Neuroleptic Malignant Syndrome

Definition and Epidemiology

Neuroleptic malignant syndrome (NMS) is a rare, life-threatening idiosyncratic reaction to dopamine receptor antagonists (antipsychotics), characterized by rigidity, fever, autonomic instability, and altered mental status. It is a medical emergency requiring ICU-level care.

- Prevalence Incidence is 0.01-0.02% in patients on antipsychotics; higher with high-potency typical antipsychotics (e.g., haloperidol). Hospitalized psychiatric patients are at greatest risk.
- Risk Factors High-dose antipsychotics, rapid dose escalation, dehydration, concurrent lithium use.
- Rare Demographics Pediatric NMS (atypical antipsychotics), elderly with parkinsonism, post-partum psychosis.

Pathophysiology

- Mechanisms NMS results from dopamine D2 receptor blockade in the nigrostriatal (rigidity), hypothalamic (hyperthermia), and mesolimbic (AMS) pathways. Reduced dopamine causes muscle rigidity and autonomic dysregulation.
- Effects Rigidity leads to rhabdomyolysis, releasing myoglobin, causing AKI. Hyperthermia from hypothalamic dysfunction risks multi-organ failure. Autonomic instability causes labile BP and tachycardia.
- Molecular Pathways D2 blockade disrupts cAMP signaling, reducing GABA inhibition. IL-6 and CPK surge from muscle breakdown. Serotonin-dopamine imbalance (e.g., SSRI co-administration) may exacerbate.
- Key Pathway D2 receptor blockade → Dopamine deficiency → Rigidity, hyperthermia, autonomic instability → Systemic complications.

Causes

Category	Common Triggers	Rare Triggers	Notes
Typical Antipsychotics	Haloperidol, chlorpromazine	Fluphenazine	High-potency drugs highest risk
Atypical Antipsychotics	Risperidone, olanzapine	Aripiprazole, clozapine	Lower risk but still significant

Category	Common Triggers	Rare Triggers	Notes
Antiemetics	Metoclopramide, prochlorperazine	Droperidol	D2 antagonism in GI tract
Other Drugs	None	Amoxapine, lithium (adjunct)	Lithium increases risk with antipsychotics
Neurological	Parkinson's (levodopa withdrawal)	MSA, DLB	Dopamine depletion mimics NMS
Genetic	None	D2 receptor polymorphisms	Rare, pharmacogenomic research

Clinical Presentation

Symptoms

- Fever, diaphoresis (temp 38-40°C)
- Lead-pipe rigidity, bradykinesia
- Confusion, delirium, mutism
- Rare Seizures, coma, dysphagia

Exam

- Generalized rigidity, tremor
- Tachycardia, labile BP (e.g., 200/110 to 90/60)
- Altered mental status (stupor to agitation)
- Rare Catatonia, cogwheel rigidity, myoclonus

Red Flags

Temp >40°C, CK >1000 U/L, SBP <90 mmHg, rigidity with AMS

Labs and Studies

Labs

- CK Elevated (>1000 U/L, rhabdomyolysis, 90% of cases)
- CMP Cr rise (AKI), K+ >5 mEq/L (rhabdomyolysis), low iron (<50 mcg/dL)
- CBC Leukocytosis (10-20K, stress), thrombocytopenia (DIC)
- Advanced Myoglobinuria, ferritin (inflammation), CSF dopamine (research)

Imaging

- CT Head Rule out stroke, ICH in AMS

- CXR Aspiration pneumonia, ARDS
- MRI Brain Rule out parkinsonism mimics (MSA, DLB)
- Advanced DAT scan (differentiate NMS from parkinsonism), PET (D2 receptor occupancy)

Other

- ECG Sinus tachycardia, QT prolongation
- EEG Non-specific slowing, rule out seizures
- Advanced Muscle biopsy (rhabdomyolysis severity), pharmacogenomics (DRD2)

Diagnosis

Criteria

DSM-5 criteria: Rigidity + fever + recent dopamine antagonist exposure + two of (AMS, tachycardia, labile BP, diaphoresis, CK elevation, leukocytosis).

Differential

Serotonin syndrome, malignant hyperthermia, catatonia, parkinsonism, meningitis.

Flowsheet

- Step 1 History/Exam Antipsychotic use, rigidity, fever, AMS
- Step 2 Labs CK, CMP, iron; rule out infection (LP, cultures)
- Step 3 Studies CT head, EEG (seizures), ECG (QT)
- Step 4 Apply DSM-5 Criteria Rigidity, fever, CK >1000 confirm
- Step 5 Differential Serotonin syndrome (clonus, rapid onset), malignant hyperthermia (anesthetics)

Treatment

General Principles

Stop offending drug, provide supportive care, and manage complications (rhabdomyolysis, hyperthermia).

