MONOAMINE OXIDASE INHIBITORS (MAOIs)

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MAOIs, Cheese, and the Hypertensive Crisis

Perhaps the most dreaded side effect in psychiatry is the interaction of MAOIs with tyramine-rich foods like cheese, which can cause a hyperten-sive crisis. This is a sharp and severe spike in blood pressure, typically to levels beyond 180/120 mmHg.

While everyday hypertension is a "silent killer," slowly damaging the body without causing the patient any symptoms, hypertensive crises are not silent. The vascular system has no time to adjust to the sudden increase in blood pressure. Vessels can burst, causing end-organ damage and stroke. Signs of hypertensive crisis include severe headache, confusion, blurry vision, chest pain, and seizures.

The MAOI-Cheese Interaction: Some Historical Perspective

In the first few years after MAOIs were introduced, nobody had an inkling of their potential dietary interactions. Then in 1961, a case report was pub-lished in *The Lancet* of a woman who died of a subarachnoid hemorrhage while taking tranylcypromine (Parnate), but clinicians were slow to blame tranylcypromine because these events occurred often enough in patients who were not taking MAOIs.

It took a psychiatric resident to save the day. Barry Blackwell, who was training at the Maudsley Hospital in London at the time, began reading about sporadic cases of high blood pressure, headache, and subarachnoid hemorrhage in patients taking MAOIs. A pharmacist told Blackwell that the pharmacist's wife, who was taking an MAOI, had developed two episodes of hypertension and headache after eating cheese. Intrigued, Blackwell and a colleague experimented on themselves. They took tranylcypromine for a week, then gorged on cheese. They felt perfectly fine. Nonetheless,

in his hospital, Blackwell consulted on several cases where patients taking MAOIs developed hypertensive headaches after eating cheese sandwiches. He published his suspicions in *Lancet* in 1963, but it still took some time before a skeptical medical community took this MAOI-cheese connection seriously, partly because there was no known mechanism to explain it. (For more details and references related to this story, see the fascinating book *The Antidepressant Era* by David Healy, Harvard University Press, 1997.)

This historical aside is interesting because it affords some perspective on the dangers of MAOI interactions. MAOIs were prescribed frequently for several years by physicians who had no knowledge of their possible drug or food interactions, and yet the rate of fatal reactions was extremely low. With our current knowledge of these interactions, the risk of serious problems is even lower.

The MAOI-Tyramine Interaction Explained

MAOIs, as their name implies, inactivate the enzyme monoamine oxidase (MAO). This MAO enzyme comes in two forms: A and B. MAO-A is the troublesome molecule in this story, because its normal function is to metabolize and break down the neurotransmitters serotonin, norepinephrine, and to some extent dopamine. Thus, tranylcypromine, phenelzine, and isocarboxazid increase levels of all three of these neurotransmitters by inhibiting MAO-A.

These changes in neurotransmitter levels ease symptoms of both depression and anxiety, and MAOI side effects are generally fairly tolerable: insomnia or sedation, orthostatic dizziness, lowered libido, and occasional weight gain. When no dangerous interactions enter the equation, MAOIs are tolerated better than tricyclic antidepressants and a bit worse than selective serotonin reuptake inhibitors (SSRIs), and they are considered by some authorities to be more effective than either tricyclics or SSRIs for depression with atypical features (overeating, oversleeping, and leaden paralysis).

Enter cheese. Certain cheeses, in addition to several other foods and beverages, contain high quantities of the amino acid tyramine. Why is tyramine potentially hazardous? To answer that, it's helpful to know that tyramine is produced from another amino acid, tyrosine. Tyrosine is (or should be) quite famous among psychiatrists, because it is the precursor of

both dopamine and norepinephrine. To return to biochemistry class for a minute, the synthetic pathway is:

Tyrosine → DOPA → Dopamine → Norepinephrine

The action of norepinephrine is terminated by the enzyme MAO-A, as well as by another enzyme, catechol-O-methyl-transferase. By a separate pathway, tyrosine can also be transformed to tyramine, which, like norepinephrine, is broken down by MAO-A. At this point, you might be thinking that because MAOIs prevent tyramine's breakdown, this leads to a buildup of tyramine's precursor, tyrosine, leading to too much dopamine and norepinephrine via the synthetic pathway outlined above. While this roundabout mechanism is part of the story, the major way that excess tyramine causes high blood pressure is via a more immediate effect on norepinephrine.

