

# Serotonin Syndrome: Information for Physicians



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**Summary:** Serotonin syndrome (aka serotonin toxicity) is a potentially life-threatening condition caused by excessive serotonergic activity, most commonly due to serotonin medications. Features include autonomic instability, mental status changes, and neuromuscular hyperactivity. In mild cases, treatment involves withdrawal of the causative serotonin agent and supportive care. In moderate to severe cases, hospitalization may be required along with IV fluids, cyproheptadine and lorazepam. Prognosis is good when appropriately recognized and managed.

## Case, Part 1

You are seeing a 16-yo teenager for a same day appointment, accompanied by her mother. She copes with a diagnosis of depression and anxiety, and has done well for many years on a stable dose of sertraline (Zoloft). Recently however, she has been started on erythromycin. About a week after starting erythromycin, she began feeling unwell and having nausea/vomiting and diarrhea. Initially, her mother thought that it was just the flu, but when she began stumbling and being confused, mother became worried and has brought her in to see you...

## Introduction

Serotonin syndrome (aka serotonin toxicity) is a potentially life-threatening condition caused by excessive serotonergic activity, most commonly due to serotonin medications. Features include autonomic instability, mental status changes, and neuromuscular hyperactivity.

## Epidemiology

Data is lacking on the incidence and prevalence of serotonin syndrome. Because many physicians are unaware of serotonin syndrome, it is felt that the majority of cases go unrecognized. Nonetheless, it is felt that the overall number of cases is increasing, due to the increasing use of SSRIs as well as polypharmacy (Boyer, 2005).

## Signs and Symptoms

Symptoms are often described as a triad of:

- Cognitive effects: headache, agitation, hypomania, mental confusion, hallucinations, coma
- Autonomic effects: shivering, sweating, hyperthermia, vasoconstriction, tachycardia, nausea, diarrhea.

- Somatic effects: myoclonus (muscle twitching), hyperreflexia (manifested by clonus), tremor.

## Mnemonic

Consider the SHIVERS mnemonic (Christensen, 2006)

- **S**hivering helps distinguish this from other hyperthermic syndromes
- **H**yperreflexia often seen in mild to moderate cases
- **I**ncreased temperature, likely due to muscular hypertonicity
- **V**itals can be unstable, with tachycardia, tachypnea or labile blood pressure
- **E**ncephalopathy with agitation, delirium, confusion can develop from hyperthermia
- **R**estlessness due to excess serotonin activity
- **S**weating as an autonomic response to excessive serotonin stimulation (as opposed to anticholinergic toxicity which has hot, dry skin)

## Pathophysiology

Serotonin syndrome is mostly iatrogenic, and occurs in situations where medications lead to increased serotonin transmission such as:

- Synergistic medication use (e.g. using more than one serotonin medication)
- Drugs which inhibit breakdown of SSRIs, e.g. drugs that inhibit cytochrome P450 isoenzymes (e.g. erythromycin)
- Exposure to high amounts of a single serotonin medication

Medications that may contribute to Serotonin Syndrome include:

- Amphetamines and derivatives
  - 3,4-methylenedioxymethamphetamine
  - Methylenedioxymetamphetamine (MDMA aka "Ecstasy")
  - Dextroamphetamine
  - Methamphetamine
  - Sibutramine (Meridia)
- Analgesics
  - Cyclobenzaprine (Flexeril)
  - Fentanyl (Duragesic)
  - Meperidine (Demerol)
  - Tramadol (Ultram)
- Antidepressants/mood stabilizers
  - Buspirone (Buspar)
  - Lithium
  - Monoamine oxidase inhibitors (e.g., phenelzine [Nardil])
  - Selective serotonin reuptake inhibitors (e.g., fluoxetine [Prozac])
  - Serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine [Effexor])
  - Serotonin 2A receptor blockers (e.g., trazodone)
  - St. John's wort (*Hypericum perforatum*)
  - Tricyclic antidepressants (e.g., amitriptyline, nortriptyline [Pamelor])
- Antiemetics
  - Metoclopramide (Reglan)
  - Ondansetron (Zofran)
- Antimigraine drugs
  - Carbamazepine (Tegretol)

- Ergot alkaloids
- Triptans
- Valproic acid (Depakene)
- Miscellaneous
  - Cocaine
  - Dextromethorphan
  - Linezolid (Zyvox)
  - L-tryptophan
  - 5-hydroxytryptophan

## History / Interviewing

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The history should include a detailed description of all medications such as:

- Prescribed medications
- Over-the-counter medications
- Recreational drugs
- Dietary supplements.

