

Serotonin syndrome: How to keep your patients safe

Justine E. Zick, PharmD, Suzanne S. Rettey, PharmD, MPA, Elizabeth A. Cunningham, DO, FAPA,
and Christopher J. Thomas, PharmD, BCPS, BCPP



Vicki L. Ellingrod,
PharmD, FCCP
Department Editor

Mr. S, age 55, comes to your clinic as a walk-in for management of major depressive disorder, insomnia, and migraines. He also has tobacco use disorder and hypertension. Several days ago, Mr. S had visited the clinic because he was continuing to experience depressive symptoms, so his sertraline was increased from 100 to 200 mg/d. His current medication regimen includes sertraline 200 mg/d, trazodone 100 mg/d, lisinopril 10 mg/d, and sumatriptan, 100 mg as needed for migraine. He says last week he used 4 or 5 doses of sumatriptan because he experienced several migraines. Mr. S also reports occasionally taking 2 tablets of trazodone instead of 1 on nights that he has trouble falling asleep.

Today, Mr. S presents with a low-grade fever, diarrhea, internal restlessness, and a racing heartbeat that started shortly after his last visit. During physical examination, he exhibits slow, continuous lateral eye movements. His vital signs are markedly elevated: blood pressure, 175/85 mm Hg; heart rate, 110 beats per minute; and temperature, 39°C (102.2°F). Based on his presentation,

the treatment team decides to send Mr. S to urgent care for closer monitoring.

Serotonin syndrome is a drug-induced syndrome caused by overstimulation of serotonin receptors. The syndrome is characterized by a classic clinical triad consisting of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities. The clinical presentation is highly variable, and the severity ranges from mild to life-threatening.¹⁻³ The incidence and prevalence of serotonin syndrome has not been well defined.³ Serotonin syndrome may be underreported because mild cases are often overlooked due to nonspecific symptoms. In addition, lack of physician awareness of drug-drug interactions, signs and symptoms, and differential diagnoses may result in underdiagnosis or misdiagnosis.¹⁻³

What causes it?

Serotonin syndrome is usually a consequence of a drug-drug interaction between 2 or more serotonergic agents.⁴ Serotonin syndrome may result following medication

Dr. Zick is a PGY-2 Psychiatric Pharmacy Resident, Chillicothe VA Medical Center, Chillicothe, Ohio. Dr. Rettey is a PGY-2 Psychiatric Pharmacy Resident, Chillicothe VA Medical Center, Chillicothe, Ohio. Dr. Cunningham is Psychiatrist, Community Health Network, Indianapolis, Indiana. Dr. Thomas is Director, PGY-1 and PGY-2 Residency Programs, Clinical Pharmacy Specialist in Psychiatry, Chillicothe Veterans Affairs Medical Center, Clinical Associate Professor of Pharmacology, Ohio University College of Osteopathic Medicine, Chillicothe, Ohio.

Disclosures

This material is the result of work supported with resources and the use of facilities at the Chillicothe Veterans Affairs Medical Center in Chillicothe, Ohio. The authors report no financial relationships with any company whose products are mentioned in this article, or with manufacturers of competing products. The content of this article does not represent the view of the Department of Veteran's Affairs of the US Government.

Practice Points

- **Recognize the clinical manifestations of serotonin syndrome**, which may include agitation, diaphoresis, hyperthermia, hyperreflexia, and clonus.
- **Act quickly and provide supportive care** for patients whom you suspect are experiencing serotonin syndrome.
- Practice safe prescribing and **minimize concomitant use of multiple serotonergic agents.**

Savvy Psychopharmacology is produced in partnership with the College of Psychiatric and Neurologic Pharmacists
cpnp.org
mhc.cpnp.org (journal)



Table 1

Medications associated with serotonin syndrome

Class	Medication(s)	Mechanism of action
Antidepressants	Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants	Serotonin reuptake inhibition
	Monoamine oxidase inhibitors	Serotonin metabolism inhibition
	Trazodone	Serotonin reuptake inhibition, serotonin receptor agonism
	Mirtazapine	Serotonin receptor agonism
Triptans	Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan	Serotonin receptor agonism
Anxiolytics	Buspirone	Serotonin receptor agonism
Antiemetics	Ondansetron, granisetron, metoclopramide	Serotonin reuptake inhibition
Herbal supplements	St. John's wort	Serotonin metabolism inhibition, serotonin reuptake inhibition
Opioids	Buprenorphine, methadone, meperidine, tapentadol, tramadol	Serotonin reuptake inhibition
Anticonvulsants	Carbamazepine, valproic acid	Serotonin receptor agonism
Illicit substances	3,4-methylenedioxymethamphetamine, methamphetamine, cocaine	Increased release of serotonin

Source: References 2-5

misuse, overdose, initiation of a serotonergic agent, or increase in the dose of a currently prescribed serotonergic agent.^{3,4} In addition to medication classes and specific agents, *Table 1*²⁻⁵ lists the drug mechanisms associated with serotonin syndrome:

- inhibition of serotonin reuptake
- inhibition of serotonin metabolism
- increased serotonin synthesis
- agonism of the serotonin receptor.

