

FIRST OF 2 PARTS



# A concise guide to monoamine oxidase inhibitors

A better understanding of the risks can lead to increased use of these highly effective agents

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### Disclosure

Dr. Meyer is a consultant to Acadia Pharmaceuticals, Neurocrine Biosciences, Inc., and Teva Pharmaceutical Industries; and is a speaker for Acadia Pharmaceuticals, Alkermes, Allergan, Merck, Neurocrine Biosciences, Inc., Otsuka America, Inc., Sunovion Pharmaceuticals, and Teva Pharmaceutical Industries.

Despite an abundance of evidenced-based literature supporting monoamine oxidase inhibitors (MAOIs) as an effective treatment for depression, use of these agents has decreased drastically in the past 3 decades. A lack of industry support and the ease of use of other agents are contributing factors, but the biggest impediments to routine use of MAOIs are unfamiliarity with their efficacy advantages and concerns about adverse effects, particularly the risk of hypertensive crises and serotonin syndrome. Many misconceptions regarding these medications are based on outdated data and studies that are no longer reliable.

The goal of this 2-part review is to provide clinicians with updated information regarding MAOIs. Part 1 provides a brief description of:

- the pharmacology of nonselective irreversible MAOIs
- the mechanism by which tyramine induces hypertension
- sources of clinically significant tyramine exposure
- what to tell patients about dietary restrictions and MAOIs.

Part 2 of this guide will cover the risk of serotonin syndrome when MAOIs are combined with inhibitors of serotonin reuptake, how to initiate MAOI therapy, and augmenting MAOIs with other agents.

## The pharmacology of MAOIs

First used clinically in the 1950s to treat tuberculosis, MAOIs have a long and interesting history (see the *Box* "A brief history of monoamine oxidase inhibitors" on [CurrentPsychiatry.com](http://CurrentPsychiatry.com)). *Table 1* (page 16) lists





## Monoamine oxidase inhibitors

### Clinical Point

**Nonselective MAOIs offer a therapeutic opportunity for patients who do not respond to single or dual-mechanism strategies**



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**Table 1**

## MAOIs available in the United States

Drug (brand name, approval date)	MAO-A/B	Dose	Comments, adverse effects
Isocarboxazid (Marplan, 7/1/59)	1:1	Start: 10 mg at bedtime Max: 60 mg/d	AEs: Sexual dysfunction, weight gain, orthostasis, hypertensive events, serotonin syndrome
Phenelzine (Nardil, 6/9/61)	1:1	Start: 15 mg at bedtime Max: 90 mg/d	AEs: Sexual dysfunction, weight gain, orthostasis, hypertensive events, serotonin syndrome
Tranylcypromine (Parnate, 2/21/61)	1:1	Start: 10 mg at bedtime Max: 60 mg/d	No known L-amphetamine metabolites, but can be stimulating at higher doses AEs: Sexual dysfunction, weight gain, orthostasis, hypertensive events, serotonin syndrome
Selegiline (transdermal) (Emsam, 2/27/06)	1:1	Start: 6 mg/24 h Max: 12 mg/24 h	No dietary restrictions at lowest dose (6 mg/24 h). Has L-methamphetamine metabolites; can be stimulating at higher doses. Also, has potential for false-positive drug screen AEs: Insomnia, site reaction, hypertensive events, serotonin syndrome
Rasagiline (Azilect, 5/16/06)	1:14	(Only used for Parkinson's disease)	Lacks L-amphetamine metabolites. No risk of hypertensive crises. No cases of serotonin syndrome when combined with antidepressants in large review (n = 1,504), <sup>1</sup> but the package insert warns about use with inhibitors of serotonin reuptake, including antidepressants, meperidine, tramadol, and methadone AEs: Adjunctive use: orthostasis and falls, peripheral edema, dyskinesia, abnormal dreams, nausea. Risk of serotonin syndrome not seen in large samples, although the package insert includes warnings
Selegiline (oral) (Eldepryl, 4/17/89)	5 mg, twice a day: 1:10 >20 mg/d: 1:1	(Only used for Parkinson's disease)	Short half-life requires multiple daily dosing. Lower plasma levels for oral than transdermal results in limited MAO-A inhibition. Oral bioavailability 4% vs 75% for transdermal AEs: Nausea, dizziness/orthostasis/falls, abdominal pain

AE: adverse effect; MAO: monoamine oxidase

MAOIs currently available in the United States, including the MAO-B-specific agent rasagiline, which is used for Parkinson's disease.

