Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects

AUTHORS: Michael Hirsch, MD, Robert J Birnbaum, MD, PhD
SECTION EDITOR: Peter P Roy-Byrne, MD
DEPUTY EDITOR: David Solomon, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Apr 15, 2023.**

INTRODUCTION

Monoamine oxidase inhibitors (MAOIs) are indicated for multiple psychiatric disorders, including treatment-resistant major depression [1-8]. The MAOIs that are most commonly used as antidepressants include isocarboxazid, moclobemide (not available in the United States), phenelzine, transdermal selegiline, and tranylcypromine.

Although MAOIs are often effective in treating major depression, they are generally reserved for treatment refractory episodes due to safety concerns arising from severe drug-drug and drug-food interactions [2,5,6,9-14]. In addition, some MAOIs (eg, isocarboxazid, phenelzine, and tranylcypromine) are relatively lethal in drug overdoses compared with other antidepressants, such as selective serotonin reuptake inhibitors [14]. Due to the potential for life-threatening outcomes, some psychiatrists never prescribe MAOIs, despite their potential utility in patients who have not responded to multiple drug trials [2,3,5,7,10,12].

MAOIs were the first class of antidepressants that were used to treat depression and were discovered largely by serendipity. As an example, the MAOI iproniazid was derived in the 1950s from an antibiotic that was ineffective for tuberculosis but effective for depressive syndromes [1,4].

This topic reviews the pharmacology, administration, safety, and adverse effects of MAOIs. Choosing a regimen for the initial treatment of major depression and treatment of resistant

depression is discussed separately, as are other antidepressant drug classes:

- (See "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Serotonin modulators: Pharmacology, administration, and side effects".)
- (See "Atypical antidepressants: Pharmacology, administration, and side effects".)
- (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

INDICATIONS

Monoamine oxidase inhibitors (MAOIs) are used to treat multiple psychiatric disorders, including [1,2,5,6,12,14-16]:

- Bulimia nervosa (see "Bulimia nervosa in adults: Pharmacotherapy", section on 'Third-line')
- Panic disorder (see "Management of panic disorder with or without agoraphobia in adults", section on 'Treatment resistance')
- Social anxiety disorder (see "Pharmacotherapy for social anxiety disorder in adults", section on 'Monoamine oxidase inhibitors')
- Persistent depressive disorder (dysthymia) unresponsive to several (eg, four to six) other pharmacotherapy regimens (see "Unipolar major depression in adults: Choosing initial treatment", section on 'Persistent depressive disorder')
- Unipolar and bipolar major depression that does not respond to several pharmacotherapy regimens (see "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Antidepressants')
- Unipolar major depression with atypical features, such as mood reactivity (feeling better in response to positive events), increased appetite/weight gain, and hypersomnia (see "Unipolar depression in adults: Assessment and diagnosis", section on 'Depressive episode subtypes (specifiers)')

  In addition, MAOIs may be indicated for Parkinson disease [17]. (See "Initial pharmacologic treatment of Parkinson disease", section on 'MAO B inhibitors'.)

Contraindications — The MAOIs isocarboxazid, phenelzine, and tranylcypromine are contraindicated in congestive heart failure, liver disease, and pheochromocytoma [1,4]. In addition, all of the MAOIs are contraindicated in patients who require medications that can cause drug-drug interactions resulting in the serotonin syndrome (serotonin toxicity) or a hypertensive crisis (see 'Safety risks' below). Due to the safety risks, clinicians need to assess the patient's ability to adhere to medication and dietary restrictions that are necessary for using MAOIs. (See 'Prescribing MAOIs' below.)

PHARMACOLOGY

MAOIs include the following antidepressants [1,2,4]:

- Isocarboxazid
- Moclobemide (not available in the United States)
- Phenelzine
- Selegiline (oral and transdermal formulations)
- Tranylcypromine

MAOIs differ in their chemical structure, in part depending upon whether the drug is a hydrazine compound (isocarboxazid and phenelzine) or a nonhydrazine (moclobemide, selegiline, and tranylcypromine) [1,6]. The structure of tranylcypromine resembles amphetamine, which may account for tranylcypromine's mild stimulating properties.