The amount of serotonergic activity most likely to cause serotonin syndrome is unclear.⁴

Pathophysiology. Serotonin, also known as 5-hydroxytryptamine (5-HT), is a metabolite of the amino acid tryptophan. This neurotransmitter is located in both the CNS and the periphery. Regulation of the serotonergic system begins in the presynaptic neurons with decarboxylation and hydroxylation of tryptophan resulting in serotonin synthesis. Once serotonin is produced, it is released into the synaptic cleft, where it binds to serotonin receptors.^{1,4,5} After receptor binding, serotonin reuptake occurs in the presynaptic

neurons, where it can be metabolized by the monoamine oxidase enzyme. Finally, the metabolites are excreted in the urine. Serotonin syndrome results when this regulatory system is disrupted due to hyperstimulation of the postsynaptic serotonin receptors, mainly via agonism of the 5-HT_{2A} and 5-HT_{1A} receptors.^{1,4,5}

A nonspecific presentation

Unfortunately, many of the symptoms of serotonin syndrome are nonspecific, and the severity varies among patients.^{2,3} The onset of symptoms usually occurs within 6 to 8 hours after ingestion of a serotonergic agent.⁵ It is important to immediately recognize the symptoms (*Table 2*,²⁻⁵ page 40) and formulate a differential diagnosis because sudden progression of symptoms is common and may lead to life-threatening circumstances.^{1,3}

In mild cases of serotonin syndrome, patients may have a low-grade fever or be afebrile. Hyperthermia tends to be present in moderate and severe cases, with temperatures >41°C (105.8°F) during life-threatening

Clinical Point

Many of the symptoms of serotonin syndrome are nonspecific, and the severity varies from mild to life-threatening



Discuss this article at
www.facebook.com/MDEdgePsychiatry

Table 2

Clinical presentation of serotonin syndrome

Altered mental status	Autonomic dysfunction	Neuromuscular abnormalities	Serious complications
Agitation	Hypertension	Tremor	Rhabdomyolysis
Confusion	Tachycardia	Clonus	Myoglobinuria
Anxiety	Diaphoresis	Hyperreflexia	Metabolic acidosis
Restlessness	Hyperthermia	Muscle rigidity	Renal failure
Excitement	Nausea	Akathisia	Respiratory failure
Delirium	Vomiting		Seizures
Coma	Diarrhea		Death
	Mydriasis		

Source: References 2-5

Clinical Point

First review the patient's medication history, specifically taking into account any recent exposure to serotonergic agents

cases. Diaphoresis and tachycardia may be present regardless of severity. Additional autonomic irregularities include hypertension, tachypnea, nausea, vomiting, diarrhea, and hyperactive bowel sounds. In terms of neuromuscular abnormalities, hyperreflexia is a primary concern, as well as myoclonus. As the severity progresses to life-threatening, the clonus may convert from inducible to spontaneous and slow, continuous lateral eye movements may be present. Additional neuromuscular symptoms include tremor, akathisia, and muscle rigidity.^{1,3-5}

Common mental status changes during mild cases include restlessness and anxiety. Abnormal mentation during moderate cases may present as increased hypervigilance and agitation, and this may advance to delirium or coma in severe cases. As the severity intensifies, the risk of developing additional physiological complications also increases. Rhabdomyolysis may occur due to muscle damage and myoglobinuria secondary to hyperreflexia, myoclonus, hypertonicity, and muscle rigidity. Muscle breakdown may then progress to further complications, such as renal failure. In rare instances, serotonin syndrome can result in seizures or death.^{1,3-5}

Medication history tips off the diagnosis

The first step in diagnosing serotonin syndrome is to conduct a thorough review of

the patient's medication history, specifically taking into account any recent exposure to serotonergic agents.^{3,5} It is important to ask about prescription medications as well as over-the-counter products, herbal supplements, and illicit substances.^{1,4} When reviewing the medication history, investigate whether there may have been a recent change in therapy with serotonergic agents. Also, determine when the patient's symptoms began in relation to exposure to serotonergic agents.⁴

