

Serotonin Syndrome vs. NMS: The Diagnostic Split

**Overstimulation.
Hyperactivity.
Serotonin
Excess.**



**Blockade.
Rigidity.
Dopamine
Antagonism.**

**A Rapid Clinical
Reference Guide**

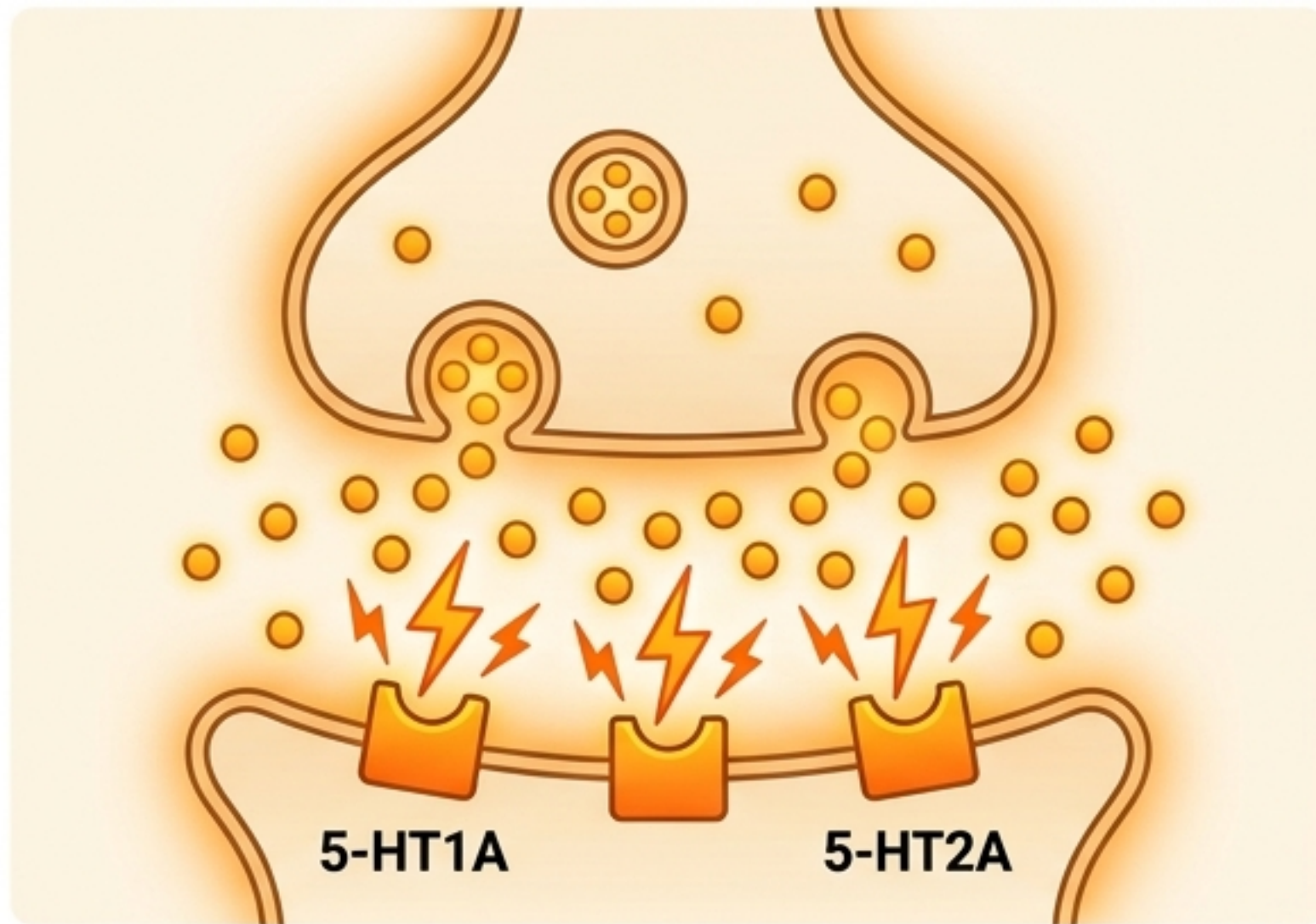
The Core Problem: Why Confusion is Deadly



Accurate differentiation dictates completely opposite pharmacological interventions.

