**Neuroleptic malignant syndrome: a guide for psychiatrists**

**Abstract**

Neuroleptic malignant syndrome is a rare idiosyncratic adverse reaction to drugs. In psychiatric practice, it is mainly associated with neuroleptic drugs. The classical presentation is that of hyperpyrexia, muscle rigidity, mental state changes, and autonomic instability. Subtle forms are difficult to recognise due to symptom overlap with other conditions. Laboratory evaluation is essential to exclude other causes of hyperthermia and detect medical complications.

Neuroleptic malignant syndrome is best considered a medical emergency and is properly managed in an acute hospital. The most important and critical intervention in the management of neuroleptic malignant syndrome is discontinuation of the antipsychotic medication. Supportive care is the mainstay of treatment. The patient should be admitted to an intensive care facility. Bromocriptine (centrally acting dopamine agonist), dantrolene (muscle relaxant) and benzodiazepines can be used. Electroconvulsive therapy should be considered for patients who have not improved after 48 hours of pharmacologic treatment.

Antipsychotic rechallenge is often required and should be attempted only after a wash out period. It is recommended to use a different agent, to be slowly titrated and closely monitored. Adjunctive treatment with an antidepressant, anxiolytic, and mood stabiliser can help avoid augmentation with antipsychotics or allow the use of lower doses of antipsychotics.

**Learning objectives**

1. Better understand the clinical presentation, the progression, as well as the risk factors for neuroleptic malignant syndrome.

2. Understand the principles of management of neuroleptic malignant syndrome.

3. Confidently reinstitute antipsychotic treatment in a patient with a history of neuroleptic malignant syndrome.

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**Introduction**

Neuroleptic malignant syndrome (NMS) is a rare idiosyncratic adverse reaction to drugs. NMS can be of variable severity ranging from mild to life-threatening cases. Subtle forms are difficult to recognise due to symptom overlap with other conditions. It is mainly associated with antipsychotic drugs, originally known as neuroleptic drugs (Pelonero et al., 1998). It was first described by Delay and colleagues; they called it ‘akinetic hypertonic syndrome’ (Delay et al., 1960). With the use of first-generation antipsychotics (FGAs), the incidence of NMS in the 80s and 90s was reported to be 0.2% (Caroff and Mann, 1993). More recent studies have reported the incidence of NMS on second-generation antipsychotics (SGAs) to be between 0.01% and 0.03% (Lally et al., 2019, Belvederi Murri et al., 2015).

Even though the widespread use of SGAs over FGAs over the years might let us think that the incidence of NMS is probably declining, no clear trend was found in a meta-analysis which included 26 studies examining the incidence of NMS (Gurrera et al., 2007). This might be due to several factors, including a probable increase of the overall and especially off-label use of antipsychotics (Procyshyn et al., 2014), increased pharmacovigilance (Tse et al., 2015), as well as several systematic biases in the published studies (Gurrera et al., 2007).

Early diagnosis is paramount in reducing mortality and relies on high clinical suspicion for diagnosis and treatment. The most important and critical intervention in the management of neuroleptic malignant syndrome in psychiatric setting is discontinuation of the antipsychotic medication (offending agent). The pathophysiology of NMS is not well understood and involves a complex interaction between antipsychotic medication and a susceptible individual. It is triggered by neuroleptic blockade of dopamine D2-receptors in the key neural pathways. It is best considered a medical emergency and is managed in an acute hospital. Supportive care is the mainstay of treatment.