After the medication review, conduct a thorough physical and neurologic examination to identify current symptoms and severity.^{1,3} No specific laboratory test is available to definitively confirm the diagnosis of serotonin syndrome.^{1,4} Monitoring of serum serotonin is not recommended because the levels do not correlate with symptom severity.³ The recommended diagnostic tool is the Hunter Serotonin Toxicity Criteria (*Figure, page 41*).^{3,4} Historically, the Sternbach's Diagnostic Criteria for serotonin syndrome were used for diagnosis; however, the Hunter Serotonin Toxicity Criteria are more sensitive (96% vs 75%) and more specific (97% vs 84%) than the Sternbach's Diagnostic Criteria for serotonin syndrome.^{1,3-5}

In addition to using the proper diagnostic tool, conduct a differential diagnosis to rule out other drug-induced syndromes, such as anticholinergic toxidrome, neuroleptic malignant syndrome, or malignant

hyperthermia.^{1,3,5} Autonomic instability, including hypertension, tachycardia, tachypnea, and hyperthermia, may be present in all of the aforementioned drug-induced syndromes.¹ As a result, the clinician must monitor for other symptoms that may differentiate the disease states to establish a clear diagnosis.

Discontinue agents, offer supportive care

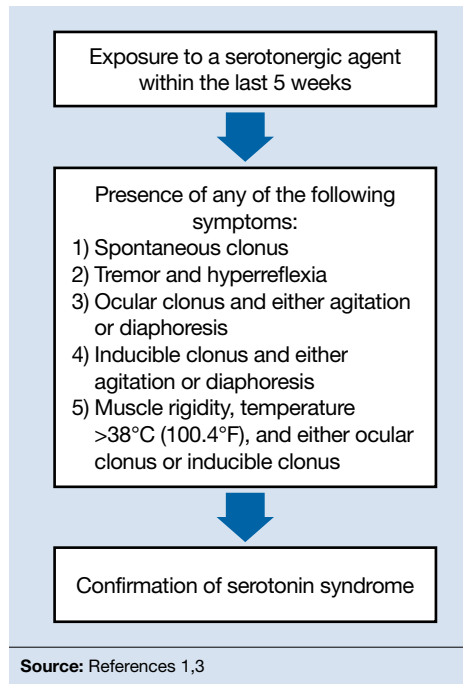
There are no official published guidelines for managing serotonin syndrome.⁵ Regardless of the severity of a patient's presentation, all serotonergic agents should be discontinued immediately. In addition, supportive care should be initiated for symptom management. Intravenous fluid replacement is recommended for hydration and to treat hyperthermia. External cooling may also be warranted to reduce body temperatures. Vital signs should be stabilized with appropriate pharmacotherapy.^{1,3-5}

Benzodiazepines are considered a mainstay for relief of agitation during serotonin syndrome of any severity. In life-threatening cases—which are characterized by hyperthermia $>41^{\circ}\text{C}$ (105.8°F)—sedation, paralysis, and intubation may be necessary to maintain the airway, breathing, and circulation.^{1,3-5} Because treatment of hyperthermia requires elimination of hyperreflexia, paralysis is recommended.¹ Nondepolarizing neuromuscular blocking agents, such as vecuronium, are preferred over depolarizing agents due to their decreased potential for rhabdomyolysis.^{1,3}

Cyproheptadine, a histamine-1 receptor antagonist and a 5-HT_{2A} receptor antagonist, is recommended for off-label treatment of serotonin syndrome to help decrease the intensity of symptoms. This should be initiated as a single dose of 12 mg followed by 2 mg every 2 hours until symptoms improve.^{1,3,5} After stabilization, a maintenance dose of 8 mg every 6 hours is recommended. Doses should not exceed the maximum recommended dose of 0.5 mg/kg/d.^{1,3,6} The most common adverse reactions associated

Figure

Hunter Serotonin Toxicity Criteria



with cyproheptadine are sedation and anticholinergic adverse effects.^{1,4,6}

Antipsychotics, such as olanzapine and chlorpromazine, have been considered treatment alternatives due to their associated 5-HT_{2A} receptor antagonism. However, there is limited data supporting such use.^{1,4} Antipsychotics should be used with caution because neuroleptic malignant syndrome may be mistaken for serotonin syndrome. Use of antipyretics is not recommended for treating fever and hyperthermia because the increase in body temperature is secondary to excessive muscle activity rather than dysfunction of the hypothalamic temperature set point.^{1,3,5} Physical restraints are also not recommended because their use may provoke further hyperthermia and increase the risk of rhabdomyolysis.^{3,5}

Ultimately, the duration of treatment will be influenced by the pharmacokinetics of the serotonergic agents that induced the serotonin syndrome. Following resolution, retrial of the offending serotonergic agents

Clinical Point

Regardless of the severity of a patient's presentation, all serotonergic agents should be discontinued immediately

Clinical Point

Patients with multiple comorbidities that result in treatment with multiple serotonergic agents are at highest risk

Related Resource

- Turner AH, Kim JJ, McCarron RM. Differentiating serotonin syndrome and neuroleptic malignant syndrome. *Current Psychiatry*. 2019;18(2):30-36.