Tyramine is sometimes termed a false neurotransmitter because it gets actively transported into neurons and displaces norepinephrine, increasing norepinephrine levels in the bloodstream (Meck JV et al, *J Cardiovasc Pharmacol* 2003;41(1):126–131). This, in turn, can result in vasoconstriction and hypertension. In fact, when volunteers who are not taking MAOIs ingest large amounts of tyramine, they experience a small rise in blood pressure, because it takes a little while for the body's MAO enzymes to metabolize this extra tyramine (VanDenBerg CM et al, *J Clin Pharmacol* 2003;43(6):604–609).

Now imagine dumping tyramine into a body that does not have any functioning MAO enzymes, as would be the situation for a patient on MAOIs. In this case, there is a double whammy of norepinephrine. First, the MAOI inhibits the breakdown of norepinephrine directly; second, the tyramine, acting as an independent false neurotransmitter, displaces norepinephrine from nerve terminals (see Figure 15-1). The combined effect floods the body with norepinephrine, causing vasoconstriction, severe hypertension, and potentially catastrophic sequelae like stroke.

EMSAM: A Safer MAOI?

Selegiline is an MAOI that we use for depression as the EMSAM patch, but it began its life as an oral medication for Parkinson's disease. Unlike traditional MAOIs, which inhibit the MAO-A receptor, selegiline is selective

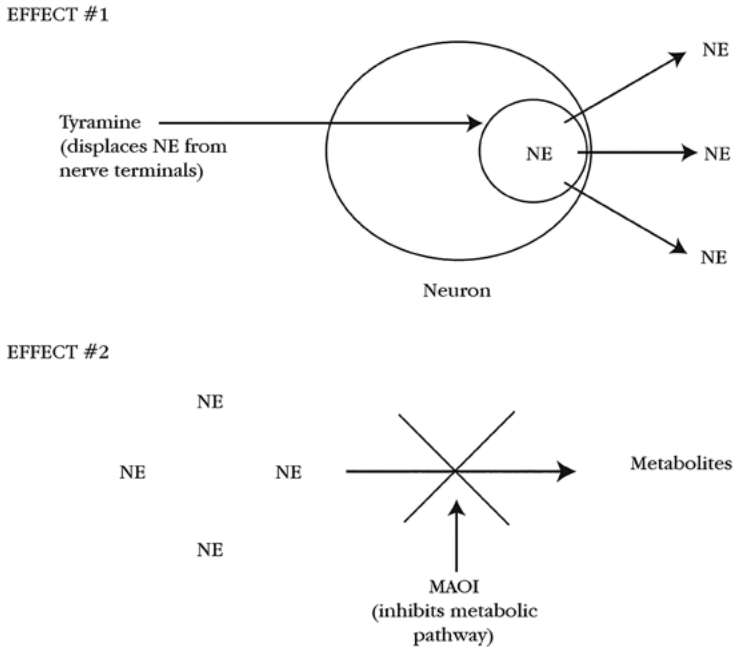

FIGURE 15-1. "Double Whammy" Effect of Ingesting Tyramine With MAOI on Board

for MAO-B. This receptor is not involved in depression, so oral selegiline's antidepressant effects don't kick in until the dose gets high enough for its inhibitor effects to spread to MAO-A (around 30 mg/day of oral selegiline). At that dose, it also inhibits MAO-A in the gut and requires the same dietary precautions as traditional MAOIs.

Transdermal selegiline (EMSAM) was developed to get around this problem. The medication passes directly into the bloodstream through the skin, bypassing the liver and GI tract. This, in turn, yields two metabolic benefits. First, because transdermal selegiline's concentration in the GI tract is much lower than the oral version, there is less inhibition of dietary tyramine's metabolism, and so less concern about dietary restrictions. Second, because there is no first-pass effect through the liver, a relatively low amount of selegiline can provide therapeutic concentrations in the brain, minimizing systemic side effects (9 mg/day of transdermal selegiline equates to 30 mg/day of oral selegiline).

