

General

Clinically Relevant Drug Interactions with Monoamine Oxidase Inhibitors

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Keywords: Monoamine oxidase inhibitors, drug interactions, hypertensive crisis, bleeding, ecstasy, weight gain, sexual dysfunction, insomnia, headache

<https://doi.org/10.52965/001c.39576>

Health Psychology Research

Vol. 10, Issue 4, 2022

Monoamine oxidase inhibitors (MAOI) are a class of drugs that were originally developed for the treatment of depression but have since been expanded to be used in management of affective and neurological disorders, as well as stroke and aging-related neurocognitive changes. Ranging from irreversible to reversible and selective to non-selective, these drugs target the monoamine oxidase (MAO) enzyme and prevent the oxidative deamination of various monoamines and catecholamines such as serotonin and dopamine, respectively. Tyramine is a potent releaser of norepinephrine (NE) and is found in high concentrations in foods such as aged cheeses and meats. Under normal conditions, NE is unable to accumulate to toxic levels due to the presence of MAO-A, an enzyme that degrades neurotransmitters, including NE. When MAO-A is inhibited, the capacity to handle tyramine intake from the diet is significantly reduced causing the brain to be vulnerable to overstimulation of postsynaptic adrenergic receptors with as little as 8-10 mg of tyramine ingested and can result in life-threatening blood pressure elevations. In addition to adverse reactions with certain foods, both older and newer MAOIs can negatively interact with both sympathomimetic and serotonergic drugs. In general, patients on a MAOI want to avoid two types of medications: those that can elevate blood pressure via sympathomimetic actions (e.g., phenylephrine and oxymetazoline) and those that can increase serotonin levels via 5-HT reuptake inhibition (e.g., dextromethorphan, chlorpheniramine, and brompheniramine). Illicit drugs that stimulate the central nervous system such as ecstasy (MDMA, 3,4-methylenedioxymethamphetamine) act as serotonin releasers. Patient involvement is also crucial to ensure any interaction within the healthcare setting includes making other providers aware of a MAOI prescription as well as avoiding certain OTC medications that can interact adversely with MAOIs.

INTRODUCTION

Monoamine oxidase inhibitors (MAOI) are a class of drugs that were originally developed for the treatment of depression but have since been expanded to be used in management of affective and neurological disorders, as well

as stroke and aging-related neurocognitive changes. Ranging from irreversible to reversible and selective to non-selective, these drugs target the monoamine oxidase (MAO) enzyme and prevent the oxidative deamination of various monoamines and catecholamines such as serotonin and dopamine, respectively.^{1,2} The two isoenzymes of MAO that can be selectively or non-selectively targeted are MAO-

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A and MAO-B and offer unique therapeutic uses tailored to specific manifestations of affective disease. Specifically, MAO-A and non-selective MAOIs are used in the treatment of atypical depression as MAO-A uniquely functions to metabolize serotonin.^{2,3} In contrast, selective MAO-B inhibitors have been found to provide therapeutic benefit in the management of Parkinson's disease.⁴⁻⁶

Despite the varied and diverse uses of MAOIs, there remains a discrepancy between the benefits offered by MAOI treatment and the actual clinical utilization of these drugs.⁷ The limited clinical use of MAOIs is a direct result of the associated significant adverse effects, specifically the cardiovascular "cheese effect" or hypertensive crisis. This adverse effect was often seen when MAOI were combined with increased intake of tyramine, typically seen at higher levels in various foods, but so named due to the presence of elevated tyramine in soft cheeses.^{1,8-10} Another concerning adverse reaction can be seen when irreversible MAOIs are combined with anti-depressant drugs, such as selective serotonin reuptake inhibitors (SSRIs) that increase serotonin to toxic levels, resulting in serotonin syndrome.^{6,11} Note, however, that these drug-drug interactions are not limited to anti-depressants and span a wide range of both prescribed and over-the-counter (OTC) medications manifesting as both serotonin syndrome and hypertensive crisis.^{5,10,12} Specifically, sympathomimetic agents such as epinephrine and OTC agents used for cough and cold symptoms can induce hypertensive crisis due to the associated surge in pressor amines.^{13,14}

