

Serotonin Syndrome

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Objectives

- Define Serotonin Syndrome
- Discuss Epidemiology and Pharmacology
- Understand Clinical Features and Diagnosis
- Highlight Prevention Strategies
- Describe Management of Serotonin Syndrome

What is Serotonin Syndrome (serotonin toxicity)?

- A potentially life-threatening condition associated with increased serotonergic activity in the central nervous system as a result of serotonergic medication use
 - The degree of serotonin buildup affects the severity of symptoms that can occur, including altered mental status, autonomic hyperactivity, and neuromuscular changes
 - Untreated disease can rapidly worsen over 24 hours, emphasizing the importance of accurate prevention, diagnosis, and treatment
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Epidemiology

Serotonin Syndrome

0.09%

Incidence of SS in insured patients exposed to serotonergic medications

0.23%

Disease incidence in patients exposed to serotonergic medications

24.3%

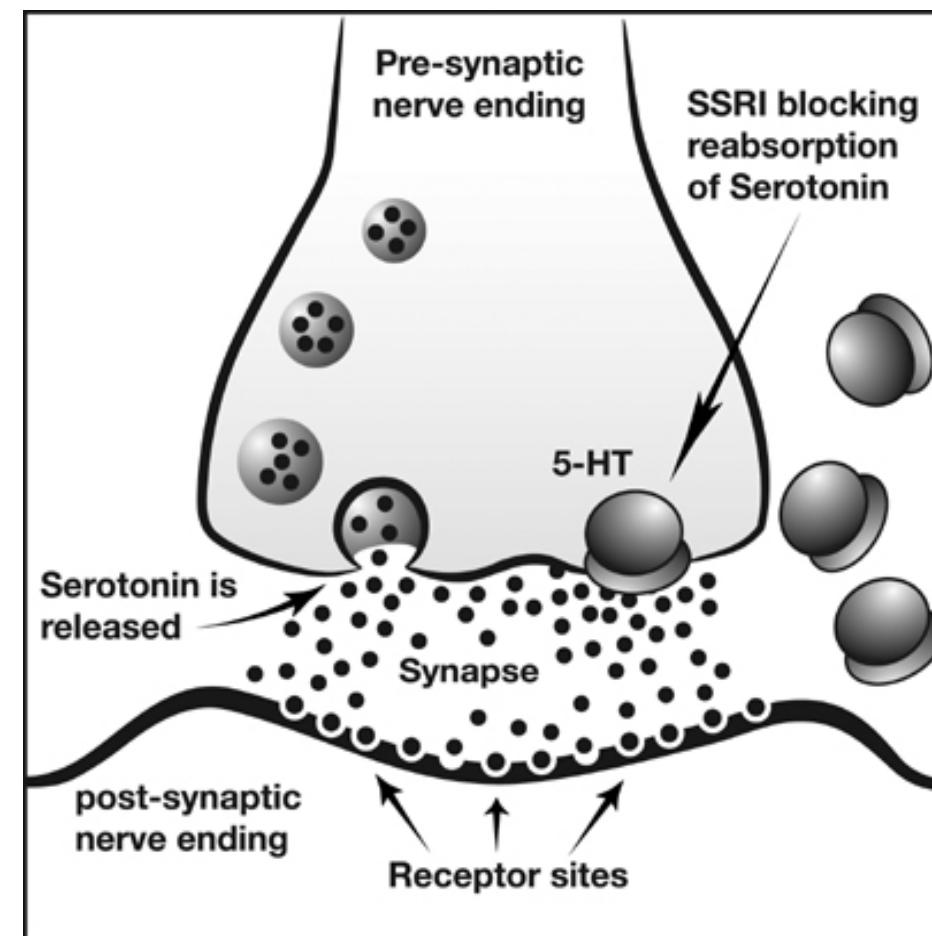
Of female patients aged 60+ use antidepressants



