APORIA · ISSUE FIVE

05

Heat and Iron.

A young man on an antipsychotic and a recently added antidepressant is rigid, febrile, and barely responsive. Four diagnoses fit the same body. Two of the treatments, given to the wrong one, will kill him.

CLINICAL DILEMMAS IN PSYCHIATRY

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01 / APORIA

The same body, four diagnoses, opposite hands

A 24-year-old man with a first episode of psychosis is three weeks into haloperidol, recently raised to 15 mg a day after agitation on the ward. Sertraline was added five days ago for low mood. Last night he stopped drinking. This morning he is mute, staring, holding a posture his hands were placed in. His temperature is 39.4 degrees Celsius, his limbs resist passive movement like bending a lead pipe, his pulse is 130, his blood pressure swings from 150 to 90 over the course of an hour, and he is drenched in sweat. The intern, who has just read about it, says serotonin syndrome and reaches to give cyproheptadine. The registrar says neuroleptic malignant syndrome and reaches to stop the haloperidol. The consultant looks at the posturing and the waxy limbs and asks for a vial of lorazepam. All three are looking at the same patient.

This is the aporia of the fifth issue. Neuroleptic malignant syndrome (NMS), malignant catatonia (MC), serotonin syndrome (SS), and the severe extrapyramidal syndromes (EPS) converge on one final common picture: rigidity, hyperthermia, altered consciousness, and autonomic instability, arising in a patient on psychotropic drugs. They share a population, a tempo, and a set of vital signs. They do not share a treatment. Stopping the antipsychotic rescues the NMS patient and is irrelevant to the serotonin patient. Giving an antipsychotic to sedate an agitated patient can be fatal in malignant catatonia. Giving an anticholinergic for presumed EPS does nothing for serotonin toxicity and worsens the hyperthermia. The diagnostic question is not academic. It selects the hand that helps from the hand that harms.

This issue walks the four-way differential from the vocabulary of rigidity and heat, through each syndrome in full, into the reasons they are confused, then to the discriminators that separate them at the bedside and in the laboratory, the bedside tools that resolve ambiguity (the lorazepam challenge above all), the mimics that are not psychiatric at all, and finally management in depth, syndrome by syndrome, including the honest algorithm for the patient you genuinely cannot classify yet. The reference list anchors every clinical claim to the canon and to the 2021 to 2025 literature, with India-specific data on drug availability where it changes what you can actually do.

> WHAT THIS ISSUE COVERS
>
> Four life-threatening hyperthermic-rigid syndromes, described in full, then separated. The structure is: definitions first, the four syndromes second (NMS, malignant catatonia, serotonin syndrome, the extrapyramidal family), the overlap that confuses them third, the discriminators and bedside tools fourth, the non-psychiatric mimics fifth, management by syndrome sixth, and the Indian frame of drug access and the law seventh. The piece closes by resolving the patient in the lede. Fourteen chapters. The evidence base is the British Association for Psychopharmacology 2023 catatonia consensus, the international NMS consensus criteria, the Hunter serotonin toxicity criteria, and recent reviews and case series current to 2025.

Why this differential matters in Indian practice

Three facts shape this differential in India specifically. First, polypharmacy is the norm, not the exception: a patient may arrive on an antipsychotic, an antidepressant, tramadol from an orthopaedic consult, and an over-the-counter cough syrup containing dextromethorphan, any combination of which can tip into serotonin toxicity or mask the picture. Second, the specific antidote for the most feared of these, intravenous dantrolene for NMS, is effectively unavailable in most Indian hospitals: it is import-dependent, brand-only, expensive, and stocked in a handful of metro centres.[22] The management that India can actually deliver leans on what is at hand, which is supportive care, benzodiazepines, bromocriptine tablets, and electroconvulsive therapy (ECT), and India is one of the few places where ECT access for malignant catatonia is a realistic same-week option. Third, the lorazepam challenge, which costs almost nothing and is available everywhere, is the single most useful disambiguating test in this differential, and it is underused.

02 / DEFINITIONS

The vocabulary of rigidity and heat

The words matter because the type of rigidity and the quality of the fever point toward different diagnoses before any test returns. Rigidity is not one thing. Hyperthermia is not the same as fever. Getting the vocabulary right is the first act of disambiguation.

> LEAD-PIPE RIGIDITY
>
> Uniform resistance to passive movement throughout the range of motion, in both flexor and extensor directions, not velocity-dependent. The hallmark of **NMS**. It reflects sustained extrapyramidal motor activation from dopamine blockade and is the engine of the heat and the muscle breakdown.

> COGWHEEL RIGIDITY
>
> Ratchet-like interrupted resistance, lead-pipe rigidity with superimposed tremor. A sign of **drug-induced parkinsonism** and milder extrapyramidal states.

> CLONUS AND HYPERREFLEXIA
>
> Rhythmic involuntary muscle contractions on sustained stretch, with brisk reflexes, typically **lower-limb predominant**. The discriminating sign of **serotonin syndrome**. Neuromuscular excitation, not the rigid hypertonia of NMS, is the serotonergic signature. Ocular clonus (slow continuous horizontal eye movements) is highly suggestive.

> WAXY FLEXIBILITY (CEREA FLEXIBILITAS) AND GEGENHALTEN
>
> In **catatonia**, limbs may hold a posture into which they are placed (waxy flexibility), or resist passive movement in proportion to the force applied (gegenhalten, paratonia). Posturing, mutism, negativism, staring, echophenomena, and stereotypy accompany the motor signs. These are the features that distinguish malignant catatonia from NMS at the bedside, when they are present.