Recent advances in knowledge surrounding MAOIs and alternative delivery systems have provided an avenue in which the use of MAOIs has become safer. As previously mentioned, the development of both selective and reversible MAOIs allowed for the production of targeted therapeutics that could selectively target specific isoenzymes or minimize the risk for hypertensive crisis, as is the case with reversible MAOIs.^{1,7,9,15} The development of a transdermal mode of delivery also limited the risk for hypertensive crisis due to the minimal inhibition of MAO-A in the gastrointestinal and hepatic system.^{16,17} Regardless, patients still need to exercise caution when using these drugs and adhere to dietary restrictions and avoid certain prescription and OTC medications.¹⁸

MONOAMINE OXYDASE INHIBITORS MECHANISM OF ACTION

The primary mechanism of MAOIs is through the inhibition of the enzyme monoamine oxidase (MAO) by binding to the enzymes active site. MAO plays a key role in the degradation process for various monoamines released by neurons and glia cells, including dopamine, serotonin, and norepinephrine.^{19,20} There are two MAO isoforms that are primary therapeutic targets MAO-A and MAO-B. The inhibitory binding site of both MOA-A and B are identical, the key difference lies in the recognition sites near their active sites. The MAO-B recognition site is smaller than that of MAO-A. This difference permits specific isoform targeting. Therefore, MAOIs can be classified based on whether they

are selective or nonselective MAO-A/MAO-B inhibitors and if their effect is reversible or irreversible.¹⁵ This allows for a wider range of therapeutic usage. Examples of nonselective and selective MAOIs include phenelzine, a nonselective MAO inhibitor, and selegiline, a selective MAO-B inhibitor. Given that MAO-A is intraneuronal with substrates of norepinephrine (NA) and serotonin (5-HT), it has generally been targeted in the treatment of depressive illnesses. However, MAO-A has also shown therapeutic potential in the treatment of narcolepsy, panic attacks, and bulimia. MAO-B has substrates of dopamine and tyramine; therefore, inhibition leads to increased levels of dopamine, which has often been used in the treatment of Parkinson's disease. It is important to note that, type A and type B MAO are not unequivocally selective in their activities, therefore at higher inhibitor concentrations the classifications between the two break down.^{1,6,21}

MONOAMINE OXIDASE INHIBITOR USES

Clinically MAOIs have been used to alleviate symptoms of various subtypes of depressive disorders. Formerly identified as the first anti-depressive agent, the use of MAOIs in the treatment of depression has mostly fallen to third or fourth line agents for treatment-resistant depression, this is largely due to the dietary restrictions, side effects, and safety concerns.²² However, in the treatment of atypical depression randomized controlled trails have shown MAOIs to be superior to other commonly used agents such as tricyclic antidepressants. Atypical depressive features include mood reactivity with two or more of the following including weight gain, hypersomnolence, leaden paralysis, and hyperphagia.^{13,23} Controlled studies have also shown efficacy in the use of monoamine oxidase inhibitors, both irreversible and reversible, in the treatment of social anxiety disorders (social phobias). Social phobias are a common psychiatric disorder, associated with considerable functional impairment and are often comorbid with depression, substance use, and anxiety disorders. Patient characteristically experience fear of being observed or evaluated by others.²⁴⁻²⁷ Phenelzine has largely been studied in patients with social anxiety disorder and has demonstrated superior efficacy when compared with placebo.²⁸ Despite substantial evidence of the efficacy of MAOIs in social anxiety disorder, they are mostly second-line agents due to their side effect profile and interactions with other agents.

Selective monoamine oxidase B inhibitors such as selegiline are frequently used to treat Parkinson's disease. The diagnosis of Parkinson's disease is typically characterized by movement disorders including tremor, rigidity, and bradykinesia. As the disease progresses patients experience neuropsychiatric disturbances including depression, anxiety, and cognitive changes. Signature neuropathological lesions such as degeneration of dopaminergic neurons in the substantia nigra pars compacta have been identified in Parkinson's disease. Therefore, activity of MAO has often been identified as a contributing factor in the neurodegeneration of Parkinson's disease. This is mostly due to the degradation of dopamine caused by MAO. Inhibition

of MAO-B through agents such as selegiline cause an increase in dopaminergic endogenous amines levels, lessening symptoms and slowing progression of the disease.^{6,29,30}