Median Cost per inpatient hospital stay

\$8,765 for Veterans Health Administration patients

\$10,792 for commercially insured patients

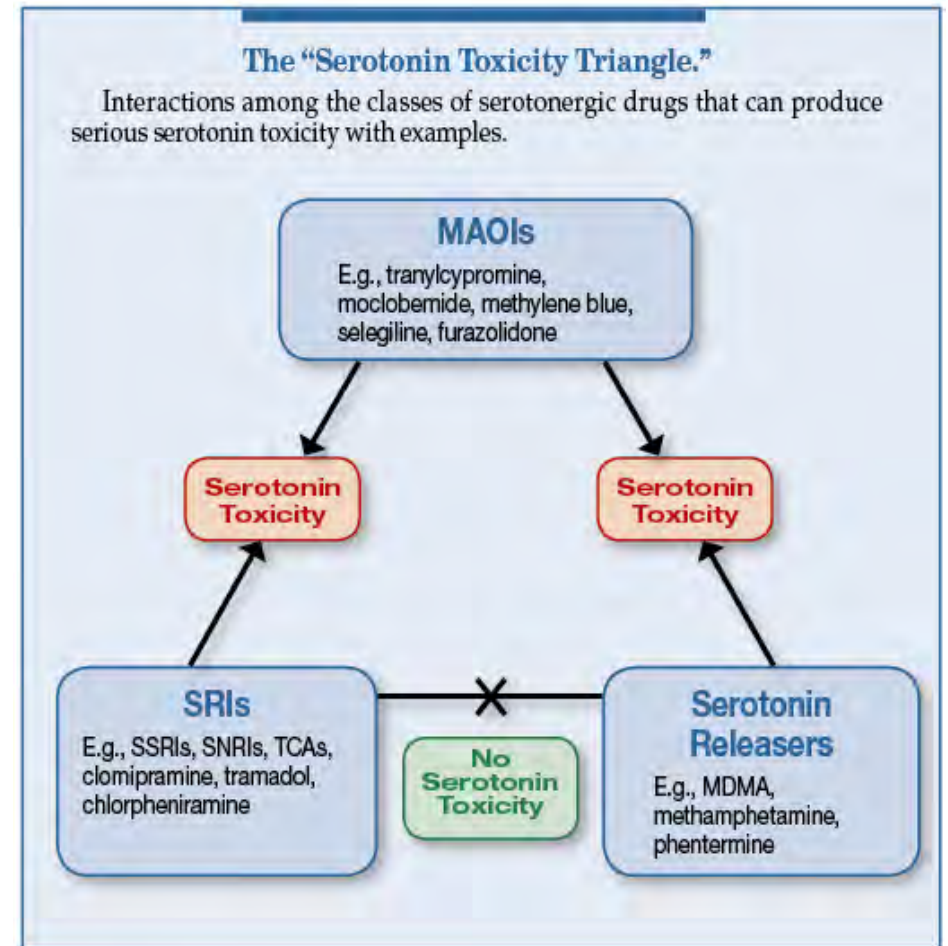


Francescangeli J, Karamchandani K, Powell M, Bonavia A. The Serotonin Syndrome: From Molecular Mechanisms to Clinical Practice. *International Journal of Molecular Sciences*. 2019; 20(9):2288. <https://doi.org/10.3390/ijms20092288>

Feeney SN. Serotonin Syndrome. *Elsevier eBooks*. Published online January 1, 2007:516-517. doi:<https://doi.org/10.1016/b978-032303506-4.10295-0>

How It Works

- **CNS** : attention, behavior, thermoregulation
- **PNS** : motility, vasoconstriction, uterine contraction, bronchoconstriction
- No single receptor is solely responsible
- Can occur after initiating one serotonergic drug or increasing doses of a serotonergic drug in sensitive individuals
- More severe episodes with MAOI (death)



Mills KC. Serotonin syndrome. A clinical update. *Crit Care Clin.* 1997;13(4):763-783. doi:10.1016/s0749-0704(05)70368-7