Manipulation of the monoamines serotonin, norepinephrine, and dopamine is fundamental to managing major depressive disorder (MDD), yet only nonselective MAOIs directly promote neurotransmission of all 3 by inhibiting MAO-A and MAO-B.<sup>2</sup> The Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study demonstrated that <50% of MDD patients achieve remission in monotherapy trials of selective serotonin reuptake inhibitors, sero-

tonin norepinephrine reuptake inhibitors, mirtazapine, or bupropion, necessitating consideration of antidepressant combinations, augmentation options, and eventually irreversible, nonselective MAOIs such as phenelzine, tranylcypromine, or isocarboxazid.<sup>3,4</sup> Nonselective MAOIs thus offer a therapeutic opportunity for patients who do not respond to single or dual-mechanism strategies; moreover, nonselective MAOIs have compelling effectiveness data for other conditions, including panic disorder and social phobia.<sup>5</sup> Although MAOIs are among the most effective pharmacologic agents for MDD,<sup>6</sup> they are underutilized

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**Monoamine oxidase inhibitors**

**Clinical Point**

**CNS MAO-A inhibition is necessary for antidepressant effects**

**Table 2**

**Substrates for monoamine oxidase enzymes**

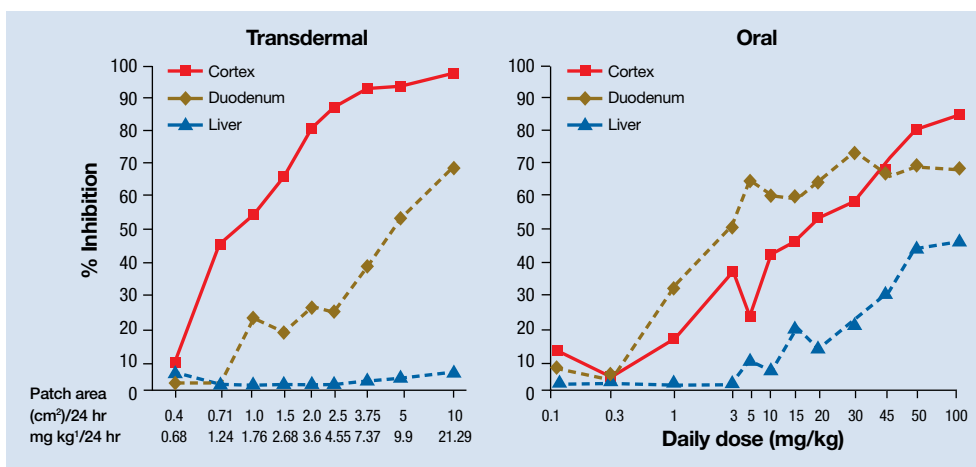
	MAO-A	MAO-B
Substrates	Serotonin Norepinephrine Dopamine Tyramine	Dopamine Phenylethylamine
Tissue localization	Brain, gut, liver, placenta, skin	Brain, platelets, lymphocytes

MAO: monoamine oxidase

Source: References 9,10

**Figure 1**

**Comparative gut monoamine oxidase inhibition of transdermal and oral selegiline in an animal model**



Source: Reference 12

because of an inadequate understanding of risk mechanisms and resultant fear of catastrophic outcomes. Because of the difficulties encountered in achieving clinical remission for MDD, the nonselective MAOIs deserve a second look.

