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# Quetiapine-Induced Atypical Neuroleptic Malignant Syndrome (NMS): A Case Report

**Charanya T[1]*, Aneelraj D[2], Sivaprakash B[3] and Eswaran S[3]**

[1]*Mental Health and Specialist Services, Gold Cost University Hospital, Gold Coast, Queensland, Australia*
[2]*Emergency Psychiatry Service, Gold Cost University Hospital, Gold Coast, Queensland, Australia*
[3]*Department of Psychiatry, Mahatma Gandhi Medical College and Research Institute, Pondicherry, India*

## Abstract

NMS is an iatrogenically caused medical emergency, by D2 receptor blocking drugs. Atypical NMS is a presentation of three of the four signs-hyperthermia, rigidity or other extrapyramidal syndromes, autonomic disturbances and mental status changes. We report a case of a 41-year-old male with multiple drug abuse, dysthymia with moderate depressive episode and hypertension who developed Atypical NMS when on treatment with quetiapine. Atypical NMS resolved within a week of discontinuation of quetiapine and with supportive care. Atypical NMS is an impending state of NMS, which needs to be identified at the earliest to avert further complications.

**Keywords:** Quetiapine; Atypical neuroleptic malignant syndrome; Adverse drug reaction; Second generation antipsychotic

## Introduction

Neuroleptic malignant syndrome is an acute, life-threatening, idiosyncratic medical complication; characterized by hyperthermia, rigidity or other extrapyramidal syndromes, autonomic disturbances and mental status changes [1]. Atypical NMS is a presentation of three of the four signs [2]. NMS is unusual with second generation antipsychotics (SGA) when compared to first generation antipsychotics (FGA). Among SGAs NMS induced by quetiapine is reported to have a different presentation, like earlier onset and rapid recovery [3]. We report a case of atypical NMS in a middle-aged male with multiple drug abuse and comorbid depressive disorder, on treatment with quetiapine 200 mg/day for 3 weeks.

## Case Report

We present a case of 41-year-old male with multiple drug dependence, dysthymia with moderate depression and essential hypertension. He had dependence to alcohol, nicotine and to prescription drugs like opioid (tramadol), pregabalin, and benzodiazepine (alprazolam, lorazepam) with history of complicated withdrawal with seizures 4 years ago but abstinent in a protected environment for a month prior to the presentation. For his depressive disorder, he was on quetiapine 200 mg/day for 3 weeks prior to presentation and he was on irregular treatment for hypertension. He presented to the emergency services with altered sensorium, staring, posturing, mutism for three days prior to presentation to the hospital.

On assessment he was agitated, had autonomic dysregulation in the form of diaphoresis, tachycardia (110 beats/min), elevated blood pressure (170/100 mm of Hg), tachypnoea (22 breaths/min), temperature of 99°F; disorientation to time and place; had rigidity of all four limbs. Medical workup was normal except for elevated total creatine phosphokinase (CPK) and CPK-MB (Table 1). Clinically, NMS was suspected. On the Naranjo adverse drug reaction scale [4] he scored eight, indicating a probable causal association between quetiapine and Atypical NMS in this patient. Multiple sets of diagnostic criteria were applied in order to enhance the diagnostic accuracy of atypical NMS (Table 2).

Other differential diagnoses such as serotonin syndrome, lethal catatonia, meningitis, encephalitis, substance/overdose or withdrawal, metabolic disturbances, seizure disorder, heat stroke were clinically ruled out. NMS rating scale (NMS-RS) [5] and Bush Francis catatonia rating scale (BFCRS) [6] were applied at frequent intervals and the improvement in the scores is represented as a graph (Figure 1).

| CPK | Day 1 | Day 2 | Day 5 |
|---|---|---|---|
| CPK- Total | 1789 | 743 | 184 |
| CPK-MB | 84 | 59 | 31 |

**Table 1:** CPK-Total and CPK-MB values.

| Criteria | Levenson | Pope | Addonizio | Adityanjee | Friedman | Caroff | DSM-5 |
|---|---|---|---|---|---|---|---|
| NMS | Yes | Yes | No | No | No | No | No |
| Atypical NMS | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