Supportive Care

- Cooling Ice packs, cooling blankets for temp >39°C

- IV Fluids NS 1-2 L bolus, 100-200 mL/h (rhabdomyolysis)
- Benzodiazepines Lorazepam 1-2 mg IV q4h PRN agitation

Specific Therapies

- Dantrolene 1-2.5 mg/kg IV q6h (muscle relaxation, hyperthermia)
- Bromocriptine 2.5-5 mg PO TID (D2 agonist, restores dopamine)
- Amantadine 100 mg PO BID (dopamine enhancer, alternative)

Advanced

Electroconvulsive therapy (ECT, refractory catatonia), plasmapheresis (severe)

Rare Triggers

Levodopa repletion (Parkinson's withdrawal), metoclopramide cessation

Monitoring

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

Complications

Acute

- Rhabdomyolysis AKI, hyperkalemia (20-30% of cases)
- Aspiration Pneumonia Dysphagia, AMS (10-15%)
- Multi-Organ Failure Sepsis, ARDS (5-10% mortality)

Long-Term

- Neurologic Sequelae Bradykinesia, cognitive deficits (<5%)
- Psychiatric Relapse, medication non-adherence

Rare

Chronic parkinsonism, tardive dyskinesia post-recovery

Clinical Scenarios

Case 1 Haloperidol-Induced NMS

- **Presentation** 50 y/o M on haloperidol for schizophrenia presents with fever, rigidity, confusion. Vitals BP 190/100, HR 120, SpO2 94%, RR 20. Exam Lead-pipe rigidity, diaphoresis.
- **Labs/Studies** CK 2000 U/L, Cr 1.8 mg/dL, iron 40 mcg/dL. CT head Normal.
- **Interpretation** NMS, haloperidol-induced.
- **Management** Stop haloperidol, dantrolene 2 mg/kg IV q6h, bromocriptine 2.5 mg PO TID. NS 150 mL/h. ICU monitoring. Symptoms resolve by day 7.

Case 2 Atypical Antipsychotic NMS

- **Presentation** 30 y/o F on risperidone presents with fever, bradykinesia, mutism. Vitals BP 90/60, HR 110, SpO2 96%, RR 18. Exam Rigidity, tremor.
- **Labs/Studies** CK 1500 U/L, WBC 15K, EEG Slowing. MRI Normal.
- **Interpretation** NMS, risperidone-induced.
- **Management** Stop risperidone, lorazepam 2 mg IV q6h, amantadine 100 mg PO BID. Cooling for temp 39°C. Stable by day 5, psychiatry follow-up.

Case 3 Metoclopramide NMS (Rare)

- **Presentation**: 65 y/o M on metoclopramide for gastroparesis presents with fever, rigidity, AMS. Vitals BP 200/110, HR 100, SpO2 92%, RR 22. Exam Cogwheel rigidity, stupor.
- **Labs/Studies:** CK 3000 U/L, Cr 2 mg/dL, myoglobinuria. ECG Tachycardia.
- **Interpretation** NMS, metoclopramide-induced.
- **Management** Stop metoclopramide, dantrolene 1.5 mg/kg IV q6h, NS 200 mL/h. Dialysis for AKI. Recovery by day 10, GI consult.

Expert Tips

- Suspect NMS in any patient on antipsychotics with fever and rigidity; onset is slower (days) than serotonin syndrome
- Check serum iron; low levels (<50 mcg/dL) are specific for NMS
- Use dantrolene for hyperthermia; bromocriptine for rigidity, AMS
- Monitor for aspiration; dysphagia is common, consider NG tube
- Avoid restarting antipsychotics for 2-4 weeks post-recovery; use low-potency agents
- Pitfall Confusing with serotonin syndrome; NMS has bradykinesia, no clonus

- Advanced ECT for refractory cases; DRD2 genotyping to assess recurrence risk

Key Pearls

- NMS is triggered by D2 antagonists (haloperidol, metoclopramide); rigidity and fever are hallmark
- DSM-5 criteria confirm diagnosis; CK >1000 U/L is near-universal
- Stop offending drug; dantrolene and bromocriptine are mainstays
- Rhabdomyolysis and AKI are major risks; hydrate aggressively
- Rare metoclopramide-induced NMS requires GI alternative (e.g., domperidone)

References

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