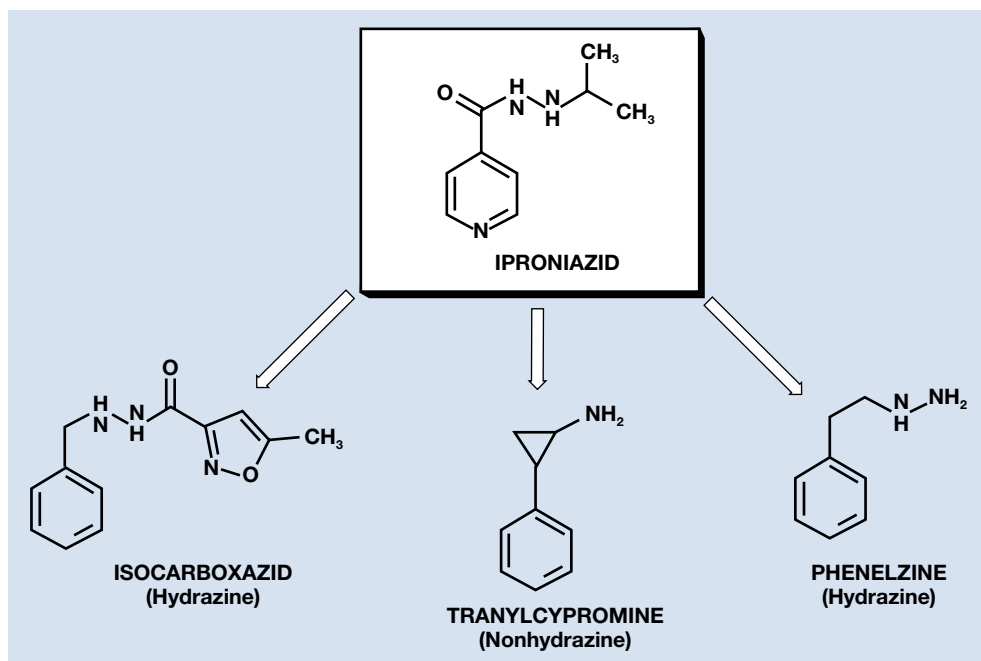
**Differentiation of MAO-A from MAO-B.** It is essential to understand the mechanism of action of MAOIs, specifically the impact of MAO-A inhibition. Although the enzyme MAO was known in the 1950s, it wasn't until 1968 that Johnston<sup>7</sup> postulated the existence of >1 form. In 1971, Goridis and Neff<sup>8</sup> used clorgyline to examine the deamination rate by MAO of tyramine and norepinephrine. They found that tyramine appeared to be a substrate of both MAO isoforms, but only 1 of the MAO types was sensitive to the inhibitory effects of clorgyline. They also

discerned that norepinephrine was only a substrate for MAO-A, and that this form of MAO was sensitive to clorgyline inhibition. Thus, the forms of MAO were characterized by their preferred substrates (Table 2<sup>9,10</sup>), and then later by their tissue distribution. Phenylethylamine is a naturally occurring compound found in foods, such as chocolate, and has an *in vitro* pharmacology similar to amphetamine but with 1 important difference: it has a short half-life of 5 to 10 minutes after oral ingestion, and therefore no appreciable CNS impact.

Within the CNS, norepinephrine and dopamine neurons possess both MAO forms, with the MAO-A content greater than MAO-B. Serotonergic neurons only contain MAO-B.<sup>11</sup> Outside of the CNS, MAO-A predominates, with only platelets and lymphocytes possessing MAO-B

Figure 2

## Chemical classification of nonselective monoamine oxidase inhibitors



### Clinical Point

Patients taking selegiline should disclose their use of this medication prior to undergoing drug testing procedures

activity.<sup>11</sup> The overall relative tissue proportions of MAO-A to MAO-B activity are: brain, 25% MAO-A, 75% MAO-B; liver, 50% MAO-A, 50% MAO-B; intestine, 80% MAO-A, 20% MAO-B; and peripheral adrenergic neurons, 90% MAO-A, 10% MAO-B.

Because of its specificity for serotonin and norepinephrine, CNS MAO-A inhibition is necessary for antidepressant effects. MAO-B inhibition by itself does not appear to raise CNS dopamine levels unless exogenous dopamine is supplied.<sup>11</sup> All MAOIs used in the United States to treat depression are *irreversible, nonselective inhibitors* of MAO-A and MAO-B.

Selegiline in oral form generates low plasma levels and primarily inhibits MAO-B. The transdermal form of selegiline achieves significantly greater systemic exposure, and at these higher plasma levels selegiline is a nonselective, irreversible MAOI effective for MDD (Figure 1,<sup>12</sup> page 18). Administering selegiline systemically via a transdermal patch avoids clinically significant MAOI effects in the gut, so no dietary warnings exist for the lowest dose (6 mg/24 hours), although there are warnings for the higher dosages (9 mg/24 hours and 12 mg/24 hours).

