

Serotonin syndrome: Unmasking the symptoms

Serotonin syndrome presents a variety of symptoms that can be difficult to diagnose. Use this information to help decipher diagnostic differentials.

By Angela Saathoff, RN, FNP-C, DNP

A 65-year-old male, Mr. R, walks to the lobby of a retail clinic during the height of the COVID-19 pandemic. Mr. R states that he would like a COVID-19 test. After checking him in, the NP asks about the reason for testing. Mr. R explains that he had a fever of 103° F (39.4° C) last night and is in town for a family celebration. The family won't let him attend until he presents a negative COVID-19 test. Mr. R said that the fever resolved last night after he smoked cannabis and took 2 mg clonazepam. Past medical history and current medications include clonazepam for anxiety, cariprazine for bipolar I disorder (manic/mixed), and escitalopram for major depressive disorder. Mr. R described his symptoms of fever, muscle spasms, eye twitching, nausea, vomiting, diarrhea, and reported shivering with goosebumps. His wife says that he's been more irritable than usual. Symptoms began a couple of days after Mr. R's psychologist increased his cariprazine dose from 1.5 mg to 3 mg. Vital signs in the clinic were: temperature 99.8° F (37.7° C), pulse 102, and BP 155/79. The patient tested negative for COVID-19.

With such a variety of symptoms, there are numerous diagnoses in the differential. However, nurses must consider the most severe life-threatening conditions first, because if not quickly recognized and treated, the patient may have a fatal outcome. This article discusses the roles of serotonin, the use of serotonergic agents, the diagnosis of serotonin syndrome, and its diagnostic differentials. Keep in mind that serotonin syndrome isn't a diagnosis that's restricted to the ED. The nurse should also be prepared to encounter patients with mild symptoms in the outpatient setting.

What is serotonin and why is it important?

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a neurotransmitter compound that's found nearly everywhere in the body. In the correct concentrations, it's essential for human life.



Did you know?

Foods that contain tryptophan¹

Tryptophan is an essential amino acid that can be found in many foods such as: milk, canned tuna and other fish, turkey, chicken, red meat, pork, tofu, beans, nuts, eggs, oats, aged cheese, bread, chocolate, bananas, and apples.

The compound is composed of tryptophan, one of the nine essential amino acids that the body can't make. Therefore, for the body to produce serotonin, there must be sufficient dietary consumption of

tryptophan (see *Did you know? Foods that contain tryptophan*).¹

Serotonin's role in the body

In the correct concentrations, serotonin is essential for human life because it's necessary for many body functions. In the central nervous system, serotonin controls attention, behavior, cognition, memory, and thermoregulation. The role of serotonin in the peripheral nervous system includes the regulation of bronchoconstriction, vasoconstriction, uterine contraction, and gastrointestinal motility.^{1,2} Serotonin is also found in blood platelets and plays a role in blood clotting by causing vasoconstriction. As serotonin affects so many bodily functions, there are numerous classes of medications that alter serotonin levels.

Serotonin syndrome

Serotonin syndrome occurs when there's an accumulation of excess serotonin within the central and peripheral nervous systems. This is a potentially life-threatening condition most attributed to a medication reaction, either from increasing the dose of a serotonergic agent or from adding another medication that has a net effect of increasing serotonin levels.^{2,3} The patient may report a triad of symptoms ranging in severity, including alterations in mental status, neuromuscular abnormalities, and autonomic hyperactivity. Symptoms of mental status alterations can include agitation, anxiety, disorientation,

restlessness, excitement, and/or agitated delirium.¹ Symptoms of neuromuscular abnormalities include tremors, clonus, hyperreflexia, muscle rigidity, and/or bilateral Babinski signs. Autonomic manifestations may include elevated BP, tachycardia, tachypnea, hyperthermia, mydriasis, diaphoresis, dry mucus membranes, flushed skin, shivering, vomiting, diarrhea, hyperactive bowel sounds, and/or arrhythmia.^{1,2}

Differential

Given the wide range of symptoms associated with serotonin syndrome, the NP must also consider other conditions such as neuroleptic malignant syndrome, anticholinergic toxicity, malignant hyperthermia, sympathomimetic toxicity, thyroid storm, cannabis toxicity, and/or meningitis/encephalitis.¹

