As the list of serotonergic agents grows, recognizing hyperthermic states and potentially dangerous drug combinations is critical to our patients’ safety.
Promptly identifying serotonin syndrome and acting decisively can keep side effects at the mild end of the spectrum. Symptoms of this potentially dangerous syndrome range from minimal in patients starting selective serotonin reuptake inhibitors (SSRIs) to fatal in those combining monoamine oxidase inhibitors (MAOIs) with serotonergic agents.

This article presents the latest evidence on how to:

- reduce the risk of serotonin syndrome
- recognize its symptoms
- and treat patients with mild to life-threatening symptoms.

**WHAT IS SEROTONIN SYNDROME?**

Serotonin syndrome is characterized by changes in autonomic, neuromotor, and cognitive-behavioral function (Table 1) triggered by increased serotonergic stimulation. It typically results from pharmacodynamic and/or pharmacokinetic interactions between drugs that increase serotonin activity.1,2

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Harvey Sternbach, MD
Clinical professor of psychiatry
UCLA Neuropsychiatric Institute
Los Angeles, CA
activity or reduced ability to secrete endothelium-derived nitric oxide may diminish the ability to metabolize serotonin.2

POTENTIALLY DANGEROUS COMBINATIONS

MAOIs. Serotonin syndrome has been reported as a result of interactions between MAOIs—including selegiline and reversible MAO-A inhibitors (RIMAs)—and various serotonergic compounds. These reports have included fatalities, some of which were preceded by severe hyperthermia with complications such as disseminated intravascular coagulation, rhabdomyolysis, and renal failure. Some cases resulted from overdoses, but others did not.

Most disturbingly, some cases occurred after patients had undergone the traditional 2-week washout from the MAOI and then took a serotonergic agent. In one instance, a patient who had discontinued fluoxetine for 6 weeks developed serotonin syndrome after starting tranylcypromine. These cases remind us to be vigilant when switching patients from irreversible MAOIs to serotonergic antidepressants or vice versa—even when recommended wash-out times are observed—and not to combine these agents acutely.

Some fatal MAOI-serotonergic interactions occur after the usual 2-week washout

The syndrome was first identified in animal studies, followed by case reports in humans. The first review—with suggested diagnostic criteria—was published in 1991.1 Since then, case reports have described serotonin syndrome with many drug combinations, including nonpsychotropics and illicit drugs. Using an irreversible MAOI with a serotonergic agent is the most toxic reported combination, but any drug or combination that increases serotonin can, in theory, cause serotonin syndrome (Table 2). A clinical scale is being developed to define and identify this potentially dangerous state, but no consensus has emerged on diagnostic criteria.

Pathophysiology. Serotonin syndrome’s symptoms and signs appear to result from stimulation of specific central and peripheral serotonin receptors, especially 5HT1a and 5HT2. Others—such as 5HT3 and 5HT4—may also be involved in causing GI symptoms and may affect dopaminergic transmission.

Damaged vascular or pulmonary endothelium, atherosclerosis, hypertension, or hypercholesterolemia may increase the risk for serotonin syndrome. In patients with these common medical conditions, reduced endothelial MAO-A

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Table 1

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic</td>
<td>Diaphoresis, hyperthermia, hypertension, tachycardia, pupillary dilatation, nausea, diarrhea, shivering</td>
</tr>
<tr>
<td>Neuromotor</td>
<td>Hyperreflexia, myoclonus, restlessness, tremor, incoordination, rigidity, clonus, teeth chattering, trismus, seizures</td>
</tr>
<tr>
<td>Cognitive-behavioral</td>
<td>Confusion, agitation, anxiety, hypomania, insomnia, hallucinations, headache</td>
</tr>
</tbody>
</table>

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Serotonin

continued on page 19
bly” consistent with serotonin syndrome.

- 2 others (0.04%) experienced serious serotonin syndrome symptoms.

Serotonin syndrome has been reported when MAO-B-selective doses of selegiline were combined with meperidine and nortriptyline. This underscores the need for caution when combining these agents, especially if transdermal selegiline—which would not be MAO-B-selective—becomes available for treating depression.