ADVERSE EFFECTS

With the continual increase in the number of available antidepressants, the use of MAOIs, relative to other antidepressants, has declined since their emergence in the early 1950s.^{31–35} Monoamine oxidase inhibitors (MAOIs) are effective antidepressants; however, many are reluctant to prescribe this class of antidepressants due to the dietary and drug restrictions that accompany MAOIs, which if not strictly followed can lead to an array of adverse effects. Despite the common misconception that MAOIs have serious side effects, the adverse effects most commonly associated with the use of oral MAOIs include weight gain, sexual dysfunction, and more general central nervous system effects such as dizziness, insomnia, or headache.³⁶ Despite the known efficacy of MAOIs in the treatment of major depressive disorder, many clinicians don't utilize this class of antidepressants. A clearer understanding of the pharmacodynamic interactions and potential adverse effects of MAOIs may help clinicians to better utilize this class of antidepressants, especially in cases of treatment-resistant and atypical depression.³⁷

SEROTONIN SYNDROME

A possible complication of monoamine oxidase inhibitors (MAOIs), although rare and largely avoidable, is the development of serotonin syndrome. Serotonin syndrome, also known as serotonin toxicity, is a potentially fatal condition believed to be caused by an excess stimulation of serotonin receptors.^{38–40} Serotonin syndrome is commonly described as a clinical triad of changes in mental status, autonomic hyperactivity, and neuromuscular abnormalities. However, it is important to note that not all of these findings are consistently present in all patients experiencing the disorder.^{41,42} Serotonin toxicity covers a broad spectrum of adverse effects ranging from mild to severe depending on the extent of excess serotonin.^{39,43} Cases commonly involve an MAOI and at least one other medication. Severe toxicity usually occurs when drugs with two different mechanisms of action on serotonin are present. MAOIs have a higher risk of inducing severe serotonin syndrome when compared to other antidepressants. Therefore, MAOIs should never be taken in combination with a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or other MAOIs as this significantly increases the likelihood of developing serotonin syndrome.⁴⁴ Moderate toxicity is also possible and has been reported to occur in overdoses with a single MAOI or from an increase in the therapeutic dose of an MAOI.

INSOMNIA

MAOIs have been reported to cause or exacerbate insomnia, leading some individuals to cease taking the medication de-

spite adequate therapeutic response. It is important that when determining if the occurrence of insomnia is associated with the prescribed MAOI that it be clearly distinguished from insomnia which results from the depression itself.^{45–49} If a patient is experiencing insomnia from MAOIs, it is suggested to first try making adjustments in the time of dosing, before resorting to discontinuing the MAOI completely.⁴⁸

Irreversible MAOIs reported to cause insomnia include isocarboxazid, tranylcypromine, and phenelzine.⁵⁰ Additionally, tranylcypromine and phenelzine have been associated with significant REM sleep suppression, which is alleviated following withdrawal of the antidepressant.⁵¹ Reversible MAOIs are less likely to cause insomnia. Moclobemide, a reversible MAOI, has been shown to exhibit less REM sleep suppression compared to traditional MAOIs.

WEIGHT GAIN

Weight gain can be a common problem experienced by individuals placed on an antidepressant. However, the link between the two is complex and can be caused by a multitude of factors and interpreted differently based on the depressive symptoms that is each patient's presentation. Weight gain associated with an antidepressant treatment can be a positive sign of improvement in patients who experience weight loss as a symptom of depression or, in contrast, it can be a residual symptom in patients who overeat when depressed.⁵² Therefore, determining the potential for weight gain when undergoing antidepressant therapy can be challenging due to the dynamic interaction between weight changes and the underlying psychiatric disorder.

