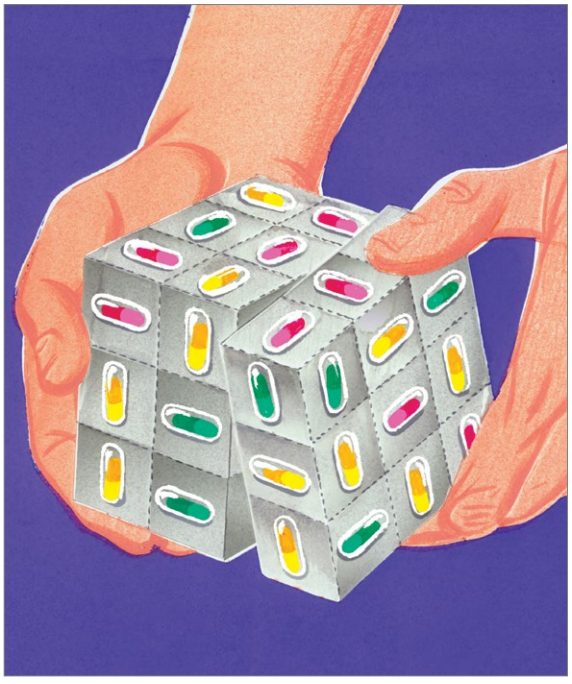
Current PSYCHIATRY

SECOND OF 2 PARTS

# A concise guide to monoamine oxidase inhibitors: How to avoid drug interactions



ALEX NABAUM

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## Use these strategies to maximize efficacy and minimize adverse effects when prescribing an MAOI

Monoamine oxidase inhibitors (MAOIs) have well-established efficacy for treating depression, panic disorder, and social phobia. However, a lack of familiarity with these agents and misconceptions about the risks associated with their use have led to MAOIs being substantially underutilized. The goal of this 2-part guide to MAOIs is to educate clinicians about this often-overlooked class of medications. Part 1 ("A concise guide to monoamine inhibitors," Current Psychiatry. December 2017, p. 14-23,47,A) described the pharmacology of MAOIs, the mechanism by which tyramine induces hypertension in patients taking MAOIs, and what to tell patients about dietary restrictions associated with these medications. Part 2 covers how to avoid potential drug interactions, including serotonin syndrome (SS) and pressor effects, that could affect patients receiving an MAOI; other factors to consider when starting a patient on an MAOI; and augmentation strategies for depressed patients who do not achieve remission from MAOI monotherapy.

### MAOIs and potential drug interactions

One source of concern in patients receiving irreversible nonselective MAOIs is the development of excessive serotonergic neurotransmission resulting in SS. In the 1960s, researchers noted that administering large doses of tryptophan to MAOI-treated patients resulted in clonus and

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Dr. Meyer is a consultant to Acadia Pharmaceuticals, Neurocrine Biosciences, Inc., and Teva Pharmaceutical Industries; and is a speaker for Acadia Pharmaceuticals, Alkermes, Allergan, Merck, Otsuka America, Inc., and Sunovion Pharmaceuticals.

Table 1

**Medications with known risk for serotonin syndrome when coadministered with nonselective MAOIs**

| Class | Examples |
|---|---|
| Tricyclic antidepressants | Imipramine, desipramine, amitriptyline, nortriptyline, clomipramine |
| SSRI antidepressants | Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, trazodone, vilazodone, vortioxetine |
| SNRI antidepressants | Duloxetine, levomilnacipran, milnacipran, desvenlafaxine, venlafaxine |
| Antipsychotics | Ziprasidone |
| Specific cold products | Dextromethorphan, chlorpheniramine |
| Synthetic analgesics | Fentanyl, meperidine, tramadol |
| Antibiotics | Linezolid |
| Drugs of abuse | MDMA, LSD |
| Other | Methylene blue |

LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxy-methamphetamine; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

**Source:** Reference 3

hyperactive reflexes without hypertensive events.[1] In 1991, Sternbach[2] provided an extensive case series and described the first set of criteria for SS. Features of SS include:

- mild symptoms: tremor, akathisia, inducible clonus
- moderate symptoms: spontaneous or sustained clonus, muscular hypertonicity
- severe symptoms: hyperthermia, diaphoresis.[2]

Although SS can be induced by significant exposure to individual agents that promote excess synaptic serotonin (eg, overdose of selective serotonin reuptake inhibitors [SSRIs]), the majority of fatal cases have occurred among patients taking MAOIs who were coadministered an agent that inhibited serotonin reuptake (***Table 1***[3]). Animal studies have determined that excessive stimulation of the 5HT2A receptor is primarily responsible for SS,[4] and that 5HT2A antagonists, such as mirtazapine, can block the development of SS in a mouse coadministered fluoxetine and tranylcypromine.[5] In addition to a patient's medication history, the clinical hallmark of SS that helps distinguish it from neuroleptic malignant syndrome, delirium, and other acute syndromes is clonus, which becomes spontaneous and sustained as the severity increases.

