22 - 29.22 Monoamine Oxidase Inhibitors

29.22 Monoamine Oxidase Inhibitors

9th edition. Vol. 2. Philadelphia: Lippincott Williams & Wilkins: 2009:3152. 29.22 Monoamine Oxidase Inhibitors Introduced in the late 1950s, MAOIs were the first class of approved antidepressant drugs. The first of these drugs, isoniazid, was intended to be used as a treatment for tuberculosis, but its antidepressant properties were discovered by chance when some treated patients experienced elevation of mood during treatment. Despite their effectiveness, prescription of MAOIs as first-line agents has always been limited by concern about the development of potentially lethal hypertension and the consequent need for a restrictive diet. Use of MAOIs declined further after the introduction of the SSRIs and other new agents. They are now mainly relegated to use in treatmentresistant cases. Thus, the second-line status of MAOIs has less to do with considerations of efficacy than with concerns for safety. The currently available MAOIs include phenelzine (Nardil), isocarboxazid (Marplan), tranylcypromine (Parnate), rasagiline (Azilect), moclobemide (Manerix), and selegiline (Eldepryl). Two subsequent advances in the field of antidepressant MAOIs involve the introduction of a selective reversible inhibitor of MAOA (RIMA), moclobemide (Manerix), in the early 1990s into most countries except the United States, and in 2005, the introduction of a transdermal delivery form of selegiline (Emsam) in the United States that is used for the treatment of parkinsonism. Other RIMA agents, including brofaromine (Consonar) and befloxatone, have not been submitted for registration despite favorable outcomes in clinical trials. PHARMACOLOGIC ACTIONS Phenelzine, tranylcypromine, and isocarboxazid are readily absorbed after oral administration and reach peak plasma concentrations within 2 hours. Whereas their plasma half-lives are in the range of 2 to 3 hours, their tissue half-lives are considerably longer. Because they irreversibly inactivate MAOs, the therapeutic effect of a single dose of irreversible MAOIs may persist for as long as 2 weeks. The RIMA moclobemide is rapidly absorbed and has a half-life of 0.5 to 3.5 hours. Because it is a reversible inhibitor, moclobemide has a much briefer clinical effect after a single dose than do irreversible MAOIs. The MAO enzymes are found on the outer membranes of mitochondria, where they degrade cytoplasmic and extraneuronal monoamine neurotransmitters such as norepinephrine, serotonin, dopamine, epinephrine, and tyramine. MAOIs act in the CNS, the sympathetic nervous system, the liver, and the GI tract. There are two types of MAOs, MAOA and MAOB. MAOA primarily metabolizes

norepinephrine, serotonin, and epinephrine; dopamine and tyramine are metabolized by both MAOA and MAOB. The structures of phenelzine and tranylcypromine are similar to those of amphetamine and have similar pharmacologic effects in that they increase the release of

dopamine and norepinephrine with attendant stimulant effects on the brain. THERAPEUTIC INDICATIONS MAOIs are used for treatment of depression. Some research indicates that phenelzine is more effective than tricyclic antidepressants (TCAs) in depressed patients with mood reactivity, extreme sensitivity to interpersonal loss or rejection, prominent anergia, hyperphagia, and hypersomnia—a constellation of symptoms conceptualized as atypical depression. Evidence also suggests that MAOIs are more effective than TCAs as a treatment for bipolar depression. Patients with panic disorder and social phobia respond well to MAOIs. MAOIs have also been used to treat bulimia nervosa, posttraumatic stress disorder (PTSD), anginal pain, atypical facial pain, migraine, attention-deficit/hyperactivity disorder (ADHD), idiopathic orthostatic hypotension, and depression associated with traumatic brain injury. PRECAUTIONS AND ADVERSE REACTIONS The most frequent adverse effects of MAOIs are orthostatic hypotension, insomnia, weight gain, edema, and sexual dysfunction. Orthostatic hypotension can lead to dizziness and falls. Thus, cautious upward tapering of the dosage should be used to determine the maximum tolerable dosage. Treatment for orthostatic hypotension includes avoidance of caffeine; intake of 2 L of fluid per day; addition of dietary salt or adjustment of antihypertensive drugs (if applicable); support stockings; and in severe cases, treatment with fludrocortisone (Florinef), a mineralocorticoid, 0.1 to 0.2 mg a day. Orthostatic hypotension associated with tranylcypromine use can usually be relieved by dividing the daily dosage. Insomnia can be treated by dividing the dose, not giving the medication after dinner, and using trazodone (Desyrel) or a benzodiazepine hypnotic if necessary. Weight gain, edema, and sexual dysfunction often do not respond to any treatment and may warrant switching to another agent. When switching from one MAOI to another, the clinician should taper and stop use of the first drug for 10 to 14 days before beginning use of the second drug. Paresthesias, myoclonus, and muscle pains are occasionally seen in persons treated with MAOIs. Paresthesias may be secondary to MAOI-induced pyridoxine deficiency, which may respond to supplementation with pyridoxine, 50 to 150 mg orally each day. Occasionally, persons complain of feeling drunk or confused, perhaps indicating that the dosage should be reduced and then increased gradually. Reports that the hydrazine MAOIs are associated with hepatotoxic effects are relatively uncommon. MAOIs are less cardiotoxic and less epileptogenic than are the tricyclic and tetracyclic drugs. The most common adverse effects of the RIMA moclobemide are dizziness, nausea, and insomnia or sleep disturbance. RIMAs cause fewer GI adverse effects than do SSRIs. Moclobemide does not have adverse anticholinergic or cardiovascular effects, and it has not been reported to interfere with sexual function.