Pathophysiology at a Glance

Serotonin Syndrome: The Flood



Excess 5-HT activity in central and peripheral nervous systems. Receptor overstimulation drives hyperkinesia and autonomic excess.

NMS: The Blockade



D2 Dopamine receptor antagonism causing central blockade in the basal ganglia and hypothalamus. Drives central rigidity and thermoregulatory failure.

The Causative Agents



Serotonin Syndrome Triggers



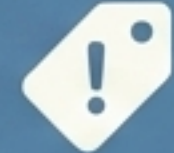
Classic Polypharmacy Combinations

- SSRI + MAOI
- SSRI + Triptan
- SSRI + Tramadol
- SSRI + Linezolid



Standalone Risks

- MDMA / Ecstasy
- St. John's Wort
- Extreme Tramadol dosage



NMS Triggers



High Risk

- First-Generation Antipsychotics (FGAs like Haloperidol)



Moderate Risk

- Second-Generation Antipsychotics (SGAs)



Overlooked Causes

- Antiemetics (Metoclopramide, Promethazine)



Distinct Mechanism

- Dopamine Agonist Withdrawal (in Parkinson's)

Diagnosing Serotonin Syndrome: The Hunter Criteria

Serotonergic Drug Initiated or Increased

CLONUS

(Rhythmic muscle jerking. The most reliable distinguishing feature.)

✓
Spontaneous
clonus

✓
Inducible clonus
+ agitation or
diaphoresis

✓
Ocular clonus
+ agitation or
diaphoresis

✓
Tremor +
hyperreflexia

✓
Hypertonia +
temp >38.5°C
+ ocular or
inducible clonus

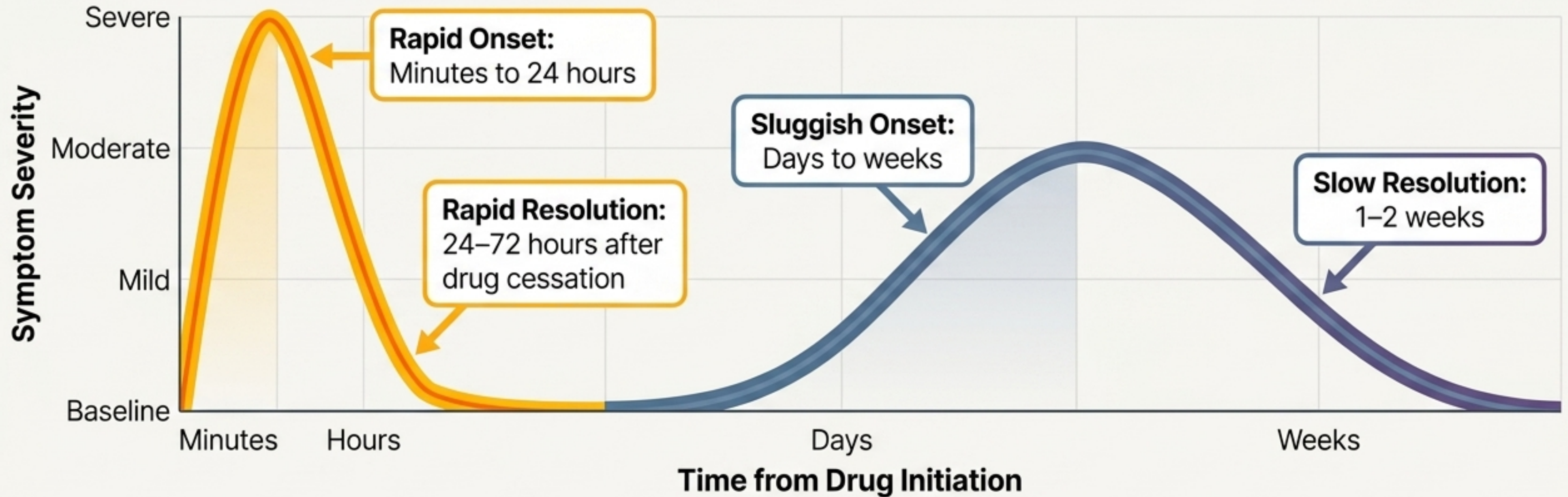
If **YES** to any branch = **Diagnosis of Serotonin Syndrome**. NMS typically lacks clonus.