Although weight gain is often considered to be a typical side effect of irreversible MAOIs, few studies have examined this issue in-depth. Early studies suggested that MAOIs were comparable to tricyclic antidepressants (TCAs) in terms of risk for weight gain during short-term treatment.^{52,53} A review of the literature suggests that the incidence of weight gain may differ depending on which MAOI is prescribed. A retrospective study compared the two classes of antidepressants and found that patients treated with either phenelzine (i.e. MAOI) or tranylcypromine (i.e. TCA) both noted weight gain during treatment, although more frequently in the phenelzine treatment group.⁵⁴ Furthermore, it has been suggested that phenelzine has a higher likelihood of causing weight gain compared to other irreversible MAOIs such as isocarboxazid and tranylcypromine, but there is a lack of sufficient evidence to support this claim.⁵²

HYPERTENSIVE CRISIS

Hypertensive reactions are a potential risk associated with the use of MAOIs. A hypertensive crisis occurs when there is a severe and abrupt elevation in blood pressure, usually defined by systolic blood pressure values greater than 180 mmHg or diastolic blood pressure values greater than 120 mmHg.⁵⁵ This potentially fatal condition is characterized by the following: headache (occipital, may radiate to frontal region), sweating (+/- fever), palpitation, tachycardia or

bradycardia (may be associated with chest pain), nausea, vomiting, dilated pupils, and stiff/sore neck.⁵⁶ Due to the risk of such adverse reactions, many clinicians have been apprehensive to utilize this class of antidepressants despite their known efficacy in the treatment of major depressive disorder.

Shortly after the introduction of MAOIs in the early 1950s, patients taking the antidepressant began to report experiencing acute episodes of throbbing headaches accompanied by elevations in blood pressure. Subsequent investigations revealed the primary cause to be what is commonly referred to now as the “cheese reaction”, a catecholamine-induced hypertensive crisis that occurs when MAOIs are combined with foods high in tyramine (i.e., cheese).⁵⁷ This adverse reaction was discovered through the observation that such acute episodes would ensue following ingestion of cheese containing high concentrations of tyramine.^{58,59}

Tyramine is a potent releaser of norepinephrine (NE) and is found in high concentrations in foods such as aged cheeses and meats. Under normal conditions, NE is unable to accumulate to toxic levels due to the presence of MAO-A, an enzyme that degrades neurotransmitters, including NE. The average person can tolerate roughly 400 mg of ingested tyramine before postsynaptic adrenergic receptors undergo excessive stimulation which then results in elevated blood pressure.⁶⁰ Generally, meals considered to be high in tyramine contain about 40 mg of this catecholamine, therefore a tyramine reaction is unlikely to occur in a normal, unmedicated person with a standard diet.⁶¹

Those on an MAOI have a heightened sensitivity to tyramine because MAOIs inhibit MAO-A. When MAO-A is inhibited, the capacity to handle tyramine intake from the diet is significantly reduced causing the brain to be vulnerable to overstimulation of postsynaptic adrenergic receptors with as little as 8-10 mg of tyramine ingested and can result in life-threatening blood pressure elevations.⁶² Such blood pressure elevations, when sudden and dramatic, can cause a hypertensive crisis requiring immediate medical intervention. This risk is largely avoidable through implementing dietary restrictions. Thus, patients taking MAOIs should be mindful of the tyramine content of foods in their diet. However, contrary to the numerous myths surrounding MAOIs, it is not necessary to restrict yourself from all cheese, wine, and beer. Aged cheeses should in general be avoided, but processed cheeses and those used by the food industry (i.e., restaurants, pizza chains) do not usually contain high levels of tyramine and are safe to consume.^{63,64} In regards to wine and beer, generally only draft and unpasteurized beer need to be avoided.^{60,63,64} Canned and bottled beer is low in tyramine, and many wines, including white wines and chianti, contain low levels of tyramine.^{63,64}

As an aside, MAOI could also precipitate an increase in histamine with certain foods. Certain fish, called Scombrotoxin fish which include skipjack and tuna, are rich in histamine.⁶⁵ MAO is involved in the breakdown of histamine as well. If MAO is inhibited, it can lead to the accumulation of histamine.⁶⁵ In contrast to the accumulation of tyramine,

the increase of histamine can actually lead to a decrease in blood pressure.

