

## REVIEW

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# Serotonin syndrome: Preventing, recognizing, and treating it

## ABSTRACT

As the use of serotonergic agents to treat depression has increased, so too has the incidence of serotonin syndrome. We identify the common agents implicated in serotonin syndrome and the clinical tools to diagnose, manage, and prevent serotonergic toxicity.

## KEY POINTS

Serotonin syndrome is caused by elevated serotonin levels in the central and peripheral nervous systems.

The classic presentation is the triad of autonomic dysfunction, neuromuscular excitation, and altered mental status. These symptoms vary based on the severity of serotonergic toxicity and often do not present concomitantly.

Early recognition is critical to ensure appropriate resuscitative measures and to limit further use of drugs that can exacerbate symptoms.

**W**ITH A SUBSTANTIAL INCREASE in antidepressant use in the United States over the last 2 decades, serotonin syndrome has become an increasingly common and significant clinical concern. In 1999, 6.5% of adults age 18 and older were taking antidepressants; by 2010, the percentage had increased to 10.4%.<sup>1</sup> Though the true incidence of serotonin syndrome is difficult to determine, the number of ingestions of selective serotonin reuptake inhibitors (SSRIs) associated with moderate to major effects reported to US poison control centers increased from 7,349 in 2002<sup>2</sup> to 8,585 in 2005.<sup>3</sup>

Though the clinical manifestations are often mild to moderate, patients with serotonin syndrome can deteriorate rapidly and require intensive care. Unlike neuroleptic malignant syndrome, serotonin syndrome should not be considered an extremely rare idiosyncratic reaction to medication, but rather a progression of serotonergic toxicity based on increasing concentration levels that can occur in any patient regardless of age.<sup>4</sup>

Because it has a nonspecific prodrome and protean manifestations, serotonin syndrome can easily be overlooked, misdiagnosed, or exacerbated if not carefully assessed. Diagnosis requires a low threshold for suspicion and a meticulous history and physical examination. In the syndrome's mildest stage, symptoms are often misattributed to other causes, and in its most severe form, it can easily be mistaken for neuroleptic malignant syndrome.

## ■ WHAT IS SEROTONIN SYNDROME?

Serotonin syndrome classically presents as the triad of autonomic dysfunction, neuromuscular excitation, and altered mental status. These symptoms are a result of increased se-

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TABLE 1

**Drug mechanisms associated with serotonin syndrome**

Mechanism	Specific agents
<b>Decreased serotonin breakdown</b>	Monoamine oxidase inhibitors <sup>a</sup> : phenelzine, tranylcypromine, isocarboxazid, moclobemide, selegiline, rasagiline Antibiotics: linezolid, tedizolid Others: methylene blue, procarbazine, Syrian rue
<b>Decreased serotonin reuptake</b>	Antidepressants: Selective serotonin reuptake inhibitors <sup>a</sup> : fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline, escitalopram Serotonin-norepinephrine reuptake inhibitors <sup>a</sup> : venlafaxine, duloxetine, milnacipran Tricyclic antidepressants <sup>a</sup> : clomipramine, imipramine St. John's wort Opioids <sup>a</sup> : meperidine, buprenorphine, tramadol, tapentadol, dextromethorphan Antiepileptics: valproate, carbamazepine Antiemetics: ondansetron, granisetron, metoclopramide
<b>Increased serotonin precursors or agonists</b>	Tryptophan, lithium, fentanyl, lysergic acid diethylamide (LSD)
<b>Increased serotonin release</b>	Central nervous system stimulants: amphetamines <sup>a</sup> Anorectics <sup>a</sup> : fenfluramine, dexfenfluramine, phentermine Drugs of abuse: methylenedioxymethamphetamine (ecstasy), <sup>a</sup> cocaine
<b>CYP2D6 and CYP3A4 inhibitors</b>	Antibiotics: erythromycin, ciprofloxacin Antifungal: fluconazole Antiretroviral: ritonavir

