Serotonin Syndrome

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Reviewed October, 2019, Expires October, 2021
Provider Information and Specifics available on our Website

By Cynthia R. Bascara, APN-C, MSN, CCRN

Course Objectives: At the completion of the course, the health care provider will be able to:

- State the definition and causes of Serotonin Syndrome
- List the clinical manifestations of Serotonin Syndrome
- Discuss how Serotonin Syndrome can be diagnosed
- Discuss the management and prevention of Serotonin Syndrome
- Discuss some differential diagnoses associated with Serotonin Syndrome
- Discuss the pediatric considerations of Serotonin Syndrome

Definition

Serotonin Syndrome is a potentially life-threatening condition manifested by increased serotonergic activity in the central nervous system (CNS) associated with therapeutic medication use such as selective serotonin reuptake inhibitor (SSRI), inadvertent interactions between drugs, intentional self-poisoning and increasing the dose of a serotonergic drug in individuals who are particularly sensitive to serotonin. Serotonin Syndrome is not an idiosyncratic drug reaction but a predictable consequence of excess serotonergic activity at CNS and peripheral serotonin receptors. For this reason, some experts strongly prefer the terms serotonin toxicity or serotonin toxidrome because these more accurately reflect the fact that it is a form of poisoning. Serotonin Syndrome may also be called serotonin sickness, serotonin storm, hyperserotonemia, or serotonergic syndrome. Serotonin Syndrome can be benign or lethal.

Epidemiology

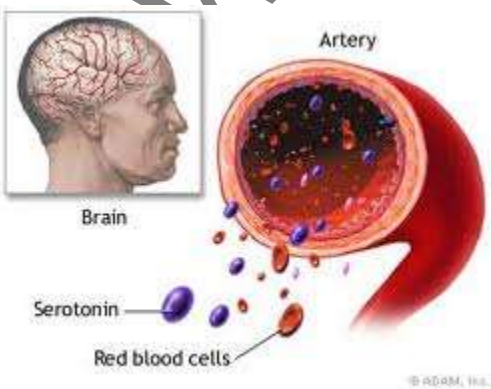
Serotonin Syndrome can occur in all age groups. There is increased incidence related to increased use of SSRI. In 2004, the Toxic Exposure

Surveillance System identified 8,187 moderate or major outcomes out of 48, 204 SSRI exposures and 103 deaths related to Serotonin Syndrome. Around 14 to 16 percent of persons who overdose on SSRIs are thought to develop Serotonin Syndrome.

The most widely recognized example of Serotonin Syndrome was the death of Libby Zion in 1984 at age 18. She had an ongoing history of depression and came to a Manhattan hospital with fever, agitation, "strange jerky motions" of her body. She also seemed disoriented at times. The emergency room physicians were unable to diagnose her condition definitively, but admitted her for hydration and observation. Her death was caused by a combination of pethidine (or meperidine (Demerol) and phenelzine. The physician who prescribed the pethidine was a medical intern. The case had an impact on graduate medical education and residency work hours. Limits were set on working hours for medical post graduates, commonly referred to as interns or residents, in hospital training programs, and there is a new requirement for a closer senior physician supervision.

Pharmacology and Cellular Toxicology

Serotonin can be found in central nervous system , peripheral nervous system and platelets. In central nervous system, serotonin modulates attention, behavior, thermoregulation, control of appetite, sleep, memory and learning and depression. In peripheral nervous system, serotonin is Involved in regulating GI motility, vasoconstriction, uterine contraction and bronchoconstriction . Serotonin promotes platelet aggregation. Stimulation of the postsynaptic 5-HT1A and 5-HT2A receptors has been implicated in serotonin syndrome but no single receptor is solely responsible.



Serotonergic drugs/agents

CLASS	DRUGS
Antidepressants	MAOIs (e.g. phenelzine-Nardil), SSRIs (e.g. Zoloft, Prozac, Paxil); TCAs (e.g. Elavil, Tofranil); SNRIs (e.g. Effexor, Cymbalta), bupropion, nefazodone, trazodone
Opiods	tramadol, pethidine, fentanyl,buprenorphine, pentazocine, oxycodone, hydrocodone
CNS stimulants	Phentermine, diethylpropion, amphetamine, sibutramine, methylphenidate, methamphetamine, cocaine
5-HT_1 agonists	triptans
Psychedelics	MDMA, MDA, 5-Methoxy-diispropyltryptamine, LSD
Herbs	St. John's wort, Syrian rue, Panax ginseng, Nutmeg, Yohimbe, tryptophan, L-Dopa, valproate, buspirone, lithium, linezolid, dextromethorpan, 5-hydroxytryptophan
OTHERS	Chlorpheniramine, risperidone, loanzapine, ondasetron, granisetron, metoclopramide, ritonavir

Diagnosis

Diagnosis is made solely on clinical grounds through a detailed history and a thorough physical and neurological examination. Serum serotonin concentrations do not correlate with clinical findings. There is no laboratory test that will confirm the diagnosis.

