

Rudy Forte, MD; Shiwani Kamath, MD, Debra Angelo, MD, Johnathan Frunzi, MD  
 Department of Internal Medicine  
 HCA Healthcare/USF Morsani College of Medicine GME Medical Center of Trinity

## Introduction

Neuroleptic Malignant Syndrome (NMS) is a rare, but potentially life threatening condition associated with dopamine blockade, particularly first-generation antipsychotics. The complex pathophysiology of NMS remains somewhat unclear and debatable as the symptoms are not fully explained by dopamine blockade alone.<sup>1</sup> D2 dopamine receptor antagonism remains responsible for most cases of NMS, however a few cases have been reported in which little to no D2 blockade activity was present.<sup>1</sup>

This poster is about an atypical presentation of NMS.

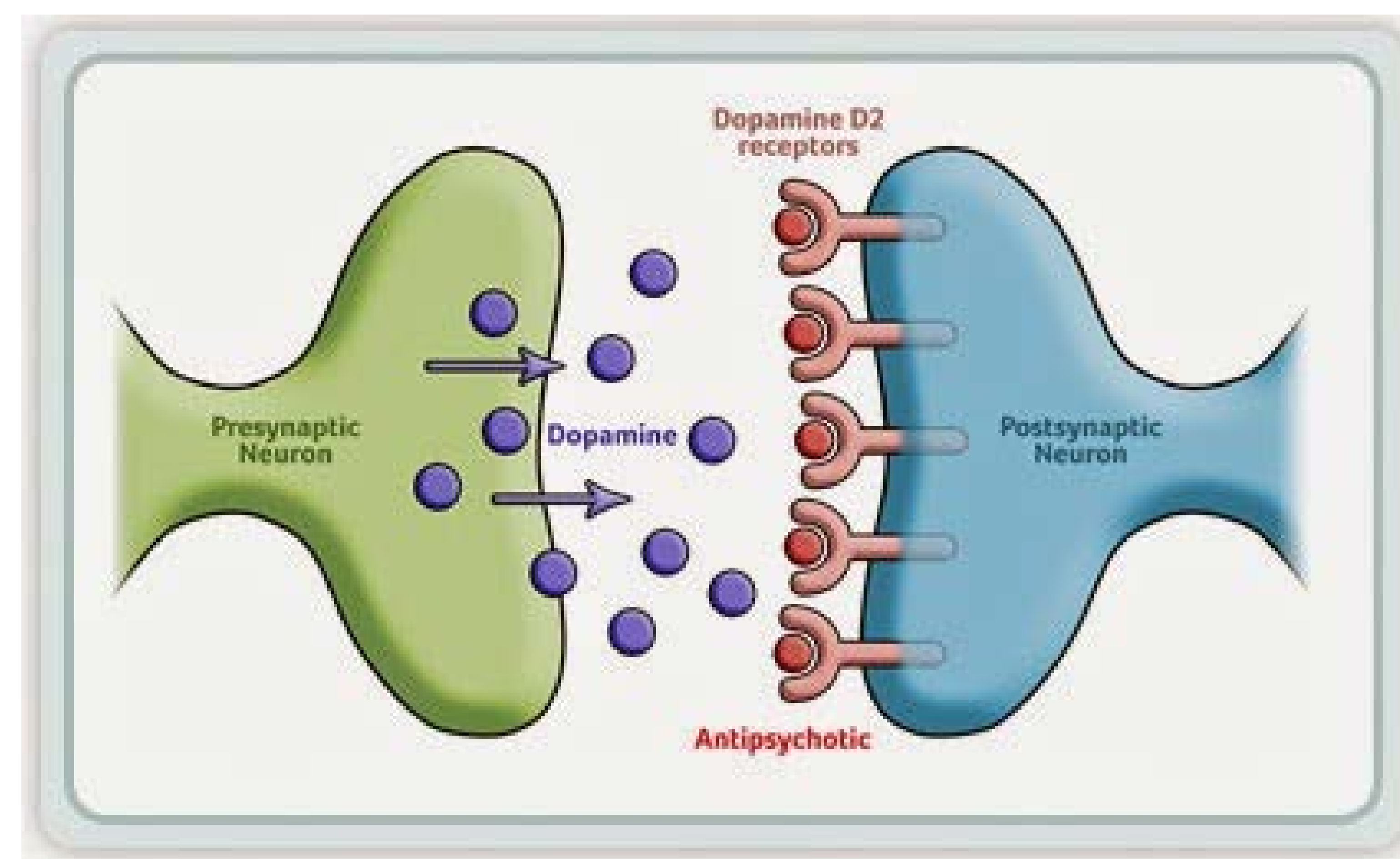
