Overview: Best Practices for Using MAOIs
Learning Objectives

• Explain the role of monoamine oxidase in the neurobiology, etiology, and presentation of psychiatric illnesses, including depression

• Identify foods and medications that interact with MAO inhibitors

• Implement safe management strategies when switching between MAO inhibitors and serotonin reuptake inhibitors

• Integrate MAO inhibitors into clinical practice according to best practices standards
Monoamine Oxidase (MAO)

- Primarily located on mitochondrial outer membranes in neurons, glia, and other cells
- ~70% of neuronal monoamine oxidase is MAO-A
- MAO-A is more often implicated in mental disorders

<table>
<thead>
<tr>
<th>Monoamine oxidase isozymes</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrates</td>
<td>5HT, NE, DA, Tyramine</td>
<td>DA, Tyramine, Phenylethylamine</td>
</tr>
<tr>
<td>Tissue distribution</td>
<td>Brain, gut, liver, placenta, skin</td>
<td>Brain, platelets, lymphocytes</td>
</tr>
</tbody>
</table>

MAO is Elevated in MDD

• The mismatch between monoamine levels raised by SSRI treatment and monoamine levels lowered by disease processes may contribute to a lack of response to SSRI treatment

MAO Elevation Predicts Depressive Relapse

Reactive Oxygen Species (ROS)

- MAO-A monoamine degradation produces ROS
  - Oxidative Stress, Peroxides, Oxygen ions
- Accumulated ROS cause oxidative damage to mitochondria, leading to increased apoptosis
- Depressed patients show:
  - Decreased mitochondrial ATP production
  - Altered cerebral energy metabolism
  - Mitochondrial dysfunction
  - Signs of cell death and oxidative damage
- Some MAO inhibitors may be neuroprotective

MAO Polymorphisms

• Both MAO-A and MAO-B are located on the X chromosome

• Two well-studied polymorphisms in the MAO-A gene
  – T941G
    • Single nucleotide polymorphism
  – MAOA-uVNTR
    • 30 bp upstream variable number tandem repeat in the promoter region
• T allele
  – Lower enzyme activity

• G allele
  – Greater enzyme activity

• The G/G genotype is associated with:
  – 75% greater MAO-A activity
  – A greater number of depressive episodes
  – Worse response to mirtazapine in females

MAOA-uVNTR

- Short 3 repeat allele
  - Lower expression of MAO-A

- Long 4 repeat allele
  - Higher expression of MAO-A
  - Risk factor for MDD
  - Predictive of worse response to fluoxetine treatment in females

# MAO Inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>MAO-A Inhibition</th>
<th>MAO-B Inhibition</th>
<th>Amphetamine Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenelzine</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>tranylcypromine</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>isocarboxazid</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>amphetamines (high-dose)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>selegiline (transdermal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>brain</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>gut</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>selegiline (oral low-dose)</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>selegiline (oral high-dose)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>rasagiline (Europe, Israel)</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>moclobemide (not in U.S.)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CX 157</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Two Major Interactions With MAOIs

- **Noradrenergic**
  - Dietary: tyramine
  - Drug: norepinephrine (NE) reuptake inhibitors and other NE-boosting drugs

- **Serotonergic**
  - Drug: serotonin (5HT) reuptake inhibitors
Noradrenergic Interactions

Dietary: Tyramine
Myth #1: The Tyramine Interaction

You can’t eat cheese, drink wine or beer, or eat lots of foods that contain tyramine, or else you will develop hypertensive crisis...

…so if you go to pizza parties or wine and cheese receptions, eat in restaurants, or follow a normal diet, you can’t take an MAOI.
Myth #1: The Tyramine Interaction

The Truth

There are a few things to avoid (which are easy to remember), but in practice, diet is not really a problem…

…unless you plan to drink a gallon of blue cheese.
Myth #1: The Tyramine Interaction

The Pharmacology

You should be cautious when combining an MAOI with anything that boosts NE because this can raise blood pressure.
Hypertensive Crisis

- Diastolic blood pressure >120 mm Hg
- Potentially fatal reaction characterized by:
  - Occipital headache that may radiate frontally
  - Palpitation
  - Neck stiffness or soreness
  - Nausea
  - Vomiting
  - Sweating (sometimes with fever)
  - Dilated pupils, photophobia
  - Tachycardia or bradycardia, which can be associated with constricting chest pain

How Much Tyramine Is Dangerous With Irreversible MAO-A Inhibitors?

