

Serotonin syndrome

How to avoid, identify, &

As the list of serotonergic agents grows, recognizing hyperthermic states and potentially dangerous drug combinations is critical to our patients' safety.

treat dangerous drug interactions

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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}

continued



Table 1

How to recognize serotonin syndrome

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

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 scale³ 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 5HT_{1a} 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

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,⁴ 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.^{5,7} In one instance,⁸ 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.

Selegiline is a relatively selective MAO-B inhibitor when used at 5 to 10 mg/d to treat Parkinson’s disease, though it loses MAO-B selectivity when used at higher dosages to treat depression. In a study⁹ of 4,568 patients with Parkinson’s disease who received selegiline (in dosages selective for MAO-B) plus an antidepressant:

- 11 (0.24%) experienced symptoms “possi-

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

continued on page 19

continued from page 16

bly” consistent with serotonin syndrome

- 2 others (0.04%) experienced serious serotonin syndrome symptoms.⁹

Serotonin syndrome has been reported when MAO-B-selective doses of selegiline were combined with meperidine¹⁰ and nortriptyline.¹¹ 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 SSRIs,¹² 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.¹³ 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.^{14,15}

In one study,¹⁶ 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

Table 2

Serotonergic agents and their actions

Actions	Agents
Inhibit serotonin reuptake	Fluoxetine, sertraline, citalopram, escitalopram, paroxetine, clomipramine, venlafaxine, fluvoxamine, tramadol, trazodone, nefazodone, tricyclic antidepressants, amphetamine, cocaine, dextromethorphan, meperidine, St. John’s wort
Increases serotonin synthesis	Tryptophan
Inhibit serotonin metabolism	Phenelzine, tranylcypromine, isocarboxazid, selegiline (deprenyl), linezolid, moclobemide
Increase serotonin release	MDMA (“Ecstasy”), amphetamine, cocaine, fenfluramine
Increase serotonin activity	Lithium, ECT
Serotonin receptor agonists	Buspirone, sumatriptan and other “triptans” used for migraine

inhibition. Cases of potential serotonin syndrome have been reported with linezolid plus paroxetine¹⁷ or sertraline.¹⁸ 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.¹ However, serotonin syndrome has been reported with combinations of risperidone with paroxetine,¹⁹ olanzapine with mirtazapine and tramadol,²⁰ and olanzapine with lithium and citalopram.²¹ The 5HT₂ antagonist effect of these atypical antipsychotics may have led indirectly to overactivation of 5HT_{1a} receptors and serotonin syndrome. In each case, neuroleptic malignant syndrome was ruled out.



Table 3

Signs and symptoms that differentiate 5 hyperthermic states

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

CPK: creatine phosphokinase

DIC: disseminated intravascular coagulation

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 sertraline²² and fluoxetine.²³ Possible causes include SSRI inhibition of CYP 2D6 metabolism of tramadol, tramadol abuse,²³ and multiple co-administered medications.²²

Sumatriptan is one of the selective 5HT_{1D} ago-

nists used in treating migraine. Gardner and Lynd²⁴ 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 5HT_{1D} agonists, using sumatriptan, zolmitriptan, rizatriptan, or almotriptan with an MAOI or within 2 weeks of discontinuing an MAOI is contraindicated. Naratriptan and

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.²⁵ 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.²⁶ 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.²⁵ 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.²⁷ 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.²⁷

Several cases of purported serotonin syndrome have been associated with St. John’s wort alone²⁸ or in combination with SSRIs, nefazodone, or fenfluramine.^{29,30} 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).

Cases of purported serotonin syndrome have been associated with St. John’s wort

MISCELLANEOUS COMBINATIONS

Antiretroviral therapy. Five cases of serotonin syndrome were reported in HIV-infected patients taking fluoxetine with antiretroviral therapy.³¹

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 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.³²

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.³³ Serotonin syndrome also developed in a 12-year-old boy with Ewing’s sarcoma when the 5HT3 antagonist ondansetron was added to mirtazapine and morphine³⁴ and in an 11-year-old girl with acute lymphoblastic leukemia when ondansetron was added to fentanyl. Interestingly, another report³⁵ 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



Table 4

Clinical signs that distinguish hyperthermic states

Signs	Possible diagnosis
Prominent muscular rigidity	Neuroleptic malignant syndrome, malignant hyperthermia, catatonia
Myoclonus/hyperreflexia	Serotonin syndrome
Diaphoresis	Serotonin syndrome, neuroleptic malignant syndrome, catatonia
Hot dry skin	Anticholinergic toxicity
Elevated creatine phosphokinase	Neuroleptic malignant syndrome, malignant hyperthermia
Family history of anesthetic-induced hyperthermia	Malignant hyperthermia

- paroxetine plus nefazodone
- fluoxetine plus clomipramine and buspirone
- fluvoxamine plus buspirone
- fluoxetine plus buspirone
- amitriptyline plus meperidine and venlafaxine
- venlafaxine and dextroamphetamine
- fluoxetine plus clomipramine.

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*),^{1,36,37} particularly with fever or hyperthermia (>40.5 °C, 105 °F). Fink³⁷ 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,² 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).

Any drug or combination that increases serotonin can, in theory, cause serotonin syndrome. Avoiding potentially dangerous drug combinations, monitoring patients carefully, and identifying and treating serotonin syndrome early can minimize its morbidity and mortality.

BottomLine

Case reports attest to these agents' potential benefit. Other clinicians have reported using mirazapine,³⁵ nitroglycerin,³⁸ and chlorpromazine.¹

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.³⁸

The rationale for using chlorpromazine 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.

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Related resources

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DRUG BRAND NAMES

Almotriptan • Axert	Nortriptyline • Pamelor
Amitriptyline • Elavil	Naratriptan, • Amerge
Bupirone • Buspar	Nefazodone • Serzone
Chlorpromazine • Thorazine	Olanzapine • Zyprexa
Citalopram • Celexa	Ondansetron • Zofran
Clomipramine • Anafranil	Paroxetine • Paxil
Cyproheptadine • Periactin	Phenelzine • Nardil
Dextroamphetamine • Dexedrine	Propranolol • Inderal
Dextromethorphan • Delsym	Risperidone • Risperdal
Efavirenz • Sustiva	Ritonavir • Norvir
Escitalopram • Lexapro	Rizatriptan • Maxalt
Fenfluramine • Pondimin	Saquinavir • Invirase
Fentanyl • Sublimaze	Selegiline • Eldepryl
Fluoxetine • Prozac	Sertraline • Zoloft
Fluvoxamine • Luvox	Sumatriptan • Imitrex
Frovatriptan • Frova	Tramadol • Ultram
Isocarboxazid • Marplan	Tranylcypromine • Parnate
Linezolid • Zyvox	Trazodone • Desyrel
Meperidine • Demerol	Venlafaxine • Effexor
Mirtazapine • Remeron	Zolmitriptan • Zomig
Moclobemide • Aurorix	

DISCLOSURE

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