## Case Report

A 47-year-old Caucasian male with past medical history of major depression, generalized anxiety disorder, and dissociative identity disorder was brought in by his wife due to generalized weakness with decreased energy and ability to care for himself. The patient, was described by his wife as a working man who, at the time, was "far from baseline." Prior to hospitalization, he was said to be experiencing occasional repetitive movements and a decreased appetite with difficulty swallowing. His medications included trazadone 100mg daily and aripiprazole 10mg twice daily, which had been prescribed 48 days prior to admission.

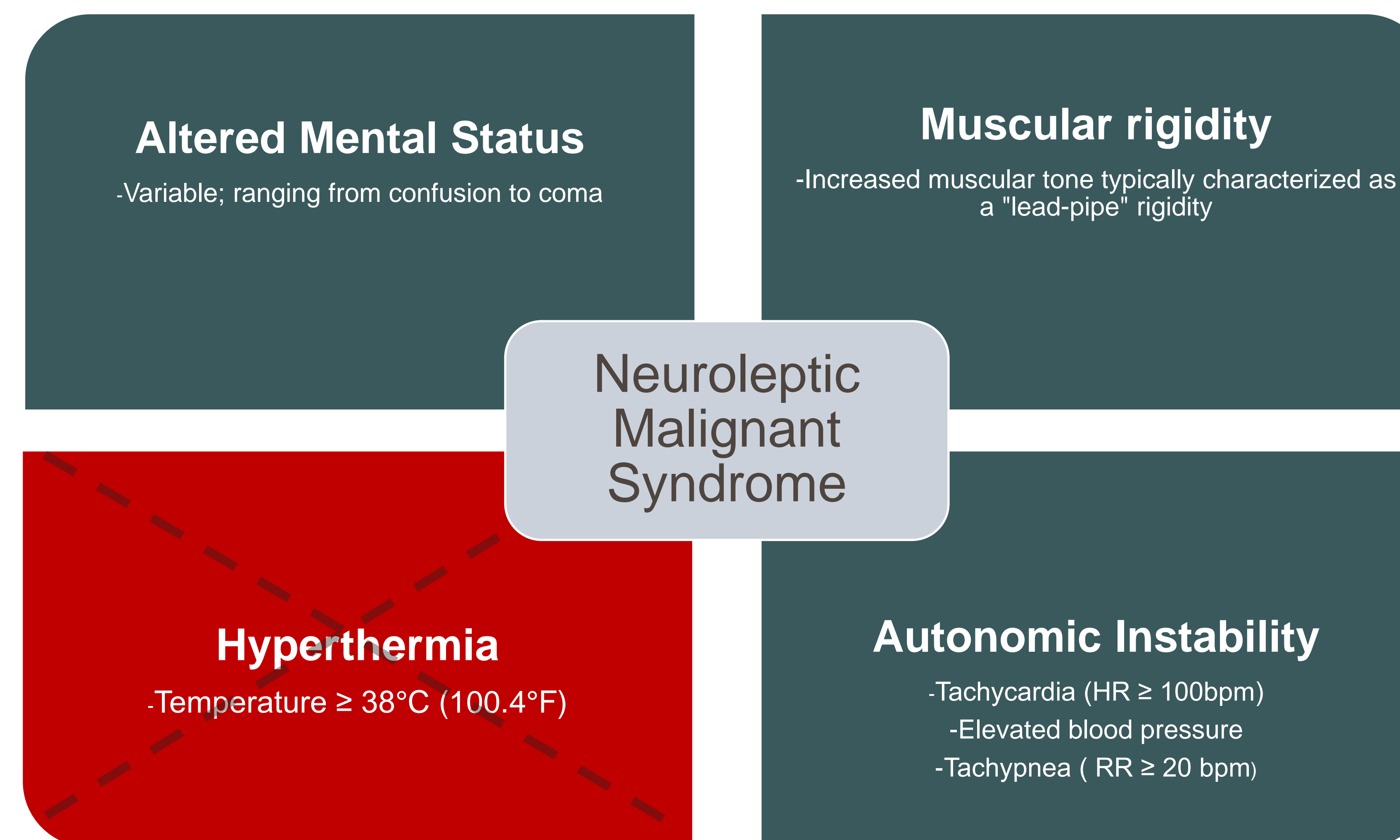
His vitals were: blood pressure 179/134 mmHg, pulse rate 119 beats per minute, oxygen saturation 91% on room air, respiratory rate 18 breaths per minute, and temperature 99°F. Despite the abnormal findings, he never had any fever.

