Individual Disclosure Statement

Faculty Editor / Presenter

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Learning Objectives

• Implement evidence-based switching strategies according to best practices standards

• Implement strategies to assess treatment effectiveness and adherence

• Modify treatment strategies in order to enhance adherence and improve patient outcomes

• Integrate appropriate treatment strategies for treatment resistance into clinical practice
Pretest Question 1

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. Meperidine
2. Morphine
3. Tramadol
4. The patient cannot take any of these medications
Switching Options

- No evidence to support preference for one agent or one class over another
- Switching within the same class or to another class are both options
- **Common options**
  - Bupropion
  - Mirtazapine
- **Under-used options**
  - Tricyclic antidepressants (TCAs)
  - Monoamine oxidase inhibitors (MAOIs)
- **New options**
  - Vilazodone
  - Trazodone ER

If At First You Don’t Succeed…

Switching to a Non-MAOI
The Usual Suspects


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Non-Remitters to Treatment With Citalopram (n=565)

STAR*D Level 2 Augmentation Results

- Similar or greater remission rates than initial treatment with citalopram alone
- Buspirone augmentation of citalopram had the same remission rates as bupropion SR augmentation of citalopram (no significant differences)
- Combining antidepressants with different mechanisms of action may be effective when monotherapy does not result in remission
- Would we be better off starting with combinations for select patients?

Mechanism of Action of Vilazodone (1)

- Vilazodone simultaneously acts as both a 5-HT$_{1A}$ partial agonist and a serotonin transport inhibitor, much like a combination of an SSRI and buspirone (SPARI-serotonin partial agonist reuptake inhibitor)

- Vilazodone’s effects at 5-HT$_{1A}$ receptors are equally potent or more potent than its effects at serotonin transporters, whereas buspirone is much weaker at 5-HT$_{1A}$ receptors than vilazodone

- Thus, vilazodone has disproportionate actions at 5-HT$_{1A}$ receptors compared to an SSRI plus buspirone
Mechanism of Action of Vilazodone (2)

- Unlike a selective 5-HT\textsubscript{1A} partial agonist, vilazodone blocks serotonin transporters; thus, like an SSRI, it immediately increases serotonin at presynaptic 5-HT\textsubscript{1A} receptors.

- Vilazodone simultaneously occupies pre- and postsynaptic 5-HT\textsubscript{1A} receptors.

- This combined action downregulates presynaptic 5-HT\textsubscript{1A} autoreceptors over time, eventually increasing the release of serotonin into postsynaptic receptors and causing antidepressant effects.

- However, due to the predominance of 5-HT\textsubscript{1A} actions, vilazodone has the low incidence of sexual dysfunction that is associated with selective 5-HT\textsubscript{1A} partial agonists and not with SSRIs.
The Hypothetical Neuron in the Depressed State

low serotonin

5-HT$_{1A}$ autoreceptors

few signals

serotonin transporters (SERT)

low serotonin
Immediate Actions of Vilazodone

- Serotonin increases at 5-HT$_{1A}$ autoreceptors
- Vilazodone - presynaptic & postsynaptic 5-HT$_{1A}$ receptors occupied
- SERTs blocked
Delayed Actions of Vilazodone: Part 1

downregulation of 5-HT$_{1A}$ autoreceptors
Delayed Actions of Vilazodone: Part 2

signals somewhat increased in the synapse

serotonin somewhat increased

anti-depressant effects & low sexual dysfunction
Vilazodone: 
Practical Tips and “Owner’s Manual”

• Usual dose: 40 mg once daily
• Take with food (like the other “-dones,” ziprasidone and lurasidone)
• Minimally effective dose not established
• Metabolized by CYP450 3A4
• Relative lack of sexual dysfunction and weight gain
• Consider for patients with comorbid anxiety
• Not well studied, but can consider 50–80 mg/day for treatment-resistant depression/OCD/anxiety

Pre-poll Question 1

To what extent do you agree with the following statement: I feel competent prescribing a tricyclic antidepressant to a patient with treatment-resistant depression?

