Key Words: neuroleptic malignant syndrome, pharmacotherapy, dantrolene, bromocriptine, amantadine, benzodiazepines, severity

An Approach to the Pharmacotherapy of Neuroleptic Malignant Syndrome

By Roland van Rensburg, Eric H. Decloedt

ABSTRACT *~ Neuroleptic malignant syndrome is a rare, idiosyncratic emergency associated with exposure to dopamine antagonists, commonly antipsychotic drugs. The typical clinical picture consists of altered consciousness, muscular rigidity, fever, and autonomic instability. While the condition has generally been well described, the pathophysiology is still poorly understood. The importance of this case report is to highlight the lack of robust evidence-based treatment for this emergency. We submit an approach to the pharmacotherapy of neuroleptic malignant syndrome based on the available evidence.* Psychopharmacology Bulletin. *2019;49(1):84–91.*

Case

A 36-year old male with autism spectrum disorder and bipolar I disorder was admitted to a primary-level hospital in Cape Town, South Africa, for a manic episode. His chronic disease management was challenging, and his latest outpatient treatment was lithium 500 mg 12-hourly, valproate 1 g 12-hourly, clozapine 100 mg 12-hourly and 75 mg at midday, sulpiride 50 mg 8-hourly, clonazepam 1 mg 8-hourly, promethazine 50 mg 8-hourly and levothyroxine 37.5 mcg daily. He was started on oral haloperidol 2.5 mg 12-hourly on admission, and his chronic medications were continued. Two weeks later he was found in the hospital bed with a decreased level of consciousness and dyspnoea (saturation 77% on room air). He was intubated and transferred to a secondary-level hospital, where he developed hyperthermia, muscle rigidity, and a severely increased creatinine kinase (CK) level (10 710 U/L, range 20–200). A mild leucocytosis was noted, but his renal function, urine dipstick, electrocardiography, and blood pressure were within normal limits. The diagnosis of neuroleptic malignant syndrome (NMS) was made, all his medications were stopped (except sodium valproate), and he was transferred to the intensive care unit (ICU) of a tertiary-level hospital the same

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day for further management. On initial admission, the patient's mother reported that he has an allergy to lorazepam and risperidone, citing that it makes him manic and dystonic, respectively. Details about the lorazepam allergy were not well interrogated at presentation.

On admission to ICU he was given dantrolene in incremental doses for 4 days. Dantrolene is not readily available in South Africa, and a recommendation was made to switch to bromocriptine, which the patient received for a total of 3 doses. He improved clinically and biochemically, and was extubated in ICU 5 days after admission.

Six days after admission to ICU the patient developed ventilator-acquired pneumonia with sepsis, and intravenous meropenem was started empirically. He decompensated and was re-intubated, but suffered cardiopulmonary failure. Resuscitation was unsuccessful, and he died in ICU. His sputum cultured multidrug-resistant *Acinetobacter baumannii*, resistant to meropenem.

Discussion

NMS is a rare, but life-threatening, idiosyncratic emergency associated with exposure to dopamine antagonists, commonly antipsychotics. It is mostly seen with high-potency first-generation antipsychotics, such as haloperidol, but can occur with any antipsychotic class.[1] Dopamine agonist withdrawal, typically antiparkinson medication, has also been implicated,[2] as well as metoclopramide.[3] NMS can occur after a single antipsychotic dose, or after years of use of the same antipsychotic on the same dose.[4] NMS is considered to be an idiosyncratic drug reaction, but dose-related increased risks have been described.[3] Comorbid mood disorders[5] and intellectual impairment[6] carry an independent risk.

The pathogenesis of NMS is unknown, but a dopamine receptor blockade is fundamental to most theories.[7] NMS may have a genetic link,[8] and polymorphisms of the dopamine 2 receptor gene have been associated with an increased risk of NMS.[9] Dysregulation of other neurotransmitters have also been implicated, including alterations of gamma-aminobutyric acid (GABA),[10,11] enhanced serotonin secretion,[12,13] and reduced acetylcholine activity.[14,15]

NMS classically presents as a tetrad of symptoms developing over 1 to 3 days: mental status change (mostly agitated delirium), muscular rigidity, fever, and autonomic instability.[5] Most patients follow a progression from impaired mental status to rigidity, followed by hyperthermia and autonomic dysfunction,[16] but clinical pictures and symptom severity may vary greatly.