MAOIs should be used with caution by persons with renal disease, cardiovascular disease, or hyperthyroidism. MAOIs may alter the dosage of a hypoglycemic agent required by persons with diabetes. MAOIs have been particularly associated with induction of mania in persons in the depressed phase of bipolar I disorder and triggering of a psychotic decompensation in persons with schizophrenia. MAOIs are contraindicated during pregnancy, although data on their teratogenic risk are minimal. MAOIs should not be taken by nursing women because the drugs can pass into the breast milk. Tyramine-Induced Hypertensive Crisis The most worrisome side effect of MAOIs is the tyramine-induced hypertensive crisis. The amino acid tyramine is normally transformed via GI metabolism. However, MAOIs inactivate GI metabolism of dietary tyramine, thus allowing intact

tyramine to enter the circulation. A hypertensive crisis may subsequently occur as a result of a powerful pressor effect of the amino acid. Tyramine-containing foods should be avoided for 2 weeks after the last dose of an irreversible MAOI to allow resynthesis of adequate concentrations of MAO enzymes. Accordingly, foods rich in tyramine (Table 29.22-1) or other sympathomimetic amines, such as ephedrine, pseudoephedrine (Sudafed), or dextromethorphan (Trocal), should be avoided by persons who are taking irreversible MAOIs. Patients should be advised to continue the dietary restrictions for 2 weeks after they stop MAOI treatment to allow the body to resynthesize the enzyme. Bee stings may cause a hypertensive crisis. In addition to severe hypertension, other symptoms may include headache, stiff neck, diaphoresis, nausea, and vomiting. A patient with these symptoms should seek immediate medical treatment. Table 29.22-1 Tyramine-Rich Foods to be Avoided in Planning Monoamine Oxidase Inhibitor Diets

An MAOI-induced hypertensive crisis should be treated with α-adrenergic antagonists —for example, phentolamine (Regitine) or chlorpromazine (Thorazine). These drugs lower blood pressure within 5 minutes. IV furosemide (Lasix) can be used to reduce fluid load, and a β-adrenergic receptor antagonist can control tachycardia. A sublingual 10mg dose of nifedipine (Procardia) can be given and repeated after 20 minutes. MAOIs should not be used by persons with thyrotoxicosis or pheochromocytoma. The risk of tyramine-induced hypertensive crises is relatively low for persons who are taking RIMAs, such as moclobemide and befloxatone. These drugs have relatively little inhibitory activity for MAOB, and because they are reversible, normal activity of existing MAOA returns within 16 to 48 hours of the last dose of a RIMA. Therefore, the dietary restrictions are less stringent for RIMAs, applying only to foods containing high concentrations of tyramine, which need be avoided for 3 days after the last dose of a RIMA. A reasonable dietary recommendation for persons taking RIMAs is to avoid eating tyramine-containing foods 1 hour before and 2 hours after taking a RIMA. Spontaneous, nontyramine-induced hypertensive crisis is a rare occurrence, usually shortly after the first exposure of an MAOI. Persons experiencing such a crisis should avoid MAOIs altogether. Withdrawal Abrupt cessation of regular doses of MAOIs may cause a self-limited discontinuation syndrome consisting of arousal, mood disturbances, and somatic symptoms. To avoid