1. 1 (strongly disagree)
2. 2
3. 3
4. 4
5. 5 (strongly agree)
Tricyclic Antidepressants

TCAs: Pharmacokinetics Tips and Pearls (1)

- Can monitor plasma drug levels of many TCAs, especially nortriptyline, amitriptyline, desipramine, imipramine, clomipramine/desmethylclomipramine
- Most TCAs are CYP2D6 substrates, so lower the dose in genetic poor metabolizers (can now genotype patients for CYP2D6)
- Lower the dose if used concomitantly with 2D6 inhibitors (e.g., fluoxetine, paroxetine, many others)
- Tertiary TCAs are metabolized to secondary TCAs by CYP1A2 (e.g., amitriptyline to nortriptyline; imipramine to desipramine; clomipramine to desmethylclomipramine), which can be inhibited by 1A2 inhibitors, such as fluvoxamine
TCAs: Pharmacokinetics Tips and Pearls (2)

• Can be exploited for the treatment of OCD by giving low-dose fluvoxamine with low-dose clomipramine to prevent the conversion of serotonergic clomipramine to noradrenergic desmethylclomipramine and thus boost net serotonergic action

• Amoxapine itself is the N-desmethyl metabolite of the conventional antipsychotic loxapine

• Amoxapine is metabolized to a D₂ antagonist; can cause EPS, but might be useful for psychotic depression
TCAs: Pharmacodynamics Tips and Pearls (1)

- Doxepin most highly antihistaminic, even at 1-10 mg
- In fact, a low-dose formulation of doxepin is now available for treating insomnia
- Don’t forget clomipramine for resistant depression, even though it is approved in US for OCD
- Low doses of many TCAs for pain or as a hypnotic
- TCAs may be the best treatment for depression in Parkinson’s disease due to anticholinergic properties
- Other uses: enuresis, cataplexy, OCD, headache
TCAs: Pharmacodynamics Tips and Pearls (2)

• Desipramine, nortriptyline, and maprotiline are more noradrenergic

• Some TCAs have 5-HT$_{2A}$ and 5-HT$_{2C}$ antagonist properties that contribute to their antidepressant action

• TCAs with potent 5-HT$_{2A}$ antagonist properties, such as amoxapine, may be best for experts to cautiously combine with MAOIs when necessary
After Multiple Failures…

Switching to an MAOI
Pre-poll Question 2

To what extent do you agree with the following statement: I feel competent prescribing a monoamine oxidase inhibitor to a patient with treatment-resistant depression?

1. 1 (strongly disagree)
2. 2
3. 3
4. 4
5. 5 (strongly agree)
MAOI Myth #1: The Tyramine Interaction

You can’t eat cheese, drink wine or beer, or have lots of foods that contain tyramine, 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.
MAOI Myth #1: The Tyramine Interaction

The Truth

There are a few things to avoid (which are easy to remember and available on a handout/card), and in practice, diet is not really a problem…

…unless you plan to eat more than 25 pieces of pizza or drink more than 25 cans of beer or 25 glasses of wine.
MAOI Myth #1: The Tyramine Interaction

The Pharmacology

You should be cautious when combining an MAOI with anything that boosts norepinephrine because this can raise blood pressure.
How Much Tyramine Is Dangerous With Irreversible MAO-A Inhibitors?

Hypertensive Crisis

• Defined by diastolic blood pressure >120 mm Hg

• Potentially fatal reaction characterized by
  – Occipital headache which 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

### MAOI Myth #1: The Tyramine Interaction

#### The Owner’s Manual

**Recommended Dietary Restrictions for MAOIs**

(not necessary for 6 mg transdermal or low-dose oral selegiline)

<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>Sauerkraut, kimchee</td>
<td></td>
</tr>
<tr>
<td>Soy products/tofu</td>
<td>Peanuts</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>

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MAOI Myth #2: The Cold Medication Interaction

You can’t take cold medications, such as decongestants, antihistamines, or cough medicines if you get a cold, so patients who get colds cannot take MAOIs.
Transdermal Selegiline Drug Interaction Trial: Pseudoephedrine (PSE)

Mean SBP and DBP (mm Hg) and HR (bpm) before and during multiple-dose treatment with PSE and/or selegiline 6 mg/24 hr

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>End of PSE Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated Control</td>
<td>selegilne</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>118.4</td>
<td>109.1</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>71.0</td>
<td>63.2</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>62.7</td>
<td>59.4</td>
</tr>
</tbody>
</table>

N=10 healthy volunteers.
Pseudoephedrine dose: 60 mg TID for 2 days.