Diagnosing NMS: The Clinical Tetrad



Timeline note: At least 3 of 4 pillars are typically present at the time of diagnosis.

The Diverging Timelines: Onset & Resolution



Serotonin Syndrome

- **Velocity:** Hyper-acute
- **Driver:** Overdose or rapid interaction.

NMS

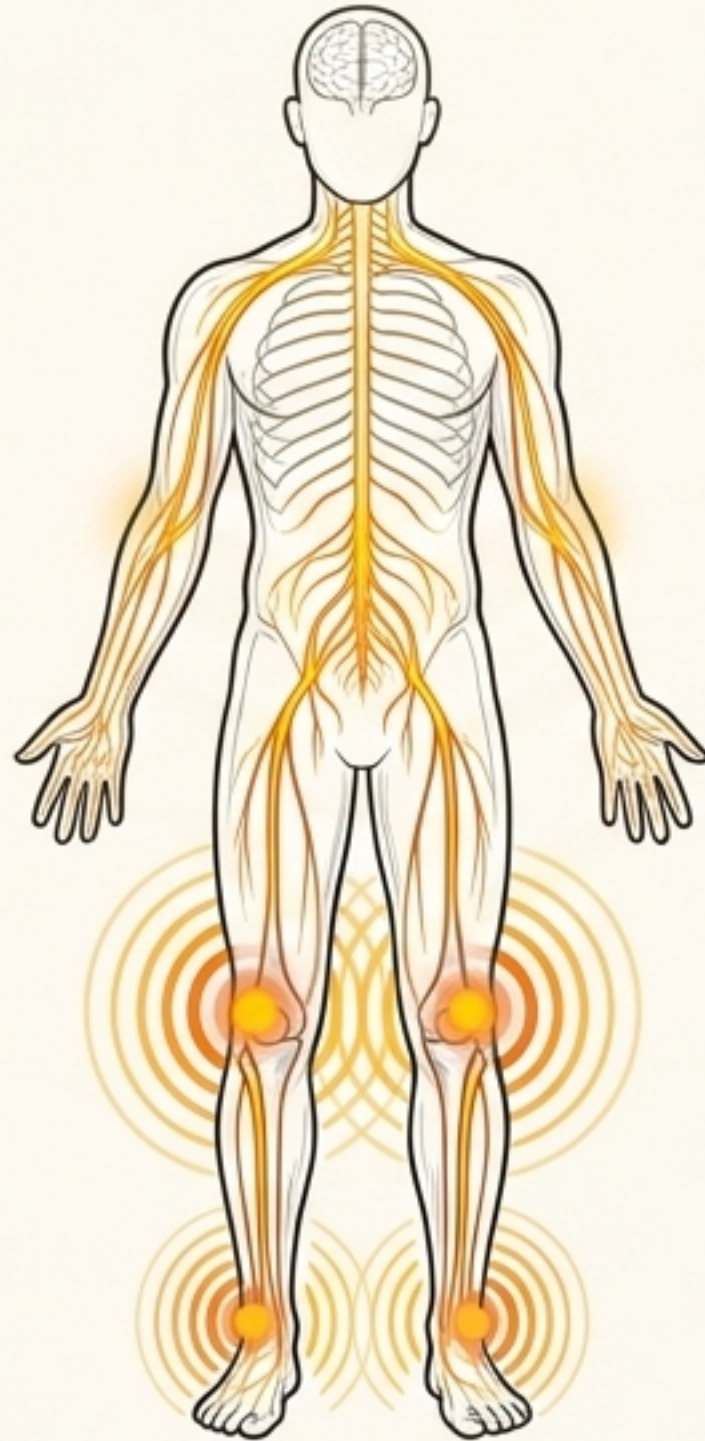
- **Velocity:** Insidious
- **Driver:** Gradual central dopamine depletion.