In addition to tyramine, hypertensive reactions can also be associated with over-the-counter sympathomimetic drugs such as ephedrine, pseudoephedrine, and phenylpropranolamine, which are found in many decongestants and cough medications. Hypertension can also arise when MAOIs are taken in combination with L-dopa, methylphenidate, dextroamphetamine, reserpine, guanethidine, or tetrabenazine.⁵⁷

The standard recommendations given to patients experiencing a hypertensive crisis while on an MAOI have changed over the years. Nifedipine, a dihydropyridine calcium antagonist that acts to lower arterial pressure via peripheral vasodilation, was widely used in cases of severe hypertension related to the use of MAOIs.^{66,67} However, concerns began to arise over reports of nifedipine causing serious adverse effects including cerebrovascular ischemia, stroke, severe hypotension, and acute myocardial infarction. Systematic studies challenged the safety and efficacy of this practice for treating hypertensive crises, which then led many experts to instead advise patients to measure their blood pressure (BP) if a severe headache transpires. Today, routine monitoring of BP remains the main recommendation for patients on an MAOI and helps to ensure the rapid detection and treatment of hypertensive reactions.⁹ In cases of hypertensive crisis, patients should seek immediate medical intervention for blood pressure control with short-acting, titratable antihypertensive agents while steadily monitoring vital signs.^{55,58}

DRUG-DRUG INTERACTIONS

Drug interactions can occur with all MAOIs. Despite the fact that MAOIs have been used for decades, the pharmacokinetic interactions for this class of antidepressants still remain poorly understood.^{68,69} In addition to adverse reactions with certain foods, both older and newer MAOIs can negatively interact with both sympathomimetic and serotonergic drugs.^{45,70-73} The most serious, although rare, adverse drug reactions that can result from the combination of MAOIs with sympathomimetic and serotonergic agents are serotonin syndrome and hypertensive crisis. The following information discusses known drug-drug interactions for MAOIs, and the potential adverse effects associated with the specific combinations.

MAOI + SSRIS/SNRIS

The general guidelines for MAOIs are to avoid combining this class of antidepressants with selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine inhibitors. Combination of an MAOI with either is dangerous due to the increased risk for serotonin syndrome.⁷⁴⁻⁷⁶ Furthermore, combination use specifically involving an SSRI has been associated with fatalities in patients receiving both therapeutic and overdose amounts.^{77,78} To avoid the potential for adverse effects, it is recommended that SSRIs or SNRIs be discontinued for a minimum of two weeks (re-

ferred to as a washout period) before starting on a MAOI, with the exception of fluoxetine, which has a longer half-life and requires a 5-week washout period.^{79,80}

MAOI + TCAS

General guidelines state MAOIs should not be combined with tricyclic antidepressants (TCAs), due to the concern for possible serotonin toxicity.⁸¹⁻⁸³ MAOIs prevent the breakdown of serotonin in the presynaptic nerve terminal and TCAs block the reuptake of serotonin in the synaptic cleft. Thus, combining the two medications is thought to lead to an increase in serotonin levels in the brain and, if such levels become toxic, precipitate serotonin syndrome. However, the literature on MAOI and TCA combination therapy is mixed, and some believe the risk of a patient developing serotonin syndrome from the combination is overestimated.⁸⁴ Interest in the use of a MAOI and TCA combination therapy has grown in recent years for its potential use as a therapy for treatment-resistant depression (TRD) where MAOIs or TCAs alone are not effective. Recent studies have also supported the use of MAOI and TCA combination therapies reporting sustained tolerability and efficacy in patients who received both medications.¹² It is important to note that if a MAOI and TCA combination therapy is used, the TCA should be introduced first or at the same time as the MAOI.⁸⁵ Studies found the risk for adverse effects increases when the MAOI is introduced first and, therefore, should always be given second to, or at the same time as, the TCA.^{12,86} Clinicians should also be aware that the TCA clomipramine displays potent inhibition of serotonin and, thus, should never be used in combination with an MAOI.⁸⁷

SWITCHING ANTIDEPRESSANTS

Irreversible MAOIs, such as phenelzine, isocarboxazid, and tranylcypromine, have a rapid absorption and clearance rate, with pharmacokinetic half-lives ranging from 1.5 - 4 hours.^{49,88} However, clinicians need to be aware that the pharmacodynamic half-life is greater than the pharmacokinetic half-life. This is due to the fact that these drugs irreversibly inhibit MAO and as a result, their physiological effects persist for up to 2-3 weeks (i.e., until new MAOs are produced). This is especially important to consider when discontinuing an irreversible MAOI and transitioning to another type of antidepressant. A 14-day drug-free washout period is necessary before starting another antidepressant to ensure the MAOI is sufficiently cleared from the system preventing any possible serious pharmacodynamic interactions.^{69,89} While it is considered safe to begin a new antidepressant after the 14-day drug-free washout period, it is recommended that patients still be monitored since cases of adverse interactions have been reported in the past.⁹⁰ When switching from one MAOI to another, similar protocols should be followed, although when both the previous and new antidepressants have the same mechanism of action, shorter drug-free washout periods have been safely performed (1-8 days). Patients switching to an MAOI from a different class of antidepressant should undergo a cleanse period of at least five half-lives specific to the antidepres-