Drug Brand Names

Almotriptan • Axert	Metoclopramide • Reglan
Buprenorphine • Subutex	Mirtazapine • Remeron
Bupropion • Wellbutrin, Zyban	Naratriptan • Amerge
Buspirone • BuSpar	Olanzapine • Zyprexa
Carbamazepine • Carbatrol, Tegretol	Ondansetron • Zofran
Chlorpromazine • Thorazine	Rizatriptan • Maxalt
Cyproheptadine • Periactin	Sertraline • Zoloft
Eletriptan • Relpax	Sumatriptan • Imitrex tablets
Frovatriptan • Frova	Tapentadol • Nucynta
Granisetron • Kytril	Tramadol • Conzip
Lisinopril • Prinivil, Zestril	Trazodone • Desyrel, Olepro
Meperidine • Demerol	Valproic acid • Depakene, Depakote
Methadone • Dolophine, Methadose	Vecuronium • Norcuron
	Zolmitriptan • Zomig

should be carefully assessed. A retriage should only be considered after an adequate wash-out period has been observed, and clinicians should consider utilizing lower doses.^{2,5}

Take steps for prevention

Patients at highest risk of developing serotonin syndrome are those who have multiple comorbidities that result in treatment with multiple serotonergic agents.³ Clinicians and patients alike need to be educated about the signs and symptoms of serotonin syndrome to promote early recognition. Also consider modifying your prescribing practices to minimize the use of multiple serotonergic agents. When switching between serotonergic agents, institute safe washout periods. Encourage patients to adhere to their prescribed medication regimens. Using electronic ordering systems can help detect drug–drug interactions.^{1,3} Prophylaxis with cyproheptadine may be considered in high-risk patients; however, no clinical trials have been conducted to evaluate using cyproheptadine to prevent serotonin syndrome.⁷

CASE CONTINUED

Upon further assessment in urgent care, Mr. S is found to have muscle rigidity in addition to ocular clonus and a temperature >38°C (100.4°F). Because Mr. S's symptoms coincide with a recent increase of sertraline and increased use of both trazodone and sumatriptan, he meets Hunter Serotonin Toxicity Criteria. Therefore, his symptoms are likely related to excessive increase in serotonergic activity. Mr. S is admitted to the hospital for closer monitoring, and his sertraline, trazodone, and sumatriptan are held. He receives IV fluids for several days as well as cyproheptadine, 8 mg every 6 hours after stabilization, until his symptoms resolve. On Day 4, Mr. S no longer experiences diarrhea and internal restlessness. His vital signs return to normal, and as a result of symptom resolution, he is discharged from the hospital. The treatment team discusses changing his medication regimen to avoid multiple serotonergic agents. Mr. S is switched from sertraline to bupropion XL, 150 mg/d. Sumatriptan, 100 mg/d as needed, is continued for acute migraine treatment. Trazodone is discontinued and replaced with melatonin, 3 mg/d. The team also counsels Mr. S on the importance of proper adherence to his medication regimen. He is advised to return to the clinic in 2 weeks for reassessment of safety and efficacy.

References

1. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352(11):1112-1120.
2. Beakley BD, Kaye AM, Kaye AD. Tramadol, pharmacology, side effects, and serotonin syndrome: a review. *Pain Physician*. 2015;18(4):395-400.
3. Wang RZ, Vashistha V, Kaur S, et al. Serotonin syndrome: preventing, recognizing, and treating it. *Cleve Clin J Med*. 2016;83(11):810-817.
4. Bartlett D. Drug-induced serotonin syndrome. *Crit Care Nurse*. 2017;37(1):49-54.
5. Frank C. Recognition and treatment of serotonin syndrome. *Can Fam Physician*. 2008;54(7):988-992.
6. Cyproheptadine hydrochloride tablets [package insert]. Hayward, CA: Impax Generics; 2017.
7. Deardorff OG, Khan T, Kulkarni G, et al. Serotonin syndrome: prophylactic treatment with cyproheptadine. *Prim Care Companion CNS Disord*. 2016;18(4). doi: 10.4088/PCC.16br01966.