The mechanism of action of MAOIs is not clear. One hypothesis is that MAOIs increase dopaminergic, noradrenergic, and serotonergic neurotransmission [1,6,14,18]. MAOIs block monoamine oxidase, which is a mitochondrial enzyme found in multiple organs, including the brain. The enzyme inactivates the neurotransmitters dopamine, norepinephrine, and serotonin; inhibition of the enzyme thus increases their concentration within neuronal synapses. In addition, the therapeutic benefit of MAOIs may involve other pharmacologic actions, such as reducing the number of adrenergic and serotonergic receptors, and inducing hippocampal neurogenesis.

There are two isomers (subtypes) of monoamine oxidase: monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) [1,4,6,14,18,19]. Both isoenzymes are found in the brain; MAO-A metabolizes dopamine, norepinephrine, and serotonin, whereas MAO-B metabolizes dopamine. The distribution of MAO-A and MAO-B in the rest of the body varies, depending upon the specific organ. Inhibition of brain MAO-A appears to be necessary for the antidepressant effects of MAOIs. Selective MAO-B inhibitors do not have significant antidepressant properties.

MAO-A and MAO-B also metabolize exogenous amines, such as dietary tyramine, a sympathomimetic amino acid that is present in multiple beverages and foods [1,2,4,7,11,20]. In the gastrointestinal system, the large majority of monoamine oxidase is MAO-A. Inhibition of MAO-A by MAOIs prevents catabolism of tyramine in the gut, which leads to release of intact tyramine into the general circulation. Tyramine then enters noradrenergic neurons and triggers the release of norepinephrine, a vasoconstrictor. As a result, MAOIs may increase the pressor effects of tyramine 10- to 20-fold and precipitate a hypertensive crisis. (See 'Hypertensive crisis' below.)

The MAOIs differ as to whether they inhibit one or both of the isoenzymes (table 1) [1,2,4]. Moclobemide selectively inhibits only MAO-A. Oral selegiline at lower doses (eg, 5 to 10 mg) selectively inhibits only MAO-B; at higher doses, selegiline is nonselective and blocks both isoenzymes. Isocarboxazid, phenelzine, and tranylcypromine inhibit both MAO-A and MAO-B, and are therefore nonselective.

MAOIs are also subdivided based upon whether inhibition of monoamine oxidase is reversible or irreversible (table 1) [1,2,4,20]. Moclobemide is a reversible MAOI, meaning that after the drug inhibits MAO-A, recovery of the enzyme's activity is relatively fast because moclobemide has a low affinity for the enzyme and is easily displaced from the enzyme by substrates such as tyramine. By contrast, isocarboxazid, phenelzine, selegiline, and tranylcypromine are irreversible; these drugs bind to and inactivate monoamine oxidase for the life of the enzyme molecule (approximately two to four weeks). Thus, recovery of enzymatic activity is slower and does not occur until the drug is discontinued and the body produces new monoamine oxidase.

The MAOIs do not appear to cause clinically meaningful pharmacokinetic drug-drug interactions [10]. However, pharmacodynamic drug-drug interactions with other serotonergic medications (table 2) can cause the serotonin syndrome (serotonin toxicity). (See 'Serotonin syndrome' below.)

SAFETY RISKS

The primary safety problems that can occur with monoamine oxidase inhibitors (MAOIs) are drug-drug interactions that cause the serotonin syndrome and drug-food and drug-drug interactions that cause a hypertensive crisis [1,2,4,6,13,14].

Serotonin syndrome — Serotonin syndrome (serotonin toxicity) is a potentially life-threatening condition caused by increased serotonergic activity in the central nervous system. It is seen with therapeutic medication use, inadvertent interactions between drugs, and intentional self-

poisoning. Serotonin syndrome may involve a spectrum of clinical findings, which often include mental status changes, autonomic hyperactivity, and neuromuscular abnormalities.

Serotonin syndrome can result from any combination of drugs that has the net effect of increasing serotonergic neurotransmission (table 2). Drug-drug interactions (including the serotonin syndrome) between MAOIs and other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Although the serotonin syndrome is classically associated with the simultaneous administration of two serotonergic agents, it can occur after initiation of a single serotonergic drug or increasing the dose of a serotonergic drug in individuals who are particularly sensitive to serotonin. Episodes of serotonin syndrome involving an MAOI may be more severe and more often lead to adverse outcomes, including death. As part of prescribing MAOIs and avoiding the serotonin syndrome, clinicians need to discuss medication restrictions with patients. (See 'Medication restrictions' below.)

Additional information about the serotonin syndrome, including its clinical features, diagnosis, and management (table 3), is discussed separately. (See "Serotonin syndrome (serotonin toxicity)".)