HYPERTHERMIA VERSUS FEVER

Fever is a regulated rise in the hypothalamic set point (infection, inflammation). **Hyperthermia** is heat production outstripping dissipation with the set point unchanged, driven here by sustained muscle activity. The hyperthermia of NMS, MC, and SS responds poorly to antipyretics and requires physical cooling and treatment of the underlying muscular hyperactivity. Temperatures above 41 degrees Celsius signal life-threatening toxicity in any of these syndromes. [6]

The three axes

Each syndrome is, mechanistically, a disturbance on one neurotransmitter axis, and the axis predicts both the offending drug and the antidote.

- **Dopamine (deficit).** NMS is acute central dopamine D2 blockade or withdrawal; the parkinsonism-hyperpyrexia syndrome is dopaminergic withdrawal in Parkinson's disease. The lever is dopamine: restore it (bromocriptine, amantadine) or remove the blocker.
- **Serotonin (excess).** SS is overstimulation of central 5-HT receptors, chiefly 5-HT2A, by serotonergic drugs alone, in overdose, or in interaction. The lever is serotonin: remove the agonists, and consider a 5-HT2A antagonist.
- **GABA (deficit) and glutamate.** Catatonia is associated with hypoactivity of cortical GABA-A signalling and dysregulated glutamate; this is why benzodiazepines (GABA-A agonists) relieve it and why the lorazepam challenge is both test and treatment. [4,12]

THE UNIFYING IDEA

All four produce heat by the same final mechanism: sustained, involuntary skeletal muscle activity that the body cannot cool fast enough. The differences are upstream, in which neurochemical lesion is driving the muscle. Read the muscle (its rigidity type), read the reflexes, read the drug list, and you are reading the axis.

03 / NMS

The dopamine-blockade emergency

Neuroleptic malignant syndrome is an idiosyncratic, life-threatening reaction to dopamine antagonism, classically to antipsychotics but also to antiemetics (metoclopramide, prochlorperazine) and to the abrupt withdrawal of dopaminergic drugs. Mortality has fallen from around 20 to 30 per cent in older series to under 10 per cent today, attributed almost entirely to earlier recognition and withdrawal of the offending drug. [2,4]

Pathophysiology

The central event is acute reduction of dopaminergic transmission. D2 blockade in the hypothalamus impairs thermoregulation; in the nigrostriatal pathway it produces rigidity; in the mesolimbic and mesocortical pathways it contributes to altered mental status. The sustained muscle contraction generates heat and breaks down myocytes, releasing creatine kinase (CK) and myoglobin. A parallel literature frames NMS as a drug-induced variant of malignant catatonia, sharing the low serum iron of the acute-phase response and a common cortico-striato-thalamo-cortical circuit disturbance. [5] This is not a semantic point: it is why benzodiazepines and ECT, the treatments for catatonia, also work in NMS.

Risk factors

- **Drug factors:** high-potency first-generation antipsychotics (haloperidol, fluphenazine), parenteral and depot formulations, rapid dose escalation, high doses, multiple antipsychotics. Second-generation agents and even aripiprazole and clozapine can cause it (clozapine-related NMS often presents with less rigidity).
- **Patient factors:** agitation, dehydration, exhaustion, restraint, intercurrent illness, iron deficiency, prior NMS (a strong predictor of recurrence), young adult males (an epidemiological signal, not a rule), catatonia preceding antipsychotic exposure.
- **Environmental:** heat, physical exertion.

Clinical features and tempo

NMS evolves over **one to three days**, more slowly than serotonin syndrome, and most cases begin within two weeks of starting or increasing the offending drug. The classic tetrad:

1. **Hyperthermia** (above 38 degrees Celsius, often above 40), poorly responsive to antipyretics.
2. **Lead-pipe rigidity**, generalised, often with tremor, dysphagia, dysarthria, sialorrhoea.
3. **Altered mental status**, classically a fluctuating encephalopathy from alert mutism to stupor and coma.
4. **Autonomic instability**: tachycardia, labile or high blood pressure, tachypnoea, diaphoresis, urinary incontinence.

Laboratory findings

- **CK markedly elevated**, frequently above 1000 IU/L and sometimes above 100,000; the international criteria use a threshold of at least four times the upper limit of normal.[1] Degree of elevation tracks severity and rhabdomyolysis risk.
- **Leukocytosis** (often 10,000 to 40,000 with left shift).
- **Low serum iron**, a sensitive though nonspecific marker shared with malignant catatonia.[5]
- Raised LDH, transaminases, metabolic acidosis; myoglobinuria and acute kidney injury in severe cases.

> INTERNATIONAL CONSENSUS CRITERIA (GURRERA 2011)
>
> A Delphi panel assigned priority weights to: recent dopamine antagonist exposure (or dopamine agonist withdrawal); hyperthermia (above 38.0 on two occasions); rigidity; mental status alteration; CK elevation (at least 4x ULN); sympathetic nervous system lability (defined by blood pressure elevation or fluctuation, diaphoresis, or incontinence); hypermetabolism (tachycardia plus tachypnoea); and a negative workup for other causes.[1] The criteria formalise what the bedside already suggests: drug exposure plus the tetrad plus a clean exclusion.