**Differentiation of MAOIs by chemical class.** The earliest MAOI, iproniazid, was a hydrazine derivative and exhibited hepatotoxicity,<sup>13</sup> as did certain other hydrazine MAOIs. This led to a search for safer hydrazine and nonhydrazine alternatives. Isocarboxazid and phenelzine are the 2 hydrazine MAOIs available in the United States, while tranylcypromine and selegiline transdermal are nonhydrazines (Figure 2).

What distinguishes the nonhydrazine medication selegiline is that its metabolism generates L-amphetamine metabolites (Figure 3,<sup>14</sup> page 20). This property was thought to be shared by other nonhydrazines, but recent studies indicate that neither tranylcypromine<sup>15</sup> nor the MAO-B-selective rasagiline possess amphetamine metabolites.<sup>16</sup> Unlike the *dextro* isomers, L-amphetamine structures do not inhibit dopamine reuptake or cause euphoria, but can cause stimulation (eg, sleep disturbance) by inhibiting norepinephrine reuptake, and also by interacting with the trace amine-associated receptor 1 (TAAR1), an intracellular receptor expressed within the presynaptic ter-

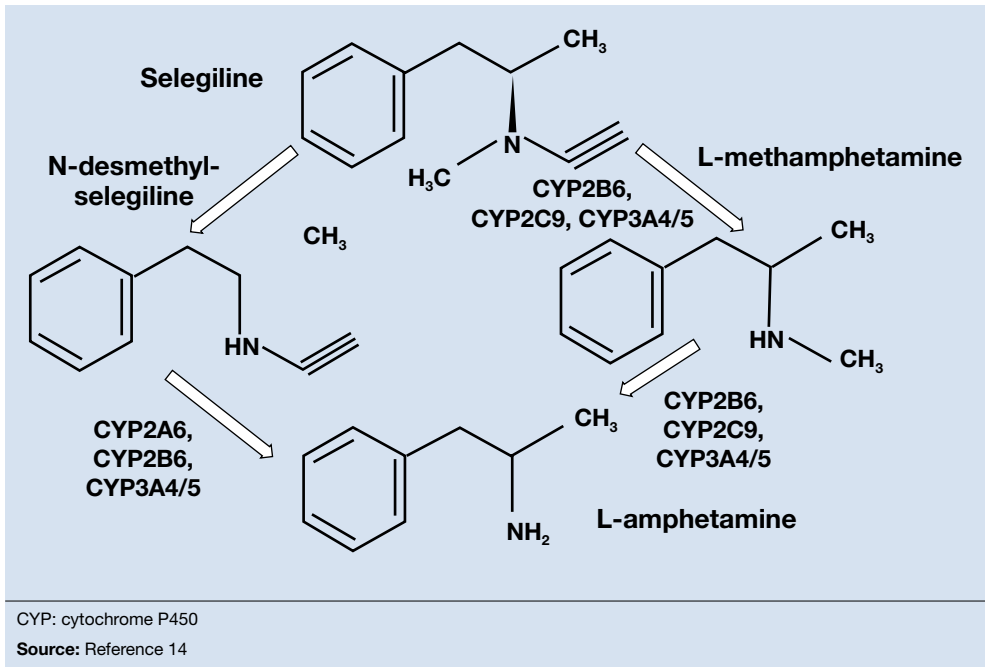


**Monoamine oxidase inhibitors**

### Clinical Point

Significant tyramine ingestion may increase BP, but the prevalence of foods high in tyramine content often is overestimated

**Figure 3**  
**Selegiline metabolism**



minimal of monoamine neurons. Activation of TAAR1 by tyramine is an important part of the hypertensive effects related to excessive tyramine exposure.<sup>17</sup> (The importance of TAAR1 and the interaction with tyramine is discussed in the next section.) Importantly, patients taking selegiline must be warned that certain drug screens may not discriminate between *levo* and *dextro* isomers of amphetamines, and that the use of selegiline should be disclosed prior to drug testing procedures.