**Clinical features of neuroleptic malignant syndrome**

The classical presentation comprises (American Psychiatric Association, 2013, Velamoor, 2017, Ware et al., 2018):

* Hyperpyrexia (>38.0°C or > 100.4°F, on at least 2 occasions measured orally). In certain cases, hyperpyrexia can be severe, and be associated with dehydration.
* muscle rigidity that is generally generalized and severe.
* In its most severe forms, it is typically described as “lead pipe” rigidity, and can lead to rhabdomyolysis, myoglobinuria, and acute renal failure. This rigidity might not respond well to antiparkinsonian medication.
* Mental state changes can range from stupor to coma. Fluctuating mental state is also common.
* Autonomic instability, as evidenced by profuse diaphoresis, tachypnoea, tachycardia, increased or fluctuating blood pressure, urinary incontinence, and pallor. Typically, blood pressure elevation in NMS is defined by systolic or diastolic increase ≥25% above baseline. Blood pressure fluctuation is generally defined by ≥20 mmHg diastolic change or ≥25 mmHg systolic change within 24 hours. Hypermetabolism is commonly defined by increased heart-rate (≥25% above baseline) and respiratory rate (≥50% above baseline).

Subtle forms are not uncommon and may be difficult to recognise due to symptom overlap with other conditions. Indeed, most of the aforementioned symptoms might be mild and go unrecognised (Velamoor, 2017). In particular, hyperpyrexia can be replaced by a febricula or falsely attributed to a co-occurring infection. Rigidity can be mild and interpreted as pseudo-parkinsonism associated with the use of antipsychotics. As mental state is commonly fluctuating in NMS, a cross-sectional assessment might miss the important diagnostic changes in mental state. Similarly, increased heart rate can be mild and falsely attributed to agitation, anxiety, or to the anticholinergic effects of psychotropic medication. Moreover, when patients are acutely disturbed, the baseline vitals might have been impossible to obtain or might have been unreliable due to agitation or psychomotor activation.

In a systematic review by Lang *et al.*, hyperthermia was present in 88% and muscle rigidity in 86% of reported cases of NMS (Lang et al., 2015). There have been reports of SGA-associated NMS often being less severe, and thus possibly more challenging to diagnose, than FGA-associated NMS. Indeed, it has been reported that SGA-associated NMS was associated with less muscle rigidity and much less severe creatinine kinase abnormalities, possibly resulting in a less severe “atypical” NMS presentation. With the common use of SGAs nowadays, it is possible that such presentations are becoming more and more common. It is important not to miss or misdiagnose these forms of NMS, since supportive management and medication adjustment are still needed in these cases (Tse et al., 2015, Belvederi Murri et al., 2015).

The order with which symptoms develop in NMS is variable. However, it is common that the initial symptoms correspond to mental status changes, followed by muscle rigidity, autonomic instability, and then hyperthermia (Tormoehlen and Rusyniak, 2018).

**Paraclinical findings in neuroleptic malignant syndrome**

Laboratory evaluation is essential to exclude other causes of hyperthermia (mainly infections, metabolic, and endocrine abnormalities, as well as drug-induced syndromes) and to detect medical complications of NMS. Laboratory findings may also help with the positive diagnosis of NMS. However, no single abnormality is specific to the diagnosis. The most commonly observed abnormality is elevated creatine kinase. The threshold that is considered to be “suggestive of NMS” varies from study to study: at least four times the upper limit of normal (Gurrera et al., 2011) or >1000 U/L (Levenson, 1985). However, even though creatine kinase elevation is often considered as the most important biological finding in favour of NMS, such an elevation may be observed in up to 70% of patients who develop fever, while on antipsychotics (without actually having NMS), and even in up to 30% of patients who develop fever, while not on any psychotropics (O'Dwyer and Sheppard, 1993). Other observed findings include elevations in catecholamines, elevations in lactate dehydrogenase, aspartate transaminase, leucocytosis, low serum iron level, metabolic acidosis, and hypoxia (Velamoor, 2017, Ware et al., 2018). Cerebrospinal fluid analysis and neuroimaging studies are generally normal and may help exclude differential diagnoses. Electroencephalography may show generalized slowing (Caroff and Mann, 1993).

