inhibitor.

as little as 6 to 8 mg of tyramine^{20,21}; however, Blackwell and Mabbitt²² consider amounts of tyramine greater than 25 mg to be potentially dangerous, although there has been a paucity of research to support this estimate.

TYRAMINE CONTENT OF FOOD

Over the years, growing concerns about this potential adverse event have led to what some consider an over-restriction of dietary factors. Foods with documented MAOI-diet interactions based on their tyramine content include aged cheeses; beer, red wine, sherry, and vermouth; yeast and protein extracts, including monosodium glutamate; fava and broad bean pods; smoked or pickled fish; beef and chicken liver; fermented meats (sausage, bologna, pepperoni); canned or overripe figs; stewed and whole bananas; soy sauce; avocado/guacamole; and chocolate.⁹ However, the actual tyramine content of many foods has been difficult to assess. Shulman et al.¹ assayed more than 100 foods purportedly associated with hypertensive reactions or thought to contain high levels of tyramine. The assays confirmed a high concentration of tyramine per serving size in aged cheeses, such as English Stilton, blue cheese, and cheddar cheese; aged meat and sausage; banana peel; sauerkraut; and concentrated yeast extract.¹ Gardner et al.²³ used a critical review of the literature and the results of their own tyramine assays to categorize foods to be absolutely restricted, taken in moderation only, or unrestricted by patients who take MAOIs (Table 1). They recommended that patients who take MAOIs avoid aged cheese; aged or cured meats; any meat, poultry, or fish that are not fresh or that are spoiled; broad (fava) bean pods; commercial concentrated yeast extract; sauerkraut; soy sauce and soy bean condiments; and tap beer. Wines and domestic bottled or canned beers are considered safe when consumed in moderation—up to 2 drinks per day. They also recommended that certain foods need not be avoided at all, such as fresh and mild cheeses, including ricotta, cottage, or cream cheese; fresh meat, fish, or poultry; monosodium glutamate; properly stored pickled or smoked fish; and yeast tablets or sprinkles. There have been some questions as to the overall safety of commercially produced pizzas, which

Table 2. Sunnybrook Health Center MAOI Diet^a

Food Group	Food to Avoid	Food Allowed
Cheese	Mature or aged cheese, casseroles made with these cheeses; all except listed opposite	Fresh cottage, cream, and ricotta cheese and processed cheese slices; all fresh milk products
Meat, fish, poultry	Fermented/dry sausage, pepperoni, salami, mortadella, improperly stored meat, fish, or poultry	All fresh packaged or processed meat, fish, or poultry; store in refrigerator, eat as soon as possible
Fruits and vegetables	Fava or broad bean pods, banana peel	Banana pulp; all others except listed opposite
Alcoholic beverages	All tap beer	Alcohol, no more than 2 domestic or canned beers or 4 oz wine/day
Miscellaneous foods	Marmite yeast concentrate, sauerkraut, soy sauce/condiments	Other yeast extracts, soy milk

^aAdapted with permission from Gardner et al.²³

Abbreviation: MAOI = monoamine oxidase inhibitor.

might include aged cheeses. Independent review of several pizzas from large chains, including those with pepperoni and double cheese, has deemed them “safe for consumption” by patients taking MAOIs.²⁴ This same review also determined the tyramine content of a variety of soy products. Marked variability was found in soy products, including clinically significant tyramine levels in tofu when stored for a week and high tyramine content in one of the soy sauces assessed. The authors concluded that all soybean products should be avoided, especially soy sauce and tofu.²⁴

Because of concern for patient safety, previous MAOI diets have probably been overly restrictive. Many of the prior restrictions have been based on unsubstantiated case reports and a limited scientific understanding of the mechanism underlying the interaction.⁹ There is some concern that overly restrictive diets may paradoxically increase the risk of hypertensive crisis by increasing noncompliance with the diet or that patients may become lax with their diets after discovering that a particular dietary restriction causes no reaction.^{25,26} With the development of evidence-based dietary restrictions, the MAOI diet has become much less burdensome. Table 2 provides a version of the MAOI diet based on the work of Gardner et al.²³ This diet was designed to improve patient compliance and quality of life in a patient population that is likely already depressed and/or anxious.

DRUG INTERACTIONS

Serotonin Syndrome

Concurrent administration of an MAOI with agents that increase the availability of serotonin may result in a reaction known as the “serotonin syndrome.” The syndrome, first described in animal models in the 1950s, was initially referred to as the “serotonin behavioral syndrome” or “hyperactivity syndrome.”²⁷ Reports of serotonin syndrome in humans followed and have become increasingly frequent since the 1960s. The earliest reports involved persons who were taking MAOIs. Some of the early reports included patients who were taking concomitant tryptophan, a serotonin precursor.^{27,28} Serotonin syndrome is characterized by a constellation of at least 3 of the following symptoms following an increase in dosage or recent addition of a serotonergic agent: mental status changes, agitation, myoclonus, hyperreflexia,

fever, shivering, diaphoresis, ataxia, and diarrhea—with or without hypertension.^{29,30} In rare cases, the symptoms may progress to seizures, hyperthermia, rhabdomyolysis, ventricular arrhythmia, respiratory arrest, or even death. Mild to moderately severe cases of serotonin syndrome usually resolve in 24 to 72 hours.²⁷ Though most cases can be treated and resolve within a week, some patients become acutely ill and require hospitalization. Optimal treatment is conservative and entails discontinuing the suspected medication and providing supportive measures, such as intravenous hydration. In some instances, patients have been admitted to the intensive care unit and required mechanical ventilation. Mortality associated with this condition is estimated to be 11%.³¹