<sup>a</sup> Confirmed to precipitate serotonin syndrome. The others have not been reliably confirmed and are based on case reports or expert opinion.

rotonin levels affecting the central and peripheral nervous systems. Serotonin affects a family of receptors that has seven members, of which 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> are most often responsible for serotonin syndrome.<sup>5</sup>

Conditions that can alter the regulation of serotonin include therapeutic doses, drug interactions, intentional or unintentional overdoses, and overlapping transitions between medications. As a result, drugs that have been associated with serotonin syndrome can be classified into the following five categories as shown below and in Table 1:

**Drugs that decrease serotonin breakdown** include monoamine oxidase inhibitors

(MAOIs), linezolid,<sup>6</sup> methylene blue, procarbazine, and Syrian rue.

**Drugs that decrease serotonin reuptake** include SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, opioids (meperidine, buprenorphine, tramadol, tapentadol, dextromethorphan), antiepileptics (carbamazepine, valproate), and antiemetics (ondansetron, granisetron, metoclopramide), and the herbal preparation St. John's wort.

**Drugs that increase serotonin precursors or agonists** include tryptophan, lithium, fentanyl, and lysergic acid diethylamide (LSD).

**Drugs that increase serotonin release in-**

TABLE 2

Spectrum of symptoms of serotonergic toxicity

Severity	Neuromuscular excitation	Altered mental status	Autonomic dysfunction
<b>Mild</b>	Hyperreflexia Tremor Myoclonus	Anxiety Restlessness Insomnia	Diaphoresis Mydriasis Tachycardia
<b>Moderate</b>	Opsoclonus Spontaneous or inducible clonus	Agitation	Hypertension Hyperthermia ( $< 40^{\circ}\text{C}$ , $< 104^{\circ}\text{F}$ ) Hyperactive bowel sounds Diarrhea, nausea, vomiting
<b>Severe</b>	Rigidity Respiratory failure Tonic-clonic seizure	Coma Delirium Confusion	Severe hyperthermia ( $\geq 40^{\circ}\text{C}$ , $\geq 104^{\circ}\text{F}$ ) Dynamic blood pressure

clude fenfluramine, amphetamines, and methylenedioxymethamphetamine (ecstasy).

Drugs that prevent breakdown of the agents listed above are CYP2D6 and CYP3A4 inhibitors, eg, erythromycin,<sup>7</sup> ciprofloxacin, fluconazole, ritonavir, and grapefruit juice.

However, the only drugs that have been reliably confirmed to precipitate serotonin syndrome are MAOIs, SSRIs, SNRIs, and serotonin releasers. Other listed drug interactions are based on case reports and have not been thoroughly evaluated.<sup>6-9</sup>

Currently, SSRIs are the most commonly prescribed antidepressant medications and, consequently, they are the ones most often implicated in serotonergic toxicity.<sup>1,10</sup> An estimated 15% of SSRI overdoses lead to mild or moderate serotonin toxicity.<sup>11</sup> Serotonergic agents used in conjunction can increase the risk for severe serotonin syndrome; an SSRI and an MAOI in combination poses the greatest risk.<sup>5</sup>

Ultimately, the incidence of serotonin syndrome is difficult to assess, but it is believed to be underreported because it is easy to misdiagnose and mild symptoms may be dismissed.

WHO IS AT RISK OF SEROTONIN SYNDROME?

Long-term antidepressant use has disproportionately increased in middle-aged and older

adults and non-Hispanic whites.<sup>1,12,13</sup> Intuitively, as the risk for depression increases dramatically in patients with chronic medical conditions, serotonin syndrome should be more prevalent among the elderly. In addition, patients with multiple comorbidities take more medications, increasing the risk of polypharmacy and adverse drug reactions.<sup>14</sup>

Although the epidemiology of serotonin syndrome has yet to be extensively studied, the combination of age and comorbidities may increase the risk for this condition.