**Risk for SS.** Most medications that promote serotonergic activity are well known for their use as antidepressants, but other agents that have 5HT reuptake properties (eg, the antihistamine chlorpheniramine) must be avoided. Although older literature suggests that the use of lower doses of certain tricyclic antidepressants concurrently with MAOIs may not be as dangerous as once believed,[6] there are sufficient reports of serious outcomes that tricyclics should be avoided in patients taking MAOIs because of the risk of SS, and also because, in general, tricyclics are poorly tolerated.[7]

Desipramine, a potent norepinephrine transporter (NET) inhibitor, blocks the entry of tyramine into cells by NET, thereby preventing hypertensive events in animal models of tyramine overexposure. However, in some assays, the affinity for the serotonin transporter is not insignificant, so at higher doses desipramine may pose the same theoretical risk for SS as seen with other tricyclics.[3]

Lastly, rasagiline is an MAO-B selective inhibitor that has been available in the United States since 2008 for the treatment of Parkinson's disease (PD). Although this drug lacks MAO-A antagonism, its package insert carries SS warnings; however, analysis of outcomes from a large multicenter rasagiline trial (N = 1,504) found no SS

**Clinical Point**

**The clinical hallmark of serotonin syndrome is clonus, which becomes spontaneous and sustained as the severity increases**

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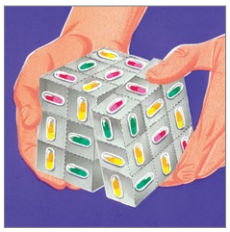



**Clinical Point**

**Orthostasis is the primary dose-limiting adverse effect associated with rapid titration or higher dosages of MAOIs**

**Table 2**

**Half-lives of newer antidepressants with potent serotonin reuptake**

| Medication | Half-life |
|---|---|
| Selective serotonin reuptake inhibitors | |
| Citalopram | 33 hours |
| Escitalopram | 30 hours |
| Fluoxetine | 87 hours |
| *Norfluoxetine* | 1 to 2 weeks |
| Fluvoxamine | 22 hours |
| Paroxetine | 21 hours |
| Sertraline | 26 hours |
| Trazodone | 7 to 10 hours |
| Vilazodone | 25 hours |
| Vortioxetine | 66 hours |
| Serotonin-norepinephrine reuptake inhibitors | |
| Desvenlafaxine | 11 hours |
| Duloxetine | 15 hours |
| Levomilnacipran | 12 hours |
| Milnacipran | 6 to 10 hours |
| Venlafaxine | 5 hours |

**Source**: References 17-22

events in the 471 patients receiving rasagiline plus antidepressants (74.5% on SSRIs).[8] Because depression is a common comorbidity in PD, clinicians who encounter rasagiline-treated patients who need antidepressant therapy should consult with the patient's neurologist regarding their experience and comfort level with combining rasagiline and SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs).

Astute clinicians will recognize that antidepressants that lack 5HT reuptake (eg, bupropion, mirtazapine) are not on this list of agents that may increase SS risk when taken with an MAOI. Older papers often list mirtazapine, but as a 5HT2A antagonist, it does not possess a plausible mechanism by which it can induce 5HT toxicity.[9,10] Most atypical antipsychotics have significant 5HT2A antagonism and can be combined with MAOIs, but ziprasidone is an exception: as a moderate SNRI, it has been associated with SS when administered with an MAOI.[11]

**Pressor reactions.** The only theoretical sources of concern for pressor effects are medications that act as norepinephrine releasers through interactions at the trace amine-associated receptor 1 (TAAR1) (for more information on TAAR1, see "A concise guide to monoamine inhibitors," Current Psychiatry. December 2017, p. 14-23,47,A). Amphetamines are one such class, but a 2004 review did not find cases of hypertensive crises when amphetamines were combined with MAOIs,[12] nor did a recent article that described the combined use of lisdexamfetamine and transdermal selegiline.[13] Presumably, the low level of intracellular exposure mitigates the risk of excessive TAAR1 agonism, but amphetamine derivatives should be approached cautiously and with careful blood pressure monitoring. On the other hand, methylphenidate is an inhibitor of dopamine reuptake with no affinity for TAAR1[14] or the serotonin transporter,[15] and does not induce a pressor response nor increase risk for SS when combined with MAOIs.[3] Concerns about the use of α1-adrenergic agonists in patients taking MAOIs are not universal, as the deleterious effects on blood pressure are seen only in certain vulnerable patients, typically those with preexisting hypertension. Nonetheless, all patients should be cautioned about the use of phenylephrine and pseudoephedrine.[16]

## Starting a patient on an MAOI

Contraindicated medications need to be tapered before beginning MAOI treatment. The duration of the washout period depends on the half-life of the medication and any active metabolites. Antidepressants with half-lives of approximately ≤24 hours should be tapered over 7 to 14 days (depending on the dose) to minimize the risk of withdrawal syndromes, while those with long half-lives (eg, fluoxetine, vortioxetine) can be stopped abruptly. After stopping a medication for 5 half-lives, 96.875% of the medication is removed, so adequate time must elapse after the last dose before starting an MAOI. ***Table 2***[17-22] lists the half-lives of commonly used newer antidepressants and any active metabolites or isomers. Clinicians should

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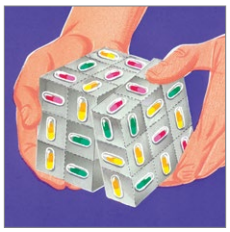

MAOIs and drug interactions

## Related Resource

- Meyer JM. A concise guide to monoamine oxidase inhibitors. First of 2 parts. Current Psychiatry. 2017;16(12):14-16,18-23,47,A.