Significantly elevated CK levels is a hallmark feature of NMS, and the degree of elevation correlates with the degree of severity and prognosis.[17]

Leucocytosis is a frequent finding, and myoglobinuria resulting from rhabdomyolysis may lead to acute renal failure.[17]

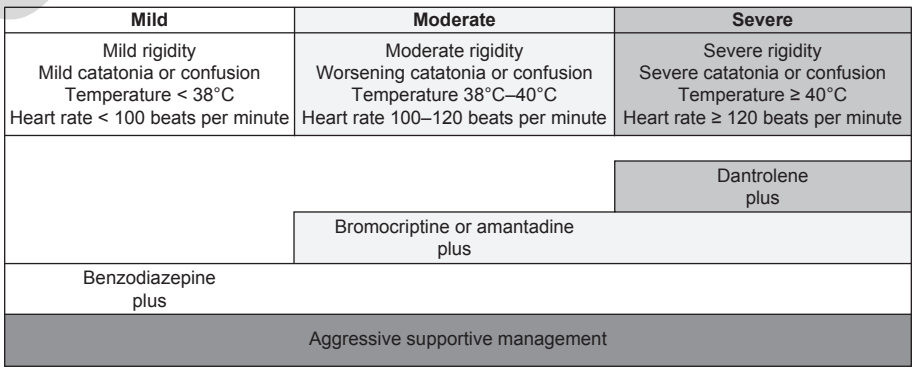
It is often difficult to distinguish NMS from other conditions with similar symptomatology, such as serotonin syndrome, malignant hyperthermia, and central nervous system infections. Serotonin syndrome is particularly difficult to distinguish from NMS, as many patients on antipsychotics are also frequently on serotonin re-uptake inhibitors. Features that may help differentiate serotonin syndrome are hyperreflexia, myoclonus, and ataxia.[18] Malignant hyperthermia will include a history of exposure to halogenated inhalational anaesthetic agents and/or suxamethonium, and central nervous system infections can be diagnosed with the use of cerebrospinal fluid analysis and neuroimaging.

The diagnosis of NMS is based on drug history and clinical presentation, as per the Diagnostic and Statistical Manual of Mental Disorders (DSM–5),[19] but efforts have been made to standardise objective criteria. In 2011 an international multispecialty consensus group released criteria for NMS diagnosis,[20] but this tool requires validation in clinical practice.

We conducted a systematic search strategy of PubMed of the following terms: *neuroleptic malignant syndrome, treatment, therapeutics, disease management/pharmacology, disease management/therapy, dantrolene, bromocriptine, amantadine, benzodiazepines*. A total of 56 publications were identified, of which 21 were relevant. These publications consisted of case reports, case series, reviews, and expert opinion. We reviewed the data and adapted a treatment approach based on NMS severity and the available evidence (Figure 1). The management of NMS is underscored by two principles: stopping the causative medicine(s) and

FIGURE 1

Neuroleptic Malignant Syndrome Severity and Pharmacotherapy (Adapted from Pileggi Et Al[23])



providing aggressive supportive care in ICU.[21] The focus of the latter is providing adequate hydration, correcting electrolyte imbalances and supporting cardiorespiratory stability.

The pharmacotherapy of NMS has been less well established, as there is lack of head-to-head studies to compare treatments. The current recommendations are based on case reports and expert opinion, and are sometimes conflicting.[22] Pharmacotherapies that have been used with success are dantrolene, bromocriptine, amantadine, and benzodiazepines (Table 1).[23] Dantrolene is a peripheral direct-acting skeletal muscle relaxant that reduces muscular rigidity, and therefore hyperthermia and increased CK levels. Dantrolene acts on peripheral skeletal muscle,[24] and may therefore be more useful in patients presenting with extreme rigidity and fever, features of severe NMS.[1] Dantrolene is registered for use in malignant hyperthermia,[25] but is routinely used off-label to treat NMS. Dantrolene is available as an oral and intravenous formulation.