Neuroleptic malignant syndrome (NMS) is a potentially life-threatening condition with symptoms that resemble serotonin syndrome and is often associated with the use of first-generation antipsychotic agents such as haloperidol and thioridazine.⁴ Notably, a clinical manifestation of NMS is a profound elevation of creatine kinase.⁴ Also, whereas serotonin syndrome usually develops within 24 hours of serotonergic agent exposure, NMS takes days to weeks for symptoms to develop.¹ In addition, unlike serotonin syndrome, myoclonus and hyperreflexia are uncommon clinical symptoms.^{2,4}

Anticholinergic toxicity. Acetylcholine functions to regulate hormone secretions, blood pressure, and contractions of the heart. The word anticholinergic means that the transmission of the neurotransmitter acetylcholine is inhibited. There are over 600 compounds known to have anticholinergic properties and, unsurprisingly, anticholinergic toxicity occurs frequently.⁵ The symptoms vary with the degree of toxicity, and onset is dependent on the half-life of the causative agent.⁶ Symptoms of anticholinergic poisoning

Consider this

Ms. A is a 22-year-old female who presents to her primary medical provider with a past medical history of major depression and generalized anxiety disorder. She reports increased feelings of depression over the last 3 months despite daily treatment of fluoxetine 20 mg. At her visit, the fluoxetine is discontinued and replaced with another SSRI, paroxetine 10 mg daily. Hydroxyzine 50 mg is added as needed twice a day for breakthrough anxiety. Later that same week, Ms. A calls her provider with symptoms of increased anxiety with depression, insomnia, and constant shaking. Her provider increases paroxetine to 30 mg daily. On follow-up 1 month later, Ms. A reports burning all over with hot flashes, fatigue, generalized weakness, body aches, and continued shaking. A slight fever of 101.2° F (38.4° C) and hyperreflexia are noted on clinical examination. Blood cultures are negative. Leukocytes are within normal limits. Using Hunter Toxicity Criteria, Ms. A is diagnosed with serotonin syndrome. Her provider discontinues paroxetine, and the clinical symptoms resolve. The provider refers the patient to a psychologist to further treat anxiety and depression.

include an altered mental status, agitation, hyperthermia, and dilated pupils, as well as a “drying” effect on the body with dry mucus membranes, urinary retention, and decreased bowel sounds. Note that with anticholinergic toxicity, reflexes and muscular tone are normal.¹ Physostigmine salicylate is the antidote for anticholinergic toxicity.⁷

Malignant hyperthermia is associated with symptoms of hyperthermia, muscle rigidity, and autonomic dysfunction.¹ Most often, malignant hyperthermia occurs when a patient with a specific autosomal dominant trait is exposed to a volatile anesthetic or a muscle relaxant such as succinylcholine.⁸

Sympathomimetic toxicity can occur from a high-dose acute exposure to agents that stimulate the sympathetic nervous system, such as cocaine, amphetamines, ketamine, 3,4-methylenedioxymethamphetamine, synthetic cannabinoids, and/or 3,4-methylenedioxypyrovalerone.⁹ Symptoms of sympathomimetic toxicity make up the mnemonic “MATHS” with mydriasis, agitation, arrhythmia, angina, tachycardia, hypertension, hyperthermia, seizures, and sweating.⁹ However, patients with serotonin syndrome will have some symptoms of neuromuscular activation, whereas patients with sympathomimetic toxicity won’t.¹

Thyroid storm symptoms often overlap with the clinical presentation of serotonin syndrome.¹⁰ However, patients presenting with thyroid storm usually have a history of thyroid disease.¹ It’s important to ask for patient history of thyroid surgery, thyroid trauma, hyperthyroidism, Graves’ disease, and/or amiodarone use.¹⁰ Note that if symptoms are due to thyroid storm, patient will have high T4/T3 and low TSH.