### Drug Brand Names

Amitriptyline • Elavil
Aripiprazole • Abilify
Asenapine • Saphris, Sycrest
Brexpiprazole • Rexulti
Bupropion • Wellbutrin XL, Zyban
Cariprazine • Vraylar
Chlorpheniramine • Chlorphen, Chlor-Trimeton
Citalopram • Celexa
Clomipramine • Anafranil
Clozapine • Clozaril
Desipramine • Norpramin
Desvenlafaxine • Pristiq
Dextromethorphan • Delsym, Robitussin
Duloxetine • Cymbalta
Escitalopram • Lexapro
Fentanyl • Duragesic, Subsys
Fludrocortisone • Florinef
Fluoxetine • Prozac, Sarafem
Fluvoxamine • Luvox
Imipramine • Tofranil
Levomilnacipran • Fetzima
Linezolid • Zyvox
Lisdexamfetamine • Vyvanse
Lithium • Eskalith, Lithobid
Lurasidone • Latuda
Meperidine • Demerol
Methylene blue • ProvayBlue
Methylphenidate • Concerta, Daytrana
Milnacipran • Savella
Mirtazapine • Remeron
Nortriptyline • Pamelor
Paroxetine • Paxil
Phenelzine • Nardil
Phenylephrine • Sudafed PE
Pseudoephedrine • Sudafed, SudoGest
Rasagiline • Azilect
Selegiline transdermal • Emsam
Sertraline • Zoloft
Tramadol • Ultram
Tranylcypromine • Parnate
Trazodone • Desyrel
Venlafaxine • Effexor
Vilazodone • Viibryd
Vortioxetine • Brintellix
Ziprasidone • Geodon

**Clinical Point**

**Methylphenidate does not induce a pressor response or increase risk for serotonin syndrome when combined with MAOIs**

always err on the side of caution before starting an MAOI, and give their patients a brief overview of SS symptoms; however, be mindful of not extending time the patient is without effective antidepressant levels.

Initiation of an MAOI is always based on whether the patient can reliably follow the basic dietary advice (see "A concise guide to monoamine inhibitors," Current Psychiatry. December 2017, p. 14-23,47,A), and they agree to check with their clinician before starting new medications. Titration of MAOIs should be based on tolerability; orthostasis is the primary dose-limiting adverse effect associated with rapid titration or higher dosages. This may be especially true in older patients with poor vasomotor tone, or those on α1-adrenergic antagonists or other agents that may induce orthostatic effects. The rapid titration schedules present in certain package inserts (eg, phenelzine[23]) should not be followed.

The orthostasis management strategy is similar to that employed for clozapine: minimize the use of concurrent α1-adrenergic antagonists, lower the doses of antihypertensives as much as possible, and encourage adequate fluid intake. For patients with ongoing orthostasis and without a history of congestive heart failure, consider using the potent mineralocorticoid fludrocortisone starting at 0.1 mg/d, and titrating every 10 to 14 days if needed to a maximum of 0.3 mg/d.[24] Older literature noted weight gain, peripheral edema, and sexual dysfunction as common adverse effects. Research on the most recently studied MAOI, selegiline transdermal, reported rates of these adverse effects as follows: weight gain: 2.1% for selegiline transdermal vs 2.4% for placebo; all forms of sexual dysfunction: 0 to 1% for selegiline transdermal vs 0 to 0.4% for placebo.[25]

## Augmentation options for patients taking MAOIs

For depressed patients who do not achieve remission of symptoms from MAOI therapy, augmentation options should be sought, as patients who respond but fail to remit are at increased risk of relapse.[26] Lithium augmentation is one of the more common strategies, with abundant data supporting its use.[27,28] Case reports dating back >12 years describe the concurrent use of bupropion and MAOIs.[12,29] A recent review of augmentation of MAOIs with second-generation antipsychotics found

# Bottom Line

When prescribing a monoamine oxidase inhibitor (MAOI), ensure that your patient isn't taking other medications that could cause an interaction that results in serotonin syndrome or pressor effects. When initiating MAOI therapy, titrate slowly to avoid orthostasis. Strategies for augmenting MAOIs include lithium, bupropion, and second-generation antipsychotics, except for ziprasidone.

multiple positive reports for most agents, including aripiprazole, with the sole exception of ziprasidone, a moderate SNRI for which cases of SS have been reported.[11] As of November 2017, there are no case reports for asenapine, lurasidone, brexpiprazole, or cariprazine. Triiodothyronine is often a neglected strategy, but older case reports of combined treatment with MAOIs found no obvious concerns beyond those related to the use of thyroid hormone.[30,31]

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**Clinical Point**

**Augmentation with lithium is a common strategy for when a patient does not achieve remission from MAOI therapy**