**Moclobemide** is a RIMA used in treating depression and anxiety, with a purported reduced risk of drug and food interactions compared with other MAOIs. Moclobemide is not approved in the United States, but some patients obtain it elsewhere.

Joffe and Bakish reported on safely combining moclobemide with SSRIIs, and a review of MAOIs—including RIMAs—indicated that moclobemide was involved in only 9 of 226 cases of adverse effects and 3 of 105 cases of defined serotonin syndrome. Most moclobemide-SSRI interactions—including fatalities—involved overdoses in suicide attempts, although toxic symptoms have been reported with clomipramine or meperidine taken at normal dosages.

In one study, 18 healthy controls received fluoxetine, 20 to 40 mg/d, for 23 days, then were given moclobemide, up to 600 mg/d, or placebo and observed for adverse effects. No indication of serotonin syndrome was observed.

**Linezolid** is an oxazolidinone antibiotic with relatively weak, nonspecific, but reversible MAO inhibition. Cases of potential serotonin syndrome have been reported with linezolid plus paroxetine or sertraline. Patients in each case were medically ill and taking several other medications, which complicates interpretation of these reports. Nonetheless, physicians should be aware of the potential risk of serotonin syndrome if this antibiotic is combined with serotonergic agents.

### Atypical antipsychotics

Original diagnostic criteria for serotonin syndrome excluded the addition of, or increase in, an antipsychotic prior to the syndrome’s onset. However, serotonin syndrome has been reported with combinations of risperidone with paroxetine, olanzapine with mirtazapine and tramadol, and olanzapine with lithium and citalopram. The 5HT2 antagonist effect of these atypical antipsychotics may have led indirectly to overactivation of 5HT1a receptors and serotonin syndrome. In each case, neuroleptic malignant syndrome was ruled out.
Gardner and Lynd concluded that most patients tolerate sumatriptan with SSRIs or lithium. They felt they could not ensure the safety of sumatriptan with MAOIs, however, because sumatriptan elimination depends on hepatic MAO activity.

Among the 5HT1D agonists, using sumatriptan, zolmitriptan, rizatriptan, or almotriptan with an MAOI or within 2 weeks of discontinuing an MAOI is contraindicated.

Tramadol is an analgesic with opioid and serotonin-reuptake inhibiting properties that is metabolized by the cytochrome P (CYP)-450 isoenzyme 2D6. Serotonin syndrome has been reported from interactions between tramadol and sertraline and fluoxetine. Possible causes include SSRI inhibition of CYP 2D6 metabolism of tramadol, tramadol abuse, and multiple co-administered medications.

Sumatriptan is one of the selective 5HT1D agonists used in treating migraine. Gardner and Lynd concluded that most patients tolerate sumatriptan with SSRIs or lithium. They felt they could not ensure the safety of sumatriptan with MAOIs, however, because sumatriptan elimination depends on hepatic MAO activity.

Table 3

<table>
<thead>
<tr>
<th>Hyperthermic state</th>
<th>Symptoms/signs</th>
<th>Lab findings</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin syndrome</td>
<td>Typically rapid onset with hyperreflexia, tremors, myoclonus, diaphoresis, confusion, agitation, or shivering; muscular rigidity not invariably present</td>
<td>Nonspecific</td>
<td>Increased serotonergic tone</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
<td>Variable rapidity of onset; severe muscular rigidity, diaphoresis, delirium, fluctuating blood pressure, tachycardia, extrapyramidal symptoms</td>
<td>Elevated CPK, leukocytosis</td>
<td>Blockade of dopamine receptors or abrupt withdrawal of a dopamine agonist</td>
</tr>
<tr>
<td>Lethal catatonia</td>
<td>Muscular rigidity, diaphoresis, delirium, alternating extreme excitement and stupor, tremors, hypertension</td>
<td>Nonspecific</td>
<td>Evidence of pre-existing psychosis (bipolar disorder, schizophrenia)</td>
</tr>
<tr>
<td>Anticholinergic toxicity</td>
<td>Hot, dry skin, pupillary dilatation, tachycardia, constipation, urinary retention, confusion, hallucinations, muscular relaxation</td>
<td>Nonspecific</td>
<td>Agents that block central and peripheral muscarinic cholinergic receptors</td>
</tr>
<tr>
<td>Malignant hyperthermia</td>
<td>Rapid onset, severe muscular rigidity, ischemia, hypotension</td>
<td>Elevated CPK, potassium, magnesium; DIC; acidosis; rhabdomyolysis</td>
<td>Inherited disorder with onset after exposure to anesthetic agents that block the neuromuscular junction</td>
</tr>
</tbody>
</table>

CPK: creatine phosphokinase  DIC: disseminated intravascular coagulation
frovatriptan appear less likely to interact with MAOIs, based on FDA-approved labeling.