Hypertensive crisis — Hypertensive crisis (hypertensive emergency) is defined as a significantly elevated blood pressure that causes signs or symptoms of acute, ongoing end-organ damage. In younger (<60 years of age) patients, the diastolic pressure is typically ≥120 mmHg, but there is no specific threshold because individuals who develop an acute rise in blood pressure can develop symptoms if the previous pressure was normal. Additional information about hypertensive crisis, including its clinical features, evaluation, diagnosis, and management, is discussed separately. (See "Evaluation and treatment of hypertensive emergencies in adults".)

Among patients treated with MAOIs, a hypertensive crisis can occur in the context of drug-food interactions or drug-drug interactions [1,2,4,7]:

- Drug-food interactions – Some MAOIs (eg, isocarboxazid, phenelzine, and tranylcypromine) can interact with tyramine, an amino acid that is found in multiple foods and beverages. Tyramine is an indirect sympathomimetic amine that can act as a vasopressor. Patients taking MAOIs that pose a risk for a hypertensive crisis must adhere to dietary restrictions that minimize exposure to tyramine (table 4). Drug-food interactions that occur typically develop within 20 to 60 minutes of ingesting tyramine. Although the hypertensive crisis resulting from the interaction is potentially lethal, death is very rare.

Other sections of this topic discuss the specific MAOIs that require dietary restrictions, the foods and beverages that are restricted, and the pharmacology of MAOIs that underlies potential drug-food interactions with tyramine. (See 'Dietary restrictions' below and 'Pharmacology' above.)

- Drug-drug interactions – Combining MAOIs (eg, isocarboxazid, moclobemide, phenelzine, selegiline, and tranylcypromine) with other medications may cause a hyperadrenergic state that leads to a hypertensive crisis. Drug-drug interactions between MAOIs and other medication can be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate. Patients taking MAOIs must adhere to medication restrictions to minimize the risk of a hypertensive crisis. (See 'Medication restrictions' below.)

In the absence of drug-food and drug-drug interactions, MAOIs may elevate blood pressure and may rarely cause a hypertensive crisis [4,20].

Overdose — Overdose (self-poisoning) of isocarboxazid, phenelzine, and tranylcypromine may be fatal and should prompt hospitalization for monitoring [6,9]. Following an overdose with these MAOIs, signs and symptoms may not appear for up to 12 hours and peak effects may be delayed for 24 to 48 hours. Patients may manifest the following clinical features: tachycardia, irregular pulse, hypertension, hypotension and vascular collapse, respiratory depression and failure, hyperpyrexia, diaphoresis, and/or cool, clammy skin, agitation, coma, convulsions, dilated pupils, dizziness, drowsiness, hallucinations, headache, opisthotonos, trismus, and precordial pain.

Treatment of overdose with isocarboxazid, phenelzine, and tranylcypromine consists of supportive measures as clinically indicated [6,9]. Drug excretion may be accelerated by acidifying the urine, and dialysis may also be helpful [20]. Dietary tyramine should be restricted for at least two weeks to allow the body to synthesize new monoamine oxidase. (See "Kidney replacement therapy (dialysis) in acute kidney injury in adults: Indications, timing, and dialysis dose".)

Overdose with moclobemide alone appears to be relatively benign [20]. Little information is available about overdose with transdermal selegiline [9].

PRESCRIBING MAOIS

Dietary restrictions — Several of the monoamine oxidase inhibitors (MAOIs) that are typically used to treat major depression require dietary restrictions to avoid interactions with foods and

beverages that contain relatively high levels of tyramine, a sympathomimetic amino acid. Exposure to tyramine can cause a hypertensive crisis (see 'Hypertensive crisis' above) [4,7,10,13,14,18]. Among patients who were treated with MAOIs prior to the advent of using dietary restrictions, it is estimated that hypertensive reactions occurred in 2 to 25 percent [6,7]. In some cases, patients suffered strokes and/or died.

The need for dietary modifications depends upon the specific MAOI that is used [1,2,4,7,9]:

- **Isocarboxazid, phenelzine, and tranylcypromine** – Patients taking these MAOIs must adhere to dietary restrictions to minimize exposure to tyramine.

