Atypical Antipsychotics and Lithium Induced Neuroleptic Malignant Syndrome associated with Acute Kidney Injury: A Case Report

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Abstract

Neuroleptic Malignant Syndrome (NMS) is a rare but serious adverse reaction to antipsychotic medications. This case report presents a 56-year-old male with bipolar disorder on a regimen of Olanzapine, Clozapine and Lithium carbonate, who developed typical NMS. He had muscle rigidity, hyperthermia, rhabdomyolysis which led to acute kidney injury. Prompt withdrawal of psychotropic medications and administration of supportive therapies was done, yet the patient's condition deteriorated, leading to Multiple Organ Dysfunction Syndrome (MODS) and eventually mortality. This case shows the complexity of managing NMS in the context of polypharmacy emphasizing the need for vigilance when prescribing antipsychotic combinations and the challenges faced in treating NMS, especially when there are associated complications.

Key words: Acute Kidney Injury, Atypical Antipsychotics, Complex Polypharmacy, Lithium, Neuroleptic Malignant Syndrome.

Introduction

Neuroleptic malignant syndrome (NMS) is a rare but severe idiosyncratic reaction to antipsychotic agents, particularly to highly potent conventional antipsychotics such as Haloperidol, Fluphenazine, Chlorpromazine, etc. The newer "atypical" antipsychotics, such as Clozapine, Risperidone, Olanzapine, etc are efficacious and proposed to have fewer extrapyramidal side effects (EPS) than conventional antipsychotics. Reports suggest that they are also associated with the NMS compromising their safety.[1] Its clinical presentation includes hyperthermia, characteristic muscle rigidity resembling "lead pipe" fluctuating blood pressure, altered sensorium, and autonomic dysregulation and elevated creatine kinase levels.[2] Notably, malignant hyperthermia in NMS can induces rhabdomyolysis which is destruction of muscle fibres which can precipitate acute kidney injury due to myoglobin's nephrotoxic effects.[3,4] Use of Complex polypharmacy (CP), that includes using three or more medications concomitantly for treating bipolar disorder, has increased over time.[5] In this case report, we present case details of a patient having bipolar disorder under a regimen of Olanzapine, Clozapine, and Lithium carbonate, who developed NMS and acute kidney injury.

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Case Details

A 56-year-old male patient, who has a history of bipolar disorder for ten years and hypothyroidism for five years, presented to our tertiary care hospital. He was disoriented, drowsy for one day, along with high fever of 100.1°F for three days, and had nausea for one- three days; according to the patient's informant, he was relatively asymptomatic 15 days ago. A day ago, he was in a private hospital which mentioned he had EPS, acute kidney injury (AKI) and experienced vomiting. Patient was taking Tab Lithium Carbonate 300 mg BD, Tab Olanzapine 10 mg OD, Tab Clozapine 12.5 mg OD, tab Diazepam 5 mg OD for 10 years for bipolar disorder and Tab Thyroxine 25 mcg OD for hypothyroidism for five years.

On admission, physical examination showed temperature of 99.5°F, HR 110/min, BP 110/70 mm of Hg and RR 24/min. The neurological examination showed that patient was partially conscious, disoriented to time, place, person, with poor eye contact (GCS - E3V2M5) and further mental status examination was not possible. Pupils were bilaterally constricted, plantar flexion normal, mild rigidity present. He was suspected to have Neuroleptic Malignant Syndrome (NMS) as he was on prescription of dual atypical antipsychotics, had elevated CPK levels (4670 U/L), high fever (100.1°F) and mild rigidity, all suggesting rhabdomyolysis along with AKI.

All psychotropic medications were immediately withdrawn and he was prescribed tab Bromocriptine 2.5 mg 1-0-1 via Ryle's tube. Patient regained partial consciousness but had seizures (suspected due to uremic encephalopathy), for which he was given Injection Levetiracetam 1 gm IV stat. Other

empirical therapies included Injection Acyclovir 400mg TDS and Injection Meropenem 500 mg IV BD till the diagnosis was confirmed. His BP was maintained at 120/80 mm of Hg on 12 ml/hr Noradrenaline and 1.8ml/hr Vasopressin. His platelet counts decreased and blood investigations were positive for Dengue IgM. (table 1)

The patient's condition continued to deteriorate, having Multiple Organ Dysfunction Syndrome (MODS). He died despite optimal treatment, due to cardiorespiratory collapse which was attributed to sepsis.

This suspected adverse drug reaction (ADR) Olanzapine, Clozapine induced Neuroleptic Malignant Syndrome has been reported to the Indian Pharmacopoeia Commission with the unique ID number IN-IPC-300823025. Causality assessment of this ADR is "Possible" since the patient was taking both Clozapine and Olanzapine and also suffered from dengue and sepsis.