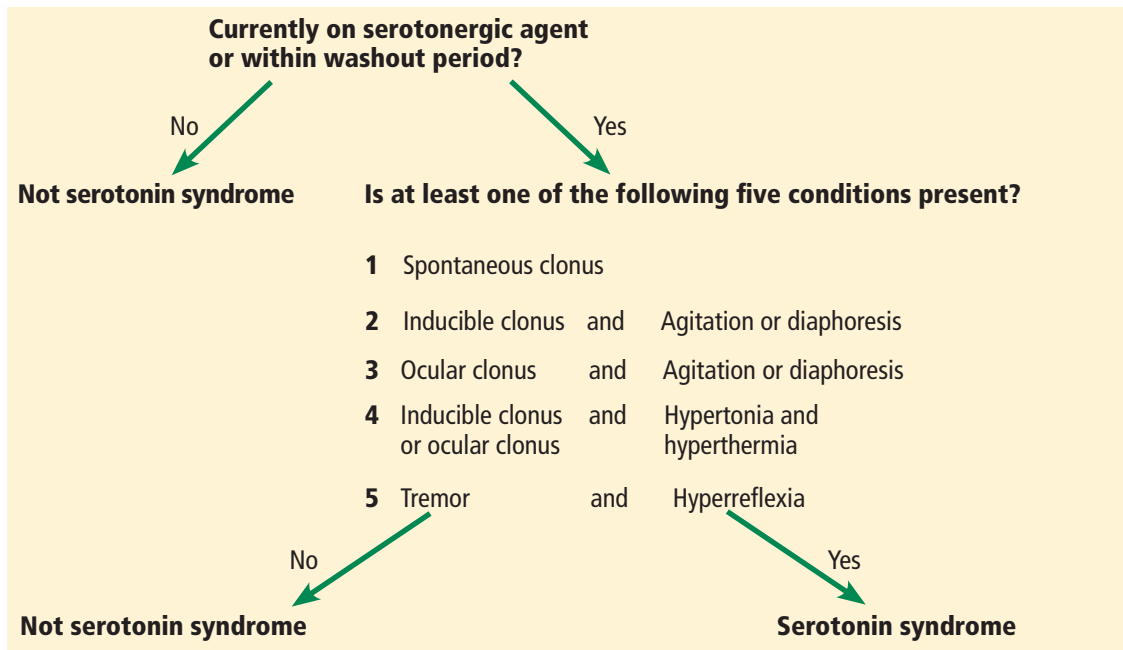
HOW DOES IT PRESENT?

Serotonin syndrome characteristically presents as the triad of autonomic dysfunction, neuromuscular excitation, and altered mental status. However, these symptoms may not occur simultaneously: autonomic dysfunction is present in 40% of patients, neuromuscular excitation in 50%, and altered mental status in 40%.<sup>15</sup> The symptoms can range from mild to life-threatening (Table 2).<sup>16</sup>

**Autonomic dysfunction.** Diaphoresis is present in 48.8% of cases, tachycardia in 44%, nausea and vomiting in 26.8%, and mydriasis in 19.5%. Other signs are hyperactive bowel sounds, diarrhea, and flushing.<sup>16</sup>

**Neuromuscular excitation.** Myoclonus is present in 48.8%, hyperreflexia in 41%, hyperthermia in 26.8%, and hypertonicity and

Serotonin syndrome can easily be overlooked, misdiagnosed, or exacerbated if not carefully assessed



**FIGURE 1.** Algorithm for clinical diagnosis of serotonin based on Hunter serotonin toxicity criteria (based on information in reference 9).

rigidity in 19.5%. Other signs are spontaneous or inducible clonus, ocular clonus (continuous rhythmic oscillations of gaze), and tremor.

**Altered mental status.** Confusion is present in 41.2% and agitation in 36.5%. Other signs are anxiety, lethargy, and coma.