## Diagnosis

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The Hunter Serotonin Toxicity Criteria are recommended for the diagnosis of serotonin syndrome (with 84% sensitivity and 97% specificity).

To fulfill the Hunter Criteria, a patient must have taken a serotonergic agent and meet at least 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 38°C plus ocular clonus or inducible clonus

## Differential Diagnosis

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- Anticholinergic syndrome
- Malignant hyperthermia
- Neuroleptic malignant syndrome (NMS):
  - Develops days to weeks after taking a dopamine antagonist (i.e. antipsychotic).
- Tetanus
- Overdose of sympathomimetic drugs
- Meningitis
- Encephalitis
- Thyroid storm
- Heat stroke
- Delirium tremens
- Sepsis

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## Physical Exam (Px)

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- General observations
  - Hyperthermia (in over 90% of cases) (Mills, 1997).
  - Shivering
  - Restlessness, agitation, confusion, akathisia (i.e. patient may be pacing)
- Head / Neck
  - Slow, continuous horizontal eye movements (ocular clonus)
  - Pupils dilated
- Vitals
  - Temperature: Hyperthermia
  - Blood pressure: Labile
  - Respiratory rate: Tachypnea
- Neurologic exam
  - Deep tendon hyperreflexia in mild to moderate cases, especially in lower extremities
  - Muscular rigidity in more severe cases
- Dermatologic:
  - Sweating

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## Investigations

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There are no specific laboratory tests for serotonin syndrome; testing is ordered to rule out other diagnoses for example:

- Leukocytosis
- Increased creatine kinase (CK) (elevated in > 90% of all cases)
- Iron deficiency

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## Management: Primary Care Interventions

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### Mild cases

- Symptoms: hyperreflexia, myoclonus in mild cases
- Stop any causative serotonergic drugs
- Supportive care
- Mild cases generally resolve within 24 to 72 hours with conservative therapy and removal of the causative drugs.
- Most patients with mild cases do not require hospital admission.

### Moderate to severe cases

- Symptoms: hypertonicity, hyperthermia, autonomic instability, or progressive cognitive changes)
- Admit to hospital
- Consider
  - IV fluids
  - For agitation / tremor

### Medications;

- Benzodiazepines.
- Chlorpromazine and olanzapine; however, note that these are not routinely used because of the potential for adverse effects and toxicity.

- Cyproheptadine, a serotonin 2A antagonist
- For hyperthermia and increased muscle rigidity in severely ill patients
- Consider neuromuscular paralysis, sedation, and possible intubation.

## Prevention of Serotonin Syndrome

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- Avoid using multiple serotonin medications, e.g. do not use more than one SSRI
- Avoid prescribing an SSRI along with a medication that blocks the metabolism of an SSRI
- Use electronic ordering systems and/or electronic medication databases to check for interactions

## When to Refer

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Serotonin syndrome is a potentially dangerous issue, and thus, close monitoring and follow-up is required. If you suspect, referral your patient to an inpatient ED.

## Case, Part 2

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You are seeing a 16-yo teenager who has been stable for many years on Sertraline. Ever since being started on erythromycin however, she has quickly deteriorated.

You look up Sertraline and Erythromycin, and discover that sertraline is metabolized by CYP3A4, and it turns out that erythromycin inhibits CYP3A4. You wonder about serotonin syndrome, and speak with the psychiatrist on call at your local emergency department. The psychiatrist agrees with your suspicion, and mother brings the patient to the emergency department, where the patient is seen by the emergency physician.

## References

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## About this Document

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