The Diagnostic Master Matrix

Premium, scannable medical command dashboard

Clinical Feature	Serotonin Syndrome	Neuroleptic Malignant Syndrome
Pathophysiology	Excess 5-HT	Dopamine Antagonism
Onset	Hours (Rapid)	Days/Weeks (Sluggish)
Key Motor Sign	✔ Clonus (spontaneous/inducible)	✔ Lead-pipe rigidity (no clonus)
Reflexes	↑ Hyperreflexia	↓ Hyporeflexia / Normal
Pupils	Mydriasis (Dilated)	Normal
Bowel Sounds	↑ Hyperactive	↓ Normal / Decreased
CK Elevation	Mild (<1,000 U/L)	⚠ Marked (1,000–5,000+ U/L)
WBC Count	Normal	⚠ Leukocytosis (10,000–20,000/ μ L)

The Deciding Factor: The Motor Exam

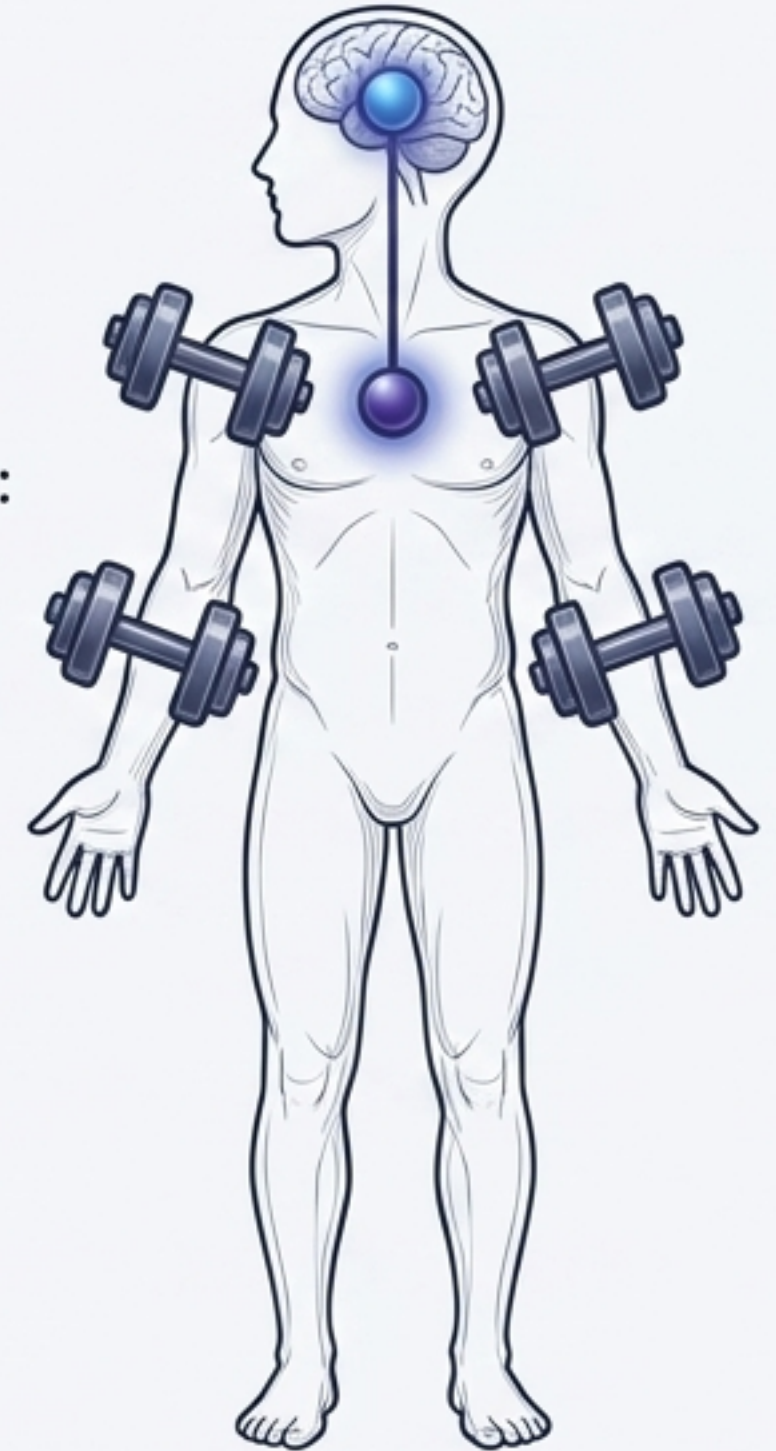


Peripheral Hyperactivity

- **CLONUS:** Rhythmic, involuntary muscle jerking.
- **HYPERREFLEXIA:** Exaggerated deep tendon reflexes.

