Serotonin syndrome recognition

Hunter criteria, Sternbach criteria, common triggers, differential from NMS, and management. Reviewed against current guidelines as of June 8, 2026.

Serotonin syndrome is a clinical diagnosis. Two decision rules are in use. Hunter criteria (Dunkley 2003) are more specific and easier to apply at the bedside. Sternbach criteria (1991) are broader and cover milder presentations. Both work. Neither replaces clinical judgment. The classic triad is autonomic instability, neuromuscular hyperactivity, and mental status change. Clonus, especially inducible or spontaneous lower-extremity clonus, is the single most useful physical sign.

Hunter criteria

In a patient exposed to a serotonergic agent, one of the following is required.

- Spontaneous clonus.
- Inducible clonus plus agitation or diaphoresis.
- Ocular clonus plus agitation or diaphoresis.
- Tremor plus hyperreflexia.
- Hypertonia plus temperature above 38 degrees C plus ocular or inducible clonus.

Sternbach criteria

A serotonergic agent added or increased, plus at least three of: mental status changes (confusion, hypomania), agitation, myoclonus, hyperreflexia, sweating, shivering, tremor, diarrhea, incoordination, fever. Other causes ruled out. No neuroleptic added or dose-increased just before symptom onset.

Common triggers

Trigger	Notes
SSRI or SNRI plus MAOI	Classic and most dangerous. 5-week wait after fluoxetine. 14 days after most other serotonergic drugs.
SSRI or SNRI plus tramadol	Common outpatient combination. Tramadol has serotonergic activity plus opioid.
SSRI or SNRI plus linezolid	Linezolid is a weak MAOI. Inpatient antibiotic that catches people off guard.
SSRI or SNRI plus methylene blue	MAOI activity. Comes up perioperatively.
SSRI or SNRI plus dextromethorphan	OTC cough syrups. Especially at high doses.
SSRI or SNRI plus triptans	Rare in practice but on the label. Ask about migraine treatment.
SSRI or SNRI plus lithium	Adds to serotonergic tone; rarely the sole trigger.
SSRI or SNRI plus St. John's wort	Patients often do not mention. Ask.
MDMA or serotonergic recreational drugs	Ecstasy plus an antidepressant is a well-documented cause.
Cross-taper of two serotonergic drugs at high doses	Usually well-tolerated; risk climbs at supratherapeutic combinations.

Serotonin syndrome vs NMS

Feature	Serotonin syndrome	Neuroleptic malignant syndrome
Onset	Hours after trigger	Days to weeks after antipsychotic start or dose change

Trigger	Serotonergic drug added or combined	Dopamine antagonist (antipsychotic) or dopaminergic drug withdrawal
Neuromuscular	Hyperreflexia, clonus (especially lower extremity), myoclonus, tremor	Lead-pipe rigidity, bradyreflexia
Mental status	Agitation, anxiety, delirium	Stupor, mutism, coma
Autonomic	Diaphoresis, tachycardia, hypertension, hyperthermia	Diaphoresis, tachycardia, labile BP, hyperthermia
Pupils	Mydriasis common	Normal
Bowel sounds	Hyperactive; diarrhea common	Normal or decreased
CK	Usually normal or mildly elevated	Markedly elevated (often over 1000)
Course	Resolves in 24 to 72 hours after stopping trigger	Days to weeks

Management

- Stop all serotonergic drugs immediately.
- Supportive care: IV fluids, cooling, benzodiazepines (lorazepam, midazolam) for agitation and clonus.
- Continuous monitoring. Autonomic instability can escalate.
- For moderate to severe cases, cyproheptadine 12 mg PO initial, then 2 mg q2 hours for continued symptoms, or 4 to 8 mg q6 hours maintenance until symptoms resolve. Max 32 mg a day.
- Avoid antipyretics for hyperthermia. The temperature is muscle-driven, not central. Cool actively.
- Avoid physical restraints when possible. Muscle activity worsens hyperthermia and rhabdomyolysis.
- ICU admission for temp above 41 degrees C, severe rigidity, seizures, or evidence of end-organ damage.
- Do not restart the offending drug without a plan. Confirm the trigger. If a serotonergic drug is still needed, restart weeks later at lower dose and monitor.

Not medical advice.