Symptoms of serotonin toxicity arise within an hour of a precipitating event (eg, ingestion) in approximately 28% of patients, and within 6 hours in 61%.<sup>16</sup> Highly diagnostic features include hyperreflexia and induced or spontaneous clonus that are generally more pronounced in the lower limbs.<sup>11</sup> Clonus can be elicited with ankle dorsiflexion.

**In mild toxicity,** patients may present with tremor or twitching and anxiety, as well as with hyperreflexia, tachycardia, diaphoresis, and mydriasis. Further investigation may uncover a recently initiated antidepressant or a cold-and-cough medication that contains dextromethorphan.<sup>15,17</sup>

**In moderate toxicity,** patients present in significant distress, with agitation and restlessness. Features may include hyperreflexia and clonus of the lower extremities, opsoclonus, hyperactive bowel sounds, diarrhea, nausea, vomiting, tachycardia, hypertension, diaphoresis, mydriasis, and hyperthermia (< 40°C, 104°F). The patient's history may re-

veal use of ecstasy or combined treatment with serotonin-potentiating agents such as an antidepressant with a proserotonergic opioid, antiepileptic, or CYP2D6 or CYP3A4 inhibitor.<sup>15</sup>

**Severe serotonin toxicity** is a life-threatening condition that can lead to multiorgan failure within hours. It can be characterized by muscle rigidity, which can cause the body temperature to elevate rapidly to over 40°C. This hypertonicity can mask the classic and diagnostic signs of hyperreflexia and clonus. Patients may have unstable and dynamic vital signs with confusion or delirium and can experience tonic-clonic seizures.

If the muscle rigidity and resulting hyperthermia are not managed properly, patients can develop cellular damage and enzyme dysfunction leading to rhabdomyolysis, myoglobinuria, renal failure, metabolic acidosis, acute respiratory distress syndrome, and disseminated intravascular coagulation.<sup>16,18</sup>

Serotonin crisis is usually caused by the co-ingestion of multiple serotonergic agents, such as an antidepressant with an aforementioned opioid and antiemetic<sup>19</sup>; combining an SSRI and an MAOI poses the greatest risk. Alternatively, patients may have recently switched antidepressants without observing a safe wash-

**Severe serotonin toxicity is a life-threatening condition that can lead to multiorgan failure within hours**

TABLE 3

Differential diagnosis of serotonin syndrome

	Serotonin syndrome	Neuroleptic malignant syndrome	Anticholinergic toxicity
<b>Causative agent</b>	Serotonergic agent	Dopamine antagonist Withdrawal from dopamine agonist	Anticholinergic agent
<b>Onset</b>	Within 24 hours	Within days to weeks	Within 1–2 hours
<b>Resolution</b>	Within 24 hours	In approximately 9 days	Within hours to days
<b>Features similar to those of serotonin syndrome</b>	—	Hyperthermia Altered mental state Diaphoresis Autonomic instability	Mydriasis Hyperthermia Agitation, delirium Visual hallucinations
<b>Distinct features</b>	Myoclonus Hyperreflexia Mydriasis Tremor Diarrhea Nausea, vomiting	Bradyreflexia Lead pipe rigidity Extrapyramidal features Absence of neuromuscular excitation	Dry skin and mucous membranes Urinary retention Decreased bowel sounds Normal muscle tone and reflexes

The Hunter criteria are more sensitive and specific than the Sternbach criteria

out period, leading to an overlap of serotonin levels.<sup>16</sup>

■ HOW DO WE DIAGNOSE SEROTONIN SYNDROME?

Serotonin syndrome is a clinical diagnosis and therefore requires a thorough review of medications and physical examination. Serum serotonin levels are an unreliable indicator of toxicity and do not correlate well with the clinical presentation.<sup>16</sup>

Currently, there are two clinical tools for diagnosing serotonin syndrome: the Hunter serotonin toxicity criteria (Figure 1) and the Sternbach criteria.