Complications

Rhabdomyolysis and acute kidney injury, aspiration pneumonia, respiratory failure from chest wall rigidity, venous thromboembolism (a major and underappreciated cause of death in immobile, hyperthermic patients), disseminated intravascular coagulation, arrhythmia, and seizures.

04 / MALIGNANT CATATONIA

Stauder's lethal form

Catatonia is a psychomotor syndrome of motor, behavioural, and autonomic signs that occurs across psychiatric and medical illness. **Malignant catatonia** (historically lethal catatonia, described by Stauder in 1934) is catatonia with fever and autonomic instability, a medical emergency with mortality that approached 50 per cent before ECT and benzodiazepines. The crucial conceptual move, codified by the British Association for Psychopharmacology 2023 consensus, is that **NMS is best understood as a drug-induced form of malignant catatonia**.[4,5] They sit on one spectrum. This reframing is what makes the differential tractable and the treatment rational.

Why this is the dangerous one to miss

Malignant catatonia is the syndrome where the reflexive psychiatric move, giving an antipsychotic to a febrile agitated or stuporous patient, is actively harmful: antipsychotics can precipitate or worsen malignant catatonia and convert it into NMS. The patient who is mute, posturing, and febrile and who is then given haloperidol for presumed agitation can deteriorate catastrophically. Recognising catatonia *before* reaching for an antipsychotic is the single most important safety habit in this entire differential.

Clinical features

Two phenotypes converge into the malignant form:

- **Stuporous (retarded) catatonia:** immobility, mutism, staring, posturing, waxy flexibility, negativism, withdrawal, refusal of food and fluid.
- **Excited catatonia:** severe psychomotor agitation, purposeless overactivity, impulsivity, autonomic arousal, which can be mistaken for mania or agitated delirium.

When fever, autonomic instability, and rigidity supervene on either, the label becomes malignant catatonia. Echophenomena (echolalia, echopraxia), automatic obedience, ambitendency, and grasp reflex may be present and are useful because they are not features of NMS or serotonin syndrome.

The Bush-Francis Catatonia Rating Scale

The Bush-Francis Catatonia Rating Scale (BFCRS) is the standard instrument: a 14-item screening subscale and a 23-item full scale rating excitement, immobility/stupor, mutism, staring, posturing, grimacing, echophenomena, stereotypy, mannerisms, negativism, waxy flexibility, withdrawal, autonomic abnormality, and others.[4,21] Two or more screening items present is the usual threshold to suspect catatonia and proceed to a lorazepam challenge. The scale also tracks treatment response: a falling BFCRS score quantifies improvement (see section 08).[13]

Aetiology

Malignant catatonia is transdiagnostic. Causes include mood disorders (the commonest psychiatric cause), schizophrenia spectrum, autism, and a long list of medical and neurological precipitants: autoimmune encephalitis (especially anti-NMDA receptor encephalitis), CNS infection, metabolic derangement, and sudden withdrawal of clozapine or benzodiazepines.[4,5,15,19] A medical cause must always be sought; catatonia is frequently the surface of a treatable organic illness.

05 / SEROTONIN SYNDROME

The 5-HT excess emergency

Serotonin syndrome, more precisely serotonin toxicity, is a dose-related spectrum of toxicity from increased central serotonergic activity, ranging from mild adverse effects to a life-threatening crisis. Incidence is rising with the prescription of serotonergic drugs.[6] Unlike NMS, it is not idiosyncratic: it is a predictable consequence of too much serotonin, and the more serotonergic agents on board, the higher the risk.

Offending drugs and interactions

- **SSRIs and SNRIs** (the commonest culprits, especially in combination or overdose).
- **MAOIs** (including linezolid, an antibiotic, and methylene blue, a dye used in surgery), which produce the most severe reactions, particularly combined with SSRIs.
- **Opioids:** tramadol, pethidine (meperidine), fentanyl, dextromethorphan (in cough syrups).
- **Others:** triptans, ondansetron, lithium, St John's wort, MDMA and amphetamines, buspirone.

The dangerous combinations in real practice are an SSRI plus tramadol, an SSRI plus linezolid, and the switch between an SSRI and an MAOI without an adequate washout.

Tempo and clinical features

Onset is **rapid**, typically within 24 hours of a dose increase or a new serotonergic drug, often within 6 hours. This speed is itself a discriminator: NMS takes days. The triad:

1. **Neuromuscular excitation:** clonus (spontaneous, inducible, or ocular), hyperreflexia, tremor, myoclonus, rigidity in severe cases. Findings are classically **lower-limb predominant**.
2. **Autonomic instability:** hyperthermia, tachycardia, hypertension, diaphoresis, mydriasis (dilated pupils), flushing, hyperactive bowel sounds, diarrhoea.
3. **Altered mental status:** agitation, anxiety, restlessness, confusion.

> HUNTER SEROTONIN TOXICITY CRITERIA
>
> In a patient who has taken a serotonergic agent, serotonin toxicity is diagnosed if **any one** of the following is present:[6,7]
>
> - Spontaneous clonus
> - Inducible clonus **with** agitation or diaphoresis
> - Ocular clonus **with** agitation or diaphoresis
> - Tremor **and** hyperreflexia
> - Hypertonia **and** temperature above 38 degrees Celsius **with** ocular clonus or inducible clonus
>
> The Hunter criteria (sensitivity ~84 per cent, specificity ~97 per cent against a toxicologist's diagnosis) outperform the older Sternbach criteria and centre on clonus, the feature that most reliably separates serotonin toxicity from NMS.

