

Neuroleptic Malignant Syndrome (NMS) — Symptoms and Treatment

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The neuroleptic malignant syndrome is a rare, idiosyncratic, and potentially life-threatening reaction to a neuroleptic (i.e. antipsychotic) drug, although other drugs can also trigger it. Although the exact cause is uncertain, one of the main mechanisms seems to be a sudden deficiency of dopamine in the central nervous system. It is important to promptly identify this condition because of high morbidity and mortality. In this article, epidemiology, etiology, pathophysiology, diagnosis, differential diagnoses, treatment and prognosis of the neuroleptic malignant syndrome are described.



Epidemiology of Neuroleptic Malignant Syndrome

The more **recent estimates of the frequency of neuroleptic malignant syndrome indicate an incidence of 0.01% to 0.07% in patients** taking antipsychotic drugs. Even though the incidence is low, it is of considerable importance because the mortality associated with this condition is quite high – around 10% (which has decreased now because of better awareness and management). In addition, if a renal failure has ensued, the mortality risk increases to as high as 50%.

Etiology of Neuroleptic Malignant Syndrome

The neuroleptic malignant syndrome is an idiosyncratic reaction to neuroleptic (antipsychotic) drugs. These **drugs are used in the treatment of schizophrenia, bipolar disorder, and other psychotic disorders**. Antipsychotic agents can be the “traditional” (or first-generation or typical) drugs or the newer (or second-generation) “atypical” drugs.

Traditional antipsychotic drugs usually act by blocking the central dopaminergic D2 receptors (as well as a variety of other receptors) and are categorized into high-potency and low-potency drugs.

High-potency drugs include:

- Fluphenazine
- Haloperidol
- Perphenazine
- Pimozide
- Thiothixene
- Trifluoperazine

Low-potency traditional antipsychotic drugs are:

- Thioridazine (rarely used now).
- Chlorpromazine (although these do not often cause neurological complications such as neuroleptic malignant syndrome, they still can).

Atypical antipsychotic drugs act on serotonin systems by inhibiting the serotonin receptors (especially 5-HT_{2A} receptors) as well as block dopaminergic D2 receptors (although some drugs like clozapine additionally block D1 and D4 receptors).

This group includes:

- Amisulpride
- Aripiprazole
- Olanzapine
- Paliperidone
- Quetiapine
- Risperidone
- Ziprasidone

Atypical drugs are less likely to cause neuroleptic malignant syndrome than the former (apart from having other advantages) and are therefore preferred as the first-line therapy for psychotic disorders.

The neuroleptic malignant syndrome is also associated with other drugs that are not antipsychotic agents. For example, **non-antipsychotic agents that block dopaminergic receptors** are:

- Amoxapine
- Droperidol
- Diatrizoate
- Metoclopramide
- Promethazine
- Tetrabenazine

Furthermore, **when dopaminergic drugs, such as levodopa are suddenly**

withdrawn, neuroleptic malignant syndrome can be triggered. Finally, certain medications with no known central dopaminergic activity have been reported to trigger neuroleptic malignant syndrome: e.g. dosulepin, lithium, and phenelzine.

Pathophysiology of Neuroleptic Malignant Syndrome

Although the exact underlying mechanism remains unclear, a **major sudden-onset decrease in the central dopaminergic activity is the trigger mechanism.** The blockade of D2 receptors within the nigrostriatal pathways leads to extrapyramidal symptoms such as rigidity and tremor. Within the hypothalamic pathways, hyperthermia; and within the mesolimbic/cortical pathways, altered mental status.

Hyperthermia may itself contribute to the altered mental status, and it may also indirectly lead to dehydration because of excessive sweating. Muscle rigidity is a state of excessive muscular contraction, which increases muscle metabolism, and is also a significant contributor to hyperthermia in neuroleptic malignant syndrome.

Two other systems have been proposed to be implicated in neuroleptic malignant syndrome.