- **Moclobemide** – Moclobemide (which is not available in the United States) can be prescribed without dietary restrictions because it increases the pressor effects of tyramine only partially. Although the drug blocks the enzyme monoamine oxidase A (MAO-A), which metabolizes tyramine in the gut, inhibition of the enzyme is reversible; moclobemide has a low affinity for the enzyme and is displaced by tyramine. Nevertheless, it is prudent to administer moclobemide after meals rather than before to avoid even mild pressor effects from tyramine.

- **Selegiline** – Patients taking selegiline at low doses (eg, transdermal selegiline 6 mg/24 hours) also do not require a low-tyramine diet. However, at higher doses (9 or 12 mg/24 hours), dietary restrictions are recommended because the safety data at these doses are relatively limited.

  Transdermal administration of selegiline bypasses the gut, which means that gastrointestinal MAO-A is not directly exposed to the drug. Thus, in phase three clinical trials that administered transdermal selegiline 6 mg/24 hours to patients (n >1600) who did not modify their diet, no hypertensive crises were observed. In addition, hypertensive crises were not reported in any of the patients (n >900) who received the selegiline patch at 9 or 12 mg/24 hours without modifying their diet. Nevertheless, patients receiving the drug at these higher doses (9 or 12 mg/24 hours) should restrict intake of tyramine due to limited safety data at these doses.

For patients who are treated with MAOIs that require dietary restrictions, we suggest avoiding the foods that are listed in the table (table 4) [1,2,4,6,9,11,13,14,21]. The table also lists related foods that are permissible. As an example, aged cheese such as cheddar is not allowed, whereas fresh cottage cheese is allowed. Clinicians should print the table for patients and discuss the restrictions with them. In addition, we suggest periodically asking about the dietary restrictions during follow-up visits to maintain patient adherence [4]. Patients who either

intentionally or inadvertently violate one dietary restriction without an adverse consequence may become less adherent with other restrictions.

The primary restrictions include aged cheeses, meats, poultry, and fish, as well as fermented, overripe, or spoiled foods [1,2,4,6,7,9,13,14,21]. As an example, if patients treated with tranylcypromine ingest approximately 0.1 lb (50 g) of aged cheddar cheese, blood pressure can increase more than 30 mmHg [4].

For patients treated with MAOIs, tyramine levels >6 mg per serving of food are generally regarded as posing a risk for a hypertensive crisis [4,7,13,14]. However, the amount of tyramine in a particular food product can vary, and some studies suggest that modern food production methods have reduced the amount of tyramine in foods and that many diet guidelines are too restrictive [10,13]. In addition, patients treated with MAOIs that require dietary restrictions appear to vary in their response to tyramine [13].

After discontinuing an MAOI that requires dietary modifications, patients should continue to restrict tyramine intake for two additional weeks, during which the body will regenerate monoamine oxidase [4,14,20].

Additional information about the pharmacology of MAOIs that underlies potential drug-food interactions with tyramine are discussed elsewhere in this topic. (See 'Pharmacology' above.)

Medication restrictions — The MAOIs isocarboxazid, moclobemide, phenelzine, selegiline (both oral and transdermal), and tranylcypromine pose a risk for clinically significant, adverse drug-drug interactions, including the serotonin syndrome (serotonin toxicity) and a hypertensive crisis [1,4,11,13,18,20]. Thus, clinicians must counsel patients about avoiding other medications that can interact with MAOIs. In addition, clinicians prescribing MAOIs should coordinate care with other clinicians who are treating the patient, and patients should be instructed to tell their other clinicians about the MAOI.

Drug-drug interactions between MAOIs and other medications can be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate. Examples of other therapeutic medications or drugs of abuse to be avoided include the following [1,2,4]:

- Serotonergic drugs – Taking MAOIs in combination or close proximity (eg, two weeks) with other serotonergic drugs (table 2) can precipitate the serotonin syndrome.

- Direct and indirect sympathomimetics – A hypertensive crisis can occur if MAOIs are combined or taken in close proximity with either direct or indirect sympathomimetics, such as the following:

- Amphetamine
- Cocaine
- Ephedrine
- Methylphenidate
- Oxymetazoline
- Phenylephrine
- Phentermine
- Pseudoephedrine

Additional information about the serotonin syndrome and hypertensive crisis is discussed elsewhere in this topic. (See 'Safety risks' above.)

Medication restrictions also include sympathomimetic vasoconstrictors that are used for local anesthesia during surgery, as well as sympathomimetic agents used for general anesthesia during surgery or electroconvulsive therapy [4,21]. Patients undergoing elective surgery generally discontinue MAOIs prior to the procedure. (See "Discontinuing antidepressant medications in adults", section on 'MAOIs'.)