Table 1: Laboratory investigation during hospital stay

	Day 1	Day 2	Day 4	Normal range[6]
CPK(U/L)	NA	4670	NA	(22 – 198)
Serum Lithium levels (mmol/L)	0.78	NA	NA	(0.6 - 1.5)
Blood Urea(mg/dL)	74.5	102.5	78.5	(19.3 - 49.2)
Creatinine serum(mg/dL)	1.80	3.38	5.9	(0.7-1.3)
Potassium serum(mmol/L)	3.46	3.19	4.65	(3.5 - 5.5)
pH	7.43	7.34	NA	(7.35 - 7.45)
Anion gap	19.4	16.9	NA	<12
WBC (cells/cumm3)	NA	18,910	21,750	(5200-12400)
Platelet count(kU/L)	238	164	85	(130-400)
CRP(mg/l)	197.72	NA	130.14	<5
Serum ALT (U/L)	195	NA	102	(10-49)
Serum AST(U/L)	325	NA	195	(0-34)

Discussion

Neuroleptic malignant syndrome (NMS) is a rare but potentially lethal EPS occurring in individuals using antipsychotic medications, with an incidence ranging from 0.02 to 3%.[4] The prevailing theory suggests that the central blockade of dopamine D2 receptors is responsible for the development of rigidity and hyperthermia and other symptoms of NMS.[7] It is an idiosyncratic reaction that can manifest unpredictably. It also has a genetic predisposition. It may occur after a single dose or years of treatment with the same medication.[8]

In some studies, Olanzapine, Clozapine and Lithium have been implicated in causing this syndrome. Olanzapine and Clozapine belong to class of atypical antipsychotics (2nd gen). Olanzapine exhibits a greater affinity for antagonizing D2 receptors in brain,[9] while Clozapine has a relatively more pronounced influence on the D4 receptor subtype.[7] Clozapine is also more associated with atypical presentation of NMS characterized by less or absence of rigidity and tremors, whereas Olanzapine has a typical NMS presentation which has rigidity, hyperthermia and elevated CK levels.[9] Lithium, a mood stabilizer used in bipolar disorder, has been reported to induce NMS when concomitant antipsychotics are used. Although, there also have been few cases of Lithium alone inducing NMS.[10] The mechanism is unclear but theorized that Lithium modifies neurotransmitter activity and diminishes dopamine effects by inhibiting the buildup of cyclic adenosine monophosphate at the intracellular level.[11] Our case documents a patient who developed NMS due to use of antipsychotic agents and mood stabilizer. He was taking Olanzapine, Clozapine and Lithium carbonate for bipolar disorder for 10 years. Our patient presented with rigidity, hyperthermia and elevated CK levels which is typical presentation of NMS. Notably, Olanzapine appears to be more likely to be offending drug in our case. While it is suggested that some patients benefit from CP treatment, it is also common for patient to not improve, yet remain on CP. 5 Evidence for the efficacy of using multiple antipsychotics of same class in bipolar disorder is limited, and risk of non-adherence and adverse effects increases, thus clinicians should be vigilant while prescribing such combinations.

Specific treatment of NMS involves use of Dantrolene, Bromocriptine, Amantadine but their efficacy is uncertain and subject to debate. Most of the current guidelines are supported by case reports of patients treated for NMS due to the rarity of NMS presentation.[12] Dantrolene directly relaxes muscles by inhibiting calcium release from sarcoplasmic reticulum. However, its mechanism in NMS remains uncertain because there is no observed abnormal calcium transport in skeletal muscle.[2] Dantrolene has potential to cause hepatotoxicity thus it should be avoided if liver function tests are very abnormal.[13] Bromocriptine is a direct D2 agonist, and reduces the recovery time of NMS than supportive therapy alone.8 Our patient was put on 2.5 mg Tab Bromocriptine. NMS mortality varies from 5 to 20%, however in cases of renal failure it may increase up to 50% (vs control 18.8%) and in liver failure it may be around 40%.[14] Our case had both altered liver profiles (elevated ALT, AST levels) and renal failure such as elevated creatinine, urea levels, metabolic acidosis, putting him at a high risk. In our case report, mortality was not directly caused by NMS, but it played as a triggering event and contributed to the cascade of events that led to the patient's mortality.

Table: 2 List of agents that have potential to cause NMS 2

Typical Antipsychotics	Atypical Neuroleptics	Antiemetics
Haloperidol	Olanzapine	Domperidone
Chlorpromazine	Clozapine	Metoclopramide
Fluphenazine	Risperidone	
Typical Antipsychotics	Quetiapine	Others
Haloperidol	Ziprasidone	Lithium

Conclusion

Neuroleptic Malignant Syndrome (NMS) is a rare drug-induced idiosyncratic reaction which can lead to serious complications like rhabdomyolysis induced acute kidney injury and is associated with high morbidity and high mortality. Atypical antipsychotics, now more commonly used, are considered to be more efficacious than conventional psychotics and thought to have fewer EPS. Nevertheless, there always remains a risk of inducing NMS. Lithium, a widely-used mood stabilizer for bipolar disorder, is also associated with NMS, especially when used concurrently with antipsychotics. However, even Lithium monotherapy is linked to this occurrence, albeit rarely. Thus, watchful and judicious administration of these drugs will help prevent NMS. Given the rise in psychiatric illness and use of these drugs, clinicians should be aware of the clinical signs of NMS as early diagnosis of NMS and prompt withdrawal of implicating drug is associated with better outcomes for the patients.

