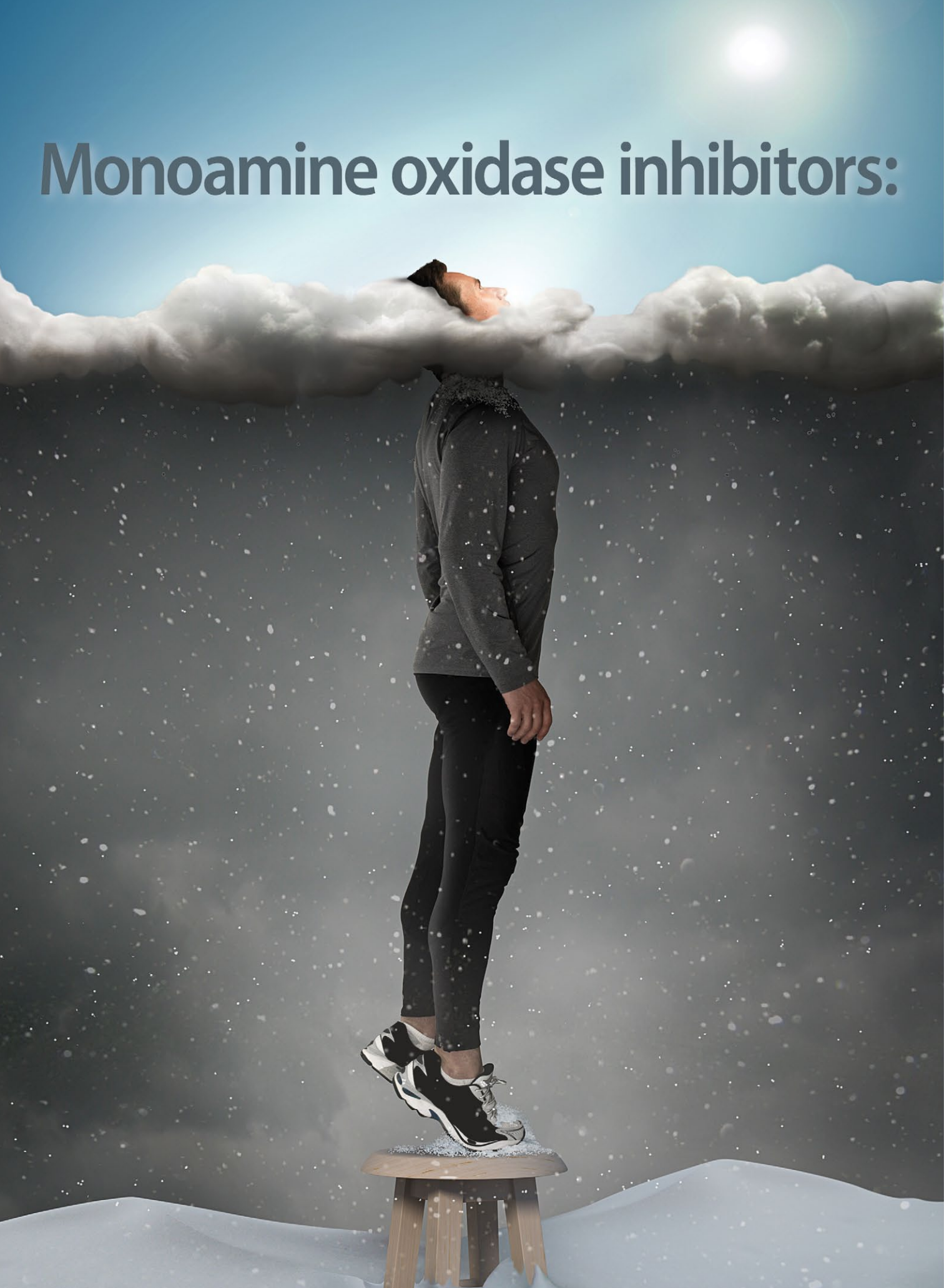
Monoamine oxidase inhibitors:



Forgotten treatment for depression

Increased knowledge of MAOIs has made these agents worthy of reconsideration

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For patients with major depressive disorder (MDD), monoamine oxidase inhibitors (MAOIs) have efficacy comparable to that of other antidepressants. However, concerns about side effects—particularly hypertensive crisis—and drug-drug interactions have led clinicians to prescribe MAOIs less often than newer antidepressants. A 1999 survey of 573 Michigan psychiatrists found that 30% had not prescribed an MAOI within the past 3 years, and 12% had never prescribed an MAOI.[1] Although there are challenges to using these agents, we prefer prescribing MAOIs to depressed patients who have not responded to previous antidepressant trials over trying untested antidepressant combinations.