Serotonin occurs naturally in the body. In the periphery, serotonin acts both as a gastrointestinal regulating agent and a modulator of blood vessel tone.³² Although only 2% of the body’s serotonin is found in the brain as a neurotransmitter, this substance has a profound effect on body functions. As a neurotransmitter, serotonin is involved in the modulation of motor function, pain perception, appetite, and outflow from the sympathetic nervous system.²⁹ Serotonin acts at receptors generally classified into 1 of 4 categories, depending upon function and location. The 4 recognized categories of serotonin receptors are 5-HT₁, 5-HT₂, 5-HT₃, and 5-HT₄. Receptor subtypes have been identified within each of these categories. For example, the 5-HT_{1D} subtype lies outside the central nervous system and is the receptor through which sumatriptan exerts its antimigraine effect. Researchers agree that the signs and symptoms associated with serotonin syndrome involve excessive stimulation of the 5-HT_{1A}^{27,33} and 5-HT₂ receptors.^{27,29} The 5-HT₂ receptors are located in the brain and peripheral blood vessels. Most cerebral functions are the result of the convergence of many different neurotransmitters, including serotonin.³⁴ This complex network of neurotransmitters makes it possible for serotonin to modulate a wide array of central nervous system functions. For example, serotonin often serves as a cotransmitter along with γ -aminobutyric acid (GABA) and norepinephrine. Serotonin antagonizes GABA_B receptors, causing up-regulation of this subtype. The activity of benzodiazepines in the treatment of serotonin syndrome is thought to occur because these compounds act as strong agonists at GABA_B receptors. Certain dopaminergic neurons have serotonin receptors, resulting in

serotonin-modulated release of dopamine in different areas of the brain.³⁵

Many case reports of the serotonin syndrome have come from patients who were prescribed an MAOI along with a serotonin reuptake inhibitor (SSRI) or a tricyclic antidepressant (TCA). The combination of MAO inhibition with inhibition of reuptake may result in a flood of serotonin and norepinephrine into the synapse, exceeding its capacity for enzymatic catabolism.³⁰ Causative agents associated with serotonin syndrome include those that increase serotonin synthesis (L-tryptophan), decrease serotonin metabolism (MAOIs), increase serotonin release, inhibit serotonin uptake (SSRIs), and stimulate certain serotonin receptors directly and provide a nonspecific increase in serotonin activity. The largest number of cases reported in the literature and the most serious consequences of serotonin syndrome have resulted from use of the MAOIs.²⁹ Most cases were reported when an MAOI was used in conjunction with meperidine, tryptophan, dextromethorphan (an ingredient in many over-the-counter products), a tricyclic antidepressant, or an SSRI antidepressant.^{28,29} The long half-life of some SSRIs and the duration of effect of the irreversible MAOIs increase the possibility of serotonin syndrome occurring several weeks after these drugs have been discontinued.²⁷ It is important to note that serotonin syndrome has been precipitated by medications that are not usually thought of as being serotonergic, including meperidine and dextromethorphan.²⁹ Patients who are currently taking MAOIs should not be given meperidine; alternative analgesics, such as fentanyl and morphine, may be used. All of the SSRIs can produce serotonin syndrome; however, the unique pharmacokinetics of fluoxetine make it especially prone to cause serotonin syndrome. The half-life of fluoxetine ranges from 1 to 4 days, and its active metabolite has a half-life of 7 to 14 days.³⁶ A 5-week abstinence period is commonly recommended once fluoxetine therapy has been stopped before initiating any other serotonergic agent. For other SSRIs or TCAs with shorter half-lives, a 1- to 2-week washout may be adequate.³⁰ Table 3 lists some medications that are contraindicated with conventional MAOIs.