The pupils and the gut

Two bedside signs are quietly decisive. **Mydriasis** (dilated pupils) and **hyperactive bowel sounds with diarrhoea** point toward serotonin toxicity; NMS and malignant catatonia do not produce them. Conversely, the rigidity of severe serotonin toxicity can mimic NMS, which is why clonus and the drug history carry the diagnosis.

06 / EPS

The extrapyramidal family and its malignant edges

The extrapyramidal syndromes are the movement disorders of dopamine blockade. Most are not emergencies and are not confused with the hyperthermic crises, but they belong in this differential for two reasons: they share the offending drugs, and two of them sit at the dangerous edge where EPS shades into, or mimics, NMS.

The four classical EPS

- **Acute dystonia:** sustained involuntary muscle contraction (oculogyric crisis, torticollis, laryngospasm), hours to days after starting or increasing an antipsychotic. Young men are at highest risk. Laryngeal dystonia is an airway emergency. Rapidly reversed by anticholinergics.
- **Akathisia:** subjective inner restlessness with an irresistible urge to move. Frequently misread as agitation or worsening psychosis, which provokes a dangerous reflex to increase the antipsychotic. Linked to distress and suicidality.
- **Drug-induced parkinsonism:** bradykinesia, cogwheel rigidity, tremor, hypomimia, shuffling gait, developing over weeks. The chronic state that, pushed far enough, blurs into NMS.
- **Tardive dyskinesia:** late-onset choreoathetoid movements (orofacial, truncal) after months to years of dopamine blockade; mechanistically distinct (receptor supersensitivity) and not part of the acute differential.

The malignant edges

Two states are the real reason EPS is in this issue:

> SEVERE PARKINSONISM VERSUS EARLY NMS
>
> Severe drug-induced parkinsonism produces marked rigidity and can raise CK modestly. The discriminator is the rest of the picture: NMS adds hyperthermia, autonomic instability, encephalopathy, and a CK that climbs steeply. Isolated rigidity without fever or dysautonomia is parkinsonism; rigidity with the tetrad is NMS. The boundary is real and clinicians watching a rigid patient on antipsychotics must monitor temperature, autonomic signs, and serial CK precisely because EPS can be the antechamber to NMS.

PARKINSONISM-HYPERPYREXIA SYNDROME (THE NMS LOOK-ALIKE FROM THE OTHER DIRECTION)

In Parkinson's disease, **abrupt withdrawal or reduction of dopaminergic medication** (levodopa, dopamine agonists), including device failure such as a blocked deep brain stimulation battery or a malfunctioning intrathecal pump, produces a syndrome clinically indistinguishable from NMS: rigidity, fever, autonomic instability, raised CK.[16] It is NMS by mechanism (dopamine deficit) but the trigger is removal of an agonist rather than addition of an antagonist. The treatment is the mirror image: **restore the dopaminergic drug immediately**. A related entity, dyskinesia-hyperpyrexia syndrome, follows dopaminergic excess. Baclofen withdrawal (a failed intrathecal pump) can produce a similar NMS-like crisis.[17]

07 / CONFUSION

Why the four collapse into one picture

They are confused because, at the moment of presentation, they genuinely look alike. Four reasons converge.

REASON 01

A shared final pathway

All four end in sustained involuntary muscle activity producing hyperthermia, raised CK, and autonomic arousal. The output is the same regardless of the upstream lesion.

REASON 02

A shared population

The same patient, on antipsychotics and antidepressants, frequently with added analgesics and antiemetics, is at risk of all four at once. The drug list rarely points to only one.

REASON 03

A genuine spectrum

NMS and malignant catatonia are not merely similar; they are one disorder seen from two angles. Antipsychotic-induced catatonia is the bridge. The overlap is real biology, not diagnostic imprecision.

REASON 04

Encephalopathy hides the signs

A stuporous or delirious patient cannot report restlessness, cannot cooperate with a reflex examination, and cannot be assessed for the subtle clonus or posturing that would settle the question. The sickest patients are the hardest to classify.

The traps that follow from the confusion

- **The agitation trap:** akathisia or excited catatonia read as psychotic agitation, met with more antipsychotic, worsening the very process.
- **The serotonin-versus-NMS trap:** a patient on both an antipsychotic and a serotonergic drug (extremely common), where rigidity is present and the question is which axis is driving it. Clonus and pupils decide it.
- **The anchoring trap:** the last thing changed gets the blame. Sertraline was added five days ago, so it must be serotonin syndrome, when the haloperidol raised three weeks ago is the actual culprit.
- **The sepsis trap:** attributing fever and altered mental status to infection and missing the rigidity, or the reverse, attributing everything to a drug syndrome and missing meningitis.

08 / DISCRIMINATORS

Telling them apart

This is the centre of the issue. The four are separated by the drug history, the tempo, the type of rigidity, the reflexes and pupils, the gut, the mental-status signature, and a small number of cheap tests. No single feature is pathognomonic; the pattern is. The comparison is split into two tables: history and examination first, then fever, laboratory, and the first treatment move.