**Diagnosis of** **neuroleptic malignant syndrome**

NMS should always be considered in patients exposed to antipsychotics who present with fever and rigidity, especially if the antipsychotic has been recently commenced or dose increased. It is important to note, however, that the majority of patients on antipsychotics who develop fever will not be suffering from NMS and it is therefore important to consider other diagnoses. By definition, NMS is a diagnosis of exclusion. Therefore, a thorough review of the case by obtaining an accurate symptom and medication history especially any temporal relationship, physical examination, and laboratory investigations can help in diagnosis and further management (Ware et al., 2018, Velamoor, 2017, Rowland et al., 2018).

The most commonly used diagnostic criteria are the DSM-5 criteria (American Psychiatric Association, 2013) and the Levenson’s criteria (Levenson, 1985) **(Table 1)**. An international multispecialty consensus group published diagnostic criteria for NMS (Gurrera, 2011) which are based on positive clinical and laboratory findings as well as the exclusion of alternative causes. However, no threshold score has been defined and validated for making a diagnosis of NMS.

These diagnostic criteria help improve diagnostic agreement, as well as diagnostic reliability and validity, thus allowing for more robust research about NMS. However, the diagnosis of NMS remains clinical, since the strict use of the criteria might make clinicians miss “atypical forms” of NMS (Tse et al., 2015).

**Differential diagnoses of** **neuroleptic malignant syndrome**

NMS is a diagnosis of exclusion. Hence, it is important to rule out other diagnoses that may present similarly **(Table 2).** These include neurological and medical conditions, substance or medication-induced syndromes, as well as psychiatric conditions. Neurological or medical conditions that need to be ruled out include central nervous system infections, inflammatory or autoimmune conditions; status epilepticus, subcortical structural lesions, as well as systemic conditions (e.g., pheochromocytoma, thyrotoxicosis, tetanus, heat stroke) (Velamoor, 2017, Ware et al., 2018).

Similar syndromes resulting from the use of other substances or medications include serotonin syndrome, Parkinsonian hyperthermia syndrome following abrupt discontinuation of dopamine agonists, alcohol or sedative withdrawal, malignant hyperthermia occurring during anaesthesia, hyperthermia associated with abuse of stimulants and hallucinogens, as well as atropine poisoning from anticholinergics. Psychiatric differential diagnoses are primarily represented by malignant catatonia associated with mood or psychotic illness (Sethi, 2004).

Indeed, individuals with schizophrenia or a mood disorder may present with malignant catatonia, which may be indistinguishable from neuroleptic malignant syndrome. Some investigators consider neuroleptic malignant syndrome to be a drug-induced form of malignant catatonia (Velamoor, 2017, Ware et al., 2018).

**Serotonin Syndrome (SS)**

SS forms an important differential diagnosis, yet hard to differentiate from NMS when it comes to clinical presentation due to overlap of symptoms. SS is described as a clinical triad of mental status changes, autonomic hyperactivity and neuromuscular changes (Sampson E, Warner JP 1999 and Martin T. 1996). However, all these may not be present in every patient with SS. SS is an adverse drug reaction caused of therapeutic drug use, intentional overdose or drug interactions leading to excessive stimulation of serotonergic receptors in the peripheral and central nervous system (Volpi-Abadie et al 2013 and Iqbal et al 2012). SS is believed to be due to excess precursors of 5-hydroxytryptamine (5-HT) and its agonists, increased release of 5-HT, decreased uptake or lower metabolism in the nervous system (Boyer EW, Shannon M 2005).

Differentiating NMS and SS can be a challenge but clinical course, signs and laboratory findings may prove to be helpful (Kimmel R. 2010). Important distinguishing clinical features pointing to the diagnosis of SS include hyper-reflexia (often in the form of clonus, more marked in the lower extremities), ocular clonus and tremors. In comparison NMS is a bradykinetic syndrome characterised by uniform ‘lead-pipe’ rigidity and hyporeflexia (Iqbal et al 2012, Boyer EW).

