

Monoamine Oxidase Inhibitors – Indirect Acting Sympathomimetics

Monoamine Oxidase (MAO) is a widely distributed enzyme that oxidizes naturally occurring monoamines such as norepinephrine, serotonin, epinephrine, and dopamine to name a few. Monoamines are responsible for homeostasis for a wide variety of physiological functions, including blood pressure, heart rate, respiratory rate and tone, and various metabolic processes. Inhibition of the enzyme that oxidizes monoamines can result in lack of homeostasis due to excessive build up of monoamines in nerve endings, leading to severe hypertension, shock, cardiac failure, arrhythmias, anaphylaxis, and respiratory difficulties.

At least two isoenzymes of MAO enzymes exist, MAO-A and MAO-B. Compounds that inhibit the MAO enzyme are classified into three groups: 1) nonselective; 2) selective for MAO-A; and 3) selective for MAO-B. MAO-A is responsible for the de-amination of epinephrine, norepinephrine, and serotonin. MAO-B is responsible for metabolizing phenylethylamine. Dopamine and tyramine are metabolized by both isoenzymes. Products that inhibit only MAO-B are less likely to have a clinically significant interaction with stimulants and other catecholamine-like agents.

Because some MAO inhibitors bind irreversibly to the MAO enzyme, they are considered suicide inhibitors. The effect of irreversible binding is that the effects can last up to two weeks for normal metabolism to be restored.

Indirect acting sympathomimetics exert their action by displacement of norepinephrine and other from storage sites in synaptic vesicles or displacement from extravesicular binding sites. Similarly, indirect acting sympathomimetics stimulate increase in endogenous serotonin leading to serotonin syndrome, a clinical condition involving altered mental status, neuromuscular abnormalities, and autonomic instability.

Type of Monoamine Oxidase Inhibitor ¹	<u>Monoamine Oxidase A Inhibitors</u>	<u>Monoamine Oxidase B Inhibitors</u>	<u>Non-Selective Monoamine Oxidase Inhibitors</u>
	Moclobemide Clorglyline	Selegiline ² Rasagiline	Isocarboxazid Phenelzine Tranylcypromine
Amphetamine	◆	■	◆
Dextroamphetamine	◆	■	◆
Cocaine	◆	■	◆
Imipramine ³	◆	■	◆
Phenmetrazine	◆	■	◆
Methamphetamine	◆	■	◆

○ = No special precautions. ■ = Assess risk and take precautions as necessary. □ ◆ = Take measures to reduce risk.

Footnotes:

1. O'Donnell JM, Shelton RC. Chapter 15. Drug Therapy of Depression and Anxiety Disorders. In: Brunton LL, Chabner BA, Knollmann BC. eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12e. New York, NY: McGraw-Hill; 2011. <http://accessmedicine.mhmedical.com/content.aspx?bookid=374&Sectionid=41266221>. Accessed September 01, 2016.
2. Selegiline reversibly inhibits primarily MAO-B at therapeutic doses, but at higher doses can inhibit MAO-A. Administration of concurrent CYP1A2 inhibitor may results in increase serum levels. Rasagiline AUC increased by 83% when ciprofloxacin was initiated in healthy volunteers (See Azilect product label).
3. Imipramine inhibits serotonin reuptake. See product labeling. Tofranil-PM(TM) oral capsules, imipramine pamoate oral capsules. Mallinckrodt Inc.

Select references:

Gillman PK. A Review of Serotonin Toxicity Data: Implications for the Mechanisms of Antidepressant Drug Action. *Biological Psychiatry* 2006; 59:1046-1051.

Vuori E, Henry JA, Ojanpera I, et al. Death following ingestion of MDMA (ecstasy) and mocabemide. *Addiction* 2003; 98(3):365-368.

Krisko I, Lewis E & Johnson JE: Severe hyperpyrexia due to tranlycypromine-amphetamine toxicity. *Ann Intern Med* 1969; 70:559-564.