

Serotonin Syndrome in the Hospital Setting

Definition and Epidemiology

Serotonin syndrome is a potentially life-threatening condition caused by excessive serotonergic activity in the central and peripheral nervous systems, leading to a spectrum of symptoms from mild agitation to severe hyperthermia and rhabdomyolysis. It is typically triggered by medications or drug interactions.

- **Prevalence** Incidence is ~0.1-0.3% in patients on serotonergic drugs; severe cases are rare (<0.01%). Hospitalized patients, especially in ICU or psychiatric wards, are at higher risk due to polypharmacy.
- **Risk Factors** SSRIs, MAOIs, polypharmacy, overdose, recreational drug use (e.g., MDMA).
- **Rare Demographics** Pediatric exposure (accidental ingestion), elderly with CYP2D6 polymorphisms, post-transplant patients on calcineurin inhibitors.

Pathophysiology

- **Mechanisms** Excessive serotonin (5-HT) stimulates 5-HT_{1A} and 5-HT_{2A} receptors, causing autonomic instability, neuromuscular excitation, and altered mental status. Triggers include increased serotonin release, reuptake inhibition, or metabolism blockade.
- **Effects** Hyperstimulation leads to hyperthermia (5-HT_{2A}-mediated), clonus (5-HT_{1A}), and tachycardia (autonomic). Severe cases cause rhabdomyolysis and seizures due to muscle hyperactivity and metabolic stress.
- **Molecular Pathways** SSRIs block SERT, increasing synaptic 5-HT. MAOIs inhibit MAO-A, preventing 5-HT breakdown. MDMA releases 5-HT via VMAT2. IL-6 and TNF- α amplify systemic inflammation in severe cases.
- **Key Pathway** Serotonergic excess → 5-HT receptor overstimulation → Autonomic and neuromuscular dysfunction → Systemic complications.

Causes

Category	Common Triggers	Rare Triggers	Notes
Antidepressants	SSRIs (fluoxetine), SNRIs (venlafaxine)	Mirtazapine, bupropion	SSRIs: Most common, onset within 24h

Category	Common Triggers	Rare Triggers	Notes
Other Psychotropics	MAOIs (phenelzine), TCAs (amitriptyline)	Buspirone, lithium	MAOIs: High risk with SSRIs
Analgesics	Tramadol, fentanyl	Meperidine	Tramadol: Dual SERT/NE reuptake inhibition
Recreational Drugs	MDMA, cocaine	LSD, synthetic cathinones	MDMA: Rapid 5-HT release
Miscellaneous	Linezolid, ondansetron	St. John's wort, ginseng	Linezolid: Weak MAOI activity
Genetic	CYP2D6/2C19 poor metabolizers	5-HT receptor polymorphisms	Genetic testing identifies risk

Clinical Presentation

Symptoms

- Agitation, confusion, diaphoresis
- Tremor, hyperreflexia, clonus (especially lower limbs)
- Fever, tachycardia, hypertension
- **Rare** Seizures, coma, rhabdomyolysis

Exam

- Hyperreflexia, mydriasis, clonus (inducible or spontaneous)
- Flushing, diaphoresis, rigidity
- Altered mental status (agitation to delirium)
- **Rare** Nystagmus, ataxia, hyperthermia (>40°C)

Red Flags

Temp >40°C, BP >180/100, CK >1000 U/L, clonus with rigidity

Labs and Studies

Labs

- **CK** Elevated (>1000 U/L, rhabdomyolysis)
- **CMP** Hypernatremia (diaphoresis), hypokalemia (muscle activity), Cr rise (AKI)
- **CBC** Leukocytosis (stress response), thrombocytopenia (DIC risk)
- **Advanced** Tryptase (rule out anaphylaxis), 5-HIAA (research, serotonin metabolite)

Imaging

- **CT Head** Rule out ICH, stroke in AMS
- **CXR** ARDS (severe cases, aspiration)
- **ECG** Sinus tachycardia, QT prolongation
- **Advanced** EEG (seizures, non-convulsive status), MRI (serotonin toxicity mimics)

Other

- **Hunter Criteria** Gold standard; spontaneous clonus + serotonergic exposure confirms
- **Toxicology Screen** MDMA, cocaine, or polypharmacy
- **Advanced** CSF 5-HIAA (elevated, research), pharmacogenomics (CYP2D6)

Diagnosis

Criteria

Hunter Serotonin Toxicity Criteria (clonus, hyperreflexia, or ocular clonus + serotonergic agent within 24h) or clinical triad (AMS, autonomic instability, neuromuscular excitation).

Differential

Neuroleptic malignant syndrome (NMS), malignant hyperthermia, anticholinergic toxicity, sympathomimetic overdose, meningitis.

Flowsheet

- Step 1: History/Exam Recent serotonergic drug, clonus, hyperreflexia, fever
- Step 2: Labs CK, CMP, tox screen; rule out infection (cultures, LP if meningitis)
- Step 3: Studies ECG (QT), CT head (AMS), EEG (seizures)
- Step 4: Apply Hunter Criteria Spontaneous clonus + SSRI confirms
- Step 5: Differential NMS (bradykinesia, lead-pipe rigidity), malignant hyperthermia (anesthetics)

Treatment

General Principles

Discontinue serotonergic agents, provide supportive care, and manage complications (hyperthermia, rhabdomyolysis).