- **Tranylcypromine and Phenelzine**: 10 mg, 80 mg, 250 mg
- **High Dose Transdermal Selegiline**: 400 mg, 400 mg+
- **Low Dose Transdermal Selegiline**: 10 mg, 80 mg, 250 mg
- **Oral Low Dose Selegiline**: 400 mg
- **Oral Tyramine Alone, Fasting**: 40 mg high tyramine meal

## Myth #1: The Tyramine Interaction
### The Owner’s Manual

<table>
<thead>
<tr>
<th>Foods to Avoid*</th>
<th>Foods Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish</td>
<td>Fresh or processed meat, poultry, and fish; properly stored pickled or smoked fish</td>
</tr>
<tr>
<td>Broad bean pods</td>
<td>All other vegetables</td>
</tr>
<tr>
<td>Aged cheeses</td>
<td>Processed cheese slices, cottage cheese, ricotta cheese, yogurt, cream cheese</td>
</tr>
<tr>
<td>Tap and unpasteurized beer</td>
<td>Canned or bottled beer and alcohol</td>
</tr>
<tr>
<td>Marmite</td>
<td>Brewer’s and baker’s yeast</td>
</tr>
<tr>
<td>Soy products/ tofu</td>
<td>Peanuts</td>
</tr>
<tr>
<td>Sauerkraut, kimchee</td>
<td></td>
</tr>
<tr>
<td>Banana peel</td>
<td>Bananas, avocados, raspberries</td>
</tr>
<tr>
<td>Tyramine-containing nutritional supplement</td>
<td></td>
</tr>
</tbody>
</table>

*Not necessary for 6 mg transdermal or low-dose oral selegiline

Noradrenergic Interactions

Cold Medications,
Stimulants, and Anesthetics
Myths #2 and #3: The Cold Medication/Stimulant Interaction

If you’re taking an MAOI, you can’t take anything with NE reuptake inhibition, which means:

You can’t take cold medications, such as decongestants, antihistamines, or cough medicines, so patients who get colds cannot take MAOIs.

You can’t take stimulants, so patients who need stimulants cannot take MAOIs.
Myths #2 and #3: The Cold Medication/Stimulant Interaction

The Truth

Sympathomimetic decongestants and stimulants should be used with caution while monitoring blood pressure in patients for which the benefits are greater than the risks and should be avoided only in high-risk/low-benefit populations.
Myths #2 and #3: The Cold Medication/Stimulant Interaction

The Pharmacology

You should be cautious when combining an MAOI with anything that boosts NE because this can raise blood pressure.

Some cold medications also inhibit 5HT reuptake; you should completely avoid combining an MAOI with anything that blocks 5HT reuptake because this can cause dangerous or fatal serotonin toxicity.
Myth #2: The Cold Medication Interaction

The Owner’s Manual

• Probably best to use antihistamines, which are safe except for two that are also 5HT reuptake inhibitors (i.e., brompheniramine and chlorpheniramine)

• Cough medicines with expectorants or codeine are safe, but avoid dextromethorphan, a weak serotonin reuptake inhibitor

Myth #3: The Stimulant Interaction

The Owner’s Manual

• Stimulants are useful as bridging medications when starting or stopping MAOIs and as augmenting medications to boost partial response to MAOIs
  – Don’t use an MAOI in a known cocaine/methamphetamine/stimulant abuser

Grady MM, Stahl SM. CNS Spectr 2012;In press.
A 35-year-old woman on an MAO inhibitor experiences a medical emergency requiring immediate surgery. Which of the following can generally be used with caution in this type of situation?

1. Benzodiazepine
2. Codeine
3. Morphine
4. Any of these can be used
5. None of these can be used
Myth #4: The Anesthetic Interaction

If you’re taking an MAOI, you can’t take anything with NE reuptake inhibition, which means:
You can’t have a local or general anesthetic, so patients who need dental work, sutures, or surgery cannot take an MAOI.
Myth #4: The Anesthetic Interaction

The Truth

Be careful using local anesthetics that contain epinephrine and general anesthesia, as both can cause blood pressure changes.
Myth #4: The Anesthetic Interaction

The Pharmacology

Pressor agents inadvertently injected intravenously can raise blood pressure; inhalation anesthetics can cause blood pressure changes.
## Myth #4: The Anesthetic Interaction

