Drug interactions between antidepressants and selective MAO-B inhibitors: Understanding and communicating safety considerations

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Parkinson disease, depression, and MAO-B inhibitors

Although Parkinson disease (PD) is typically thought of as a motor disease, it is also characterized by a number of nonmotor features. These include psychiatric symptoms such as depression. One-quarter to nearly three-quarters of patients with PD also suffer from depression. Depression is not just a reaction to PD, it is also part of the illness because PD causes dysfunction in dopaminergic, noradrenergic, and serotonergic neurotransmission. Depression is associated with worse motor function, greater impairment in activities of daily living, and an earlier need for symptomatic therapy for PD. However, depression often goes undiagnosed in patients with PD because clinical symptoms of depression (e.g., flat affect, inability to work, fatigue, loss of desire, preoccupation with illness) can overlap with and even be mistaken for PD.

Selective serotonin reuptake inhibitors (SSRIs) are the treatment of choice for managing depression in patients with PD. However, their use in PD patients is complicated by their ability to exacerbate parkinsonian symptoms and by a potential, albeit rare, drug interaction with one class of PD medications, selective monoamine oxidase (MAO) type B (MAO-B) inhibitors.

MAO inhibitors can be classified according to their selectivity for the two subtypes of MAO (type A and type B). Nonselective MAO inhibitors block both type A and type B activity. Selective MAO inhibitors block only MAO-B or only MAO-A activity. Nonselective MAO inhibitors used in the United States are antidepressants and include isocarboxazid (Marplan—Validus), phenelzine (Nardil—Pfizer), and tranylcypromine (Framine—GlaxoSmithKline). Outside of the United States, therapies selective for MAO-A (e.g., moclobemide) are also used in the treatment of depression. Selegiline (Emsam—Bristol-Myers Squibb) and rasagiline (Azilect—Teva), at FDA-approved doses, are selective MAO-B inhibitors indicated for use in the treatment of PD. A transdermal formulation of selegiline is also approved to treat depression.

Learning objectives

At the completion of this activity, the pharmacist will be able to:

■ Describe the causes, clinical features, and treatment of serotonin syndrome.
■ Recognize the potential for, and clinical significance of, drug interactions with the coadministration of antidepressants and MAO-B inhibitors in Parkinson disease.
■ List tips for counseling patients and caregivers and communicating with physicians regarding this potential interaction.

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Drug interactions associated with MAO inhibitors are largely attributable to inhibition of MAO-A and are therefore less common with the selective MAO-B inhibitors.

Concurrent use of any antidepressant that affects serotonin levels with any MAO inhibitor potentially increases the risk of serotonin syndrome. The most serious reactions have occurred with therapies that inhibit MAO-A, including non-selective MAO inhibitors. The risk remains theoretical with MAO-B inhibitors. However, most drug interaction screens do not differentiate between MAO inhibitor classes and “flag” any use of an MAO inhibitor and antidepressant as a potential drug interaction. Pharmacists have a unique knowledge base and therefore are in a primary position to determine clinical significance of drug interactions and work with prescribers on these issues.

Serotonin syndrome

Serotonin syndrome is caused by excessive activation of serotonin receptors in the central nervous system. Clinical manifestations (Table 1) represent a concentration-dependent spectrum of toxicity ranging from barely noticeable to seizures, coma, and death. Early recognition and treatment are therefore essential. Serotonin syndrome is usually precipitated or suddenly exacerbated when a new serotonergic medication is added to ongoing serotonergic medications, when doses are increased, or after an overdose of a serotonergic medication. Onset can be rapid, within minutes to hours of ingestion.

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<th>Behavioral/cognitive symptoms</th>
<th>Autonomic effects</th>
<th>Somatic effects</th>
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<td>Confusion</td>
<td>Syncope</td>
<td>Muscular rigidity</td>
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<td>Hypomania</td>
<td>Shivering</td>
<td>Myoclonus</td>
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<td>Hallucinations</td>
<td>Sweating</td>
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<td>Headache</td>
<td>Tachycardia</td>
<td>clonus</td>
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<td>Delirium</td>
<td>Nausea</td>
<td>Tremor</td>
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<td>Coma</td>
<td>Increased bowel</td>
<td>Akathisia*</td>
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<td>sounds/diarrhea</td>
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<td>Mydriasis*</td>
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*Loss of consciousness resulting from decrease in blood pressure.
*Inner restlessness.
*Dilated pupils.
*Source: References 6 and 10.