PART A: HISTORY AND EXAMINATION

FEATURE	NMS	MALIGNANT CATATONIA	SEROTONIN SYNDROME	SEVERE EPS
Offending drug	Dopamine antagonist started/raised; or dopaminergic withdrawal	Often antipsychotic, but may precede any drug; medical/autoimmune triggers	Serotonergic agent(s), interaction, or overdose	Dopamine antagonist; dose-related
Onset / tempo	Days (1 to 3), within 2 weeks of change	Days, may evolve from psychiatric prodrome	Rapid, within 24 h (often 6 h)	Hours (dystonia) to weeks (parkinsonism)
Rigidity type	Lead-pipe, generalised, severe	Rigidity plus posturing, waxy flexibility, gegenhalten	Hypertonia, lower-limb predominant (severe cases)	Cogwheel; sustained dystonic contraction
Reflexes / clonus	Normal or reduced reflexes; no clonus	Variable; no clonus	Hyperreflexia, clonus (spontaneous/inducible/ocular)	Normal
Pupils	Normal	Normal	Mydriasis (dilated)	Normal
Bowel sounds	Normal or reduced	Normal or reduced	Hyperactive, diarrhoea	Normal
Mental status	Stupor, mutism, fluctuating encephalopathy	Mutism, staring, negativism, echophenomena, posturing	Agitation, anxiety, restlessness	Alert (akathisia restless); normal sensorium

PART B: FEVER, LABORATORY, AND FIRST MOVE

FEATURE	NMS	MALIGNANT CATATONIA	SEROTONIN SYNDROME	SEVERE EPS
Fever	High, hours to days, antipyretic-resistant	High in malignant form	Proportional to severity; can exceed 41 C	Absent (except parkinsonism-hyperpyrexia)
CK	Markedly high (often >1000; ≥4x ULN)	Often raised	Mild to moderate (severe if rigid)	Normal or mildly raised
Serum iron	Low	Low	Normal	Normal
Lorazepam challenge	Partial benefit (spectrum overlap)	Often responds (test and treatment)	Sedates, reduces tone	No specific catatonic response
First treatment move	Stop antagonist; supportive; dopaminergic agent	Lorazepam; ECT; avoid antipsychotics	Stop serotonergic; benzodiazepine; cooling	Anticholinergic (dystonia); reduce dose

> *Clonus points to serotonin. Lead-pipe rigidity points to dopamine. Waxy flexibility and posturing point to catatonia. The drug that changed, and when, points to all three at once, so let the body, not the prescription chart alone, cast the deciding vote.*
>
> THE BEDSIDE HEURISTIC

The bedside tools, in order of usefulness

T1 **The lorazepam challenge.** Give 1 to 2 mg of lorazepam intravenously (or intramuscularly), and reassess in 5 to 10 minutes, repeating once if needed. Marked relief of mutism, rigidity, and posturing supports catatonia and is simultaneously the start of treatment. The test is cheap, fast, and available everywhere. In a pediatric multisite cohort, BFCRS fell from 16.6 to 9.5 after lorazepam, a large effect; in Indian tertiary-care data the challenge predicted response best in the first week.[13,14] Where ECT access is limited, zolpidem 5 to 10 mg has emerging evidence as an alternative challenge agent.[12]

T2 **The reflex and clonus examination.** Knees, ankles, and a careful look for ocular clonus. Hyperreflexia and clonus, lower-limb predominant, separate serotonin toxicity from the hyporeflexic rigidity of NMS. This single examination is the most discriminating physical finding in the differential.

T3 **The Hunter criteria** for serotonin toxicity and the **BFCRS** for catatonia. Apply both deliberately; they structure the examination and document the reasoning.

T4 **Serial CK and serum iron.** A steeply rising CK and a low serum iron support the NMS/malignant-catatonia end of the spectrum. A single value is less useful than the trend.

T5 **Tests to exclude mimics:** full blood count, cultures, lumbar puncture and neuroimaging where infection or encephalitis is possible, EEG (to exclude non-convulsive status and to support encephalitis), thyroid function, anti-NMDA receptor antibodies when catatonia is unexplained or refractory.[19]

Patient and life-stage factors

- **Children and adolescents:** catatonia is under-recognised, especially in autism and neurodevelopmental disability; the lorazepam challenge is effective and safe in this group.[13] NMS occurs and may be missed.
- **Older adults:** higher serotonin-syndrome risk with antidepressant polypharmacy; presentations are often milder and attributed to other causes.[18] Parkinson's disease raises the stakes for parkinsonism-hyperpyrexia.
- **Pregnancy and the perinatal period:** catatonia and NMS both occur; the BAP guideline addresses perinatal management specifically, and the threat of dehydration and venous thromboembolism is heightened.[4]
- **Medical and neurological comorbidity:** cerebral palsy, intellectual disability, autism, and Parkinson's disease change both the baseline motor examination and the differential, and demand a search for device failure (intrathecal baclofen, DBS) and medication withdrawal.[16,17]
- **Prior episodes:** a previous episode of NMS or catatonia strongly predicts recurrence and reshapes the risk-benefit of rechallenge.

Course and prognosis

- **NMS:** resolves over 1 to 2 weeks after the offending drug is stopped (longer with depot antipsychotics). Mortality under 10 per cent with early recognition; death is from rhabdomyolysis-related kidney injury, respiratory failure, thromboembolism, and arrhythmia.[2,4]
- **Malignant catatonia:** historically up to 50 per cent mortality untreated; excellent response to benzodiazepines and ECT when recognised early. Delay is the enemy.
- **Serotonin syndrome:** usually resolves within 24 to 72 hours of stopping serotonergic drugs and supportive care; severe cases with hyperthermia above 41 degrees carry significant mortality.[6]
- **EPS:** acute dystonia reverses in minutes with treatment; akathisia and parkinsonism resolve over days to weeks with dose adjustment; parkinsonism-hyperpyrexia carries NMS-level risk if not reversed.