### The Owner’s Manual

<table>
<thead>
<tr>
<th>Local anesthetic</th>
<th>Elective surgery</th>
<th>Urgent or elective surgery while on an MAOI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choose an agent that does not contain vasoconstrictors</td>
<td>Wash out the MAOI 10 days prior to surgery (if possible)</td>
<td>Cautiously use a benzodiazepine, mivacurium, rapacuronium, morphine, or codeine</td>
</tr>
</tbody>
</table>

## Summary:
Noradrenergic Drug Interactions

<table>
<thead>
<tr>
<th>Decongestants</th>
<th>Stimulants</th>
<th>Antidepressants With NRIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td>Amphetamine</td>
<td>Some TCAs</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Methylphenidate</td>
<td>NRIs</td>
</tr>
<tr>
<td></td>
<td>Modafinil</td>
<td>NDRIs</td>
</tr>
<tr>
<td></td>
<td>Armodafinil</td>
<td></td>
</tr>
</tbody>
</table>

Serotonergic Interactions

Tricyclic Antidepressants (TCAs), Pain Medications, and Other Psychototropic Medications
A clinician is considering options for a 45-year-old man with severe treatment-resistant depression who has exhibited only partial response to first-line and older-generation antidepressants and who is unwilling to attempt electroconvulsive therapy or other stimulation therapy. One option, undertaken with extreme caution and under expert guidance, is to combine a monoamine oxidase inhibitor (MAOI) with a tricyclic antidepressant; however, which of the following should absolutely NOT be used in combination with an MAOI?

1. Amitriptyline
2. Clomipramine
3. Nortriptyline
4. Any of these can be used
5. None of these can be used
Myth #5: The Tricyclic Interaction

Tricyclic antidepressants are so dangerous that patients on MAO inhibitors cannot take them or anything that resembles them, including carbamazepine and cyclobenzaprine.
Myth #5: The Tricyclic Interaction

The Truth

Other than clomipramine, tricyclic antidepressants and related agents can be used with caution in patients taking MAO inhibitors.
Myth #5: The Tricyclic Interaction

The Pharmacology

You should completely avoid combining an MAOI with anything that blocks 5HT reuptake because this can cause dangerous or fatal serotonin toxicity.

**Some TCAs also increase NE:
You should be cautious when combining an MAOI with anything that boosts NE because this can raise blood pressure.
Myth #5: The Tricyclic Interaction

The Owner’s Manual

• Contraindicated: clomipramine

• Other TCAs can be used with caution for severe TRD

• If an MAOI and a TCA are combined:
  – DO NOT START THE MAOI FIRST!
  – Start the MAOI at the same time as the TCA (both at low doses) after an appropriate drug washout
  – Alternately increase the doses of these agents every few days to a week as tolerated

• Cyclobenzaprine, carbamazepine, and oxcarbazepine can be used with caution because they do not block 5HT or NE reuptake

A 54-year-old man with a history of treatment-resistant depression has been successfully treated with a monoamine oxidase inhibitor (MAOI) for the last year. He recently suffered a severe back injury and is in quite a bit of pain. In light of potential interactions with the MAOI, which of the following would be an acceptable pain management option for this patient?

1. Hydrocodone
2. Meperidine
3. Tramadol
4. The patient cannot take any of these medications
Myth #6: The Painkiller Interaction

You can’t take painkillers with MAOIs because they will kill you, so patients who have sprained ankles, sore muscles, dental extractions, or surgeries cannot take MAOIs, as they must avoid all opiate and non-opiate painkillers.
Myth #6: The Painkiller Interaction

The Truth

There are a few things to avoid (which are easy to remember), and in practice, this is not really a problem.
Myth #6: The Painkiller Interaction

The Pharmacology

There is no interaction of MAOIs with opiate mechanisms.

Meperidine is a potent 5HT reuptake inhibitor and should be avoided.

Fentanyl, methadone, and tramadol are weak 5HT reuptake inhibitors and should be avoided.

Tapentadol is an NE reuptake inhibitor and should be avoided.
## Myth #6: The Painkiller Interaction

### The Owner’s Manual

<table>
<thead>
<tr>
<th>Use With MAOIs Should Be Cautious</th>
<th>Use With MAOIs May Sometimes Be Done By Experts (NE Effects)</th>
<th>Use With MAOIs Strictly Prohibited (5HT Reuptake or Strong NE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetaminophen</td>
<td>hydromorphone</td>
<td>fentanyl</td>
</tr>
<tr>
<td>aspirin</td>
<td>morphine</td>
<td>meperidine</td>
</tr>
<tr>
<td>buprenorphine</td>
<td>oxycodone</td>
<td>methadone</td>
</tr>
<tr>
<td>butorphanol</td>
<td>oxymorphone</td>
<td>tapentadol</td>
</tr>
<tr>
<td>codeine</td>
<td></td>
<td>tramadol</td>
</tr>
<tr>
<td>hydrocodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nalbuphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pentazocine</td>
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</tr>
</tbody>
</table>

A 36-year-old man with depression has had 3 therapeutic trials of serotonin reuptake inhibitors (SRIs) without notable improvement. His clinician is now considering switching the patient's SRI to a monoamine oxidase inhibitor (MAOI). Which of the following is an appropriate switching strategy in this situation?