### MAOIs and tyramine: Dietary requirements

Clinicians who are familiar with MAOIs recognize that there are dietary restrictions to minimize patients' exposure to tyramine. As most clinicians know, significant tyramine ingestion may cause an increase in blood pressure (BP) in patients taking an MAOI, but many overestimate the prevalence of foods high in tyramine content since the original reports emerged in the early 1960s.<sup>18</sup> In a recent monograph, one of the leading experts on MAOIs, Professor Ken Gillman, stated:

Very few foods now contain problematically high tyramine levels, that is a result of great changes in international food production methods and hygiene regulations. Cheese is the only food that, in the past, has been associated with documented fatalities resulting from hypertension. Nowadays most cheeses are quite safe, and even 'matured' cheeses are usually safe in healthy-sized portions. The variability of sensitivity to tyramine between individuals, and the sometimes unpredictable amount of tyramine content in foods, means a little knowledge and care are still required.<sup>19</sup>

**What is tyramine?** Tyramine is a biogenic amine that is virtually absent in fresh animal protein sources but is enriched after decay or fermentation.<sup>20</sup> Modern food processing and handling methods have significantly limited the tyramine content in processed foods, with the exception of certain cheeses and sauces, as discussed below. Moreover, modern assaying techniques using high-performance liquid chromatography have generated extremely accurate assessments

**Table 3**

**A select list of foods high in tyramine<sup>a</sup>**

	Maximal tyramine content per kg or L	Serving required to ingest 25 mg of tyramine
<b>Cheeses</b>		
Highly aged artisanal cheeses	1,000 mg	25 g (0.88 oz)
Aged feta	250 mg	100 g (3.5 oz)
Commercial cheeses and cheddar	200 mg	125 g (4.4 oz)
Grana padano, pecorino, provolone, ripened goat cheese, emmental, taleggio, bel paese	200 mg	125 g (4.4 oz)
Parmigiano reggiano	150 mg	167 g (5.9 oz)
Edam	120 mg	208 g (7.3 oz)
Gouda, gruyere	100 mg	250 g (8.8 oz)
<b>Dried aged sausages</b>		
Various, from Europe (primarily)	200 mg (rare reports up to 600 mg)	125 g (4.4 oz) (if 600 mg: 42 g; 1.5 oz)
<b>Sauces, spreads, vegetables, wine, beer</b>		
Fermented yeast (Marmite, Vegemite)	300 mg	75 g (2.64 oz) <sup>b</sup>
Specialty soy sauce	940 mg	27 g (0.94 oz) <sup>c</sup>
Fish sauce (eg, Nam-pla, etc.)	500 mg	50 g (1.8 oz) <sup>c</sup>
Commercial soy sauce	200 mg	125 g (4.4 oz) <sup>c</sup>
Sauerkraut	200 mg (rare reports up to 900 mg)	125 g (4.4 oz) (if 900 mg: 28 g; 0.98 oz)
Kimchi	120 mg	208 g (7.33 oz)
Wines	none exceeded 10 g/L	>2.5 L
Beers	majority <10 g/L (rare 30 to 100 mg/L)	>2.5 L (if 30 to 100 mg: 250 mL to 833 mL)
<sup>a</sup> For an exhaustive list, see <a href="http://www.psychotropical.com/images/Publications-pdfs/MAOI_diet_drug_interactions_2017.pdf">www.psychotropical.com/images/Publications-pdfs/MAOI_diet_drug_interactions_2017.pdf</a>		
<sup>b</sup> 1 oz = 28.35 g; 100 g = 3.53 oz; 3.53 oz = 0.22 lb		
<sup>c</sup> Usual serving: 5 g (5 mL)		
<b>Source:</b> Reference 19		

**Clinical Point**

**Data on the tyramine content of specific foods that was published prior to 2000 are not reliable because outdated methods were used**

of the tyramine content of specific foods.<sup>21</sup> Data published prior to 2000 are not reliable, because many of these publications employed outdated methods.<sup>17</sup>

When ingested, tyramine is metabolized by gut MAO-A, with doses up to 400 mg causing no known effects, although most people rarely ingest >25 mg during a meal.<sup>22</sup> In addition to being a substrate for MAO-A, tyramine is also a substrate for the dopamine transporter, norepinephrine transporter (NET), the vesicular monoamine transporter 2, and TAAR1.<sup>23</sup> Tyramine enters the cell via NET, where it interacts with TAAR1, a G protein-coupled receptor that

is responsive to trace amines, such as tyramine, as well as amphetamines.<sup>20</sup> The agonist properties at TAAR1 are the presumed site of action for the BP effects of tyramine, because binding results in potent release of norepinephrine.<sup>20,24</sup> When tyramine is supplied to an animal in which MAO-A is inhibited, the decreased peripheral catabolism of tyramine results in markedly increased norepinephrine release by peripheral adrenergic neurons. Moreover, the absence of MAO-A activity in those neurons prevents any norepinephrine breakdown, resulting in robust synaptic norepinephrine delivery and peripheral effects.