Management of postoperative pain in patients taking MAOIs should avoid serotonergic analgesics (eg, fentanyl, meperidine, and tramadol). If postoperative patients require narcotic analgesia, morphine is typically used [1].

Patients who switch from any antidepressant to an MAOI, or vice versa, need to wait a sufficient amount of time between the last dose of the discontinued drug and the first dose of the new drug to avoid precipitating the serotonin syndrome or a hypertensive crisis. Details about switching to or from an MAOI, including the waiting period, are discussed separately. (See "Switching antidepressant medications in adults", section on 'Switching to or from MAOIs'.)

Other guidelines for patients — Prior to prescribing MAOIs, clinicians should discuss [1,4]:

- Wearing a medical alert bracelet or carrying a card – We suggest that patients taking an MAOI wear a medical alert bracelet or carry a card to alert first responders that the patient is taking an MAOI (in the event that the patient is incapacitated).
- Side effects.
- Time to response.
- Discontinuing the medication.

Common and serious side effects (table 5) and the need to take the medication as prescribed rather than on an as needed basis should be reviewed. Patients should also be informed that although some response may occur within the first two weeks of treatment, it may take many weeks (eg, 8 to 12) for a full response; severity of illness and comorbidities may affect the rate of response. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Duration of an adequate trial' and "Unipolar major depression in adults: Choosing initial treatment".)

In addition, clinicians should caution patients that abruptly discontinuing MAOIs may precipitate symptoms such as anxiety, agitation, insomnia, chills, diaphoresis, headache, irritability, malaise, and nausea. This discontinuation syndrome may be more common with phenelzine and tranylcypromine. Additional information about the discontinuation syndrome and stopping MAOIs is discussed separately. (See "Discontinuing antidepressant medications in adults".)

Medical tests, monitoring, and serum levels — Before starting isocarboxazid, phenelzine, and tranylcypromine, we suggest obtaining baseline liver function tests and periodically thereafter (eg, every three to six months). These drugs may injure the liver and increase liver enzymes (eg, alanine aminotransferase and aspartate aminotransferase) in 3 to 5 percent of patients [1]. However, hepatotoxicity is rare. Subsequent to starting MAOIs, symptoms such as jaundice and new onset fatigue should prompt drawing a set of liver function tests.

Isocarboxazid, phenelzine, and tranylcypromine may also cause postural hypotension. Thus, blood pressure should be assessed prior to starting an MAOI and monitored during treatment. As an example, blood pressure can initially be checked every one to two weeks for the first month of treatment and then every one to two months for the next six months of treatment. Thereafter, monitoring can occur every three to six months. This schedule may be adjusted depending upon the dose; relatively low doses (eg, phenelzine 15 to 30 mg per day) would be expected to have fewer effects upon blood pressure. Managing hypotension is discussed elsewhere in this topic. (See 'Side effects' below.)

Drug serum concentrations are not routinely monitored because they are not correlated with clinical response [6].

Administration — MAOIs are largely used for treatment-resistant depression. Care must be exercised when switching from the drug that failed to achieve response to an MAOI. Switching to an MAOI is discussed separately. (See "Switching antidepressant medications in adults", section on 'Switching to or from MAOIs'.)

Isocarboxazid — The initial dose of isocarboxazid is 10 mg once or twice daily [2,5,6,11,14]. For patients who start with 10 mg/day and tolerate the drug, the dose is generally increased within a week to 10 mg twice daily. Patients who tolerate 20 mg/day, but do not achieve a satisfactory response after one to four weeks, should increase the dose by increments of 10 mg/day every one to two weeks until response occurs. The maximum dose is 60 mg/day; doses ≥20 mg/day are divided into two to four doses.

Moclobemide — The starting dose of moclobemide is 150 mg once or twice daily [2,5,11,12,20]. For patients who start with 150 mg/day and tolerate the drug, the dose is generally increased within a week to 150 mg twice daily. Patients who tolerate 300 mg/day, but do not achieve a satisfactory response after one to four weeks, should increase the dose by increments of 150 mg/day every one to four weeks until response occurs. The maximum dose is 600 mg/day; doses ≥300 mg/day are divided into two doses.

We suggest administering moclobemide after meals rather than before to avoid even mild pressor effects from tyramine. (See 'Dietary restrictions' above.)