Reference

1. Faay MD, Czobor P, Sommer IE. Efficacy of typical and atypical antipsychotic medication on hostility in patients with psychosis-spectrum disorders: a review and meta-analysis. Neuropsychopharmacology. 2018 Nov;43(12):2340-9. doi: 10.1038/s41386-018-0161-2
2. Khonsary SA. Goodman and Gilman's The Pharmacological Basis of Therapeutics. Surg Neurol Int 2023;14:91
3. Rojas-Valverde D, Sánchez-Ureña B, Crowe J, Timón R, Olcina GJ. Exertional rhabdomyolysis and acute kidney injury in endurance sports: a systematic review. European journal of sport science. 2021 Feb 1;21(2):261-74. doi: 10.1080/17461391.2020.1746837
4. Malhotra SD, Mistry AR, Gupta SD. Neuroleptic Malignant Syndrome Associated with Rhabdomyolysis Induced by Antipsychotic Agents: A Rare Occurrence. European Journal of Clinical Medicine. 2021 Aug 30;2(4):4-6. doi: 10.24018/ejclinicmed.2021.2.4.117
5. Fung VC, Overhage LN, Sylvia LG, Reilly-Harrington NA, Kamali M, Gao K, Shelton RC, Ketter TA, Bobo WV, Thase ME, Calabrese JR, Tohen M, Deckersbach T, Nierenberg AA. Complex polypharmacy in bipolar disorder: Side effect burden, adherence, and response predictors. J Affect Disord. 2019 Oct 1;257:17-22. https://doi.org/10.1016/j.jad.2019.06.050. Epub 2019 Jul 2. PMID: 31299400; PMCID: PMC6711795.
6. Normal range of lab report reference: Farinde A. Lab Values, Normal Adult: Laboratory Reference Ranges in Healthy Adults [Internet]. Medscape.com. 2019. Available from: https://emedicine.medscape.com/article/2172316-overview.
7. Szota A, Ogłodek E, Araszkiewicz A. Fever development in neuroleptic malignant syndrome during treatment with olanzapine and clozapine. Pharmacological Reports. 2013 Mar;65(2):279-87. doi: 10.1016/s1734-1140(13)71004-1.
8. Kuhlwilm L, Schönfeldt-Lecuona C, Gahr M, Connemann BJ, Keller F, Sartorius A. The neuroleptic malignant on therapy regimes and outcome. Acta Psychiatrica Scandinavica. 2020 Sep;142(3):233-41. doi: 10.1111/acps.13215.
9. Trollor JN, Chen X, Chitty K, Sachdev PS. Comparison of neuroleptic malignant syndrome induced by first- and second-generation antipsychotics. The British Journal of Psychiatry. Cambridge University Press; 2012;201(1):52–6. (DOI: https://doi.org/10.1192/bjp.bp.111.105189)
10. Ramadas S, Nitin Murali T N, Krishnan J, Andrade C. Neuroleptic Malignant Syndrome with Low Dose Lithium, Without Concomitant Antipsychotics. Indian J Psychol Med. 2023 Jan;45(1):92-94. https://doi.org/10.1177/02537176221099307. Epub 2022 Jun 26. PMID: 36778604; PMCID: PMC9896103.
11. Patil V, Gupta R, Verma R, Balhara YP. Neuroleptic Malignant Syndrome Associated with Lithium Toxicity. Oman Med J. 2016 Jul;31(4):309-11. https://doi.org/10.5001/omj.2016.59. PMID: 27403245; PMCID: PMC4927730.
12. Ngo V, Guerrero A, Lanum D, Burgett-Moreno M, Fenati G, Barr S, Neeki MM. Emergent treatment of neuroleptic malignant syndrome induced by antipsychotic monotherapy using dantrolene. Clinical Practice and Cases in Emergency Medicine. 2019 Feb;3(1):16. doi: 10.5811/cpcem.2018.11.39667
13. Bhanushali MJ, Tuite PJ. The evaluation and management of patients with neuroleptic malignant syndrome. Neurol Clin. 2004 May;22(2):389-411. https://doi.org/10.1016/j.ncl.2003.12.006. PMID: 15062519.
14. Modi S, Dharaiya D, Schultz L, Varelas P. Neuroleptic Malignant Syndrome: Complications, Outcomes, and Mortality. Neurocrit Care. 2016 Feb;24(1):97-103. doi: https://doi.org/10.1007/s12028-015-0162-5. PMID: 26223336.