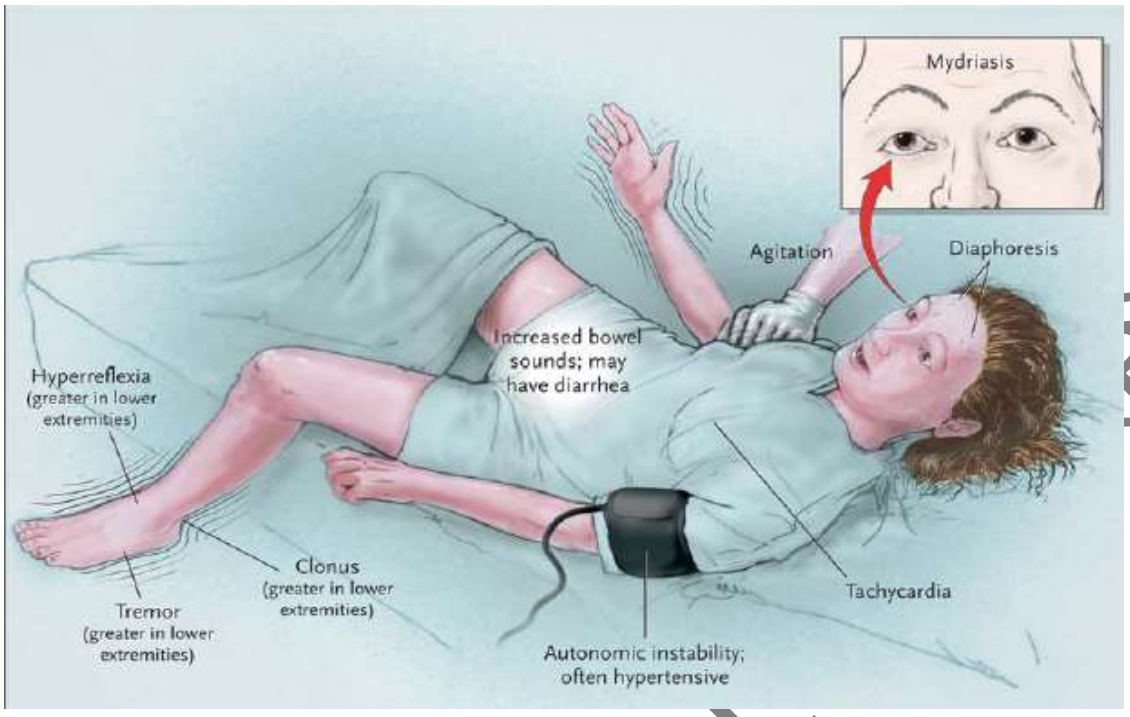
Clinical Features

Serotonin Syndrome encompasses a spectrum of disease where the intensity of clinical findings is thought to reflect the degree of serotonergic activity. Mental status changes include anxiety, agitated delirium, restlessness, disorientation and patient startles easily. Some of the autonomic manifestations include diaphoresis, tachycardia, hyperthermia, hypertension, vomiting and diarrhea. Neuromuscular hyperactivity may manifest as tremors, muscle rigidity which is pronounced in lower extremities, myoclonus and hypereflexia which are commom and bilateral Babinski sign.

Dignostic Criteria (Hunter Criteria): Patient must have taken a serotonergic agent and have

of the following:

- Spontaneous clonus
- Inducible clonus plus agitation or diaphoresis
- Ocular clonus plus agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia
- Temperature above 38ºC (100.4 ºF) plus ocular clonus or inducible clonus



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Differential Diagnosis

Neuroleptic Malignant Syndrome (NMS)	***Serotonin Syndrome***
Develops over days to weeks	Develops over 24 hours
Involves sluggish neuromuscular responses (rigidity, bradyreflexia)	Involves neuromuscular hyperactivity (tremor, hyperreflexia, myoclonus)

Resolution: average nine days	Resolution: usually less than 24 hours

In severe cases of NMS and Serotonin Syndrome , hyperthermia, altered mental status, muscle rigidity, leukocytosis, elevated creatinine phospokinase, elevated hepatic transaminase, and metabolic acidosis can be seen in both conditions. This is the same reason why thorough history and physical examination are important in diagnosing Serotonin Syndrome.

Differential Diagnosis

Anticholinergic Toxicity	***Serotonin Syndrome***
Hyperthermia, agitation,altered mental status, mydriasis, dry mucus membrane, urinary retention, decreased bowel sounds	Hyperthermia, agitation, ocular clonus, tremor, akathisia, deep tendon hyperreflexia, inducible or spontaneous clonus, bilateral Babinski, dilated pupils, dry mucus membranes, increased bowel sounds, flushed skin, diaphoresis
Muscular tone and reflexes are normal	Muscle rigidity

Management

1. Discontinuation of all serotonergic agents.

   Syndrome resolves often within 24 hours of discontinuation. With drugs with long half-lives or active metabolites, the symptoms persist.