- Sympathetic nervous system
- Peripheral skeletal muscle system

Diagnosis of Neuroleptic Malignant Syndrome

The neuroleptic malignant syndrome is always secondary to exposure to a neuroleptic drug.

Clinical

The **cardinal features of the neuroleptic malignant syndrome** are:

- High temperature (above 38° C).
- Alteration in the level of consciousness.
- Autonomic dysregulation.
- Severe muscular rigidity (typically, lead pipe rigidity).

Autonomic dysregulation is identified by the presence of:

- Excessive sweating (diaphoresis)
- Tachycardia
- Tachypnea
- Sialorrhea
- Increased blood pressure
- Hypoxemia

Other signs and symptoms are as follows:

- Pallor
- Dysphagia
- Dyspnea
- Tremors
- Incontinence

- Mental state alteration – delirium, stupor, or coma
- Urinary incontinence (in some cases)

Laboratory

The **diagnosis of the neuroleptic malignant syndrome is mainly clinical.**

Laboratory investigations are performed to rule out other conditions or complications. Abnormal liver function test parameters, electrolyte abnormalities such as hyperkalemia, leukocytosis, proteinuria, etc. can be found in cases with the neuroleptic malignant syndrome.

As per Diagnostic and Statistical Manual of mental disorders, 5th edition (DSM-5), the **neuroleptic malignant syndrome is diagnosed in the presence of any combination of the following symptoms**, as long as exposure to a known neuroleptic malignant syndrome-causing agent is documented, and other medical causes have been ruled out.

- Hyperthermia (over 38° C on at least two occasions).
- Rigidity.
- Altered level of consciousness (reduced or fluctuating).
- Elevated creatine phosphokinase (at least four times higher).

Sympathetic nervous system lability, defined as at least two of the following:

- Elevated blood pressure (at least 25% above baseline).
- Fluctuating blood pressure (a change of ≥ 20 mmHg diastolic or ≥ 25 mmHg systolic change in 24 hours).
- Excessive sweating.
- Urinary incontinence.

Hypermetabolism: Tachycardia (at least 25% above baseline) and tachypnea (at least 50% above baseline).

Differential Diagnoses of Neuroleptic Malignant Syndrome

- Heatstroke
- Infections of the central nervous system
- Toxic encephalopathies
- Agitated delirium
- Status epilepticus
- Other drug-induced syndromes
- Alcohol or sedative withdrawal
- Malignant hyperthermia
- Malignant catatonia
- Serotonin syndrome
- Lethal catatonia

Differentiating neuroleptic malignant syndrome from serotonin syndrome and malignant hyperthermia is very important as they have similar clinical presentations. They all present with hyperthermia, autonomic dysregulation, and muscular rigidity. Malignant hyperthermia occurs secondary to the use of halogenated inhalational anesthetic agents and succinylcholine.

In serotonin syndrome, the rigidity is not “lead pipe” but is characterized by hyperkinesia and clonus. Also, the laboratory profile of proteinuria, elevated creatine kinase, elevated liver enzymes, and leukocytosis is associated more with the neuroleptic malignant syndrome than with serotonin syndrome. **Serotonin hyperactivity is also associated with gastrointestinal symptoms** such as nausea and vomiting, which are not seen in neuroleptic malignant syndrome cases.

Treatment of Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome being a potentially life-threatening condition is a medical emergency. While there is a lack of definitive evidence-based treatment for neuroleptic malignant syndrome, the **first step is to stop all the potential causative drugs**, if not already stopped.

Of course, if neuroleptic malignant syndrome has occurred due to the sudden stopping of a dopaminergic drug, then it should be promptly reinstated. In most cases, the **symptoms should start subsiding after discontinuation and resolve within 10 days**.

Supportive treatment: Apart from this, the treatment is mainly supportive.

- Correction of metabolic abnormalities.
- Administration of intravenous fluids for hydration.
- Controlling hyperthermia by antipyretics or ice packs.
- Alkalinization of urine (bicarbonate overload) to prevent renal failure.