What all this means is that EMSAM does not require any dietary restrictions, but this is true only at the starting dose of 6 mg/day. At the higher

doses of 9 and 12 mg/day, all the usual restrictions apply, because at these doses enough of the medication gets into the gut to inhibit the metabolism of tyramine. However, if you take a look at the raw data used by the FDA to make these crucial dosing decisions, you come away with the sense that they were extremely cautious, and that in fact the 9 mg dose is likely to be quite safe without dietary restrictions. In clinical practice, this means you can be somewhat less insistent that patients follow their MAOI diet when they are on EMSAM 9 mg than if they are on the highest dose, 12 mg.

To increase the confusion, the entire discussion above applies only to MAOI food interactions and not MAOI drug interactions. EMSAM is considered dangerous to combine with serotonergic drugs at *all* doses, including the 6 mg dose. This is because these drug interactions have nothing to do with tyramine and generally involve excessive serotonin. However, since EMSAM was released, there have been many cases of patients taking supposedly forbidden medications without suffering serotonin syndrome. (For a comprehensive review of EMSAM's safety record, see Asnis G and Henderson M, *Neuropsychiatr Dis Treat* 2014;10:1911–1923.)

So, is EMSAM a safer MAOI? Probably so, and as we gain more experience using it, we'll all likely become more comfortable with it, which is a good thing for those patients who have failed all the usual antidepressant suspects.

Tyramine in the Diet

How do foods get to be high in tyramine? Through the action of bacteria on tyrosine, which high-protein foods have lots of. Bacteria such as *Enterococcus* and *Lactobacillus* contain tyrosine decarboxylase, which converts tyrosine to tyramine. Hence, foods that contain amino acids (eg, have protein) and have a lot of bacteria in them are likely to be loaded with tyramine. One of the best ways for bacteria to grow is by allowing food to sit around for a long time, which is why aged foods of all sorts are on the high tyramine list: stinky cheeses, smoked meats, and fermented liquids (beer, certain wines, soy sauce). This is also why we tell patients on MAOIs to eat foods when they are fresh. The longer cheese or meat is left in the fridge, the more bacteria, and hence the more tyramine.

The internet is awash with lists of foods to avoid with MAOIs, but most of those are out of date. It's only in the past two decades that we've had the technology to accurately measure tyramine in food. Since then, the

restrictions have relaxed a bit, most importantly with pizza. Researchers at the University of Toronto found that pizzas from major food chains had safe quantities of tyramine, including a Domino's double-cheese, double-pepperoni pizza (Shulman KI and Walker SE, *J Clin Psychiatry* 1999;60(3):191–193). The serving sizes were liberal: half of a medium pizza.

TABLE 15-2. A Modernized MAOI Diet

Avoid completely	Highly aged cheeses and aged beef (eg, charcuterie boards) Freshly baked sourdough bread Fermented soy bean products (found in Asian foods like tempeh, miso, pickled tofu, and bean paste) Fermented meat or fish Raw meat or fish that has not been refrigerated properly or is past its use-by date Homemade beer or wine
OK in small portions (less than a typical serving size)	Specialty soy sauce Dried, aged sausage and salami (prosciutto is OK) Sauerkraut Beer that is microbrewed, on tap, or requires refrigeration (no more than 1 standard drink)
OK in normal portions (but don't overindulge)	Cheeses that are not highly aged Chocolate Caffeinated beverages Wine from a commercial producer (no more than 2 glasses) Beer that is shelf-stable or pasteurized (no more than 2 pints) Fresh beef or fish Fava beans Bananas and avocados that aren't overly ripe Soy sauce or fish sauce from grocery store brands Worcestershire sauce Kimchi Commercially produced sourdough bread Fermented yeast products (Marmite and Vegemite)
No restrictions (barely any tyramine here)	Milk, yogurt, cream Non-matured, soft cheese (mozzarella, American, ricotta, cottage cheese, cream cheese) Dry, cured meats (prosciutto, pepperoni) Smoked or pickled fish Fresh chicken, duck, pork, and sausage Stock cubes, powder, or bullion Non-fermented soy bean products

Sources: psychotropical.com; Finberg JPM and Gillman K, *Int Rev Neurobiol* 2011;100:169–190

MAOIs, SSRIs, and Serotonin Syndrome

The tyramine "cheese" effect may be the most famous and feared MAOI interaction, but serotonin syndrome is probably more common and can be just as serious. In fact, the most infamous case involving MAOIs, the Libby Zion case, involved a death due to serotonin syndrome in which an MAOI was combined with the serotonergic opioid meperidine, causing malignant hyperthermia and death from cardiac arrest. The resident who prescribed this combination to Zion had been awake for 18 hours, and it was this case that set in motion the restrictions in on-call hours that residents (and patients) now benefit from.