Currently, MAOIs are used primarily for patients who have not responded to other antidepressant trials and are considered treatment resistant. Treatment-resistant depression (TRD) typically is defined as nonresponse to ≥3 adequate antidepressant trials. TRD is a major cause of disability and loss of productivity. These patients tend to do poorly over the long term, with high rates of hospitalization and suicide attempts. Several controlled trials have shown that patients who fail other antidepressants may respond to MAOIs.[2-4]

Our knowledge regarding MAOIs has grown considerably. We have learned more about depression subtypes that MAOIs may help. As we learned more about dietary restrictions for patients taking MAOIs, the list of "forbidden foods" has decreased. Advances in treating a hypertensive crisis have decreased the need for hospitalization. By educating ourselves and our patients about MAOIs, we can provide another option for treating MDD.

continued

Monoamine oxidase inhibitors

Table 1

Recommended dosages of monoamine oxidase inhibitors

Medication	Starting dosages	Usual therapeutic dosage
Isocarboxazid	10 mg twice a day	30 to 60 mg/d
Phenelzine	15 mg twice a day	45 to 90 mg/d
Selegiline transdermal	6 mg patch/d	6 to 12 mg patch/d
Tranylcypromine	10 mg, 2 or 3 times a day	30 to 60 mg/d

Source: Adapted from reference 8

Clinical Point

Several trials have found MAOIs may benefit outpatients with MDD who have not responded to other antidepressants

An older antidepressant class

MAOIs were introduced approximately 60 years ago. Their potential for treating depression was discovered when a tuberculosis treatment—iproniazid—was found to reduce depressive symptoms. Researchers determined iproniazid's antidepressant effects were the result of blocking removal of the amine group by monoamine oxidase (MAO) from dopamine, norepinephrine, and serotonin.[5] A second MAOI, tranylcypromine, was discovered when it was found to be ineffective for treating decongestion.[6]

MAOI use in psychiatric practice has undergone significant changes since these medications were introduced. The discovery of hypertensive crises related to tyramine consumption led to decreased MAOI use, as did the rise of tricyclic antidepressants (TCAs) shortly thereafter. In the 1960s, research compared the relative efficacy of MAOIs to TCAs, and they became second-line antidepressants after the TCAs. In the late 1980s, the introduction of fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) resulted in a significant drop-off in MAOI use.

Pharmacologic effects

MAO is a class of enzymes that initiate oxidation of extracellular neurotransmitters such as serotonin, norepinephrine, and dopamine. MAOIs can be classified based on their relative affinity to MAO as well as their enzyme selectivity. The first distinguishing characteristic is whether the drug binds to MAO in a reversible or irreversible manner. Currently, all MAOIs that are FDA-approved for treating depression bind irreversibly to MAO. As a result, the body must renew its MAO levels before a patient is no longer at risk for a hypertensive crisis, a process that may take up to 2 weeks. Clinicians must take care to ensure their patients avoid foods that contain tyramine and medications contraindicated with MAOIs during this period.

MAOIs also differ from each other in enzyme selectivity. There are 2 subtypes of MAO enzymes—MAO_A and MAO_B. Generally, the antidepressant activity of MAOIs appears to be directed toward MAO_A inhibition. MAO_A has been found to be more specific for binding to serotonin and norepinephrine and MAO_B to be more specific for phenylethylamine. Dopamine is equally deaminated by both MAO_A and MAO_B.

Reversible MAO_A inhibitors require fewer restrictions on diet or concurrent medications, but efficacy data of reversible MAO_A inhibitors is mixed.

Clinical use of MAOIs

Four MAOIs are available in the United States: tranylcypromine, phenelzine, isocarboxazid, and selegiline. Selegiline is the only MAOI available as a transdermal patch. Transdermal administration results in fewer effects on MAO in the gastrointestinal tract, which means no dietary restrictions at the 6 mg/d starting dose, although the manufacturer recommends patients follow the MAO diet at 9 mg/d and 12 mg/d doses.[7] Although selegiline is selective for MAO_B at low doses, it becomes nonselective at therapeutic doses for depression. Recommended dosages for MAOIs can be found in ***Table 1***.[8]

Depression subtypes. Researchers have observed that MAOIs are effective for

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treating atypical depression.[9] Atypical depression is characterized by significant increases in sleep, appetite, or weight; leaden paralysis; and a pattern of extreme sensitivity to interpersonal loss often referred to as "rejection sensitivity." Other subtypes of depression—such as depression with melancholic features and dysthymia—respond to MAOIs.[10,11]