Pharmacology

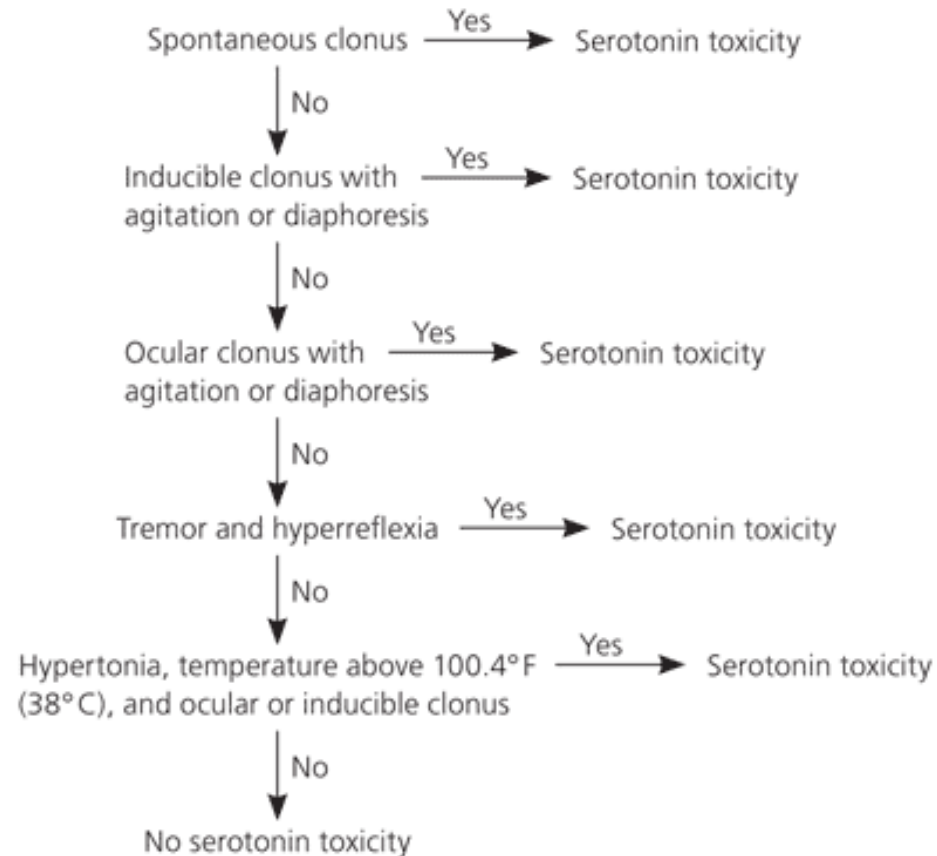
MECHANISM	AGENTS INVOLVED
Increases serotonin formation	Tryptophan, Oxitriptan
Increases release of serotonin	Amphetamines (including Dextroamphetamine, Methamphetamine), MDMA (ecstasy), Amphetamine derivatives (including Fenfluramine, Dexfenfluramine, Phentermine), Cocaine, Mirtazapine
Impairs serotonin reuptake from the synaptic cleft into the presynaptic neuron	Cocaine, MDMA, Meperidine, Tramadol, Pentazocine, Dextromethorphan, SSRIs, SNRIs, Sibutramine, Bupropion, serotonin modulators, cyclic antidepressants, St. John's wort, 5HT3 receptor antagonists, Cyclobenzaprine, Methylphenidate, dexamethylphenidate
Inhibits serotonin metabolism by inhibition of MAO	MAO non-selective inhibitors, MAO-A inhibitors, MAO-B inhibitors
Direct serotonin receptor agonist	Buspirone, Triptans, Ergot derivatives, Fentanyl, Lysergic acid diethylamide (LSD), Lasmiditan, Lorcaserin, Metaxalone
Increases sensitivity of postsynaptic serotonin receptor	Lithium

Pharmacology

Severe SS usually occurs with concomitant administration of **2 or more** serotonergic agents even at therapeutic doses

DRUG CLASS	DRUG COMBINATIONS
MAOIs	MAOIs + SSRIs or SNRIs
SSRIs	SSRIs + MAOIs or TCAs or SNRIs or opiates or triptans
SNRIs	SNRIs +TCAs or MAOIs or opiates or triptans
Other antidepressants	Mirtazapine + SSRIs Trazodone + amitriptyline + lithium
Opiates	Opiates + MAOIs or SSRIs or SNRIs or triptans
Cold remedies	Dextromethorphan + SSRIs or TCAs or atypical antipsychotics
Atypical antipsychotics	Olanzapine + citalopram and lithium Risperidone + paroxetine or fluoxetine
Antibiotics/antifungals	Linezolid + SSRIs or tapentadol Fluconazole + citalopram Ciprofloxacin + methadone + venlafaxine

Hunter Serotonin Toxicity Criteria for Diagnosis



- Must include a ***serotonergic agent*** + at least (1) of the following conditions:
 - Spontaneous clonus
 - Inducible clonus **plus** agitation or diaphoresis
 - Ocular clonus **plus** agitation or diaphoresis
 - Tremor **plus** hyperreflexia
 - Hypertonia **plus** temperature >100.4°F (38°C) **plus** ocular clonus or inducible clonus

Serotonergic Agents

- Overdose with a serotonergic agent, except a **direct serotonin receptor agonist**
 - › **Direct serotonin receptor agonists** are less likely to cause excessive stimulation of 5-HT1A and 5-HT2 serotonin receptors on their own
- Drug-drug interaction of two serotonergic agents, except when *both* are direct serotonin receptor agonists
- Initiation or increase in dose of a serotonergic agent or agent that decreases metabolism of serotonergic agent

Clinical Features

PHYSICAL EXAM

- **Hyperthermia**
- Agitation
- **Slow, continuous, horizontal eye movement (ocular clonus)**
- Dilated pupils
- Tremor
- Akathisia
- **Deep tendon hyperreflexia**
- **Inducible or spontaneous muscle clonus**
- Muscle rigidity
- Bilateral Babinski signs
- Dry mucus membranes
- Flushed skin and diaphoresis
- Increased bowel sounds