**Table 2:** Diagnostic criteria sets for NMS and atypical NMS met.

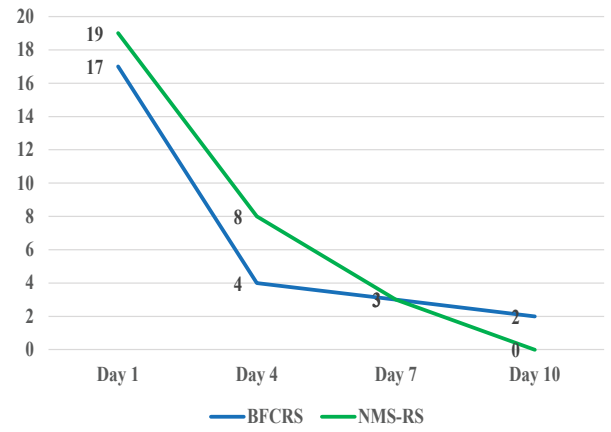


**Figure 1:** Graph depicting NMS-RS and BFCRS scores.

***Corresponding author:** Charanya T, Mental Health and Specialist Services, Gold Cost University Hospital, Gold Coast, Queensland, Australia, Tel: + 476993227; E-mail: drcharanya.t@gmail.com

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According to the Woodbury staging [7], patient had stage III- mild, early NMS characterized by mild rigidity; catatonia or confusion; ≤ 38°C (100.4°F); heart rate ≤ 100/min. Quetiapine was discontinued; supportive care was provided along with injection lorazepam 2 mg every 6 hours, for 2 days, which was tapered over one week and stopped. Patient improved significantly within the first week of admission. In discussion with the patient, Bupropion was added and titrated to 300 mg/day as an antidepressant. Divalproex was also added and titrated to 1 g/day, in view of both risk of complicated withdrawal and lower abuse potential, as patient had multiple prescription drug abuse in the past.

## Discussion

NMS is underdiagnosed as there is no clear consensus on diagnosis and at present there are 7 sets of criteria for the diagnosis of NMS [8], which further contributes to the difficulty in diagnosing atypical NMS. NMS has a mortality rate of up to 30% [9] and atypical cases represent a state of impending NMS which may progress to typical NMS [2]. Hence, it's important to identify Atypical/early presentations of NMS.

Although risk of neurological disorders has been reduced by SGAs, NMS remains a risk for patients who are susceptible. However, this risk is less with SGAs as opposed to FGAs. Abrupt and profound dopamine D2 receptor blockade by antipsychotic drugs has been proposed to be the cause of NMS. It has been reported that 16% of NMS cases had their onset within 24 hours, 66% within a week and virtually all cases within 30 days, after initiation of antipsychotic drugs [10]. In this patient, the onset was within 3 weeks of initiating quetiapine with no recent increase in dosage, which suggests clinicians to be aware regarding the possibility of NMS up to 1 month after initiating an antipsychotic.

Reviews suggest that three of the four cardinal signs of NMS are required to diagnose atypical NMS [2]. Consequently, this puts greater emphasis on ancillary measures, such as CPK level. Even though it is not specific for NMS, it is important to monitor CPK levels in NMS, especially in cases with an atypical presentation. The cause of increased CPK levels in NMS is attributed to rhabdomyolysis, physical muscle injury, agitation, hyperactivity, and medication [11].

Risk factors in this patient was male gender, affective disorder, substance dependence, dehydration, psychomotor agitation, confusion, disorganization, extrapyramidal signs and catatonia. Other risk factors like dyselectrolytemia, infections, concurrent dementia, use of neuroactive medications, use of higher doses of neuroleptics, recent increase in dosage of neuroleptics, parenteral administration of neuroleptics, prior history of NMS, medical or neurologic illness were absent in this patient [12].

## Conclusion

Atypical cases of NMS have been reported, where patients have presented without muscle rigidity and/or hyperthermia. Hence, the absence of hyperthermia as in this case should not prevent from diagnosing NMS when the rest of the clinical picture strongly points towards this diagnosis. For patients with atypical or impending NMS, as in this case, supportive care such as discontinuation of antipsychotic and maintaining adequate hydration, careful clinical monitoring and hastening the recovery by lorazepam would be enough. Hence, vigilant detection of atypical or impending NMS and intervention can prevent further progression to severe NMS, thereby reducing the probability of morbidity and mortality.

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