MDMA. 3,4-methylenedioxyamphetamine (MDMA, “Ecstasy”) is widely used as a recreational drug, especially at crowded dances (“raves”) and with other drugs. This illicit amphetamine derivative stimulates the release of serotonin and inhibits its reuptake.

Kaskey reported the rapid onset of serotonin syndrome when a patient taking lithium and phenelzine ingested MDMA. Signs and symptoms of serotonin syndrome also may develop when MDMA is used alone, facilitated by the high ambient temperatures on crowded dance floors and the dancers’ relative dehydration.

Fatalities have been blamed on complications including disseminated intravascular coagulation, rhabdomyolysis, and acute hepatic, renal, or cardiac failure. Cases are difficult to interpret because of uncertainty about whether the victim ingested MDMA or another agent or combination.

St. John’s wort (Hypericum perforatum) contains numerous constituents, including hypericin and hyperforin, which have been found to inhibit the synaptic uptake of monoamines, including serotonin. Which constituents are responsible for its clinical effect is unclear. Adverse effects from monotherapy include GI symptoms, confusion, dry mouth, dizziness, headache, fatigue, allergic skin reactions, photosensitivity, and urinary frequency.

Several cases of purported serotonin syndrome have been associated with St. John’s wort alone or in combination with SSRIs, nefazodone, or fenfluramine. GI symptoms and anxiety were the primary complaints and resolved without complications (adjunctive cyproheptadine was prescribed in two cases, though it is not clear that this agent contributed to resolution).

## MISCELLANEOUS COMBINATIONS

### Antiretroviral therapy

Five cases of serotonin syndrome were reported in HIV-infected patients taking fluoxetine with antiretroviral therapy. In particular, the use or addition of ritonavir—a potent CYP 2D6 inhibitor—was implicated, though saquinavir, efavirenz, or grapefruit juice (all primarily CYP 3A4 inhibitors) were also used, suggesting that pharmacokinetic interactions increased serotonergic stimulation. All five patients were taking multiple additional medications and had complex medical and/or psychiatric histories. Reducing SSRI dosages by one-half when used with ritonavir has been recommended to minimize adverse effects from a pharmacokinetic interaction.

### Erythromycin

Erythromycin was reported to induce serotonin syndrome in a 12-year-old boy when added to ongoing treatment with sertraline, an effect believed to be secondary to CYP 3A4 inhibition of sertraline metabolism.

### Mirtazapine

Mirtazapine was reported to induce serotonin syndrome in an elderly man 8 days after it was added to a regimen he had been taking for several years to treat chronic obstructive pulmonary disease. Serotonin syndrome also developed in a 12-year-old boy with Ewing’s sarcoma when the 5HT3 antagonist ondansetron was added to mirtazapine and morphine and in an 11-year-old girl with acute lymphoblastic leukemia when ondansetron was added to fentanyl. Interestingly, another report suggested using mirtazapine to treat serotonin syndrome caused by serotonergic antagonist effects.

Reports have associated the following combinations with serotonin syndrome, perhaps as the result of pharmacodynamic and/or pharmacokinetic interactions:

- paroxetine plus dextromethorphan and pseudoephedrine
HOW TO RECOGNIZE SEROTONIN SYNDROME

Signs and symptoms of serotonin syndrome can overlap with those seen in neuroleptic malignant syndrome, lethal catatonia, malignant hyperthermia, and anticholinergic toxicity (Table 3), particularly with fever or hyperthermia (>40.5 °C, 105 °F). Fink has opined that acute neurotoxic syndromes such as serotonin syndrome and neuroleptic malignant syndrome also meet criteria for catatonia and are therefore subtypes of catatonia. The types of drugs involved and clinical findings can help distinguish the various hyperthermic states (Table 4).