continued



## Monoamine oxidase inhibitors

### Clinical Point

Only a small number of highly aged foods contain high quantities of tyramine, and even these can be enjoyed in small amounts

All orally administered irreversible MAOIs potentially inhibit gut and systemic MAO-A, and are susceptible to the impact of significant tyramine ingestion. The exception is selegiline transdermal (*Figure 1*,<sup>12</sup> *page 18*), as appreciable gut MAO-A inhibition does not occur until doses >6 mg/24 hours are reached.<sup>22</sup> No significant pressor response was seen in participants taking selegiline transdermal, 6 mg/24 hours for 13 days, who consumed a meal that provided 400 mg of tyramine.<sup>22</sup> Conversely, for oral agents that produce gut MAO-A inhibition, tyramine doses as low as 8 to 10 mg (when administered as tyramine capsules) may increase systolic pressure by 30 mm Hg.<sup>25</sup> The dietary warnings do not apply to rasagiline, which is a selective MAO-B inhibitor, although rasagiline may have an impact on resting BP; the prescribing information for rasagiline includes warnings about hypotension and hypertension.<sup>26</sup>

### What to tell patients about tyramine.

Although administering pure tyramine capsules can induce a measurable change in systolic BP, when ingested as food, tyramine doses <50 mg are unlikely to cause an increase in BP sufficient to warrant clinical intervention, although some individuals can be sensitive to 10 to 25 mg.<sup>19</sup> When discussing with patients safety issues related to diet, there are a few important concepts to remember<sup>19</sup>:

- In an era when the tyramine content of foods was much higher (1960 to 1964) and MAOI users received no dietary guidance, only 14 deaths were reported among an estimated 1.5 million patients who took MAOIs.
- MAOIs do not raise BP, and their use is associated with orthostasis in some patients.
- Routine exercise or other vigorous activities (eg, weightlifting) can raise systolic pressure well above 200 mm Hg, and routine baseline systolic pressures, ranging from 180 to 220 mm Hg, do not increase the risk of subarachnoid hemorrhage.
- Hospital evaluation is needed only if a substantial amount of tyramine is ingested (eg, estimated  $\geq 100$  mg),

and self-monitoring shows a systolic BP  $\geq 220$  mm Hg over a prolonged period (eg, 2 hours). Ingestion of 100 mg of tyramine would almost certainly have to be intentional, as it would require one to consume 3.5 oz of the most highly tyramine-laden cheeses.

Emphasize to patients that only a small number of highly aged cheeses, foods, and sauces contain high quantities of tyramine, and that even these foods can be enjoyed in small amounts. All patients who are prescribed an MAOI also should purchase a portable BP cuff for those rare instances when a dietary indiscretion may have occurred and the person experiences a headache within 1 to 2 hours after tyramine ingestion. Most reactions are self-limited and resolve over 2 to 4 hours.

Patients who ingest  $\geq 100$  mg of tyramine should be evaluated by a physician. Under no circumstances should a patient be given a prescription for nifedipine or other medications that can abruptly lower BP, because this may result in complications, including myocardial infarction.<sup>27,28</sup> Counsel patients to remain calm. Some clinicians endorse the use of low doses of benzodiazepines (the equivalent of alprazolam 0.5 mg) to facilitate this, because anxiety elevates BP. A recent emergency room study of patients with an initial systolic BP  $\geq 160$  mm Hg or diastolic BP  $\geq 100$  mm Hg without end organ damage demonstrated that alprazolam, 0.5 mg, was as effective as captopril, 25 mg, in lowering BP.<sup>29</sup>

Also, tell patients that if a food is unfamiliar and *highly* aged or fermented, they should avoid it until they can further inquire about it. In a review, Gillman<sup>19</sup> provides the tyramine content of an exhaustive list of cheeses, aged meats, and sauces (see *Related Resources*). For other products, patients often can obtain information directly from the manufacturer. In many parts of the world, assays for tyramine content are required as a demonstration of adequate product safety procedures. Even the most highly aged cheeses with a tyramine content of 1,000 g/kg can be enjoyed in small amounts (<1 oz), and most products would require heroic intake to achieve clinically significant tyramine ingestion (*Table 3*,<sup>19</sup> *page 21*).