Several case reports illustrate the array of interactions between MAOIs and other agents. A case reported in 1994 involved a 48-year-old man brought to the emergency room due to agitation and confusion.³⁷ He had a 3-year history of depression, which was being treated with tranylcypromine. The tranylcypromine was discontinued prior to his presentation at the emergency department. Fourteen days after the MAOI was discontinued, fluoxetine (40 mg daily) was begun. Over the next 72 hours, the patient developed agitation, diaphoresis, and confusion. During his hospital stay, he developed tachycardia and profound muscle rigidity, requiring intubation. In addition to supportive measures, the patient received diazepam and propranolol to relieve muscle rigidity, hypertension, and tachycardia. By the third hospital day, his temperature returned to normal, and he rapidly recovered. He was released on the fifth day.³⁷ This case underlines

Table 3. Drugs Contraindicated With Conventional MAOIs

Drug
Sympathomimetics
Ephedrine, phenylephedrine, pseudoephedrine
Central stimulants
Amphetamine and amphetamine-like compounds, cocaine
Centrally acting antihypertensives
Guanethidine, methyl dopa, reserpine
Opioid analgesics
Pethidine (meperidine), dextromethorphan

Abbreviation: MAOI = monoamine oxidase inhibitor.

the extreme importance of implementing a “washout” period after the discontinuation of 1 serotonergic drug before the implementation of another. Even after 2 weeks, the effect of tranylcypromine was still active enough to cause a serotonergic crisis when therapy with fluoxetine was begun.

Another case reports a 72-year-old man who was admitted to the hospital for presumed Parkinson’s disease and depression.³⁸ He was placed on selegiline and fluoxetine. After 9 weeks of treatment, he presented to the hospital with acute delirium that progressed to lethargy, malaise, myoclonic jerking, and grand mal seizures. The fluoxetine was discontinued, but 7 days later, he experienced acute delirium and convulsions and became unresponsive. The selegiline was discontinued. Five days later, the symptoms resolved completely. This case demonstrates the ability of fluoxetine to exert its serotonergic effects for a few days up to weeks after discontinuation. The effect probably is due to the long half-life of both fluoxetine and its active metabolite, norfluoxetine.

Hypertensive crisis is known to occur when the irreversible, nonspecific MAOIs are taken along with other drugs, and as a result, many medications are contraindicated in patients taking MAOIs. The concurrent use of MAOIs and indirectly acting sympathomimetics (amphetamines, ephedrine, phenylpropanolamine, pseudoephedrine) can result in hypertensive urgency or hypertensive crisis—a rapid and serious rise in blood pressure, accompanied by tachycardia, chest pains, and severe occipital headache. Neck stiffness, flushing, sweating, nausea, vomiting, hypertonicity of the limbs, and sometimes epileptiform convulsions can also occur. Infrequently, fatal intracranial hemorrhage, cardiac arrhythmias, and cardiac arrest may result.³⁹ One early case report describes a woman taking pargyline who was given phenylpropanolamine for nasal decongestion on the eve of surgery, which promptly caused a hypertensive reaction.⁴⁰ Her blood pressure rose rapidly from 130/80 to 220/160 mm Hg, and she complained of occipital headache, photophobia, and nausea. She also exhibited sweating and vomited. Two intravenous injections of phentolamine 5 mg controlled her blood pressure.⁴⁰ Patients taking MAOIs should be taught to avoid over-the-counter compounds that contain indirectly acting sympathomimetics. If these drugs are used together and hypertensive crisis develops, agents such as phentolamine, chlorpromazine, nicardipine, and labetalol,

along with intravenous hydration, may be administered in the emergency room. Effects of nonselective MAOIs should be assumed to persist for 2 weeks after they are discontinued, so clinicians should not administer sympathomimetics until after this time period.

Phentolamine and chlorpromazine are traditional drug treatments for MAOI hypertensive emergencies. Newer drug treatments have evolved in the last decade for treating hypertensive emergencies, but are not necessarily yet reflected in the psychiatric or emergency medicine literature on treating MAOI-induced hypertensive states. Nifedipine, diazoxide, or sodium nitroprusside appear to be more rational choices for the treatment of hypertensive crises.⁴¹

CONCLUSION

Monoamine oxidase inhibitors are underutilized in the treatment of major depressive disorder and other psychiatric disorders, in part because of fears about serotonin syndrome, hypertensive reactions, adverse interactions with foods, and the need for a restricted diet. Less rigid, evidence-based dietary guidelines are now available that should help enhance patient adherence. The development of delivery systems that reduce the risk of tyramine-related hypertensive crisis are likely to increase the use of MAOIs again. Patients taking MAOIs should be encouraged to consult with their clinician prior to adding either a prescription or an over-the-counter medication to their regimen. Serotonin syndrome is an important drug-related complication that may occur when 2 or more serotonergic drugs are given concurrently. It is imperative that clinicians recognize and avoid potential serotonergic drug interactions. In general, MAOIs can be used safely as long as the physician and patient clearly understand some simple principles that will decrease the risk of food and/or drug-drug interactions.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), diazepam (Valium and others), diazoxide (Proglycem), fentanyl (Duragesic, Fentora, and others), fluoxetine (Prozac and others), isocarboxazid (Marplan), labetalol (Trandate and others), meperidine (Demerol and others), morphine (Kadian, Avinza, and others), nifedipine (Cardene and others), nifedipine (Procardia, Adalat, and others), phenelzine (Nardil), phentolamine (Regitine and others), propranolol (Innopran, Inderal, and others), reserpine (Serpalan and others), selegiline (Eldepryl, Zelapar, and others), selegiline transdermal system (EMSAM), sodium nitroprusside (Nitropress and others), sumatriptan (Imitrex), tranlycypromine (Parnate and others).

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