Bromocriptine and amantadine are both dopamine agonists that displace antipsychotic dopamine antagonists.[23] Both bromocriptine and amantadine are only available as oral formulations. Benzodiazepines are usually used in combination with other pharmacotherapies.[1] Benzodiazepine efficacy is attributed to its muscle relaxation properties and effect on the altered GABA system in NMS.[23]

In a retrospective analysis of case reports the time to complete clinical recovery was 9 days with dantrolene, 10 days with bromocriptine, and 15 days with supportive care only.[26] Dantrolene use had higher mortality rates compared to bromocriptine when used as monotherapy (8.6 vs. 7.8%) in an retrospective analysis of 734 case reports.[27] Mortality was 21% in the group receiving supportive care alone. The use of dantrolene in combination with bromocriptine has been suggested to be effective for severe NMS cases,[22] but mortality rates remain high (7.3%).[18] In cases of NMS refractory to supportive and pharmacological interventions, responses to electroconvulsive therapy have been described.[28]

The cessation of antipsychotics following NMS may increase the risk of relapse of the underlying condition. An antipsychotic will in most cases need to be re-initiated. Rechallenge carries the risk of recurrence of NMS, but the reported prevalence varies, and may be as high as 30%.[23] If the patient's clinical condition requires a rapid antipsychotic rechallenge, it may be done as soon as 5 days after NMS symptom resolution.[29] If the clinical picture is not as pressing, a washout period of at least 14 days after symptom resolution has been suggested.[30] Our patient was classified as having severe NMS[31] with excessive rigidity, but no benzodiazepine was given due to the history

TABLE 1

Neuroleptic Malignant Syndrome Key Diagnostic Features and Specific Pharmacotherapy

Diagnosis:
- History of neuroleptic (antipsychotic) use
- Mental status change
- Muscular rigidity
- Hyperthermia
- Autonomic instability

Management:
- Stop precipitating medicine(s)
- Aggressive supportive management (including):
  - Adequate hydration
  - Correct electrolyte imbalances
  - Support cardiorespiratory stability

PHARMACOTHERAPY	DOSE*,†	ADVERSE EFFECTS[24,32–34]	CLINICAL INDICATION[23]
Benzodiazepines			
Lorazepam	1 to 2 mg intramuscular or intravenously 4 to 6-hourly[35]	Delirium Sedation Hypotension	Mild or early NMS
Diazepam	10 mg intravenously 8-hourly[35]		
Bromocriptine	2.5 mg 8 to 12-hourly via nasogastric tube (maximum 45 mg/day)[1]	Hypotension Gastrointestinal ulcer Psychosis‡	Moderate NMS, in addition to benzodiazepines
Amantadine	200 to 400 mg daily in 2 or 3 divided doses[1,35]	Orthostatic hypotension Agitation Urinary tract infection Nausea	Moderate NMS, in addition to benzodiazepines Alternative to bromocriptine
Dantrolene	1 to 2.5 mg/kg initially via intravenous infusion, followed by 1 mg/kg infusion 6-hourly (maximum 10 mg/kg/day)[1]	Anaphylaxis Hepatotoxicity Flushing Heart failure Tachycardia Muscle weakness Somnolence Nausea, diarrhoea	Severe NMS, in addition to bromocriptine and benzodiazepines

*Increase dose to effect. †Continue bromocriptine and/or dantrolene for at least 10 days followed by slow taper to minimize relapse.[36] ‡Bromocriptine appears to be well-tolerated by psychotic patients.[37]

given by the family that he had previously suffered an adverse drug reaction to lorazepam. Resolution of NMS usually occurs within two weeks,[3] and our patient showed signs of improvement by day 5 of his ICU admission.

Conclusion

This case report highlights the important aspects of NMS, in particular the place of pharmacotherapy. While the condition is still poorly understood and diagnostic criteria yet to be validated, numerous case reports support benzodiazepine, bromocriptine, amantadine, and dantrolene as treatment options. Aggressive supportive management is the basis of treatment of NMS, and a reasonable pharmacotherapeutic approach based on drug efficacy, availability, and experience would be to start drug therapy with a benzodiazepine and bromocriptine, and escalate to the addition of dantrolene in severe cases. ✤

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Consent

Verbal consent was obtained from the parents of the patient to use this case.

Conflict of interest

None.

Author contributions

Roland van Rensburg: Data collection and drafting of the manuscript. Eric Decloedt: Reviewing of the manuscript.

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