Several controlled trials have found a better response rate to MAOI therapy in outpatients with MDD who have not responded to other antidepressants.[2,12] In a 6-week, double-blind trial, Vallejo et al[10] reported that the TCA imipramine and high-dose phenelzine were equally efficacious in 32 patients with major depression with melancholia. In 32 dysthymic patients, high-dose phenelzine was superior to imipramine. Himmelhoch et al[13] compared efficacy of tranylcypromine with that of imipramine in treating anergic bipolar depressive illness. Patients receiving tranylcypromine experienced significantly greater symptomatic improvement and higher global response without increased risk of treatment-emergent hypomania or mania.

Serum monitoring of MAOIs is not clinically indicated and there are no correlations between drug levels and effectiveness.[14] In a study that examined the correlation of inhibiting platelet MAO and MAOIs' antidepressant effects, researchers found that a higher dose of phenelzine (60 mg/d) was significantly better in treating depression and anxiety than a lower dose (30 mg/d), and only the higher dose achieved 80% of platelet MAO inhibition.[15] Further studies with other MAOIs did not reproduce this effect and platelet MAO inhibition is not regularly used to assess adequate dosing.

A refined view of side effects

Clinicians often consider hypertensive crisis to be the most serious side effect of MAOIs. Many clinicians recommend that their patients wear bracelets stating they are taking MAOIs in case they become unconscious in an emergency. Consumption of tyramine, a substrate for the MAO enzyme, may trigger a hypertensive crisis. Although the exact mechanism by which tyramine causes hypertensive crises is unknown, it is thought that if a patient with depleted MAO levels ingests tyramine, it may displace intracellular norepinephrine, leading to a rapid rise in blood pressure. Hypertensive crises are rare among patients who adhere to a tyramine-free diet.

In a hypertensive crisis, patients experience significant hypertension, headaches, tachycardia, diaphoresis, and vomiting. Intravenous phentolamine—an α-adrenergic receptor blocker—can be used as an antidote; often a single dose is effective.[16] Alternatively, calcium channel blockers such as nifedipine can be prescribed. A patient can take 10 mg/hour and be observed in the emergency room until symptoms are relieved (usually only 1 or 2 doses are needed) without being admitted to the hospital.

Dietary restrictions. In the 1970s and 1980s, the "MAOI diet" list of prohibited foods contained >70 items. As patients on an overly inclusive diet began to "cheat," they struggled to differentiate foods that

Table 2

Food restrictions with MAOIs

Severe
Aged cheeses
Aged meats (pepperoni, sausage, salami)
Sauerkraut
Soy sauce
Fava or broad bean pods
Banana peels
All beers on tap
Use in moderation (≤2 servings/d)
Red wine (4 oz)
White wine (4 oz)
Bottled or canned beers (12 oz)
Mild to none
Avocados
Banana pulp
Bouillon
Chocolate
Fresh cheeses (cottage cheese, cream cheese, processed cheese slices)
Fresh or processed meat

MAOIs: monoamine oxidase inhibitors
Source: Adapted from references 4,17,18

Clinical Point

Hypertensive crisis is the most serious side effect of MAOIs, but often it can be treated without hospitalization

Monoamine oxidase inhibitors

Table 3

MAOIs: Stay vigilant for side effects

Medication	Common side effects
Isocarboxazid	Anxiety, blurred vision, constipation, dizziness, headache, insomnia, mania, somnolence, weight gain, xerostomia
Phenelzine	Constipation, disorder of ejaculation and/or orgasm, dizziness, edema, fatigue, headache, hyperreflexia, impotence, elevated values on liver function tests, orthostatic hypotension, sleep disorders, somnolence, tremor, weight gain, xerostomia
Selegiline transdermal	Application site reaction, decreased systolic blood pressure, diarrhea, headache, indigestion, insomnia, orthostatic hypotension, weight loss, xerostomia
Tranylcypromine	Agitation, anxiety, constipation, diarrhea, dizziness, headache, impotence, insomnia, loss of appetite, mania, nausea, orthostatic hypotension, somnolence, weight gain, xerostomia

MAOIs: monoamine oxidase inhibitors

Source: Adapted from reference 20

Clinical Point

Based on rigorous reviews of tyramine content, the number of 'forbidden foods' for patients taking an MAOI has decreased

were moderately safe from those that were highly dangerous. Over time, in addition to foods that contained tyramine, foods that contained compounds that caused symptoms similar to those of a hypertensive crisis were added to many MAOI diets. For example, chocolate, which contains phenylethylamine, is associated with migraine headaches, which can be confused with MAOI-related emergencies. Likewise, tannic acids found in red wines caused similar symptoms. In recent years, the number of "forbidden foods" on the MAO diet has decreased. ***Table 2*** (***page 23***)[4,17,18] contains an up-to-date list of foods with elevated tyramine content, based on systematic reviews and more rigorous evaluations of tyramine content of foods.