09 / EXCLUDE

The mimics that are not psychiatric

Before settling on a drug-induced syndrome, exclude the conditions that present identically and that a psychiatric anchor will cause you to miss. A negative workup for these is part of the NMS criteria for a reason.[1]

MIMIC	DISCRIMINATING FEATURES	TEST
CNS infection (meningitis, encephalitis)	Meningism, headache, focal signs, prodromal illness; fever precedes rigidity	Lumbar puncture, neuroimaging, blood cultures
Anti-NMDA receptor encephalitis	Subacute psychosis, catatonia, seizures, dyskinesia, autonomic instability; young women, often refractory catatonia	CSF and serum NMDAR antibodies, EEG, MRI, pelvic imaging (teratoma) [19]
Malignant hyperthermia	Within minutes of volatile anaesthetic or succinylcholine; masseter spasm, hypercarbia; family history	Anaesthetic history, rising end-tidal CO2; dantrolene [10]
Sepsis / heat stroke	Source of infection or environmental heat exposure; often hyporeflexic, vasodilated	Cultures, lactate, imaging, exposure history
Anticholinergic toxidrome	Dry skin and mucosae (not diaphoretic), flushing, urinary retention, absent bowel sounds, mydriasis	Drug history (antihistamines, TCAs, datura); clinical
Sympathomimetic toxicity	Cocaine, amphetamines; diaphoresis, mydriasis, severe hypertension; intact reflexes	Drug history, urine toxicology
Thyroid storm	Goitre, ophthalmopathy, atrial fibrillation, diarrhoea, precipitant	TSH, free T4 and T3
Non-convulsive status epilepticus	Altered consciousness without obvious convulsion; subtle eye or facial movements	EEG
Withdrawal (alcohol, benzodiazepine, baclofen)	Tremor, autonomic arousal, seizures; baclofen pump failure mimics NMS	History, device interrogation [17]

> THE DISCIPLINE
>
> The anticholinergic toxidrome is the most elegant near-miss: it shares mydriasis and agitation with serotonin syndrome but the skin is **dry**, the bowel sounds are **absent**, and there is no clonus, the inverse of the serotonergic gut and the serotonergic reflexes. Touch the skin and listen to the abdomen before you commit.

10 / MANAGEMENT

By syndrome, in depth

Management has two layers: the supportive care that every one of these patients needs from the first minute, and the syndrome-specific therapy that follows the diagnosis. The supportive layer buys the time in which the diagnosis declares itself.

Shared supportive care (all four)

- **Stop the offending agent** (antipsychotic for NMS; all serotonergic drugs for SS) or **restore the missing one** (dopaminergic drug in parkinsonism-hyperpyrexia). This is the first and most important step.
- **Resuscitation and monitoring:** airway protection if obtunded, oxygen, continuous cardiac and temperature monitoring, ICU or high-dependency care for severe cases.
- **Aggressive cooling:** physical measures (cooling blankets, ice packs, cold IV fluids); antipyretics are largely ineffective because the set point is normal. Temperatures above 41 degrees require sedation, paralysis,

and intubation.[7]

- **Fluids and renal protection:** aggressive intravenous hydration to prevent and treat rhabdomyolysis-induced acute kidney injury; monitor CK, renal function, and potassium; consider urinary alkalinisation in severe rhabdomyolysis.
- **Prophylaxis:** venous thromboembolism prophylaxis (a leading preventable cause of death), aspiration precautions, pressure-area care.
- **Benzodiazepines** are useful across the board for agitation and rigidity and are first-line specific therapy for catatonia.

NMS-specific

- **Withdraw the dopamine antagonist** (or reinstate the dopaminergic agent if withdrawal-induced).
- **Benzodiazepines:** lorazepam 1 to 2 mg parenterally, repeated, for milder cases and to treat any catatonic component.
- **Dantrolene:** for severe hyperthermia and rigidity, 1 to 2.5 mg/kg intravenously initially, then 1 mg/kg every 6 hours, to a maximum of 10 mg/kg/day, tapering or switching to oral over days.[24] A direct skeletal muscle relaxant; reduces rigidity, heat, and CK.
- **Bromocriptine:** a dopamine agonist, 2.5 mg orally two to three times daily, titrated up to 45 mg/day; restores dopaminergic tone. Amantadine 200 to 400 mg/day orally or by nasogastric tube is an alternative.[24]
- **ECT:** for cases refractory to supportive care and pharmacotherapy, or where malignant catatonia cannot be excluded. ECT treats both NMS and malignant catatonia, which is exactly why it is the rational fallback when the two cannot be separated.[4]
- **Rechallenge:** if an antipsychotic is later essential, wait at least two weeks after full recovery, choose a low-potency or second-generation agent at a low dose, titrate slowly, and monitor. Prior NMS is a strong recurrence risk.