Serotonin syndrome is best thought of as serotonin toxicity, and it occurs on a spectrum, from barely recognizable to potentially lethal. At the mild level are serotonergic side effects like jitteriness, insomnia, GI disturbances, and cognitive problems like word-finding difficulties or general spaciness. As these serotonergic effects become more extreme, they eventually cross a line and become the serotonin syndrome. Think of "shaking, sweaty, and confused" to remember its hallmark symptoms:

- Shaking: muscle jerking (myoclonus), tremor, akathisia
- Sweaty: fever, sweating
- Confused: mental status changes, delirium

Of all these symptoms, the most reliable for accurately diagnosing serotonin syndrome are the neuromuscular symptoms, such as myoclonus (rapid alternating relaxation and contraction of muscles, often measured by flexing the patient's foot and watching for rhythmic contractions of the ankle), hyperreflexia, and muscular rigidity. These can help differentiate it from neuroleptic malignant syndrome (NMS), a rare reaction to antipsychotics. Both syndromes can present with autonomic instability, mental status changes, and rigidity, but unlike NMS, serotonin syndrome is rapidly progressive and includes hyperreflexia in addition to the rigidity.

A Controversial Issue: How Relevant Is Serotonin Syndrome in Clinical Practice?

While there is no disagreement in the field about the fact that serotonin syndrome exists and can be deadly, there is much controversy about how common it is and which drug combinations cause it. As with any

controversial topic in medicine, there are different factions arguing their points. The inclusive faction argues that serotonin syndrome is more common and less predictable than appreciated, while the purist faction argues that the syndrome occurs primarily in clear situations of serotonin toxicity.

In the next section, we'll take a hard-nosed look at which medication combinations are most likely to lead to serotonin syndrome.

Specific Drug Combinations: An Evaluation of the Dangers

Serotonin syndrome can occur from an overdose of serotonergic medication or from a drug interaction between two serotonergics. Although SSRIs are prone to this interaction, it is with MAOIs that serotonin syndrome is the most common and most dangerous. MAOIs increase serotonin by blocking the MAO-A enzyme. When used on their own, this effect is therapeutic. But when another serotonergic medication is added in, the body is unable to break down the excess serotonin, resulting in toxicity.

The risk of this interaction is illustrated by a large database of 2222 cases of serotonergic drug overdose in the Newcastle region of Australia from 1987 to 2002. Overdoses on an SSRI led to serotonin syndrome 15% of the time, but when the overdose involved both an SSRI and MAOI, the rate of serotonin syndrome rose to 50%. The cases involving MAOIs were also much more severe (Dunkley EJC et al, *QJM* 2003;96(9):635–642).

That same Australian group also gathered a practical list of medications you should avoid with MAOIs, and we've updated and reprinted that information in Table 15-3. Most of these medications can also cause serotonin syndrome when combined with SSRIs, but there the risk is much lower than it is with MAOIs. In the case of the sympathomimetics, which include psychostimulants, phentermine, and cocaine, combination with MAOIs risks not only serotonin syndrome but also hypertensive crisis.

Besides the usual round of antidepressants, we should also watch out for ziprasidone, the lone antipsychotic that can't be taken with an MAOI. Ziprasidone is a serotonin 1A agonist with a track record for triggering serotonin syndrome in case reports. In addition to psychiatric medications, the list includes a few opioids with serotonergic properties. Morphine, codeine, oxycodone, and buprenorphine (the active ingredient in Suboxone) are safe. There are also a few over-the-counter medications to warn patients about.