Potential drug-drug interactions. Concomitant use of SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), opioids, clomipramine, epinephrine, local anesthetics containing sympathomimetic agents, and decongestants with MAOIs could cause serotonin syndrome. Serotonin syndrome is characterized by hypertonicity, autonomic signs, hallucinations, rhabdomyolysis, and hyperthermia, and can be fatal if not promptly treated. Treatment is guided by presentation severity and discontinuing the causative medications is of utmost importance. Interventions include aggressive treatment for hyperthermia, including external cooling and hydration, and supportive care such as administering IV fluids.

Orthostatic hypotension is a common cardiovascular side effect of MAOIs that may lead to dizziness or syncope. Typically this is seen 2 to 3 weeks after initiating MAOI treatment. If hypotension remains a problem, mineralocorticoids can be prescribed with monitoring of serum potassium for hypokalemia. Increasing doses of tranylcypromine can increase supine—but not standing—diastolic blood pressure.[19] Distinguish this type of blood pressure elevation from a hypertensive crisis by monitoring blood pressure with the patient sitting and standing and before and after he or she walks for 60 seconds.

Insomnia and day-night shifting—sleeping during the day and staying awake at night—are common and patients often cite these as reasons for discontinuing MAOIs. Many patients who respond to MAOIs report periods of substantial sleepiness in the mid to late afternoon. ***Table 3***[20] provides a more complete list of reported side effects and their frequencies.

Practice guidelines

The American Psychiatric Association's practice guidelines for treating major depression state that MAOIs are effective in treating subgroups of patients with MDD with atypical features who have failed TCA trials.[21] These guidelines also state that MAOIs have been shown to be effec-

tive treatment for some patients who have failed other antidepressants. However, for TRD patients who have not responded to SSRIs or SNRIs, the effectiveness of MAOIs compared with other strategies is unclear.[22]

One study found adding lithium to an MAOI may provide more rapid or more efficacious response than MAOI monotherapy.[23] Guze et al[24] evaluated the effects of high-dose MAOI treatment for 2 TRD patients; both patients improved without any side effects.

MAOIs have been used for >6 decades, and published studies continue to document their efficacy and safety when patients are monitored appropriately.[11,12,14,15,25] However, based on our observations we suspect MAOIs are underutilized in clinical practice today. We are concerned that such practices can trickle down into residency training programs. Psychiatric residents typically do not receive adequate training in prescribing MAOIs, largely because many training faculty are not prescribing MAOIs themselves. Despite MAOIs' limitations, concerns about an increased risk of suicide in patients with TRD[26] and the high likelihood of a poor outcome associated with persistent nonresponse to prior treatments must be weighed against the relatively low risk of a hypertensive event with MAOIs.[6]

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continued

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Practice guidelines state MAOIs are effective for patients with depression with atypical features who have failed tricyclic antidepressants

Monoamine oxidase inhibitors

Clinical Point

Studies continue to document MAOIs' safety and efficacy when patients are monitored appropriately

Related Resources

- McCabe-Sellers BJ, Staggs CG, Bogle ML. Tyramine in foods and monoamine oxidase inhibitor drugs: a crossroad where medicine, nutrition, pharmacy, and food industry converge. Journal of Food Composition and Analysis. 2006;19(suppl):S58-S65.
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Drug Brand Names

Clomipramine • Anafranil
Epinephrine • Adrenalin, EpiPen
Fluoxetine • Prozac
Imipramine • Tofranil
Isocarboxazid • Marplan
Lithium • Eskalith, Lithobid
Nifedipine • Adalat, Afeditab
Phenelzine • Nardil
Phentolamine • OraVerse, Regitine
Selegiline • EMSAM
Tranylcypromine • Parnate

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Bottom Line

The efficacy of monoamine oxidase inhibitors (MAOIs) for depression is comparable to that of other antidepressants. Concerns about side effects—primarily hypertensive crisis—and dietary restrictions have lead many clinicians to curtail their use of MAOIs, but increased knowledge of these drugs can help psychiatrists reconsider this treatment option, particularly for patients with atypical depression.