Malignant catatonia-specific

- **Lorazepam** first-line, and at higher doses than many clinicians expect: titrate from 1 to 2 mg upward, with total daily doses of 8 to 16 mg or more used in responsive cases under monitoring.[4]
- **ECT** is the definitive treatment for malignant catatonia and should not be delayed when the patient is deteriorating or fails to respond to benzodiazepines; it is first-line, not a last resort, in the malignant form.[4]
- **Avoid antipsychotics**, which can precipitate or worsen malignant catatonia and tip it into NMS. If an underlying psychosis must eventually be treated, do so only after the catatonia has resolved, cautiously.
- **Treat the cause:** investigate and treat any medical or autoimmune precipitant (anti-NMDA receptor encephalitis requires immunotherapy and tumour removal, not benzodiazepines alone).[19]

Serotonin syndrome-specific

- **Discontinue all serotonergic agents.** This alone resolves most cases within 24 to 72 hours.
- **Benzodiazepines** for agitation, tremor, and to blunt autonomic arousal; the mainstay of pharmacological control.
- **Cyproheptadine**, a 5-HT2A antagonist, for moderate-to-severe cases not settling with supportive care: 12 mg orally (or by nasogastric tube) initially, then 2 mg every 2 hours until response, to roughly 32 mg/day.

The evidence is weak (case-level only) and it is an adjunct, never a substitute for stopping the drugs and supporting the patient.[8,9] It is oral-only, which matters in the obtunded patient.

- **Severe toxicity** (temperature above 41 degrees, rigidity compromising ventilation): intubation, sedation, and neuromuscular paralysis with a non-depolarising agent, plus active cooling. Avoid physical restraints alone, which worsen lactic acidosis and hyperthermia.
- Do not give antipyretics (ineffective) or bromocriptine/dantrolene as primary therapy (not indicated for SS, and dantrolene has no proven benefit here).

EPS-specific

- **Acute dystonia:** intramuscular or intravenous anticholinergic (promethazine, or benztropine/trihexyphenidyl where available) or diphenhydramine; relief within minutes. Treat laryngeal dystonia as an airway emergency.
- **Akathisia:** reduce the antipsychotic dose; propranolol is first-line; consider a benzodiazepine; mirtazapine has evidence. Crucially, do not mistake it for agitation and increase the antipsychotic.
- **Drug-induced parkinsonism:** reduce the dose or switch to a lower-potency agent; anticholinergics help but carry cognitive cost in the elderly.
- **Parkinsonism-hyperpyrexia syndrome: reinstate dopaminergic medication immediately** (restart levodopa or the agonist, restore the device), plus supportive care; this is the mirror image of NMS treatment.[16] Baclofen-withdrawal crises require baclofen reinstatement.[17]

The honest algorithm for the patient you cannot yet classify

Often the diagnosis is not clear in the first hour, and the patient cannot wait. A safe empirical sequence:

01 **Stop the suspects and support.** Withhold all antipsychotics and all serotonergic drugs at once; never give an antipsychotic to sedate. Begin cooling, fluids, monitoring, and VTE prophylaxis.

`This is safe whichever of the four it turns out to be.`

02 **Examine for the discriminators.** Clonus and pupils (serotonin), lead-pipe rigidity (NMS), posturing and waxy flexibility (catatonia). Send CK, serum iron, FBC, renal function, and screen for mimics.

03 **Give a benzodiazepine.** Lorazepam 1 to 2 mg parenterally serves three purposes at once: it treats agitation, it is therapeutic for catatonia and NMS, and a clear catatonic response is diagnostic.

`Responds:` favour catatonia, continue and escalate lorazepam.

04 **If serotonergic drugs are implicated and clonus is present,** treat as serotonin syndrome (supportive plus cyproheptadine if needed). **If lead-pipe rigidity, high CK, and the tetrad dominate,** treat as NMS (dantrolene, dopamine agonist).

05 **If the patient is deteriorating and you still cannot separate NMS from malignant catatonia,** proceed to ECT. It treats both, and indecision is more dangerous than ECT.

`ECT is the unifying answer at the dangerous end of the spectrum.`

11 / INDIAN FRAME

Availability, access, and the law

The textbook algorithm assumes a pharmacy that India often does not have. What you can do depends on what is on the shelf, and the gap reshapes the priorities.

The dantrolene problem

Intravenous dantrolene, the muscle relaxant for severe NMS (and the specific antidote for malignant hyperthermia), is **not reliably available in India**. It is import-dependent, brand-only with no generic, expensive, and stocked in a small number of metropolitan centres; it is often obtained on a named-patient import basis, and shelf life is short. [22] The practical consequence: Indian management of severe NMS leans more heavily on the universally available levers, namely stopping the antipsychotic, aggressive supportive care, benzodiazepines, oral bromocriptine and amantadine, and early ECT. A clinician should know in advance whether their hospital can obtain dantrolene at all, because discovering the answer during a crisis is too late.

What is available and cheap

- **Lorazepam** (oral and parenteral) is widely available and is the workhorse of this differential, for the challenge test and for treatment.
- **Bromocriptine and amantadine** are available as oral tablets.
- **Cyproheptadine** is inexpensive and ubiquitous (brands such as Practin and Ciplactin, around template strip prices of a few rupees per tablet) but is **oral-only**, which limits it in the obtunded serotonin-syndrome patient who needs nasogastric administration. [23]
- **Anticholinergics** for dystonia (promethazine, trihexyphenidyl) are universally stocked.

ECT and the law

India is, in one respect, well placed: ECT is widely practised and accessible, which matters because ECT is the definitive treatment for malignant catatonia and the fallback for NMS that cannot be separated from it. Under the **Mental Healthcare Act 2017**, ECT requires modified technique (anaesthesia and muscle relaxation), is prohibited for minors without Mental Health Review Board approval, and ordinarily requires informed consent. In the emergency of malignant catatonia, where the patient lacks capacity and delay is life-threatening, ECT may proceed under the Act's emergency provisions with the appropriate consent pathway (nominated representative, and Board processes as applicable). Document capacity, the emergency, the consent route, and the clinical reasoning carefully; this is both good practice and medicolegal protection.

