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Case Study
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# Venlafaxine Rechallenge - Associated with Neuroleptic Malignant Syndrome

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## Abstract

Neuroleptic Malignant Syndrome (NMS) is an infrequent but a potentially life-threatening emergency, associated with the use of neuroleptic and antipsychotic medications. It is characterized by tetrad of symptoms including fever, rigidity, altered mental status and autonomic dysfunction. Although NMS is most commonly seen as a reaction to neuroleptics, its development has also been seen with use of non-neuroleptics agents that blocks central dopamine pathway.

NMS was first described in 1960 with the use of Haloperidol. It has been associated with virtually all neuroleptics including newer atypical antipsychotics. The incidence rate ranges from 0.02% to 3%. However, the incidence rate as decreased with newer neuroleptics to 0.01% to 0.02%. Due to its life-threatening nature, NMS requires prompt diagnosis and treatment, ruling out similar conditions such as Serotonin Syndrome and Malignant Hyperthermia.

**Keywords: Neuroleptic Malignant Syndrome (NMS); Parkinson disease; Hyperthermia; ED; CK; COVID**

## Introduction

A 60 year old female was admitted with one week of paranoia, hallucination, incomprehensible speech and a background history of Parkinson disease, anxiety and depression. She was on Sinemet, Amantadine and half Sinemet, Venlafaxine. Her Amantadine was stopped in community and Venlafaxine was stopped on admission. Few days later she developed persistent hyperthermia, raised CK and Lactate. A diagnosis of NMS was made, and improvement was seen with Dantrolene along with supportive measures. Patient was stabilized for discharge and her Venlafaxine was reintroduced. She had a relapse of her symptoms with high grade fever, confusion and rigidity. This case emphasizes the need and importance of rechallenging non-neuroleptic medications which resulted in relapse of NMS.

## Case Study

A 60 year old was admitted with one-week history of paranoia, hallucination, agitation, falls and seemed more confused than normal. She had history of Parkinson's disease, anxiety and depression. Her Parkinson's disease was well controlled on Sinemet and half Sinemet along with Amantadine which was stopped a week ago prior to admission by Parkinson's nurse specialist. She was also on Venlafaxine for her depression. She was due to see a psychiatrist but the visit was delayed due to the COVID pandemic.

On admission to ED, she was combative, agitated which made it difficult to get any observations or perform clinical examination. ED team managed to get her cannulated along with a VBG sample. She received 1 mg of Lorazepam IV in ED which calmed her down. Subsequently, she underwent full observations and clinical examination which did not show any abnormality. Her urine test came back normal. No acute findings noted on ECG. She also had head CT which showed no acute intracranial abnormality. So far, the only abnormality noted was in her VBG which was lactate and high at 3.1. She was given IV fluids in ED and referred to the medical team.

On admission to medical ward, she was treated as sepsis with differential including UTI or encephalitis. She was started on broad spectrum IV antibiotics with sepsis bundle. She had additional investigations including blood and urine culture which all came back negative. She was referred to neurology team to rule out encephalitis. A lumbar puncture and MRI head were performed. All came back as normal.

Patient did not improve on sepsis protocol instead remained quite rigid, confused. On day 5

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of admission she became hyperthermic with temperature of 38.9°C and developed a brief seizure. She was started on Phenytoin and had repeat blood cultures with full routine bloods including CK this time in keeping with differentials of malignant hyperthermia, Serotonin Syndrome and Neuroleptic Malignant Syndrome. Her Venlafaxine was stopped, and she was put on Rotigotine patch for her Parkinson's. Her routine bloods all came back as completely normal with no signs of infective picture. Her electrolytes, LFTS and C. Ca were all within range including CRP remaining <1, throughout her admission. Her CK came back as 739 u/l which went up to 2584 u/l on 3rd day of her hyperthermia.

The patient was treated with Dantrolene IV along with supportive cooling measures and IV fluids. She had RIG tube inserted to facilitate her Parkinson's medication. After almost 10 to 12 days patient showed progress and her symptoms resolved. She became orientated and started engaging in rehabilitation therapy. She was optimized for discharge with review of her medication and was rechallenged on her Venlafaxine. After 48 h of re-introduction of Venlafaxine, she became hyperthermic again with temperature of 38.9°C reaching up to 40°C with altered mental status, autonomic instability and rigidity. She had full sets of bloods repeated including, COVID, B C/S, urine C/S, and CK. Again, the only abnormality noted was raised CK of 1146 u/l. Treatment was initiated for relapse of Neuroleptic Malignant Syndrome, related to her antipsychotic medication, with IV Dantrolene, cooling and supportive measures. Her Venlafaxine was stopped; patient became better and was finally discharged to her own home with carer support.

## Discussion

NMS is commonly associated with high potency antipsychotic agents, formerly called as neuroleptic agents (e.g. Haloperidol, Fluphenazine) [1-2]. However, every class of antipsychotics has been implicated including low potency such as Chlorpromazine and newer atypical antipsychotic drugs including Clozapine, Risperidone, Olanzapine. Other associated medications include Antiemetics including Metoclopramide, Promethazine and Levosulpride.

Symptoms usually develop during the first two weeks of starting the therapy however; the association of NMS with antipsychotics is idiosyncratic. It can occur after single dose or after treatment with same agent at the same dose for many years. Other commonly associated risk factors include concomitant use of lithium, trauma, surgery, infection, dehydration, and malnutrition and post-partum period.

NMS is also seen in patients treated for Parkinson's disease in settling of withdrawal of L-dopa or dopamine agonist therapy, as well as with dose reductions and switch from one agent to another [3-5].

Pathogenesis of NMS is unknown. It is thought to be due to decreased dopamine activity in CNS as a result of reduced dopamine signaling due to sudden withdrawal of dopaminergic agents and introduction of Da blocking agents. Among the four dopamine receptors it is D2 receptor blockade that leads to NMS.

Disruption of central dopamine pathway in hypothalamus results in hyperthermia and other autonomic instability. Whereas interference with nigrostriatal pathway leads to Parkinson's type rigidity and tremor [6]. A primary role has also been proposed for a disrupted modulation of the sympathetic nervous system, manifesting in increased muscle tone and metabolism and unregulated sudomotor and vasomotor activity; these in turn lead to ineffective heat dissipation, and labile blood pressure and heart rate [7].

The occurrence of NMS in some families suggest familial disposition. Studies have found presence of specific allele of the D2 receptor gene is over presented in NMS. And this allele is associated with reduce density and function of dopamine receptors as well as decrease dopaminergic activity and metabolism [8,9].

Although there is no diagnostic test for NMS, typical laboratory abnormalities help to confirm the clinical diagnosis and to rule out other common differentials such as serotonin syndrome, malignant hyperthermia and common medical conditions, (CNS infections, stroke, status epilepticus, acute intermittent porphyria, thyroid storm, heat stroke, sepsis) mimicking NMS [10,11].

Elevated CK level is more specific for NMS. Leucocytosis, mildly elevated LDH, electrolyte abnormalities hypocalcaemia, hypo – hyperkalemia, hypomagnesemia and metabolic acidosis are frequently observed. Evaluation with CT head and Lumbar puncture is also important.

## Conclusion

In patients who have experienced an episode of Neuroleptic Malignant Syndrome, the risk of recurrence is strongly related to the elapsed time between the episode and restarting antipsychotics. Following guidelines may minimize the risks of recurrence, however none of these guarantees either success or failure.

- 1-wait for at least two weeks before re-starting therapy
- 2- start with low dose and titrate upward slowly
- 3-avoid dehydration
- 4-avoid concomitant use drugs &
- 5- Use low potency drug

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