## Related Resource

- Gillman PK. Monoamine oxidase inhibitors: a review concerning dietary tyramine and drug interactions. *PsychoTropical Commentaries*. 2016;16(6):1-97.

### Drug Brand Names

Alprazolam • Xanax	Mirtazapine • Remeron
Bupropion • Wellbutrin, Zyban	Nifedipine • Adalat, Procardia
Captopril • Capoten	Norepinephrine • Levophed
Clozapine • Clozaril	Phenelzine • Nardil
Imipramine • Tofranil	Rasagiline • Azilect
Iproniazid • Marsilid	Selegiline oral • Eldepryl
Isocarboxazid • Marplan	Selegiline transdermal • Emsam
Lithium • Eskalith, Lithobid	Tramadol • Ultram
Meperidine • Demerol	Tranlycypromine • Parnate
Methadone • Dolophine, Methadose	

## Improved education can clarify the risks

Medications such as lithium, clozapine, and MAOIs have a proven record of efficacy, yet often are underused due to fears engendered by lack of systematic training. A recent initiative in New York thus aimed to increase rates of clozapine prescribing by providing clinicians with an education consultation center.<sup>30</sup> Similarly, enhanced education regarding MAOIs could increase the use of these highly effective medications. With a better understanding of MAOIs, clinicians can become adept at using these medications, and therefore expand the armamentarium of agents available to patients with MDD, as well as to those with panic disorder and social phobia.

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## Clinical Point

**Tell patients if a food is unfamiliar and highly aged or fermented, they should avoid it until they can further inquire about it**

## Bottom Line

Monoamine oxidase inhibitors (MAOIs) are among the most effective medications for treating depression but are underutilized because of misunderstanding of risk mechanisms and fear of catastrophic outcomes. Through education, astute clinicians can master the proper use of MAOIs and add these agents to their treatment armamentarium.

## Monoamine oxidase inhibitors

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## A brief history of monoamine oxidase inhibitors

Following World War II, large supplies of leftover hydrazine used for V2 rocket fuel were given to the pharmaceutical industry. In 1951, isonicotinylhydrazine was rediscovered, found to have antitubercular properties by independent groups at Hoffman-La Roche and Squibb, and released in 1952 as isoniazid.<sup>a</sup> Based on the success of isoniazid, numerous derivatives were synthesized, including iproniazid. In 1952, Ernst Albert Zeller demonstrated that iproniazid but not isoniazid was a monoamine oxidase inhibitor, although the significance at that time was unclear. However, later that year, the psychostimulant effects of iproniazid were noted in clinical trials of tuberculosis (TB) patients, although the CNS stimulatory findings were thought to be an adverse effect.

Nonetheless, several astute clinicians saw the opportunity presented by iproniazid, and from 1953 to 1954 a small number of case series were published on its use in psychiatric patients and depressed TB patients.<sup>a</sup> Preclinical work by Charles Scott at Warner-Lambert (1956) found that pretreatment of animals with iproniazid prevented the lethargy induced by

reserpine, and in 1957, George Crane, Frank Ayd, and Nathan Kline presented separate reports at the American Psychiatric Association (APA) Annual Meeting on iproniazid's mood-elevating effects in non-TB depressed patients. Later that year, Hoffman-La Roche organized a symposium on iproniazid, but medical directors at the company lost interest in marketing the drug as an antidepressant, because no such class of agents existed.<sup>a</sup> Kuhn's first report of imipramine's effectiveness would not appear until the end of 1957, and then only written in German in a Swiss medical journal.<sup>b</sup>

Nathan Kline subsequently held a secret meeting with the Hoffman-La Roche president to convince him to pursue iproniazid as a mood elevator, and threatened to publish the data presented at that year's APA without their support and over their objections.<sup>a</sup> Although iproniazid and certain other hydrazine-based monoamine oxidase inhibitors exhibited hepatotoxicity, numerous hydrazine and nonhydrazine structures were subsequently synthesized, and many have remained commercially available for more than 50 years.

### References

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