sant being discontinued.^{80,89} Fluoxetine, a selective serotonin reuptake inhibitor, is a particular challenge due to its long half-life and requires a 5-to-6-week drug-free washout period before cautiously starting a low-dose MAOI.

MAOI + COLD MEDICATIONS

Individuals taking a MAOI should avoid taking cold and cough medications that contain certain ingredients. These include drugs that increase adrenergic stimulation by a mechanism other than MAO inhibition. If such medications are added to an MAOI, a potentially dangerous hypertensive crisis can occur. Decongestant medications taken orally have the ability to increase blood pressure by themselves, especially in patients with preexisting hypertension or those whose hypertension is poorly controlled. Therefore, when such medications are combined with MAOIs the likelihood of elevated blood pressure significantly increases as well as the potential for a hypertensive crisis.⁶⁰ Decongestants to be avoided mainly include the over-the-counter α 1-adrenoceptor agonists, phenylephrine and oxymetazoline. Ephedrine, phenylpropanolamine, and pseudoephedrine are also contraindicated with MAOI use; however, these medications have been either withdrawn from the United States or only available upon signing for them at a pharmacy. These decongestants have adverse drug interactions with MAOIs because they add to the pro-noradrenergic actions of MAO inhibition to promote overstimulation of alpha 1 postsynaptic vascular receptors.⁷² These receptors determine both the arteriole resistance and venous capacitance. Thus, excessive stimulation of these receptors leads to a direct increase in blood pressure and, in severe cases, a hypertensive crisis.⁹¹ Dextromethorphan is an additional ingredient found in cold medicines. This opiate derivative is a cough suppressant and should not be combined with MAOIs. Dextromethorphan is a weak 5-HT reuptake inhibitor, making it a much more dangerous medication than adrenergic stimulants for those on an MAOI. When a 5-HT reuptake inhibitor is combined with an MAOI, postsynaptic 5-HT receptors become overstimulated and can lead to serotonin syndrome.

It is important for clinicians, as well as patients, to be aware that not all cough or cold medications must be avoided when taking an MAOI. In general, patients on a MAOI want to avoid two types of medications: those that can elevate blood pressure via sympathomimetic actions (e.g., phenylephrine and oxymetazoline) and those that can increase serotonin levels via 5-HT reuptake inhibition (e.g., dextromethorphan, chlorpheniramine, and brompheniramine). Other cough and cold medications not included in either of these categories are, in general, suitable to use with MAOIs. Antihistamines (excluding chlorpheniramine and brompheniramine) and cough medicines with expectorants or codeine (excluding dextromethorphan) are safe to use with MAOIs.^{14,56}

MAOI + SYNTHETIC ANALGESICS

Analgesics with serotonergic activity should not be combined with MAOIs. The properties of the two when com-

bined can produce life-threatening serotonin toxicity. Knowledge of these drugs' properties can help to prevent such adverse reactions from occurring as well as ensure appropriate treatment is administered if such adverse events do occur. Analgesics that are known to be weak serotonin reuptake inhibitors (SRIs) and should therefore be avoided by patients on an MAOI include phenylpiperidine opioids, meperidine (pethidine, Demerol), tramadol, methadone, and dextromethorphan. Another opioid medication that can cause buprenorphine. This is important to consider if you have a patient that needs treatment with an antidepressant medication and is on opioid replacement treatment. Innocuous analgesics available to patients on an MAOI include morphine, codeine, oxycodone, and buprenorphine. These analgesics are not known to be SRIs and therefore would not produce serotonin toxicity.