MAOI Myth #3: The Stimulant Interaction

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

The Pharmacology

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

You should avoid combining an MAOI with anything that blocks serotonin reuptake because this can cause a dangerous or fatal serotonin syndrome.
Drugs That Boost Norepinephrine and Thus Should Be Used With Caution to Avoid Hypertensive Episodes

<table>
<thead>
<tr>
<th>Decongestants</th>
<th>Stimulants</th>
<th>Antidepressants With NRIs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td>Amphetamine</td>
<td>Most TCAs</td>
<td>Phentermine</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Methylphenidate</td>
<td>NRIs</td>
<td>Local anesthetics containing vasoconstrictors</td>
</tr>
<tr>
<td></td>
<td>Modafinil</td>
<td>SNRIs</td>
<td>Tramadol</td>
</tr>
<tr>
<td></td>
<td>Armodafinil</td>
<td>NDRIs</td>
<td>Cocaine, methamphetamine</td>
</tr>
</tbody>
</table>

MAOI Myths #2 and #3: The Cold Medication/Stimulant Interaction
The Owner’s Manual

- Probably best to use antihistamines, which are safe except for two that are also serotonin reuptake inhibitors; cough medicines with expectorants or codeine are safe, but avoid dextromethorphan, a weak serotonin reuptake inhibitor

- 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
MAOI Myth #4: The Anesthetic Interaction

You can’t have a local or a general anesthetic, so patients who need dental work, stitches, or surgery cannot take an MAOI.
MAOI Myth #4: The Anesthetic Interaction

The Truth

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

The Pharmacology

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

• Use local anesthetics that do not contain vasoconstrictors

• For elective surgery, wash out of MAOI for 10 days

• For urgent or elective surgery while taking an MAOI, use benzodiazepines, mivacurium, rapacuronium, morphine, and codeine cautiously
MAOI Myth #5: The Tricyclic Interaction

Tricyclics are so dangerous that you cannot take them or anything that resembles them, including carbamazepine, cyclobenzaprine, and your daughter’s tricycle.
MAOI Myth #5: The Tricyclic Interaction
The Pharmacology

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

You should avoid combining an MAOI with anything that blocks serotonin reuptake because this can cause a dangerous or fatal serotonin syndrome.
MAOI Myth #5: The Tricyclic Interaction
The Owner’s Manual

• The only tricyclic to be strictly avoided is clomipramine; other TCAs can be used with caution.

• Cyclobenzaprine, carbamazepine, and oxcarbazepine can be used with caution because they don’t block serotonin or norepinephrine reuptake.

• And your daughter can ride her tricycle if you take an MAOI.
MAOI 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.
MAOI Myth #6: The Painkiller Interaction

The Truth

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

The Pharmacology

There is no interaction of MAOIs with opiate mechanisms; however, mepirididine is a potent serotonin reuptake inhibitor and should be avoided.

Methadone and tramadol are weak serotonin reuptake inhibitors and should be avoided.
MAOI Myth #6: The Painkiller Interaction
The Owner’s Manual

- Avoid meperidine, methadone, and tramadol; use morphine, codeine, oxycodone, hydrocodone, suboxone, and NSAIDs
MAOI Myth #7: The Psychotropic Concomitant Medication Interaction Myth

Since you can’t take any medications that block serotonin reuptake while taking an MAOI, 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, you cannot get there from here because in order to start an MAOI, you have to disrupt everything, stopping all other meds 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 meds for another 2 weeks. This is an unacceptable risk and a hassle.
MAOI Myth #7: The Psychotropic Concomitant Medication Interaction Myth

The Pharmacology

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

You should avoid combining an MAOI with anything that blocks serotonin reuptake because this can cause a dangerous or fatal serotonin syndrome.
Serotonin Syndrome/Toxicity*