No laboratory test exists that can confirm high levels of serotonin; therefore, serotonin syndrome must be diagnosed clinically based on history and symptoms. Multiple diagnostic criteria have been proposed, but the Hunter Serotonin Toxicity Criteria are the most sensitive and specific. According to Hunter’s criteria, serotonin syndrome is diagnosed in the presence of any one of the following in a patient taking a serotonergic agent:

- Spontaneous clonus (rhythmic muscular contractions)
- Inducible clonus and either agitation or diaphoresis (excessive sweating)
- Ocular clonus and either agitation or diaphoresis
- Tremor and hyperreflexia (overactive reflexes)
- Hypertonia (increased muscle tone) and temperature greater than 38°C and either ocular clonus or inducible clonus

Most cases of serotonin syndrome are mild and can be managed by discontinuing the precipitating drugs and providing supportive care. Supportive measures may include hemodynamic stabilization, sedation, cooling, hydration, and monitoring for complications. Benzodiazepines (e.g., diazepam) may help relieve agitation and tremor, regardless of syndrome severity. After treatment is instituted and the offending drugs withdrawn, mild serotonin syndrome typically resolves within 24 to 72 hours. Drugs with longer half-lives, active metabolites, or long durations of action may result in more persistent symptoms.

Patients with moderate to severe cases in which they also have hypotonicity, hyperthermia, autonomic instability, or progressive cognitive changes should be hospitalized and may require neuromuscular paralysis, external cooling, sedation, and intubation. For these cases, therapies with antiserotonergic activity can be beneficial. Cyproheptadine is the most commonly used. This use of cyproheptadine is not approved by FDA, and no prospective controlled trials exist. Cyproheptadine is usually given as an initial 12-mg dose followed by 2 mg every 2 hours to a maximum 32 mg in 24 hours if symptoms continue, then a maintenance dose of 8 mg every 6 hours. Sedation as a potential adverse effect of cyproheptadine is not undesirable because it may aid in relieving some of the symptoms of serotonin syndrome. Antipyretics do not have a role because hyperthermia associated with serotonin syndrome results from increased muscle activity rather than central nervous system activity.

MAO-B inhibitors and antidepressants: Potential drug interaction

A theoretical risk of serotonin syndrome exists when selective MAO-B inhibitors are used in combination with drugs that have serotonergic activity (e.g., SSRI, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, tryptophan, dextromethorphan, meperidine). In theory, select antidepressants with low serotonergic potential (e.g., bupropion, nortriptyline, desipramine, doxepin, amoxapine) might have a lower risk of serotonin syndrome. Risk of serotonin syndrome is also increased if MAO-B inhibitors are used in combination.
with cytochrome P450 (CYP) enzyme inhibitors or at doses greater than 10 mg/day for selegiline or greater than 1 mg/day for rasagiline. Rasagiline is a substrate of CYP1A2, and selegiline is a substrate of CYP2B6 and CYP3A4. Concurrent use of rasagiline or selegiline with inhibitors of these enzymes may increase the rasagiline or selegiline concentration, which theoretically may increase the risk of serotonin syndrome.

Serotonin syndrome resulting from the combination of MAO-B inhibitors and antidepressants is rare. The Parkinson Study Group found that of 4,568 PD patients treated with an antidepressant and selegiline, only 11 (0.24%) reported symptoms consistent with serotonin syndrome. Only two patients (0.04%) experienced serious symptoms, and no fatalities occurred. In a recent study of 12 healthy male volunteers, 1 week of combination rasagiline 1 mg/day and escitalopram 10 mg/day was well tolerated, without evidence of serotonin syndrome.

Many pharmacy drug database systems do not differentiate between contraindications and warnings/precautions listed in product labeling. A drug is labeled as contraindicated only if a known (not theoretical) hazard exists and the risk from use clearly outweighs potential benefit. A warning/precaution describes a potential adverse reaction or drug interaction, giving clinicians information about the risk, risk factors, and steps to take to reduce the risk or manage the reaction if it occurs. FDA labeling for rasagiline and selegiline contains a warning/precaution informing health professionals about the potential for severe central nervous system toxicity with concurrent use of antidepressants and selective or nonselective MAO inhibitors. The warning/precaution states that, in general, avoiding the combination of MAO-B inhibitors and any antidepressant is prudent and that a reasonable washout period should occur between them; however, this is not labeled as an absolute contraindication to concurrent use. In routine practice, MAO-B inhibitors and antidepressants, including SSRIs, are commonly used together. Use of meperidine, tramadol, methadone, propoxyphene, dextromethorphan, St. John’s wort, and other MAO inhibitors (selective or nonselective) concurrent with MAO-B inhibitors is contraindicated, however. In clinical trials of rasagiline, fluoxetine and fluvoxamine were not permitted, but the following antidepressants and doses were allowed: amitriptyline 50 mg or less per day, trazodone 100 mg or less per day, citalopram 20 mg or less per day, sertraline 100 mg or less per day, and paroxetine 30 mg or less per day. No cases of serotonin syndrome have been reported in rasagiline clinical trials to date. A subgroup analysis of patients from a clinical trial of rasagiline as adjunct to carbidopa/levodopa reported that no increase in the prevalence of adverse effects occurred when rasagiline and an SSRI were used concurrently. Pharmacists should discuss with prescribers the risks and benefits of concomitant administration of MAO-B inhibitors and antidepressants for specific patients. If a decision is made to use these agents in combination, pharmacists and prescribers should be aware of the potential for serotonin syndrome and monitor accordingly.