TABLE 15-3. Medications That Can Cause Serotonin Syndrome With MAOIs*

Serotonergic psychotropics	Serotonergic antidepressants (SSRIs, SNRIs, other MAOIs, vortioxetine, vilazodone, clomipramine, imipramine, and possibly trazodone and nefazodone); ketamine, esketamine, viloxazine, ziprasidone, and possibly lithium and buspirone
Stimulants	Amphetamine, methylphenidate, phentermine, and local anesthetics that contain sympathomimetics
Serotonergic opioids	Fentanyl, methadone, meperidine, oxycodone, propoxyphene, tramadol
Other	Fenfluramine, linezolid, methylene blue, moclobemide
Over-the-counter	L-tryptophan, SAMe, St. John's wort, and decongestants containing phenylephrine, pseudoephedrine, dextromethorphan, or chlorpheniramine
Drugs of abuse	Cocaine, amphetamines, LSD, MDMA, ecstasy, bath salts

*These meds can also cause serotonin syndrome with SSRIs and SNRIs, but the risk with these combinations is much lower

One of them—pseudoephedrine—is now kept behind the counter to prevent diversion into meth labs, but it is still available without a prescription.

The savvy reader may also notice a few medications that are missing from the list. Some medicines were thought to cause serotonin syndrome on theoretical grounds, but those concerns did not hold up over time. For example, the triptans treat migraines by activating serotonin 1B and 1D receptors. Those receptors are not implicated in serotonin syndrome, and a database of over 19,000 patients who took triptans with serotonergic antidepressants also failed to implicate them (Orlova Y et al, *JAMA Neurol* 2018;75(5):566–572). Although triptans' association with serotonin syndrome is increasingly in doubt, it's worth knowing that the following triptans are considered safest: almotriptan (Axert), naratriptan (Amerge), eletriptan (Relpax), and frovatriptan (Frova).

Carbamazepine is another medication we gave a pass to. This anticonvulsant has a structural resemblance to the tricyclic antidepressants, which generated concerns that it might interact with MAOIs, but those suspicions have not panned out. Also missing from our list are the alpha-antagonists like clonidine and guanfacine, which appear on some "do not combine with MAOIs" lists. We left them off because here the risk is not serotonin syndrome but orthostatic hypotension, a common problem with MAOIs that antihypertensives can exacerbate.

Controversy: Antidepressant Augmentation of MAOIs

Combining a serotonergic antidepressant with an MAOI is potentially lethal, but what about adding a non-serotonergic antidepressant? This strategy is controversial, but as reassuring case series have built up over the years it has become slightly more acceptable. Among the tricyclic antidepressants, the noradrenergic tricyclics (e.g., desipramine) are probably safe, but the serotonergic tricyclics should be avoided (imipramine and—the most serotoner-gic of all—clomipramine). Bupropion, mirtazapine, and trazodone (which has been used successfully to treat MAOI-induced insomnia) are all relatively low risk.

Another risky strategy is combining psychostimulants with MAOIs, which can cause both serotonin syndrome and a hypertensive crisis. However, both of these problems are fairly rare, with only a few case reports in the past 50 years. Some experts utilize this combination in refractory depression to create a "triple reuptake inhibitor" that raises serotonin, norepinephrine, and dopamine. Among the two stimulants, methylphenidate is safer to combine with MAOIs than the amphetamines. The risk is further reduced by adding stimulants to MAOIs slowly and at low doses.

While these MAOI combination strategies may be appropriate for patients with severe, refractory depression in the hands of careful, experienced clinicians, they're not for everyday use. At the very least, monitor blood pressure when embarking on them.

Switching to and From MAOIs

To prevent serotonin syndrome, a washout period is required between stopping a serotonergic drug and replacing it with an MAOI. Once the old drug is completely stopped, wait at least 5–7 half-lives for it to clear before starting the MAOI. Technically, 5 half-lives should be enough, but there may still be some residual reuptake inhibition after all the actual medication has washed out of the patient's system. For most antidepressants that means waiting 1–2 weeks, for fluoxetine the wait is 4–5 weeks, and for vortioxetine it's 2–3 weeks. Patients will worry about going that long without an antidepressant, but reassure them that the drug is still in their

system and use benzodiazepines if any serious distress arises during the washout (alprazolam, in particular, had rapid effects against depression in over a dozen controlled trials).

When switching from any MAOI to a serotonergic medication, wait 14 days before starting the new medication. Because most MAOIs have a half-life of 24 hours (or less), a 14-day washout is conservative. That time period takes into account the fact that currently available MAOIs are *irreversible* inhibitors of MAO, meaning that the enzyme is essentially destroyed. After the drug is gone, the body needs another week or so to remanufacture enough MAO in order to safely deal with the SSRI/SNRI. This same rule applies when switching from one MAOI to another.