these symptoms when discontinuing use to an MAOI, dosages should be gradually tapered over several weeks. Overdose There is often an asymptomatic period of 1 to 6 hours after an MAOI overdose before the occurrence of the symptoms of toxicity. MAOI overdose is characterized by agitation that can progress to coma with hyperthermia, hypertension, tachypnea, tachycardia, dilated pupils, and hyperactive deep tendon reflexes. Involuntary movements may be present, particularly in the face and the jaw. Acidification of the urine markedly hastens the excretion of MAOIs, and dialysis can be of some use. Phentolamine or chlorpromazine may be useful if hypertension is a problem. Moclobemide alone in overdosage causes relatively mild and reversible symptoms. DRUG INTERACTIONS The major drug–drug interactions involving MAOIs are listed in Table 29.22-2. Most antidepressants as well as precursor agents should be avoided. Persons should be instructed to tell any other physicians or dentists who are treating them that they are taking an MAOI. MAOIs may potentiate the action of CNS depressants, including alcohol and barbiturates. MAOIs should not be coadministered with serotonergic drugs, such as SSRIs and clomipramine (Anafranil), because this combination can trigger a serotonin syndrome. Use of lithium or tryptophan with an irreversible MAOI may also induce a serotonin syndrome. Initial symptoms of a serotonin syndrome can include tremor, hypertonicity, myoclonus, and autonomic signs, which can

then progress to hallucinosis, hyperthermia, and even death. Fatal reactions have occurred when MAOIs were combined with meperidine (Demerol) or fentanyl (Sublimaze). Table 29.22-2 Drugs to be Avoided During Monoamine Oxidase Inhibitor Treatment (Part of Listing)

When switching from an irreversible MAOI to any other type of antidepressant drug, persons should wait at least 14 days after the last dose of the MAOI before beginning use of the next drug to allow replenishment of the body's MAOs. When switching from an antidepressant to an irreversible MAOI, persons should wait 10 to 14 days (or 5 weeks for fluoxetine [Prozac]) before starting use of the MAOI to avoid drug–drug interactions. In contrast, MAO activity recovers completely 24 to 48 hours after the last dose of a RIMA. The effects of the MAOIs on hepatic enzymes are poorly studied. Tranylcypromine inhibits CYP2C19. Moclobemide inhibits CYP2D6, CYP2C19, and CYP1A2 and is a substrate for 2C19. Cimetidine (Tagamet) and fluoxetine significantly reduce the elimination of moclobemide. Modest doses of fluoxetine and moclobemide administered concurrently may be well tolerated, with no significant pharmacodynamic or pharmacokinetic interactions. LABORATORY INTERFERENCES MAOIs may lower blood glucose concentrations. MAOIs artificially raise urinary metanephrine concentrations and may cause a false-positive test result for pheochromocytoma or neuroblastoma. MAOIs have been reported to be associated with a minimal false elevation in thyroid function test results. DOSAGE AND CLINICAL GUIDELINES There is no definitive rationale for choosing one irreversible MAOI over another. Table

29.22-3 lists MAOI preparations and typical dosages. Phenelzine use should begin with a test dose of 15 mg on the first day. The dosage can be increased to 15 mg three times daily during the first week and increased by 15 mg a day each week thereafter until the dosage of 90 mg a day, in divided doses, is reached by the end of the fourth week. Tranylcypromine and isocarboxazid use should begin with a test dosage of 10 mg and may be increased to 10 mg three times daily by the end of the first week. Many clinicians and researchers have recommended upper limits of 50 mg a day for isocarboxazid and 40 mg a day for tranylcypromine. Administration of tranylcypromine in multiple small daily doses may reduce its hypotensive effects. Table 29.22-3 Typical Dosage Forms and Recommended Dosages for Currently Available Monoamine Oxidase Inhibitors Even though coadministration of MAOIs with TCAs, SSRIs, or lithium is generally contraindicated, these combinations have been used successfully and safely to treat patients with refractory depression. However, they should be used with extreme caution. Hepatic transaminase serum concentrations should be monitored periodically because of the potential for hepatotoxicity, especially with phenelzine and isocarboxazid. Elderly persons may be more sensitive to MAOI adverse effects than are younger adults. MAO activity increases with age, so MAOI dosages for elderly persons are the same as those required for younger adults. The use of MAOIs for children has had minimal study. Studies have suggested that transdermal selegiline has antidepressant properties. Although selegiline is a type B inhibitor at low doses, it becomes less selective as the dose is increased. REFERENCES Adli M, Pilhatsch M, Bauer M, Köberle U, Ricken R, Janssen G, Ulrich S, Bschor T. Safety of high-intensity treatment with the irreversible monoamine oxidase inhibitor tranylcypromine in patients with treatment-resistant depression. Pharmacopsychiatry. 2008;41:252. Amsterdam JD, Bodkin JA. Selegiline transdermal system in the prevention of relapse of major depressive disorder: A 52week, double-blind, placebo-substitution, parallel-group clinical trial. J Clin Psychopharmacol. 2006;26:579. Balu DT, Hoshaw BA, Malberg JE. Differential regulation of central BDNF protein levels by antidepressant and non-

Revision #1
Created 2026-01-04 19:51:48 UTC by Omar Ayman
Updated 2026-01-04 19:51:48 UTC by Omar Ayman