Discussion with patients and prescribers
Ultimately, as the medication expert, the role of the pharmacist is to ensure that patients receive safe and effective medication therapy, get the most benefit from the medication that is prescribed, and achieve optimal outcomes related to their medication therapy. A key element of the pharmacist’s responsibility in safe medication use is to identify drug interactions and determine the potential severity and clinical significance of the interaction. Pharmacists should identify situations in which a selective MAO-B inhibitor is being prescribed concurrently with an antidepressant that may increase serotonin levels. When this situation arises, pharmacists must determine whether patients need to be counseled or whether the interaction requires physician notification. Pharmacists can ask patients what they were told by their physician and then provide reinforcement—a strategy that is usually much appreciated by both patients and physicians.

Pharmacists can make physicians aware when an interaction potentially exists between an MAO-B inhibitor and an antidepressant and assist physicians in determining the clinical significance and whether medication and/or dosage adjustments are needed or whether monitoring patients is adequate. Pharmacists may suggest changing to an antidepressant with lower serotonergic potential (e.g., bupropion, amoxapine, doxepin, desipramine, nortriptyline), adjusting the dose of the antidepressant, changing PD therapy, or initiating active monitoring for patients remaining on the combination. Pharmacists and prescribers should discuss these options in the context of the individual patient’s needs. Pharmacists should approach...
Tips for counseling patients

Speak to patients in a quiet area that affords privacy and minimizes disruptions.

Ask patients what their physician has already told them regarding rasagiline/selegiline and the antidepressant; reinforce the physician’s teaching.

Inform patients that the drug interaction is rare but that a physician should be contacted if they experience any symptoms such as muscle stiffness or jerkiness, agitation or confusion, sweating, or other unusual symptoms.

Explain the situation in a way that does not undermine the physician–patient relationship.

Use lay language and look patients in the eyes.

Be respectful.

Be sensitive to patients’ level of comprehension and cultural background/belief systems.

Avoid inciting undue alarm and be careful not to create patient anxiety that may lead to poor adherence.

Actively listen to patient concerns and express empathy by responding and restating what patients say.

Document the discussion.

Tips for communicating with prescribers

Be aware of the prescriber’s specialty. Most movement disorder specialists and neurologists have considerable experience using selective MAO-B inhibitors and antidepressants in combination, whereas internists and family practice physicians may have less experience with this patient population and these combinations of medications.

Phone or type messages directly to the prescriber; avoid handwritten notes and messages conveyed through others.

Confirm that the prescriber is aware of the potential drug interaction, citing or providing clinical references as support if necessary.

Keep the focus on the patient’s welfare.

Initiate discussion of the risk-to-benefit ratio of the two therapies, actively listening to and showing respect for the prescriber’s perspective.

When pointing out a potential problem, describe the problem succinctly and provide potential solutions.

Pay attention to word choice; maintain a nonconfrontational tone.

Avoid escalating the conversation into an exchange of who is “right” or “wrong.”

Be clear on what the prescriber’s final decision is: what, if any, change is needed to the patient’s medications?

If the decision is made to continue with both MAO-B inhibitor and antidepressant, discuss a plan for monitoring the patient.

Document the discussion.

Assessing your communication skills

Reflect on the last few conversations you have had with patients and prescribers regarding potential drug interactions. How well did they go? What could you have done to improve communication?

Conclusion

Selective MAO-B inhibitors and antidepressants theoretically increase the risk of serotonin syndrome when used concurrently. Although serotonin syndrome is potentially serious, it is an extremely rare occurrence and often mild. When serotonin syndrome is recognized promptly and managed appropriately, prognosis is favorable. Pharmacists should discuss with the patient’s provider the risks and benefits of combined selective MAO-B inhibitor and antidepressant therapy for individual PD patients. Pharmacists should provide counseling to patients taking these combinations so that they can be alert to and report the onset of any symptoms, but should also help patients keep the risks in perspective.

References


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