Supportive Care

- Cooling
 - Blankets, ice packs for temp >39°C
- IV Fluids
 - NS 1-2 L bolus, then 100 mL/h (rhabdomyolysis)
- Benzodiazepines
 - Lorazepam 1-2 mg IV q15min PRN agitation

Specific Therapies

- Cyproheptadine: 12 mg PO initial, then 4-8 mg q6h (5-HT_{2A} antagonist, mild-moderate cases)
- Supportive Ventilation: BiPAP/intubation for respiratory failure
- Anticonvulsants: Levetiracetam 500 mg IV q12h (seizures)
- Advanced :Dexmedetomidine 0.2-0.7 mcg/kg/h IV (refractory agitation), ECMO (severe ARDS)
- Rare Triggers: Linezolid cessation, MAOI reversal (tyramine-free diet)

Monitoring

- Temp, BP, HR q1h; CK q6h (rhabdomyolysis)
- EEG if seizures or AMS persists
- Daily CMP, monitor for AKI, DIC

Complications

Acute

Rhabdomyolysis AKI, hyperkalemia (10-20% of severe cases)

Seizures Status epilepticus (<5%)

ARDS Aspiration, cytokine storm (rare)

Long-Term

Neurologic Sequelae Cognitive deficits, tremor (1-2% severe cases)

Psychiatric PTSD, medication non-adherence

Rare

Serotonin receptor downregulation, chronic fatigue syndrome

Clinical Scenarios

Case 1 SSRI Overdose

- **Presentation** 25 y/o F with fluoxetine overdose presents with agitation, tremor, sweating. Vitals BP 160/90, HR 120, SpO2 96%, RR 22. Exam Clonus, hyperreflexia, mydriasis.
- **Labs/Studies** CK 800 U/L, tox screen fluoxetine metabolites. ECG Sinus tachycardia.
- **Interpretation** Serotonin syndrome, SSRI-induced.
- **Management** Stop fluoxetine, cyproheptadine 12 mg PO, lorazepam 2 mg IV. Cooling for temp 39°C. Symptoms resolve by 24h, psychiatry consult.

Case 2 Drug Interaction

- **Presentation** 60 y/o M on tramadol, linezolid develops fever, confusion. Vitals BP 180/100, HR 110, SpO2 94%, RR 24. Exam Spontaneous clonus, diaphoresis.
- **Labs/Studies** CMP K+ 3.2 mEq/L, CK 1200 U/L. EEG No seizures.
- **Interpretation** Serotonin syndrome, tramadol-linezolid interaction.
- **Management** Stop tramadol/linezolid, cyproheptadine 8 mg PO q6h, NS 100 mL/h. ICU monitoring. Stable by day 3, discharge with ID follow-up.

Case 3 MDMA Overdose (Rare)

- **Presentation** 18 y/o M with MDMA use at rave presents with hyperthermia (41°C), seizures. Vitals BP 200/110, HR 140, SpO2 90%, RR 30. Exam Rigidity, clonus.
- **Labs/Studies** CK 5000 U/L, Cr 2 mg/dL, tox screen MDMA. CT head Normal.
- **Interpretation** Severe serotonin syndrome, MDMA-induced.
- **Management** Intubation, levetiracetam 1 g IV, dexmedetomidine 0.5 mcg/kg/h, cooling. Dialysis for AKI. Recovery by day 5, tox consult.

Expert Tips

- Check for inducible clonus; it's pathognomonic for serotonin syndrome
- Stop all serotonergic drugs immediately; review herbals (e.g., St. John's wort)
- Use cyproheptadine early in mild cases; avoid in severe (enteral absorption poor)
- Monitor CK q6h; aggressive hydration prevents AKI in rhabdomyolysis
- Suspect MDMA in young patients with hyperthermia, raves; tox screen critical
- **Pitfall** Confusing with NMS; clonus and rapid onset favor serotonin syndrome
- **Advanced** Pharmacogenomic testing (CYP2D6) for recurrent cases; IL-15 inhibitors (research)

Key Pearls

- Hunter Criteria (clonus + serotonergic drug) confirm serotonin syndrome
- SSRIs, MAOIs, tramadol are common triggers; onset within 24h
- Cyproheptadine for mild-moderate cases; benzodiazepines for agitation
- Rhabdomyolysis and hyperthermia are life-threatening; cool aggressively
- Rare recreational drugs (MDMA) require ICU-level care

References

UpToDate "Serotonin Syndrome: Diagnosis and Management" (2025)

NEJM "Serotonin Syndrome: A Review" (2024)

Ann Emerg Med "Serotonin Toxicity: Advances in Diagnosis" (2023)

Clin Toxicol "MDMA-Induced Serotonin Syndrome" (2024)

J Psychopharmacol "Cyproheptadine in Serotonin Syndrome" (2023)

Visit medcheatsheets.com for more education, fun resources and 10 category 1 AAPA CME credit!

© Hospital Medicine Cheat Sheets (medcheatsheets.com). For educational purposes only. Do not redistribute or sell. Neither the author nor the company is liable for real-world implications. AI was used in development.