Pharmacological treatment: Pharmacological treatment of neuroleptic malignant syndrome entails administration of nondepolarizing neuromuscular blocking agents such as pancuronium or muscle relaxants such as dantrolene (1 mg/kg every 6 hours intravenously, can be switched to oral later) to decrease muscular rigidity and, thereby, the contribution to hyperthermia by muscular contraction.

In addition, administration of dopaminergic drugs such as bromocriptine (2.5 mg orally two times a day, can be gradually increased to 45 mg if needed) or amantadine (200–400 mg/day orally in divided doses) is a usual practice in neuroleptic malignant syndrome to reverse the dopamine deficiency in the central nervous system.

Electroconvulsive therapy: In some cases, even the combination of supportive care and pharmacotherapy is ineffective. In such cases, **electroconvulsive therapy can be tried**. For neuroleptic malignant syndrome cases, the regime would be 4–10 treatments with electrodes placed bilaterally.

Anesthetic agents in these patients should be used with caution and should be individualized. For example, succinylcholine should be avoided in neuroleptic malignant syndrome patients with severe rhabdomyolysis to prevent hyperkalemia.

Progression and Prognosis of Neuroleptic Malignant Syndrome

Because of its effects on water and electrolyte balance, there **can be many complications of the neuroleptic malignant syndrome**. The risk of morbidity is high in these patients. The main complications include dehydration, acute renal failure, and deep venous thrombosis.

Dehydration can occur because of inadequate fluid intake or resuscitation, as well as excessive sweating and hyperthermia. Renal failure can result because of rhabdomyolysis. Deep venous thrombosis, as well as pulmonary embolism, can set in because of generalized rigidity and extended immobilization (this can, in turn, lead to disseminated intravascular coagulation).

Other complications include:

- Cardiopulmonary failure
- Seizures
- Arrhythmias
- Myocardial infarction
- Aspiration pneumonia
- Sepsis

Note: If the neuroleptic malignant syndrome is left untreated, death can occur in as many as 10% of the patients.

Post-neuroleptic malignant syndrome antipsychotic use: The patients who developed neuroleptic malignant syndrome were most likely taking antipsychotics for schizophrenia or other psychotic disorders, which are best treated with neuroleptic drugs. Thus, the question arises whether antipsychotic drugs can be reinstated (known as antipsychotic rechallenge) after neuroleptic malignant syndrome and whether it is safe.

Although the chance of relapse can be as high as 30% in some cases, if appropriate cautions are taken, **antipsychotics can be safely re-administered in most cases.** They should be resumed at least 2 weeks after recovery (i.e. complete resolution of symptoms) from the neuroleptic malignant syndrome, else the chances of relapse increase.

Precautions include assessing and reducing risk factors and starting with the lowest dose of a safer atypical antipsychotic.

Review Questions

1. Which of the following drug/route combinations is not appropriate in the treatment of neuroleptic malignant syndrome?

- A. Dantrolene, intravenously
- B. Bromocriptine, via nasogastric tube
- C. Amantadine, orally
- D. Dantrolene, orally
- E. Dantrolene, via nasogastric tube

2. A 40-year-old woman was hospitalized for an acute manic episode and was prescribed haloperidol. Two days after admission, she developed muscular rigidity, high temperature, profuse sweating, and tachypnea. Which of the following is the most probable diagnosis?

- A. Neuroleptic malignant syndrome
- B. Malignant hyperthermia
- C. Serotonin toxicity
- D. Status epilepticus
- E. Heatstroke

3. A 31-year-old man with depression and psychotic features was switched from

olanzapine monotherapy to a combination of olanzapine and fluoxetine. Five hours after the first dose, he developed tremors, muscular rigidity, hyperthermia, and excessive sweating. Tachycardia and tachypnea were also observed. Which of the following is the most probable diagnosis?

- A. Neuroleptic malignant syndrome
- B. Malignant hyperthermia
- C. Serotonin toxicity
- D. Status epilepticus
- E. Heatstroke

References

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Correct answers: 1E; 2 A; 3 C

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