In the instance where an MAOI is co-ingested with an SRI, it is critical that the appropriate intervention be promptly initiated to prevent rapid deterioration and death.⁹²⁻⁹⁴ Many reports suggest 5-HT_{2A} antagonists (e.g., chlorpromazine via i.v. administration) are the most effective treatment for severe cases of serotonin toxicity.^{92,95,96} It is also important to note that reports have shown the cessation of the drugs and supportive care are not enough to treat these patients, as some will die before the effects of the ingested medications wear off.⁹²⁻⁹⁴ More proactive interventions, such as cooling and 5-HT_{2A} antagonists, need to be implemented to treat for serotonin toxicity caused by MAOI + SRI co-ingestion.^{92,95}

MAOI + ANTIBIOTICS

Patients taking MAOIs or other serotonergic psychiatric medications should avoid taking the antibacterial drug linezolid. Clinicians, as well as patients, may not realize that linezolid possesses MAOI properties. Linezolid belongs to the class of oxazolidinone antibiotics which are antibacterial agents that selectively prevent bacterial protein synthesis through the inhibition of monoamine oxidase. Although the exact mechanism of the drug interaction between linezolid and MAOIs is unclear, linezolid is understood to be a reversible MAOI that selectively inhibits human MAO-A and thus prevents the breakdown of serotonin in the brain.^{72,97} It is suggested that when linezolid is combined with a MAOI antidepressant (or other serotonergic psychiatric medications), toxic levels of serotonin accumulate in the brain causing serotonin syndrome. Therefore, general guidelines suggest linezolid should be not be prescribed to patients on an MAOI (or other serotonergic psychiatric medications). However, the exception being life-threatening conditions that require immediate treatment with linezolid such as vancomycin-resistant *Enterococcus faecium* (VRE) infections and infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA).⁹⁸

MAOI + ILLICIT DRUGS

Illicit drugs that stimulate the central nervous system (CNS) such as ecstasy (MDMA, 3,4-methylenedioxymethamphetamine) act as serotonin releasers. Com-

binning serotonin releasers with MAOIs can cause a severe and potentially fatal degree of serotonin toxicity.^{99,100} Growth in the antidepressant market and the widespread use of illicit drugs, stresses the need to emphasize the potential harms associated with the concomitant use of MAOIs (and other serotonergic drugs) with serotonin releasers (i.e., ecstasy). Ecstasy alone can induce severe serotonin syndrome, therefore combining this illicit drug with an MAOI significantly increases the likelihood of provoking serotonin syndrome. Furthermore, MAOIs are noted to be the most likely of all the serotonergic drugs to lead to toxic increases in serotonin when used with ecstasy.¹⁰⁰ It is also important for patients to be aware of the long half-life of some MAOIs (e.g., phenelzine, tranylcypromine) meaning an individual could still be susceptible to adverse interactions with ecstasy up to two weeks after cessation of the antidepressant.^{101,102}

MAOI + METHYLENE BLUE

Methylene blue (methylthioninium chloride) is a synthetic, basic dye that has several notable uses in clinical medicine. Examples include use as a tissue dye in diagnostic procedures for the selective staining of certain body tissues during surgery.^{103,104} It also serves as a medication to treat various medical conditions including methemoglobinemia, vasoplegic syndrome, and ifosfamide-induced encephalopathy. The dye has been clinically used for many years with few reports of toxicity. Early experiments found oral administration of methylene blue to be innocuous.¹⁰⁵ However, more recent studies have confirmed that methylene blue is, in fact, not an innocuous substance and acts on a larger array of enzymes and proteins than previously believed.

In the interest of MAOIs, the FDA now labels methylene blue as "a potent, reversible monoamine oxidase inhibitor" that has the potential to cause serotonin syndrome when combined with a serotonergic psychiatric medication. This discovery emerged after several reports of serotonin toxicity following administration of methylene blue exclusively in patients on a serotonergic psychiatric medication (e.g., MAOI or SSRI), indicating methylene blue must have an influence on the 5-hydroxytryptamine (5-HT, serotonin) system.¹⁰⁶ Studies examined the effects of methylene blue on the two monoamine oxidase isoforms, MAO-A and MAO-B, and found methylene blue to be a very potent inhibitor of MAO-A with a K_i of 27 nM and binds to the active site of MAO-A. In contrast, MAO B did not appear to be a target of action for methylene blue and no significant inhibition of the enzyme was observed.^{105,107}

For clinical use of methylene blue, clinicians should be aware of its properties as a potent MAOI and avoid administering the dye to patients on a MAOI antidepressant or any other type of serotonergic medication. Combining methylene blue with a MAOI increases MAO inhibition which in turn directly increases levels of serotonin at the synaptic cleft. High levels of serotonin can become toxic to the body and induce serotonin syndrome.