As mentioned above, original diagnostic criteria for serotonin syndrome excluded the addition of, or increase in, an antipsychotic agent. This exclusion was intended to avoid confusion between serotonin syndrome and neuroleptic malignant syndrome. Co-administering antipsychotic and serotonergic agents requires heightened awareness for both neurotoxic syndromes.

TREATING MILD TO SEVERE CASES

If a patient develops serotonin syndrome, immediately discontinue the suspected agent(s) and observe carefully. In most cases, serotonin syndrome will resolve within 24 hours.

In mild cases, lorazepam, 1 to 2 mg slow IV push every 30 minutes until excessive sedation develops, may help. In moderate to severe cases, agents that block serotonin’s action are recommended, including:

- cyproheptadine (4 mg po every 4 hours as needed, up to 20 mg in 24 hours)
- propranolol (1 to 3 mg IV every 5 minutes, up to 0.1 mg/kg).

Table 4 Clinical signs that distinguish hyperthermic states

<table>
<thead>
<tr>
<th>Signs</th>
<th>Possible diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prominent muscular rigidity</td>
<td>Neuroleptic malignant syndrome, malignant hyperthermia, catatonia</td>
</tr>
<tr>
<td>Myoclonus/hyperreflexia</td>
<td>Serotonin syndrome</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Serotonin syndrome, neuroleptic malignant syndrome, catatonia</td>
</tr>
<tr>
<td>Hot dry skin</td>
<td>Anticholinergic toxicity</td>
</tr>
<tr>
<td>Elevated creatine phosphokinase</td>
<td>Neuroleptic malignant syndrome, malignant hyperthermia</td>
</tr>
<tr>
<td>Family history of anesthetic-induced hyperthermia</td>
<td>Malignant hyperthermia</td>
</tr>
</tbody>
</table>
Case reports attest to these agents’ potential benefit. Other clinicians have reported using mirtazapine, nitroglycerin, and chloropromazine.

Serotonin syndrome symptoms resolved within minutes when IV nitroglycerin was used in a patient with serotonin syndrome and cardiac ischemia. The authors hypothesized that nitroglycerin, via nitric acid, provided an “off” signal for serotonin, though they did not advocate this as a routine treatment.

The rationale for using chloropromazine is its potential to block serotonin receptors. I would avoid the routine use of any antipsychotic agent in this setting, however, to minimize the risk of neuroleptic malignant syndrome.

Severe cases. Intensive care observation and treatment is required for patients with severe serotonin syndrome, including evidence of hyperthermia, DIC, rhabdomyolysis, renal failure, or aspiration. In cases of hyperthermia, supportive measures and standard treatments include muscle relaxants, cooling, and endotracheal intubation.

Severe complications are most likely with interactions between MAOIs and serotonergic agents, especially in overdose. Therefore, using such combinations requires close observation.

References


Drugs

Almotriptan • Axert
Amitriptyline • Elavil
Buspirone • Buspar
Chlorpromazine • Thorazine
Citalopram • Celexa
Clomipramine • Anafranil
Cyproheptadine • Periactin
Dextroamphetamine • Dexamfetamine
Dextromethorphan • Delsym
Etivizine • Sustiva
Escitalopram • Lexapro
Fenfluramine • Pondimin
Fentanyl • Sublimaze
Fluoxetine • Prozac
Fluvoxamine • Luvox
Frovatriptan • Frova
Isocarboxazid • Marplan
Linezolid • Zyvox
Meperidine • Demerol
Mirtazapine • Remeron
Moclobemide • Aurorix
Nortriptyline • Pamelor
Naratriptan • Amerge
Nefazodone • Serzone
Olanzapine • Zyproxa
Ondansetron • Zofran
Paroxetine • Paxil
Phenelzine • Naridil
Proprazol • Inderal
Risperidone • Risperdal
Ritonavir • Norvir
Rizatryptan • Maxalt
Saquinavir • Invirase
Selegline • Eldepryl
Sertraline • Zoloft
Sumatriptan • Imitrex
Tramadol • Ultram
Tranclorpromazine • Parnate
Trazodon • Desyrel
Venlafaxine • Effexor
Zolmitriptan • Zomig

Disclosure

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