Phenelzine — The initial dose of phenelzine is 15 mg once, twice, or three times daily [2,5,6,11,12,14]. For patients who start with 15 mg/day and tolerate the drug, the dose is generally increased within a week 15 mg twice daily. Patients who tolerate 30 or 45 mg/day, but do not achieve a satisfactory response after one to four weeks, should increase the dose by increments 15 mg/day every one to four weeks until response occurs. The maximum dose is 90 mg/day; doses ≥45 mg/day are divided into three doses.

Selegiline — Selegiline is available as transdermal and oral formulations [1,4,7,14,18]. Transdermal selegiline is preferred because it avoids first-pass metabolism; thus, bioavailability is greater with transdermal administration than oral selegiline (approximately 75 versus 5 percent). The result is that a lower dose of transdermal selegiline provides a higher serum concentration for a longer time. Also, transdermal selegiline is absorbed gradually over 24 hours and decreases absorption peaks, which may mitigate adverse effects and improve tolerability.

The starting dose of transdermal selegiline is 6 mg; the patch is applied once daily and left in place for 24 hours [2,4,9,11,12]. For patients who tolerate the drug but do not achieve a satisfactory response after two to four weeks, the dose is titrated up to 9 mg/24 hours. If response after two to four weeks remains unsatisfactory, the dose is increased to a maximum of 12 mg/24 hours.

Tranylcypromine — The initial dose of tranylcypromine is 10 mg once or twice daily [2,3,5,6,11,12,14]. For patients who start with 10 mg/day and tolerate the drug, the dose is

generally increased within a week to 10 mg twice daily. Patients who tolerate 20 mg/day but do not achieve a satisfactory response after one to three weeks should increase the dose by increments of 10 mg/day every one to three weeks until response occurs. The maximum dose is 60 mg/day; doses ≥20 mg/day are divided into two doses.

SIDE EFFECTS

The monoamine oxidase inhibitors (MAOIs) can cause drug-drug interactions that lead to the serotonin syndrome and drug-food and drug-drug interactions that can result in a hypertensive crisis [1,2]. (See 'Safety risks' above.)

Other adverse effects may also occur with MAOIs, depending upon the specific drug (table 5).

- **Isocarboxazid, phenelzine, and tranylcypromine** – The most common side effects of these MAOIs include [1,2,4]:
  - Blurred vision
  - Constipation
  - Dry mouth
  - Headache
  - Insomnia
  - Liver enzyme elevation
  - Myoclonus
  - Nausea
  - Orthostatic hypotension
  - Paresthesias
  - Peripheral edema
  - Sedation
  - Sexual dysfunction
  - Urinary hesitancy
  - Weight gain

  Insomnia may be more common with tranylcypromine than isocarboxazid and phenelzine and may respond to administering the nighttime dose earlier [6]. In addition, benzodiazepines such as clonazepam or lorazepam are permissible with MAOIs.

  Although liver enzyme elevation is relatively common, hepatotoxicity is rare [1,22]. Liver enzyme elevation may manifest with jaundice and new onset anorexia, fatigue, nausea,

and weakness; these symptoms should prompt assessment with liver function tests.

Orthostatic hypotension is especially common with isocarboxazid, phenelzine, and tranylcypromine and may manifest with dizziness [1,2,4,20]. Older adult patients may be both more sensitive to hypotension and more likely to fall and sustain fractures. Management of orthostasis includes rising slowly if sitting or lying down, adjusting any concomitant antihypertensive drugs, increasing fluids (eg, consuming two liters/day), adding dietary salt, and wearing elastic support stockings; severe cases may necessitate the salt-retaining steroid fludrocortisone. General measures for managing orthostasis and other adverse effects include slowly increasing the dose and dividing the daily doses [4]. Additional information about managing orthostatic hypotension is discussed separately. (See "Treatment of orthostatic and postprandial hypotension".)

Weight gain is also common, especially with isocarboxazid and phenelzine [1,2]. Switching from these drugs to tranylcypromine may alleviate the problem [1]. In addition, a combination of diet, exercise, and behavioral modification can help manage weight gain. (See "Obesity in adults: Overview of management".)

Paresthesias may be alleviated by adding pyridoxine (vitamin B6) [4,20].

Sexual dysfunction can include decreased libido, impotence, delayed ejaculation, and anorgasmia.

- **Moclobemide** – Moclobemide is relatively well tolerated [1]. In randomized trials, the only side effect that occurred more frequently with moclobemide than placebo was nausea.