The Hunter criteria are based more heavily on physical findings. The patient must have taken a serotonergic agent and have one of the following:

- Spontaneous clonus
- Inducible clonus plus agitation or diaphoresis
- Ocular clonus plus agitation or diaphoresis
- Inducible clonus or ocular clonus, plus hyper-

pertonia and hyperthermia

- Tremor plus hyperreflexia.

The Sternbach criteria. The patient must be using a serotonergic agent, must have no other causes of symptoms, must not have recently used a neuroleptic agent, and must have three of the following:

- Mental status changes
- Agitation
- Hyperreflexia
- Myoclonus
- Diaphoresis
- Shivering
- Tremor
- Diarrhea
- Incoordination
- Fever.

The Hunter criteria are recommended and are more specific (97% vs 96%) and more sensitive (84% vs 75%) than the Sternbach criteria when compared with the gold standard of diagnosis by a clinical toxicologist.<sup>1</sup> The Hunter criteria are also less likely to yield false-positive results.<sup>11</sup>

### Differential diagnosis

The differential diagnosis for serotonin syndrome includes neuroleptic malignant syndrome, anticholinergic poisoning (Table 3), metastatic carcinoma, central nervous system infection, gastroenteritis, and sepsis.

**Neuroleptic malignant syndrome**, the disorder most often misdiagnosed as serotonin syndrome, is an idiosyncratic reaction to a dopamine antagonist (eg, haloperidol, fluphenazine) that develops over days to weeks.<sup>20</sup> In 70% of patients, agitated delirium with confusion appears first, followed by lead pipe rigidity and cogwheel tremor, then hyperthermia with body temperature greater than 40°C, and finally, profuse diaphoresis, tachycardia, hypertension, and tachypnea.<sup>21</sup>

Key elements that distinguish neuroleptic malignant syndrome are the timeline of the clinical course, bradyreflexia, and the absence of clonus. Prodromal symptoms of nausea, vomiting, and diarrhea are also rare in neuroleptic malignant syndrome. Neuroleptic malignant syndrome typically requires an average of 9 days to resolve.

**Anticholinergic poisoning** usually develops within 1 to 2 hours of oral ingestion. Symptoms include flushing, anhidrosis, anhidrotic hyperthermia, mydriasis, urinary retention, decreased bowel sounds, agitated delirium, and visual hallucinations. In contrast to serotonin syndrome, reflexes and muscle tone are normal with anticholinergic poisoning.

### ■ HOW CAN WE TREAT SEROTONIN SYNDROME?

The two mainstays of serotonin syndrome management are to discontinue the serotonergic agent and to give supportive care. Most patients improve within 24 hours of stopping the precipitating drug and starting therapy.<sup>16</sup>

**For mild serotonin syndrome**, treatment involves discontinuing the offending agent and supportive therapy with intravenous fluids, correction of vital signs, and symptomatic treatment with a benzodiazepine. Patients should be admitted and observed for 12 to 24 hours to prevent exacerbation.

**For moderate serotonin syndrome**, treatment also involves stopping the serotonergic agent and giving supportive care. Symptom-

atic treatment with a benzodiazepine and nonserotonergic antiemetics is recommended, and standard cooling measures should be implemented for hyperthermia. Patients should be admitted and observed for 12 to 24 hours to prevent exacerbation.

**For severe serotonin toxicity**, treatment should focus on management of airway, breathing, and circulation—ie, the “ABCs.” The two primary life-threatening concerns are hyperthermia (temperature > 40°C or 104°F) and rigidity, which can lead to hypoventilation.<sup>1,22</sup> Controlling hyperthermia and rigidity can prevent other grave complications. Patients with severe serotonin toxicity should be sedated, paralyzed, and intubated.<sup>21</sup> This will reverse ventilatory hypertonia and allow for mechanical ventilation. Paralysis will also prevent the exacerbation of hyperthermia, which is caused by muscle rigidity. Antipyretics have no role in the treatment of serotonin syndrome since the hyperthermia is not caused by a change in the hypothalamic temperature set point.<sup>21</sup> Standard cooling measures should be used to manage hyperthermia.