> DOCUMENTATION IN THE INDIAN MEDICOLEGAL CONTEXT
>
> These are high-mortality syndromes in patients who frequently lack capacity, on drugs the clinician prescribed. Record the indication for the original drug, the recognition of the syndrome, the time the offending drug was stopped, the consent pathway for ECT, and the involvement of family or nominated representative. A clear contemporaneous record is the single best defence if an outcome is poor.

12 / THE PATIENT

The case in the lede, resolved

Return to the 24-year-old. He is on haloperidol, raised three weeks ago, and sertraline, added five days ago. He is mute and posturing, with limbs that hold the position they are placed in, lead-pipe in quality, febrile at 39.4, tachycardic, labile, diaphoretic. The intern saw the recent sertraline and thought serotonin syndrome. But there is **no clonus, no hyperreflexia, no mydriasis, and no diarrhoea**: the serotonergic signature is absent. The registrar saw the haloperidol and the lead-pipe rigidity and high suspicion of a rising CK, and thought NMS, which is closer. The consultant saw the **posturing, the waxy flexibility, the mutism**, and recognised that NMS and malignant catatonia are the same spectrum, and that the safest and most informative next move is not an antipsychotic and not cyproheptadine but a **vial of lorazepam**.

Lorazepam 2 mg is given intravenously. Within ten minutes the posturing eases and he speaks a few words. The picture is malignant catatonia, very likely antipsychotic-related, on the NMS-catatonia spectrum. The haloperidol is stopped, the sertraline is held, supportive care and VTE prophylaxis begin, CK returns at 4,200 IU/L and serum iron is low (consistent with the spectrum), and the meningitis and encephalitis workup is sent and is clean. He is escalated on lorazepam and, because he remains febrile and rigid the next morning, ECT is started. He recovers over a week. The antipsychotic question is deferred until the catatonia has fully resolved, and is then approached with a low-dose second-generation agent under close monitoring.

The lesson of the case is the lesson of the issue. The most recently changed drug is not always the culprit. The serotonergic signature is specific, and its absence matters as much as its presence. And when the dangerous end of the spectrum cannot be parsed into NMS versus malignant catatonia, the benzodiazepine challenge and then ECT answer the question by treating both.

13 / PEARLS

Short clinical pearls

01	**Clonus is the keystone.** Lower-limb-predominant clonus and hyperreflexia mean serotonin until proven otherwise. NMS does not produce clonus.
02	**Read the rigidity.** Lead-pipe is dopamine (NMS). Waxy flexibility and posturing are catatonia. Cogwheel is parkinsonism.
03	**Tempo separates.** Hours to one day favours serotonin syndrome. One to three days favours NMS.
04	**Pupils and gut.** Mydriasis, hyperactive bowel sounds, and diarrhoea point to serotonin; their absence argues against it.
05	**Never give an antipsychotic to sedate a febrile rigid patient** until you have excluded malignant catatonia. It can be fatal.
06	**The lorazepam challenge is test and treatment.** Cheap, fast, available, and diagnostic. Use it early.
07	**NMS and malignant catatonia are one spectrum.** ECT treats both, so it is the answer when you cannot separate them.

08 **Don't anchor on the last drug changed.** The antipsychotic raised three weeks ago can be the culprit, not the antidepressant added last week.

09 **Dry skin, absent bowel sounds, no clonus** with agitation and mydriasis is anticholinergic toxicity, not serotonin syndrome.

10 **Parkinson's patient, fever, rigidity?** Ask what dopaminergic drug was stopped or which device failed. Restart it; do not stop it.

11 **Cyproheptadine is an adjunct, not a rescue.** Stopping the drugs and supporting the patient is the cornerstone of serotonin-syndrome care.

12 **Know your dantrolene access before the crisis.** In much of India it is unavailable; plan for supportive care, bromocriptine, and ECT.

13 **Refractory catatonia in a young patient?** Send anti-NMDA receptor antibodies and look for a tumour. Immunotherapy, not benzodiazepines alone.

14 **Venous thromboembolism kills.** Immobile, hyperthermic, dehydrated patients need prophylaxis from hour one.

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Educational note. This clinical-reasoning essay is for clinicians and students. It is educational, not treatment advice for any individual. Care decisions belong with the treating clinician. At Weave, care is led by Dr. Niharika Reddy, Consultant Psychiatrist.

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Aporia 05 - Heat and Iron. Built from the British Association for Psychopharmacology 2023 catatonia consensus guideline, the Gurrera international NMS consensus criteria, the Hunter Serotonin Toxicity Criteria, and reviews and case series current to 2025, cross-checked against the Maudsley Prescribing Guidelines (15th ed). Drug doses, the Hunter decision rule, and the lorazepam-challenge technique were verified against primary sources during the build. This issue is a clinical reasoning aid for qualified clinicians, not a protocol; it does not replace local emergency and ICU pathways, senior consultation, or the prescribing information for any drug. Doses must be checked against current references and the individual patient before administration. **Dr. Wilfred D'souza**, Weave - Centre for Integrative Psychiatry. Series: *Aporia - clinical dilemmas in psychiatry.*