- Neuromuscular hyperactivity
  - Akathisia, tremor, clonus, myoclonus, hyperreflexia, rigidity, nystagmus

- Autonomic hyperactivity
  - Diaphoresis, fever, tachycardia, tachypnea

- Altered mental status
  - Agitation, excitement, confusion

*Presents abruptly and can progress quickly

# Drugs to Avoid Due to Risk of Serotonin Syndrome

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Drugs of Abuse</th>
<th>Opioids</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>MDMA (ecstasy)</td>
<td>meperidine</td>
<td></td>
</tr>
<tr>
<td>SNRIs</td>
<td>cocaine</td>
<td>tramadol</td>
<td>non-subcutaneous sumatriptan</td>
</tr>
<tr>
<td>clomipramine</td>
<td>methamphetamine</td>
<td>methadone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-dose or injected amphetamine</td>
<td></td>
<td>chlorpheniramine</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td></td>
<td></td>
<td>dextromethorphan brompheniramine procarbazine?</td>
</tr>
</tbody>
</table>
MAOI Myth #7: The Psychotropic Concomitant Medication Interaction Myth

The Truth

You must 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.
MAOI Myth #7: The Psychotropic Concomitant Medication Interaction Myth
The Owner’s Manual

- Learn how to switch and how to bridge
Switching: From a Serotonergic Drug to an MAOI

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

Switching: From an MAOI to a Serotonergic Drug

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

How to Bridge: Use These Drugs While Waiting to Start an MAOI or When Discontinuing an MAOI

- Benzodiazepines
- Z drug hypnotics
- Trazodone
- Lamotrigine
- Valproate
- Gabapentin, pregabalin, topiramate, carbamazepine, oxcarbazepine
- Stimulants
- Atypical antipsychotics
After Multiple Failures…

Neurostimulation
Electroconvulsive Therapy (ECT)

- Highest rates of response and remission of any antidepressant treatment
  - Best data are for acute treatment, maintenance data not as clear cut
- Response often occurs after a few sessions
- Acute course: typically 6–12 treatments, does not generally exceed 20
- Treatment should continue until symptoms remit or plateau; relapse rates are higher if ECT is discontinued prematurely
- Right unilateral ECT has been reported to have fewer memory side effects than bilateral ECT
- Frequency of ECT can also affect memory side effects, as patients may not have sufficient time to recover from memory effects prior to the next session
- No clear evidence to support any particular medicine for maintaining response after ECT
  - Best research is in older literature and suggests nortriptyline or lithium

Transcranial Magnetic Stimulation (TMS)

- Approved for treatment-resistant depression
  - Usually mild to moderate resistance
- Generally done on an outpatient basis
- Electromagnetic coil is placed against the scalp near the forehead and turned on and off repeatedly; each session typically lasts 30–50 min.
- Typical treatment duration is 5 treatments per week for 4 to 6 weeks
- Ongoing use for maintenance?

Deep Brain Stimulation (DBS)

- In trials for treatment-resistant depression
- Involves two surgical procedures, one to implant electrodes in the brain and a second to implant a neurostimulator in the chest
- Stimulation is generally constant but can be temporarily turned off by holding a handheld magnetic device over the area of the chest where the neurostimulator is located
- Response to treatment appears to be rapid

Vagal Nerve Stimulation

- Approved for treatment-resistant depression but no longer on the market for depression and very difficult to get reimbursement through insurance
- Involves surgical implant of a stimulation device in the upper left side of the chest
- Stimulation is intermittent and can be temporarily turned off by holding a hand-held magnetic device over the area of the chest where the neurostimulator is located
- Response to treatment appears to be slow

Summary

• TCAs and MAOIs still have a role in modern psychopharmacology

• Distinct and understandable pharmacological mechanisms account for MAOIs and their:
  – Therapeutic actions
  – Serotonin syndrome
  – Sympathomimetic drug interactions
  – Dietary tyramine interactions with MAO inhibitors

• Neurostimulation should be considered for patients with severe MDD that is not responsive to pharmacotherapy or psychotherapy