### Serotonin antagonists

Serotonin antagonists have had some success in case reports, but further studies are needed to confirm this.<sup>4,23,24</sup>

**Cyproheptadine** is a potent 5-HT<sub>2A</sub> antagonist; patients usually respond within 1 to 2 hours of administration. Signs and symptoms have resolved completely within times ranging from 20 minutes to 48 hours, depending on the severity of toxicity.

The recommended initial dose of cyproheptadine is 12 mg, followed by 2 mg every 2 hours if symptoms continue.<sup>16</sup> Maintenance dosing with 8 mg every 6 hours should be prescribed once stabilization is achieved. The total daily dose for adults should not exceed 0.5 mg/kg/day. Cyproheptadine is available only in oral form but can be crushed and administered via a nasogastric tube.<sup>21</sup>

**Chlorpromazine** is a 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> antagonist and can be given intramuscularly. Despite case reports citing its effectiveness, the risk of hypotension, dystonic reactions, and neuroleptic malignant syndrome may make it a less desirable option.<sup>4,25</sup>

Cyproheptadine, chlorpromazine, and other

**Mainstays of management: stop the serotonergic agent and give supportive care**



serotonin receptor antagonists require further investigation beyond individual case reports to determine their effectiveness and reliability in treating serotonin syndrome.

## Other agents

**Benzodiazepines** are considered a mainstay for symptomatic relief because of their anxiolytic and muscle relaxant effects.<sup>26</sup> However, animal studies showed that treatment with benzodiazepines attenuated hyperthermia but had no effect on time to recovery or outcome.<sup>27</sup>

**Neuromuscular blocking agents.** The suggested neuromuscular blocking agent for severe toxicity is a nondepolarizing agent such as vecuronium. Succinylcholine should be avoided, as it can exacerbate rhabdomyolysis and hyperkalemia.<sup>21</sup>

Dantrolene has also been suggested for its muscle-relaxing effects and use in malignant hyperthermia. However, this treatment has not been successful in isolated case reports and has been ineffective in animal models.<sup>4,28</sup>

**Physical restraints are ill-advised**, since isometric muscle contractions can exacerbate hyperthermia and lactic acidosis in agitated patients.<sup>21</sup> If physical restraints are necessary to deliver medications, they should be removed as soon as possible.

## ■ HOW CAN WE PREVENT SEROTONIN SYNDROME?

Prevention of serotonin syndrome begins with improving education and awareness in patients and healthcare providers. Patients should be primarily concerned with taking their medications carefully as prescribed and recognizing early signs and symptoms of serotonin toxicity.

As use of antidepressants among an aging population continues to increase, and as physicians in multiple disciplines prescribe them for evolving indications (eg, duloxetine to treat osteoarthritis, diabetic neuropathy, fibromyalgia, and chemotherapy-induced peripheral neuropathy), healthcare providers need to be prepared to see more cases of serotonin syndrome and its deleterious effects.<sup>29–31</sup> Physicians should be vigilant in minimizing unnecessary use of serotonergic agents and reviewing drug regimens regularly to limit polypharmacy.

Electronic ordering systems should be designed to detect and alert the prescriber to possible interactions that can potentiate serotonin syndrome, and to not place the order until the prescriber overrides the alert. Combinations of SSRIs and MAOIs have the highest risk for inducing severe serotonin syndrome and should always be avoided.

If a patient is transitioning between serotonergic agents, physicians should observe a safe washout period to prevent overlap.<sup>16,32</sup> Washout periods may differ among medications depending on their half-lives. For example, sertraline has a washout period of 2 weeks, while fluoxetine requires a washout period of 5 to 6 weeks.<sup>33</sup> Consulting a pharmacist may be helpful when considering half-lives and washout periods.

We believe that educating both patients and physicians regarding prevention will help minimize the risk for serotonergic syndrome and will improve efficiency in assessment and management should toxicity develop. ■

If transitioning between serotonergic agents, observe a safe washout period

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