Cannabis toxicity should also be considered as a differential, especially with the increasing availability in the US. Patients have exhibited symptoms of agitation, lower extremity clonus, hyperreflexes, tachycardia, and elevated BP, which are also symptoms of serotonin syndrome. Reports note the use of “dabbing” with concentrated tetrahydrocannabinol.¹¹ Also, cannabinoid receptor agonists have demonstrated the activation of 5-HT receptors and tetrahydrocannabinol is known to decrease the reuptake of serotonin.¹¹

Meningitis/encephalitis is a central nervous system infection that can also produce symptoms like serotonin syndrome. Patients with meningitis may report headaches, fever, nausea, and vomiting.¹² The clinical presentation of encephalitis may include a wide range of altered mental status, from mild agitation to complete unresponsiveness along with hyperreflexes.¹²

Deepen your knowledge: MAOIs¹⁷

Medications in the MAOI class	Foods to avoid while taking MAOIs	Adverse reactions associated with MAOIs
Isocarboxazid, phenelzine, selegiline, and tranylcypromine	aged cheese, aged meat, aged fish, overripe fruits and vegetables, draft beer, any fermented food products, concentrated yeast extract, soy sauce, tofu, and any foods containing tyramine	hypertensive crisis, orthostatic hypotension, serotonin syndrome, blurred vision, constipation, dry mouth, headache, insomnia, liver enzyme elevation, myoclonus, nausea, paresthesia, peripheral edema, sedation, sexual dysfunction, urinary hesitancy, and weight gain

Serotonergic agents

These are any compounds that alter the effects of serotonin within the body. Any medication that increases the concentration of serotonin can contribute to the development of serotonin syndrome.¹ Of note, in rare cases, serotonin syndrome has been associated with monotherapy of a serotonergic agent.¹³ The medications discussed in this article are the most documented contributors to serotonin syndrome. However, this article doesn't contain a comprehensive collection of all known compounds that can cause serotonin syndrome.

Selective serotonin reuptake inhibitors (SSRIs) are among the first-line medications used to treat depression, largely due to their efficacy and tolerability.¹³ The SSRI class includes citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. As the name implies, these medications selectively inhibit reuptake of serotonin, which allow for more serotonin in the synaptic gap and enables the post synaptic receptors to become more sensitive to the remaining serotonin. SSRIs are the most implicated class of medications linked to serotonin syndrome.¹ However, cases of

serotonin syndrome associated with SSRI use often involve an additional serotonergic agent.¹³

Serotonin-norepinephrine reuptake inhibitors (SNRIs) inhibit the reabsorption of serotonin and norepinephrine in the central nervous system, resulting in an elevated mood.¹⁴ SNRIs are indicated for the treatment of unipolar major depression and anxiety disorders. They include desvenlafaxine, duloxetine, levomilnacipran, milnacipran, and venlafaxine. SNRI overdose, either intentional or unintentional, can result in serotonin syndrome.^{14,15}

Tricyclic antidepressants are used to treat depression and other psychiatric disorders, including posttraumatic stress disorder, bulimia, smoking cessation, panic attacks, and anxiety.¹⁶ Tricyclic antidepressants inhibit the reuptake of serotonin and norepinephrine, which increases these neurotransmitters in the synaptic cleft. Fatal overdoses of tricyclic antidepressants may occur with as little as 10 times the daily dose and are usually associated with prolongation of the QT interval.¹⁶ However, both anticholinergic toxicity and serotonin syndrome can also manifest from an overdose of tricyclic

antidepressants. NPs can differentiate them by the presence of diaphoresis in serotonin syndrome and the dry skin of an anticholinergic response.^{6,7} Medications in this class include amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine, as well as the tetracyclic antidepressant maprotiline.

Monoamine oxidase inhibitors (MAOIs) work by decreasing the effectiveness of monoamine oxidase (MAO). The MAO enzyme breaks down neurotransmitters like norepinephrine, dopamine, and serotonin.¹⁷ Thus, if the enzyme is less effective, there will be higher concentrations of these neurotransmitters. MAOIs include isocarboxazid, phenelzine, selegiline, and tranylcypromine and are effective in the treatment of depression. However, due to multiple food and drug interactions, as well as a plethora of adverse reactions, this class is reserved for patients who are treatment-resistant to other antidepressant classes.¹⁷ (See *Deepen your knowledge: MAOIs*.) Note that episodes of serotonin syndrome due to MAOI drug-to-drug interactions are usually more complicated and are more likely to lead to fatal adverse outcomes.^{1,17}

Serotonin modulators such as nefazodone, trazodone, vilazodone, and vortioxetine work by inhibiting the reuptake of postsynaptic serotonin and have little effect on norepinephrine.¹⁸ These drugs may elevate serotonin levels, potentially resulting in serotonin syndrome when combined with other medications that increase the availability of serotonin within the central nervous system.¹⁸