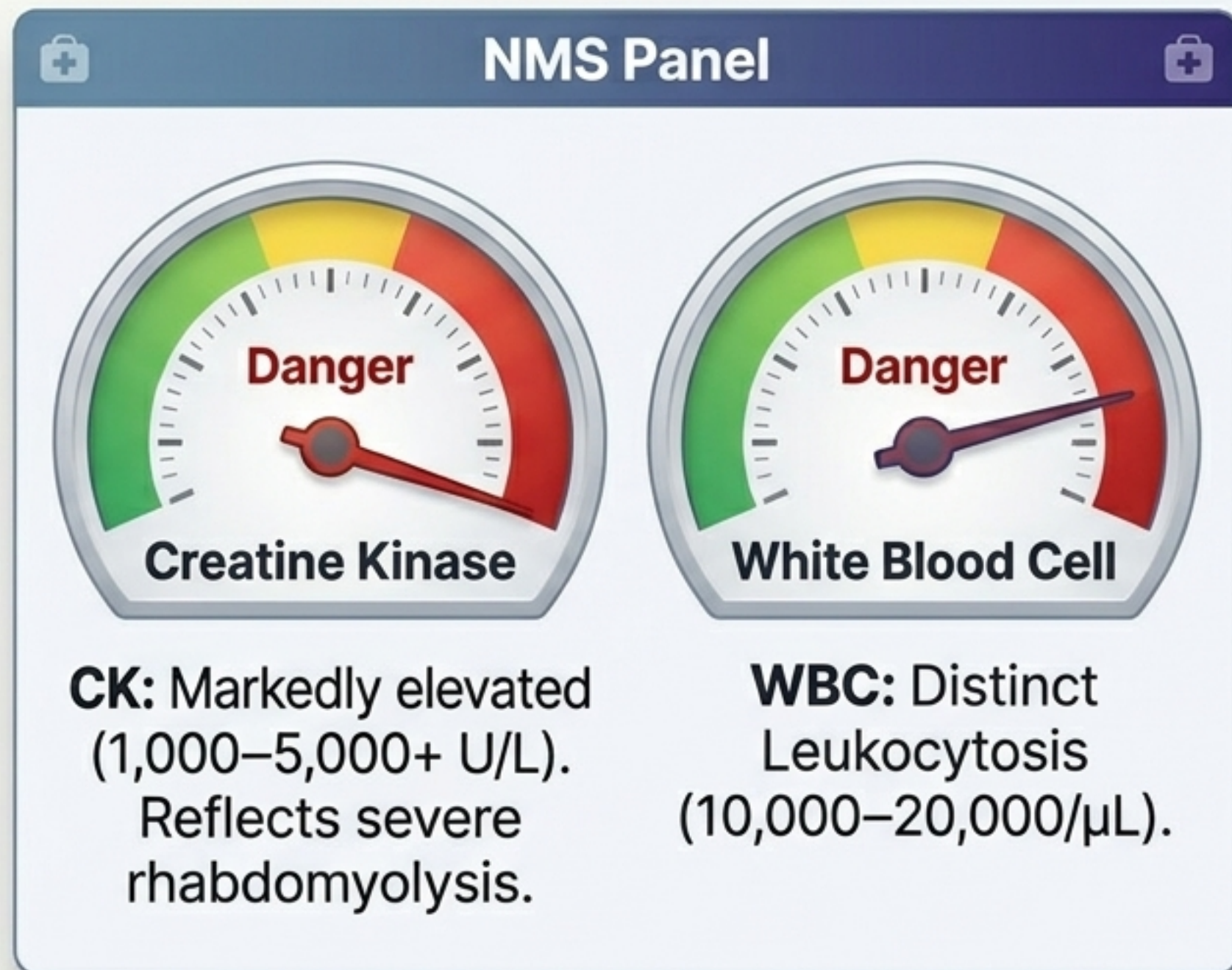