LABORATORY FINDINGS

- **Complete blood count (CBC)**
- **Basic serum electrolytes (BMP)**
- BUN and creatinine
- **Creatine phosphokinase**
- Hepatic transaminase concentrations
- Coagulation studies
- Blood culture
- Urinalysis and urine culture
- Plain chest radiograph
- Cerebrospinal fluid analysis and culture
- Head computed tomography (CT)

Clinical Features

SEVERE COMPLICATIONS

- Disseminated intravascular coagulation
- Rhabdomyolysis
- Metabolic acidosis
- Renal failure
- Myoglobinuria
- Acute respiratory distress syndrome



****If suspected intentional overdose, measure **acetaminophen** and **salicylate** concentrations plus obtain an **ECG*****

PREVENTION

Prevention

Strategy 1

- Begins with awareness of the toxicity potential from serotonergic drugs
- Providers play a key role
- Computerized ordering system and medical software can help identify possible interactions
- No established guidelines for prevention



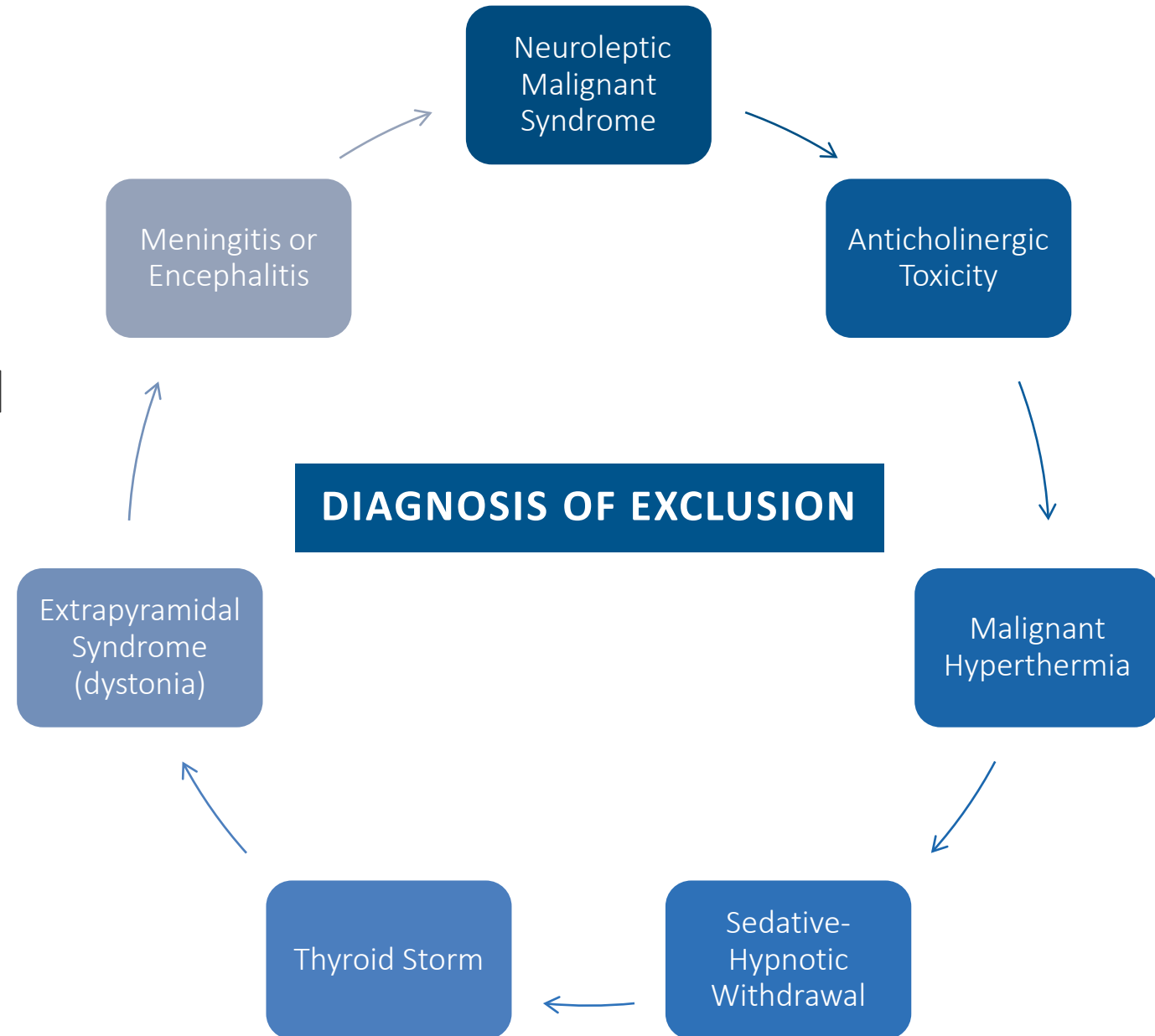
Prevention

Strategy 2

Other conditions may look similar to serotonin toxicity, so it is crucial to understand symptoms for each