Triptans include almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan and are commonly prescribed for migraine therapy.¹⁹ There are several mechanisms of actions for this medication class. However, they activate the 5-HT receptors in

Hunter Toxicity Criteria

To meet Hunter Toxicity Criteria, a patient must have the presence of a serotonergic agent and meet **one** of the following conditions:

- Spontaneous clonus
- Inducible clonus **plus** agitation or diaphoresis
- Ocular clonus **plus** agitation or diaphoresis
- Tremor **plus** hyperreflexia
- Hypertonia **plus** temperature above 100° F (37.8° C) **plus** ocular clonus or inducible clonus

the descending brainstem which increases the neurotransmission of serotonin.¹⁹

Psychoactive drugs such as lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine, also known as “Molly” or “ecstasy,” and 5-MeO-DIPT, also known as “Foxy Methoxy,” are recognized agents that have the potential to cause or contribute to serotonin syndrome.^{20,21}

Diagnosis

Unfortunately, serotonin syndrome must be clinically diagnosed because there’s not a lab test to confirm the diagnosis. There exists a test for serum serotonin concentration; however, the concentration levels don’t correspond with clinical findings.^{1,3} Therefore, a detailed patient history, including dosage changes of all medications, including over-the-counter medications, dietary supplements, and the use of recreational or illicit drugs, is necessary. The history should also include details of each of the patient’s symptoms, including symptom onset, severity, and rate of change. The spectrum of symptom severity can range from extremely mild to very severe, including death. It’s also necessary to inquire if the exposure was intentional and if the increased levels of serotonin are the result of an attempt to self-harm.¹ Note that the Hunter Toxicity Criteria, Sternbach Criteria, and/or Radomski Criteria may provide some help in diagnosing serotonin syndrome.³ (See *Hunter Toxicity Criteria*.)

Did you know?

MAOIs were discovered in the 1950s and was the first class of medication used to treat depression.

Treatment

Treatment of serotonin syndrome is largely based on the severity of the symptoms. Consult with a medical toxicologist in moderate to severe cases. The initial treatment is a decrease or discontinuation of the causing or contributing serotonergic agents. Here, the NP must consider the patient's underlying conditions, treatment of those conditions, and medication half-lives. Benzodiazepines may be titrated to decrease symptoms of agitation, tremors, tachycardia, and elevated BP. Implement supportive care such as I.V. fluids, oxygen, sedation, and continuous cardiac monitoring as needed. In cases of extreme hyperthermia, rapid sequence intubation with sedation and paralytic may be needed. Note that antipyretic agents won't lower the patient's temperature because these agents don't affect the increase in muscle activity which is what's causing the hyperthermia.¹

Cyproheptadine is considered the antidote to serotonin because it has antagonistic properties on the 5-HT receptors. However, it's only indicated when benzodiazepines and supportive care aren't effective. Monitoring is required with cyproheptadine administration because sedation and hypotension may occur.¹

Prognosis

Serotonin syndrome is a potentially life-threatening condition that, if left untreated, may result in death. However, if the syndrome is recognized and treated appropriately, the symptoms usually resolve within 24 hours of discontinuing the causing agent.¹

Did Mr. R have serotonin syndrome?

It's difficult to say. Indeed, a mild case of serotonin syndrome should be included in the differential. The following evidence supports the diagnosis of serotonin syndrome:

- Mr. R was taking escitalopram, an SSRI and a known contributor to serotonin syndrome.
- He had a recent dose increase of cariprazine, an antipsychotic second-generation medication that partially agonizes the serotonin 5-HT_{1A} receptor but is an antagonist of the serotonin 5-HT_{2A} receptor. This could cause a mild increase in serotonin.
- The patient's reported muscle spasms and eye twitches could have represented a clonus. This, combined with a fever and agitation, meets the Hunter Toxicity Criteria for a diagnosis of serotonin syndrome. However, the patient's partial symptom relief and overall mild symptoms could be due to the use of clonazepam. Clonazepam is a benzodiazepine that's also used to treat serotonin syndrome.

The NP referred the patient to the local ED, where he was evaluated and discharged home the same day with instructions to decrease his cariprazine to 1.5 mg and follow up with his psychologist within a week. ■

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