The Hyperthermic Toxidromes

NMS, serotonin syndrome and their mimics · Examine the legs and take the timeline, and the diagnosis falls out

CLONUS vs RIGIDITY
serotonin vs NMS

THE TWO DISCRIMINATORS *speed of onset and what the neuromuscular exam shows*

SEROTONIN SYNDROME — fast

Within hours of a dose increase or a new serotonergic drug, usually under 24 hours. **Neuromuscular excitation: clonus, hyperreflexia and tremor, all worse in the legs than the arms.** Plus **mydriasis, diarrhea and hyperactive bowel sounds**. **Resolves within about 24 hours** of stopping the drug.

NMS — slow

Evolves over days to weeks after starting or increasing a dopamine antagonist. **Generalized lead-pipe rigidity with bradykinesia and normal or reduced reflexes — no clonus. Very high creatine kinase**, leukocytosis, and marked hyperthermia. **Takes days to weeks to resolve.**

THE DRUG HISTORY DECIDES

Serotonergic: SSRIs and SNRIs, MAO inhibitors, **tramadol, fentanyl, linezolid, methylene blue**, triptans, ondansetron, St John's wort, MDMA. **Dopamine-blocking:** antipsychotics, and the ones that are forgotten — **metoclopramide and prochlorperazine**. **Also abrupt withdrawal of levodopa** causes NMS.

DISTINGUISH FROM THE MIMICS *each has a different antidote*

Diagnosis	Distinguishing features
Malignant hyperthermia	**Minutes after a volatile anesthetic or succinylcholine**, in a genetically susceptible patient. **A rising end-tidal CO_2 is the earliest sign**, with masseter spasm, rigidity and severe mixed acidosis. **Dantrolene is definitive and must not be delayed.**
Anticholinergic	**Hot, red and dry.** Mydriasis, **absent bowel sounds and urinary retention**, mumbling delirium. **No rigidity and normal reflexes. Dry skin is the key separator from serotonin syndrome**, which is drenched in sweat. Physostigmine in selected cases.
Sympathomimetic	Cocaine, amphetamines. Agitation, mydriasis, hypertension and tachycardia, but **diaphoretic with present bowel sounds**. **Benzodiazepines are the treatment**; avoid unopposed beta-blockade.
Sepsis and CNS infection	**Always in the differential, and can coexist. Do not anchor on the drug chart** — consider meningitis, encephalitis and an intracranial event, and have a low threshold for cultures, imaging and lumbar puncture.
Thyroid storm	Fever, tachyarrhythmia, agitation and tremor, with a **goitre, ophthalmopathy or a precipitating illness**. Reflexes are brisk but **there is no clonus or lead-pipe rigidity**. Send thyroid function early.

CONFIRM SEROTONIN SYNDROME *the Hunter criteria, which outperform clinical impression*

THE RULE

A serotonergic agent must be on board, plus **any one** of the following: **spontaneous clonus**; **inducible clonus with agitation or diaphoresis**; **ocular clonus with agitation or diaphoresis**; **tremor with hyperreflexia**; or **hypertonia with a temperature above 38°C plus ocular or inducible clonus**.

HOW TO ELICIT IT

Test for clonus at the ankles — dorsiflex the foot briskly and hold. **Lower limb findings dominate**, so an examination confined to the arms will miss it. **Look for ocular clonus** with slow horizontal tracking. **Rigidity severe enough to mask clonus is a marker of severity**, not evidence against the diagnosis.

TREAT *shared principles, then the specific agent*

1. **Stop every causative drug immediately** and review the whole chart including patches, infusions and recently ceased agents with long half-lives. **In NMS from levodopa withdrawal, restart the levodopa.**
2. **Benzodiazepines are the shared first-line treatment** for agitation, rigidity and hyperthermia in both syndromes, and they reduce muscular heat production directly. **Titrate generously.**
3. **Cool actively. Antipyretics do not work** — the heat is generated by muscle, not by a raised hypothalamic set point. Use external cooling and cold fluids. **Above about 41°C, intubate, sedate and paralyze with a non-depolarising agent**, which stops the muscular heat production at source.
4. **Then the specific agent. Serotonin syndrome: cyproheptadine. NMS: consider dantrolene, bromocriptine or amantadine in severe or prolonged cases**, though the evidence is weaker than for supportive care. **Dantrolene is definitive only in malignant hyperthermia.**
5. **Support the complications. Rhabdomyolysis with acute kidney injury, hyperkalemia, DIC, seizures and arrhythmia.** Give **generous intravenous fluid** and monitor creatine kinase, potassium and renal function. Most patients need critical care.

WHAT MAKES IT WORSE *the interventions that harm*

AVOID

Physical restraint — isometric struggling against restraints drives lactic acidosis and hyperthermia and has caused deaths; **sedate chemically instead**. **Antipsychotics in serotonin syndrome**, which worsen it and confuse the picture. **Succinylcholine** where rhabdomyolysis is likely, because of hyperkalemic arrest. **Bromocriptine in serotonin syndrome**, since it is itself serotonergic.

PREVENT THE NEXT ONE

Document the reaction prominently as an allergy or adverse drug reaction before discharge, and name the specific drug. **Rechallenge with a dopamine antagonist after NMS should be delayed at least 2 weeks** beyond full recovery, at a low dose of a lower-potency agent, with monitoring. **Watch for the linezolid and tramadol interactions with antidepressants** — both are prescribed by people who do not realise they are serotonergic, and they are a recurring cause.

PEARLS & PITFALLS

- **The antidote doses, since both syndromes name a drug and rarely quantify it: cyproheptadine 12 mg orally or by tube, then 2 mg every 2 h** until response (about 32 mg/day maximum) for serotonin syndrome; **dantrolene 1-2.5 mg/kg IV** and **bromocriptine 2.5-5 mg every 8 h** for severe NMS.
- **Clonus means serotonin; lead-pipe rigidity means NMS.** Examine the ankles, not just the arms.
- **Hours means serotonin, days means NMS.** The timeline is as discriminating as the examination.
- **Metoclopramide and prochlorperazine cause NMS.** Everyone remembers antipsychotics and forgets the antiemetics.
- **Acetaminophen will not touch this fever.** The heat is muscular, so cool physically and paralyze if extreme.
- **Do not restrain a struggling hyperthermic patient** — isometric activity worsens acidosis and temperature. Sedate.
- **Check for linezolid, tramadol and methylene blue** in any patient on an antidepressant. These combinations are the classic trigger.

References: Hunter Serotonin Toxicity Criteria (Dunkley et al., QJM 2003) · Boyer and Shannon, the serotonin syndrome (NEJM) · consensus diagnostic criteria for neuroleptic malignant syndrome · MHAUS guidance on malignant hyperthermia and dantrolene.

Educational aid; verify against local toxicology and critical care protocol and patient factors.

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