Poison Control Center (US)

1-800-222-1222



Prevention



Strategy 3

- ***Before prescribing a serotonergic drug and at checkups***, ask patients about **OTC drug, herbal, and illicit or recreational drug use**
- ***When prescribing***, use the **lowest effective dose** and **avoid the use** of 2 high-dose serotonin drugs at the same time
- ***If stopping or switching drugs***, check for **tapering** and **washout** periods and stress careful adherence
- ***After prescribing***, **follow-up** with patients in a few days and annually

MANAGEMENT

Key Management Principles

- Discontinuation of all serotonergic agents
- Supportive care to normalize vital signs
- Sedation with benzodiazepines
- Administration of serotonin antagonists
- Assess need to resume use of serotonergic agents after resolution of symptoms

Supportive Care and Sedation for Mild Cases

- **Oxygen** to maintain O₂ saturation at ≥ 94%
- **IV fluids** (10-20 mL/kg crystalloids initially) for vol depletion
- **IV benzodiazepines** for significant agitation, repeat every 5 to 10 min based on patient response
 - Lorazepam 2 to 4 mg IV
 - Diazepam 5 to 10 mg IV



**Butyrophenones (i.e. droperidol, haloperidol) should be avoided as they can inhibit sweating and release of body heat*

Antidote Treatment for Severe Cases

- ***Cyproheptadine***
 - MOA: competitive histamine-1 receptor antagonist with nonspecific 5-HT_{1A}/5-HT_{2A} antagonistic properties and weak anticholinergic activity
 - Available as 4 mg tablets or 2 mg/5 mL oral syrup
 - Initial Adult Dose: **12 mg, then 2 mg every 2 hours** if patient remains symptomatic (Max dose: 32 mg in 24 hours)
 - › Tablets may be crushed and administered via a nasogastric tube



Other Treatments for Severe Cases

Hypotension

- Direct-acting vasopressors (**norepinephrine, epinephrine, phenylephrine**)
- *Indirect agents (dopamine) should be avoided as they must be metabolized to epi/norepinephrine and MAO may be inhibited*



Hyperthermia

- Aggressive benzodiazepines and nondepolarizing paralytics (**rocuronium, vecuronium, pancuronium**) + external cooling
- *Antipyretic agents (APAP) should be avoided since the hypothalamic temperature set point is not affected*



Hypertensive Emergency and Tachycardia

- Short-acting agents (**esmolol, nicardipine, nitroprusside**)
- *Long-acting agents (propranolol) should be avoided due to rapid changes in BP and HR*



Summary

- Serotonin syndrome is a drug-induced condition caused by too much serotonin in the synapses in the brain
- In some cases, medical intervention is not needed and could be managed by discontinuing the drug or lowering the dose
- It is crucial for both the providers and patients to understand prevention and symptoms of serotonin syndrome for better management

References

Boyer EW, Shannon M. The serotonin syndrome. *New England Journal of Medicine*. 2005;352(11):1112-1120. doi:10.1056/nejmra041867

Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The hunter serotonin toxicity criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003;96(9):635-642. doi:10.1093/qjmed/hcg109

Feeney SN. Serotonin Syndrome. *Elsevier eBooks*. Published online January 1, 2007:516-517. doi:https://doi.org/10.1016/b978-032303506-4.10295-0

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Martin TG. Serotonin syndrome. *Ann Emerg Med*. 1996;28(5):520-526. doi:10.1016/s0196-0644(96)70116-6

Mason PJ, Morris VA, Balcezak TJ. Serotonin syndrome presentation of 2 cases and review of the literature. *Medicine*. 2000;79(4):201-209. doi:10.1097/00005792-200007000-00001

Mills KC. Serotonin syndrome. A clinical update. *Crit Care Clin*. 1997;13(4):763-783. doi:10.1016/s0749-0704(05)70368-7

Scotton WJ, Hill LJ, Williams AC, Barnes NM. Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions. *Int J Tryptophan Res*. 2019 Sep 9;12:1178646919873925. doi: 10.1177/1178646919873925. PMID: 31523132; PMCID: PMC6734608.