Noteworthy labs, included: white blood cell count 16,350 per microliter with 84.2% neutrophils, sodium 149 mmol/L, creatinine 1.7 mg/dL, and a creatine kinase 1711 unit/L. Urine showed positive 3,4-Methylenedioxymethamphetamine and metabolites. Magnetic resonance imaging of the head was unremarkable.

## Imaging & Pathology



("D2 dopamine receptor blockade" 2014)



Classic NMS tetrad  
 Our case, particularly, presented without fever (highlighted in red)

## Discussion

Second generation antipsychotics (SGA), such as aripiprazole, have long been presumed as being free of NMS risk.<sup>3</sup> Our case was particularly interesting in that not only did he have an aripiprazole-induced NMS, but also presented without fever.

SGA were identified as causative agents of NMS in a systematic review and case report analysis by Murri et al.<sup>3</sup> Reported cases were shown to have a milder clinical presentation characterized as "lower incidence, lower clinical severity, and less frequent lethal outcome" when compared to first generation antipsychotic-induced NMS.<sup>3</sup> Aripiprazole was found to be the least likely to cause fever.<sup>3</sup>

In another systematic review of case reports by Singhai et al., absence of fever along with absence of muscle rigidity were the most common atypical findings found in SGA-induced NMS patients.<sup>2</sup> While our patient did not have a recorded fever Trollor et al. reported that hyperthermia was seen in 78% of aripiprazole-induced NMS.<sup>4</sup> However, the average temperature of the fevers in aripiprazole patients was found to be substantially lower compared to other atypical drugs.<sup>4</sup>

Our case along with others in the peer-reviewed literature demonstrate the potential of SGA, including aripiprazole, to cause NMS. However, SGA-induced NMS incidence is infrequent and their clinical presentation variable, for reasons unknown. There seems to be more variability in body temperature in aripiprazole-induced NMS compared to other second generation antipsychotics.<sup>4</sup> Despite several reported cases of atypical NMS, diagnostic criteria remains unchanged.

## Conclusion

The possibility, albeit rare, of NMS should be explained to the patient along other potential side-effects before starting any antipsychotic medication. Despite its infrequency, physicians should have low threshold for NMS in patients taking SGA and be aware of the possibility of atypical presentations. Further studies are needed to establish new diagnostic criteria for atypical NMS.

## References

1. Berman Brian D. "Neuroleptic malignant syndrome: a review for neurohospitalists". *The Neurohospitalist* 1.1 (Jan.2011): 41-47.
2. Singhai Kartik, Kuppli Pooja Patnaik and Nebhinani Naresh. "Atypical neuroleptic malignant syndrome: A systematic review of case reports". *General hospital psychiatry* 60(Sep.2019): 12-19.
3. Belvederi Murri Martino, Guaglianone Argentina, Bugliani Michele, et al. "Second-generation antipsychotics and neuroleptic malignant syndrome: systematic review and case report analysis". *Drugs in R&D* 15.1(Mar.2015): 45-62.
4. Trollor Julian N., Chen Xiaohua and Sachdev Perminder S. "Neuroleptic malignant syndrome associated with atypical antipsychotic drugs". *CNS drugs* 23.6 (May.2009): 477-492.
5. Simon Leslie V., Hashmi Muhammad F. and Callahan Avery L. "StatPearls".
6. Dopamine Blockade by Antipsychotics. 9 Apr. 2014, [http://4.bp.blogspot.com/-PguBX1E3\\_vc/U0SSRHfwSUI/AAAAAAAAAIQ/dOp887KuLUE/s1600/D2\\_receptors.jpg](http://4.bp.blogspot.com/-PguBX1E3_vc/U0SSRHfwSUI/AAAAAAAAAIQ/dOp887KuLUE/s1600/D2_receptors.jpg).