In irreversible MAOIs, resolution may take several days. With selective SSRIs, symptoms may last several weeks.

2. Supportive care aimed at normalization of vital signs
   Patient will need oxygen and intravenous fluids for fluid depletion and hyperthermia. Patient is placed on continuous cardiac monitoring. For severe hypertension and tachycardia, short-acting agents like esmolol or nitroprusside may be employed. For hypotension from MAOIs, low doses of direct-acting sympathomimetic amines such as phenyleprine, epinephrine, or norepinephrine may be used. Hyperthermia: > 41°C (105.8ºF) will need immediate sedation, paralysis and endotracheal intubation. Control of hyperthermia involves eliminating excessive muscle activity Effective control of hyperthermia can minimize complications of serotonin syndrome such as seizures, coma, DIC, hypotension, ventricular tachycardia and metabolic acidosis. There is no role for antipyretic for hyperthermia due to Serotonin Syndrome. The increase in temperature is not due to an alteration in the hypothalamic temperature set point, but rather an increase in muscular activity
3. Sedation with benzodiazepines
   Chemical restraint is preferred over physical restraint for agitated patients. Physical restraint can cause isometric muscle contractions which can cause profound lactic acidosis and hyperthermia. Benzodiazepine is used for control of agitation and correction of mild increase in blood pressure and heart rate.
4. Administration of serotonin antagonists
   Cyproheptadine is the recommended antidote. It can only be given orally. Initial dose is 12mg by mouth or crushed through NGT, then 2mg every 2 hours until clinical response seen. Possible effects are sedation which is consistent with the treatment goal and transient hypotension which usually responds to intravenous fluids.
5. Assessment of the need to resume use of causative serotonergic agents after resolution of symptoms

In mild cases, discontinuation of causing agents, supportive care, and sedation with benzodiazepines is generally sufficient. Moderately ill patients require more aggressive treatment of autonomic instability and possibly

treatment with a serotonin antagonist. Hyperthermic patients are critically ill and often require paralysis and endotracheal intubation.

Common management pitfalls include failure to recognize Serotonin Syndrome, misdiagnosis, and failure to understand Serotonin Syndrome's potentially rapid rate of progression. Even if the diagnosis is unclear, the clinician should withhold serotonergic agent when Serotonin Syndrome is suspected.

Consultation with any of the following is necessary once serotonin syndrome occurs to provide assistance with decision making:

- Clinical pharmacologist
- Medical toxicologist
- Poison control center

Prevention

Serotonin Syndrome can be avoided by:

- Applying pharmacologic principles
- Educating clinicians
- Modifying prescription practices
- Avoiding multi-drug regimens

Pediatric Considerations

The pathophysiology, diagnostic criteria, manifestations and management of Serotonin Syndrome in children are similar to that of the adults. Hyperreflexia, clonus, and hyperthermia are also common in children.

Diagnosis of Serotonin Syndrome is even more difficult in children. Children may not be able to communicate vague symptoms. Health care providers may not consider the syndrome a pediatric problem. Adolescents may be reluctant to disclose recreational drug use, which may include serotonergic agents, such as methylenedioxymethamphetamine (MDMA; "Ecstasy") or dextromethorphan.

The basic principles of management are applied to the pediatric populations. Any serotonergic agent should be discontinued. Supportive care is provided with adequate patient sedation and normal vital signs as treatment goals. Standard interventions include oxygen, intravenous fluids, continuous cardiac monitoring. Autonomic instability and hyperthermia require aggressive treatment. Sedation with weight-based doses of benzodiazepines is recommended for the treatment of agitation.

In patients with severe Serotonin Syndrome, serotonergic antagonists can be given. Cyproheptadine may be used in pediatric patients with a dose of 0.25 mg/kg/day divided every six hours. Doses should be titrated to maintain adequate sedation. General dosing is as follows:

- Children younger than two years can be given approximately 0.06 mg/kg per dose every six hours, if needed (not to exceed 0. 25 mg/kg/day).
- Children two to six years can be given 2 mg every six hours, if needed (not to exceed 12 mg/day).
- Children 7 to 14 years can be given 4 mg every six hours, if needed (not to exceed 16 mg/day).

Severe cases of Serotonin Syndrome in pediatric patients require management in intensive care unit. Patients with mild to moderate symptoms require continuous cardiac monitoring and admission for observation. Prognosis is generally favorable if Serotonin Syndrome is recognized early and complications treated appropriately.

There are rare reports of neonates with symptoms resembling Serotonin Syndrome. One small study showed that infants exposed to SSRIs late in pregnancy were at increased risk for adverse CNS effects. The most common findings were restlessness, tremor and rigidity. Myoclonus and hyperreflexia occurred less often. Symptoms appeared to subside quickly without any specific intervention.

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