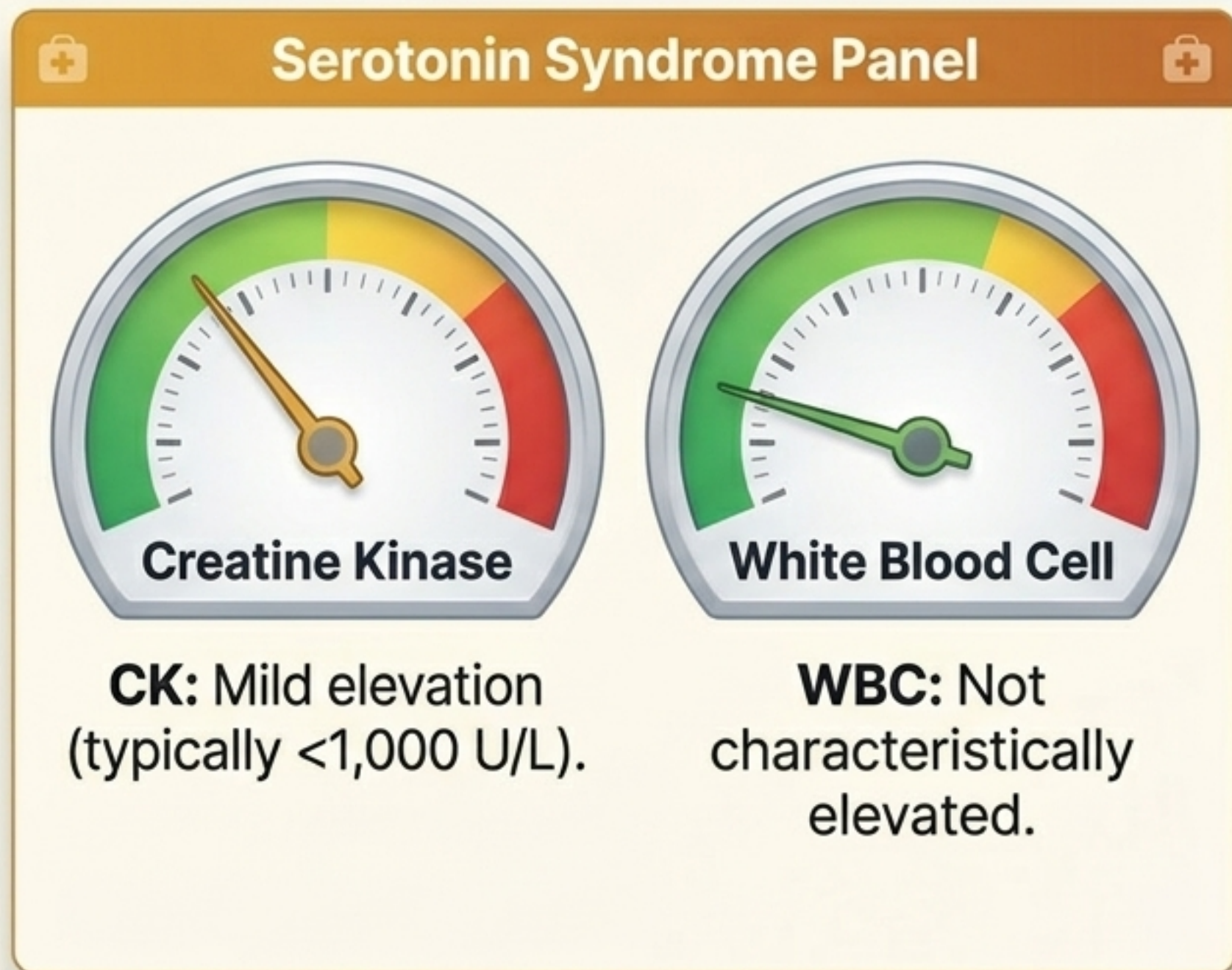
Central Blockade