1. Cross-titr ate SRI with MAOI
2. Discontinue SRI, then initiate MAOI
3. Discontinue SRI, then wait 5 half-lives before initiating MAOI
4. Discontinue SRI, then wait 14 days before initiating MAOI
Myth #7: The Psychototropic Medication Interaction

You can’t take any medications that block 5HT reuptake, which means you can’t take any psychotropic medications. Since all patients who are candidates for an MAOI need concomitant medications, no one can take an MAOI.

Besides, in order to start an MAOI, you have to stop all other medications for 2 weeks after taper. And if you have to stop an MAOI to go back to a psychotropic medication, you have to go without all medications for another 2 weeks. This is an unacceptable risk and a hassle.
Myth #7: The Psychototropic Medication Interaction

The Truth

You must completely avoid only agents that block serotonin reuptake. There are many options for not only bridging between serotonin reuptake inhibitors and MAOIs, but also augmenting MAOIs.
Myth #7: The Psychotropic Medication Interaction

The Pharmacology

You should completely avoid combining an MAOI with anything that blocks 5HT reuptake because this can cause dangerous or fatal serotonin toxicity.

You should be cautious when combining an MAOI with anything that boosts NE because this can raise blood pressure.
# Serotonin Syndrome/Toxicity*

<table>
<thead>
<tr>
<th>Neuromuscular hyperactivity</th>
<th>Autonomic hyperactivity</th>
<th>Altered mental status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>Diaphoresis</td>
<td>Agitation</td>
</tr>
<tr>
<td>Tremor</td>
<td>Fever</td>
<td>Excitement</td>
</tr>
<tr>
<td>Clonus</td>
<td>Tachycardia</td>
<td>Confusion</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Tachypnea</td>
<td></td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nystagmus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Presents abruptly and can progress quickly

### Myth #7: The Psychototropic Medication Interaction

#### The Owner’s Manual:
**Drugs to Avoid Due to Risk of Serotonin Toxicity**

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Drugs of Abuse</th>
<th>Opioids</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>MDMA (ecstasy)</td>
<td>meperidine</td>
<td>non-subcutaneous sumatriptan</td>
</tr>
<tr>
<td>SNRIs</td>
<td>cocaine</td>
<td>tramadol</td>
<td>chlorpheniramine</td>
</tr>
<tr>
<td>clomipramine</td>
<td>methamphetamine</td>
<td>methadone</td>
<td>brompheniramine</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>High-dose or injected amphetamine</td>
<td>fentanyl</td>
<td>dextromethorphan</td>
</tr>
</tbody>
</table>

Myth #7: The Psychototropic Medication Interaction

The Owner’s Manual: Switching From a Serotonergic Drug to an MAOI

**Titration schedule for MAOI may differ depending on the individual agent**

Myth #7: The Psychotropic Medication Interaction

The Owner’s Manual: Switching From an MAOI to a Serotonergic Drug

**Titration schedule for 5HT drug may differ depending on the individual agent

Myth #7: The Psychototropic Medication Interaction

The Owner’s Manual: How to Bridge Use These Drugs While Waiting to Start an MAOI or When Discontinuing an MAOI

- Benzodiazepines, Z-drug hypnotics, trazodone
- Lamotrigine, valproate, lithium
- Gabapentin, pregabalin, topiramate, carbamazepine, oxcarbazepine
- Stimulants
- Atypical antipsychotics

Grady MM, Stahl SM. CNS Spectr 2012;In press.
Summary

• MAOIs still have a role in modern psychopharmacology

• Distinct and understandable pharmacological mechanisms account for MAOIs and their therapeutic, drug, and dietary interactions

• Bottom line:
  – Be cautious when combining an MAOI with anything that boosts NE because this can raise blood pressure
  – Completely avoid combining an MAOI with anything that blocks 5HT reuptake because this can cause dangerous or fatal serotonin toxicity