- **Selegiline** – Transdermal selegiline is also well tolerated [7,11,18]. In randomized trials, which compared transdermal selegiline (3 to 12 mg/24 hours) with placebo in depressed patients (total n >1400) for up to eight weeks, the only adverse effect that was greater with transdermal selegiline than placebo was skin irritation at the patch application site (24 versus 12 percent). This mild contact dermatitis can be managed by changing the application site each day and not applying the patch to areas that are hairy or shaved. Cleaning the patch site with warm soapy water and applying moisturizers can also help, as can low potency topical steroids for two to three days.

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading

level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see "Patient education: Coping with high drug prices (The Basics)")
- Beyond the Basics topics (see "Patient education: Depression treatment options for adults (Beyond the Basics)" and "Patient education: Depression in adults (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

The National Institute of Mental Health also has educational material explaining the symptoms, causes, and treatment for depression in a booklet entitled "Depression," which is available online at the website, or by calling a toll-free number, 866-615-6464. The website also provides references, summaries of study results in language intended for the lay public, and information about clinical trials currently recruiting patients.

The Depression and Bipolar Support Alliance (available at the website or 800-826-3632) is a national organization whose mission is to educate members about depression and how to cope with it. Other functions include increasing public awareness of the illness and advocating for more research and services. The organization is administered and maintained by patients and family members, and has local chapters.

The National Alliance on Mental Illness (available at the website or 800-950-6264) is a similarly structured organization devoted to providing education, support, and advocacy for patients with any mental illness. Depression is one of their priorities.

SUMMARY

- Monoamine oxidase inhibitors (MAOIs) are used to treat multiple psychiatric disorders, including bulimia nervosa, panic disorder, social anxiety disorder, and treatment-resistant depressive syndromes, including unipolar major depression with atypical features. The

MAOIs that are most commonly used as antidepressants include isocarboxazid, moclobemide (not available in the United States), phenelzine, selegiline, and tranylcypromine. Isocarboxazid, phenelzine, and tranylcypromine are contraindicated in congestive heart failure, liver disease, and pheochromocytoma. (See 'Introduction' above and 'Indications' above.)

- The mechanism of action of MAOIs is not clear. One hypothesis is that MAOIs increase dopaminergic, noradrenergic, and serotonergic neurotransmission by inhibiting/blocking monoamine oxidase, which is an enzyme that inactivates these neurotransmitters. Inhibition of monoamine oxidase also prevents metabolism of tyramine (a sympathomimetic amino acid) in the gastrointestinal tract; this allows tyramine to enter the general circulation, which may subsequently lead to a hypertensive crisis. (See 'Pharmacology' above.)

- The primary safety problems that can occur with MAOIs are drug-drug interactions that cause the serotonin syndrome and drug-food and drug-drug interactions that cause a hypertensive crisis. Use of MAOIs thus necessitates dietary restrictions (table 4) and medication restrictions. (See 'Safety risks' above and 'Dietary restrictions' above and 'Medication restrictions' above.)

- It is prudent for patients taking an MAOI wear a medical alert bracelet or carry a card to alert first responders that the individual is taking an MAOI. (See 'Other guidelines for patients' above.)

- MAOIs are largely used for treatment-resistant depression. Care must be exercised when discontinuing the drug that failed to achieve response and switching to the MAOI. (See "Switching antidepressant medications in adults", section on 'Switching to or from MAOIs'.)

- MAOIs are started at relatively low doses and then titrated up according to response and tolerability. Initial and maximum daily doses are as follows:

  - Isocarboxazid – 10 mg once or twice daily; 60 mg/day divided into two to four doses.

  - Moclobemide – 150 mg once or twice daily; 600 mg/day divided into two doses.

  - Phenelzine – 15 mg once, twice, or three times daily; 90 mg/day divided into three doses.

  - Selegiline (transdermal) – 6 mg once daily; 12 mg once daily.

- Tranylcypromine – 10 mg once or twice daily; 60 mg/day; doses ≥20 mg/day are divided into two doses.

(See 'Administration' above.)

- Beyond the serotonin syndrome and hypertensive crisis, other adverse effects may also occur with MAOIs, depending upon the specific drug (table 5). Isocarboxazid, phenelzine, and tranylcypromine can cause several side effects, including orthostasis and weight gain. By contrast, moclobemide and transdermal selegiline are relatively well tolerated. (See 'Side effects' above.)

Topic 1715 Version 21.0

→