Table 1. Drugs Contraindicated with MAOIs

Agent	Adverse Reactions	Additional Comments
Antibiotics		
Linezolid	Serotonin syndrome	Reversible MAOI; selectively inhibits MAO-A. Combination with MAOI produces toxic levels of serotonin.
Antidepressants		
Other MAOIs	Hypertensive crisis	Increase risk for severe side effects; convulsions
SNRIs	Serotonin syndrome, hypertensive crisis	Severe hypertensive crisis and serotonin syndrome
SSRIs	Serotonin syndrome	Severe serotonin toxicity and strongly associated with fatalities.
TCA's		
Clomipramine	Severe serotonin toxicity	Causes potent inhibition of serotonin and should never be combined with an MAOI
Other TCAs (e.g., cyclobenzaprine, carbamazepine, oxcarbazepine)	Possible serotonin toxicity	Combination therapy with MAOI + TCA can be used for severe TRD with caution. Never start the MAOI first; take at the same time as TCA or after beginning the TCA first. Low doses should be given for both and titrated to a tolerable dose
Cold Medications		
Decongestant		
Oxymetazoline	Hypertensive crisis	Over-the-counter α 1-adrenoceptor agonist
Phenylephrine	Hypertensive crisis	Over-the-counter α 1-adrenoceptor agonist
Cough suppressant		
Dextromethorphan	Serotonin syndrome	Weak 5-HT reuptake inhibitor
Illicit Drugs		
Ecstasy	Severe serotonin syndrome	Acts as a serotonin releaser; can cause severe, fatal serotonin toxicity
Methylene Blue	Serotonin syndrome	Potent, reversible MAOI
Synthetic analgesics / Opioids	Serotonin syndrome	Analgesics that are weak SRIs should be avoided. Safe analgesics to use include morphine, codeine, oxycodone, and buprenorphine
Fluphenazine	May prolong or intensify the hypotensive, anticholinergic, or sedative effects of either agent	Due to the potential for additive CNS and cardiovascular effects, MAOIs and phenothiazines should be used together cautiously
Cimetidine	May increase steady-state plasma concentrations of MAOI	Dose of MAOI may have to be reduced for the duration of cimetidine treatment

MAOI + OTHER

Phenothiazine antipsychotics, such as fluphenazine, are known to increase concentrations of tranylcypromine (a nonselective, irreversible MAOI). Tranylcypromine is also an inhibitor of CYP2C19, which metabolizes proton pump inhibitors such as omeprazole, a medication used to treat stomach and esophagus problems.^{69,108} In addition, cimetidine, a medication also used for gastroesophageal issues, has been shown to reduce the clearance of moclobemide (a reversible MAOI). Therefore, when using the two medications in combination it is recommended the dose of moclobemide be cut in half.¹⁰⁹ Table one summarizes drugs that are contraindicated with MAOIs.

CONCLUSION

MAOIs are an old yet evolving drug class that were initially developed for the treatment of depression but have since expanded to neurocognitive disorders, stroke management, and even neuroprotection. Despite the efficacy in various atypical and treatment-resistant depression, these therapeutics remain underutilized due to significant associated adverse effects, specifically hypertensive crisis and serotonin syndrome. This concern is further exacerbated due to the robust list of drugs and foods that must be avoided or consumed with caution in order to minimize the potential for adverse reactions. Therefore, it is critical that the oversight of a trained psychiatrist is an integral part of prescribing MAOI. Patient involvement is also crucial to ensure any interaction within the healthcare setting includes making other providers aware of a MAOI prescription as

well as avoiding certain OTC medications that can interact adversely with MAOIs. However, advancements in isoenzyme target specificity, reversibility of action and mode of drug delivery have provided alternatives to the original ir-

reversible, non-selective MAOIs that function to minimize the risk for adverse events.

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