- **LEAD-PIPE RIGIDITY:** Diffuse, uniform resistance to passive movement.
- **BRADYKINESIA:** Sluggish, slowed movements.



The Laboratory Signatures

Premium, scannable medical command dashboard



Note: Serum serotonin levels are not clinically useful in emergency settings. Rely on clinical signs and proxy markers.

Emergency Management: Serotonin Syndrome

1 Immediate Discontinuation

Stop all serotonergic agents.
Often sufficient for mild cases.

2 Supportive Care

IV fluids, active cooling.
Administer Lorazepam (1-4 mg IV q1-2h) for agitation and rigidity.



Step 3: 5-HT Antagonist
(Moderate-Severe Cases)

Cyproheptadine ^{Rx}

- 12 mg PO Loading Dose
- Followed by 2 mg PO every 2-4 hours.
- (Max 32 mg/day)



Emergency Management: NMS

1

Immediate Discontinuation

Stop offending antipsychotic **immediately**.

2

Aggressive Supportive Care

Aggressive hydration (**goal 200–300 mL/hr urine output**) to prevent myoglobin precipitation. Cooling measures.

Rx

Muscle Relaxant

Dantrolene Sodium

- 1–2.5 mg/kg IV
- (q5-10 min until rigidity resolves, max 10 mg/kg)

Rx

Dopamine Agonist

Bromocriptine

- 2.5 mg PO TID
- (Titrate up to 5 mg TID). Continues 5-10 days.

Clinical Traps & Atypical Presentations



Trap 1: SS Without Fever

Mild cases may completely lack hyperthermia.

Diagnosis relies entirely on the presence of **clonus** and **hyperreflexia**, not temperature.

Do not rule out **SS** simply because the patient is afebrile.



Trap 2: Rapid-Onset NMS

While typically slow and insidious, **NMS** can develop rapidly within 24 hours of receiving **high-dose** or parenteral **Haloperidol**.

This aggressive timeline perfectly mimics the rapid onset of **Serotonin Syndrome**.



Trap 3: The Overlap Patient

A patient concurrently on **SSRIs** and **antipsychotics** who presents with systemic symptoms.

Requires **stopping both** drug classes simultaneously and initiating combined medical management (**Cyproheptadine + Dantrolene**).

The Re-Challenge: Post-Recovery Protocols



Serotonin Syndrome Strategy

Wait **24–48 hours** post-resolution.

Can safely restart monotherapy at a low dose.

RULE: Permanently avoid the specific polypharmacy combination that caused the crisis.



NMS Strategy (High Risk)

~60% Recurrence Rate



Wait >2 weeks post-resolution.



Switch class: Use the lowest-potency atypical antipsychotic available.



Micro-dose: Start ultra-low, titrate slowly.



Provide Dantrolene prophylaxis during the re-challenge period.

RAPID + JERKY → SS

(Clonus)

GIVE CYPROHEPTADINE

SLOW + STIFF → NMS

(Lead-Pipe)

GIVE DANTROLENE + BROMOCRIPTINE