Symptoms of SS are also frequently seen within the first 24 hours of starting serotonergic agents and resolve within a few days of starting treatment and omitting the medication. On the other hand NMS can often be slower in onset and usually takes 9–14 days to remit in spite of appropriate treatment. (Perry PJ 2012, Kimmel R. 2010)

**Aetiology and pathophysiology of neuroleptic malignant syndrome**

NMS is caused due to exposure to dopamine antagonists. It can occur at any time during antipsychotic therapy but the risk is highest immediately after starting the medication or following a dose increase. NMS has been noted to occur within the first four weeks in 96% of cases (Sethi, 2004, Berman, 2011).

Most antipsychotics have been implicated, and NMS usually occurs within the therapeutic dosage range of antipsychotics. Typical antipsychotic agents have been reported in the literature to cause NMS more frequently than other agents, which may reflect their long history of use (Nakamura et al., 2012). Dopamine antagonists used in medical settings (e.g., metoclopramide, prochlorperazine) could also induce NMS (American Psychiatric Association, 2013).

The pathophysiology of NMS is not well understood and involves a complex interaction between antipsychotic medication and a susceptible individual. It is triggered by neuroleptic blockade of dopamine D2-receptors in the key neural pathways that affect thermoregulation (hypothalamus), motor tone (nigrostriatum and brain stem) and mental status (reticular activating system). However, central thermoregulation is mediated by noradrenergic, serotonergic and cholinergic pathways, as well as the dopaminergic pathways and it is therefore unlikely that NMS is due to central dopamine blockade alone. To date, however, none of the theories put forth as the underlying cause of NMS, have been able to explain why only a small fraction of patients exposed to neuroleptics develop this condition. Furthermore, it remains unknown why patients who develop NMS are usually able to continue being treated with similar medications and, at times, even the same offending agent (Berman, 2011, Khaldi et al., 2008).

**Neuroleptic malignant syndrome risk factors**

Both age and gender distributions correspond with the distribution of the exposure to neuroleptic agents. Hence, age and gender are not risk factors, per se (Caroff and Mann, 1993).

The previous history of NMS may increase the risk of NMS. Indeed, about 15%-20% of NMS patients will have experienced a similar episode (Ouyang and Chu, 2013). There is limited evidence to suggest genetic susceptibility, possibly through a reduction in the D2 dopamine receptor function (Berman, 2011).

Other medical risk factors include catatonia, organic brain syndrome or previous brain injury, Parkinson’s disease, hyperthyroidism, alcoholism, use of restraints, iron deficiency, exhaustion, dehydration and agitation (Berman, 2011, Stroup and Gray, 2018).

Medication-related factors include antipsychotic polypharmacy, high-potency or high-dose antipsychotics, adjunctive psychotropic medications, e.g. lithium, rapid titration of antipsychotics, abrupt discontinuation of antipsychotic medication, poorly controlled or treatment resistant antipsychotic-induced extrapyramidal symptoms, as well as withdrawal of antiparkinsonian medications (Stroup and Gray, 2018).

*Atypical versus conventional antipsychotics*

NMS was originally described with conventional or typical antipsychotics. Although atypical antipsychotics or SGAs are overall less likely to induce severe hyperthermia or rigidity, NMS has been reported with virtually all atypical antipsychotics (Velamoor, 2017, Anzai et al., 2019), including those with weak anti-D2 effects such as quetiapine and clozapine (Teo et al., 2018) and those with partial D2 agonist effects, e.g. aripiprazole (Agrawal et al., 2019). Yet, apart from possibly blonanserin and perospirone, atypical antipsychotics appear to be significantly less associated with NMS than haloperidol, with clozapine being possibly the safest in this regard, followed by quetiapine (Anzai et al., 2019).

**Course and complications**

There is substantial variation in NMS clinical presentations ranging from mild to life-threatening presentation.

NMS presents a challenge as the outcome depends on its prompt recognition and treatment. Although relatively uncommon, NMS can be fatal. However, in most cases, if the offending agent is discontinued, NMS is self-limited. Indeed, following antipsychotic discontinuation, patients recover within an average of 7 to 10 days. Nonetheless, the duration may be prolonged when long-acting antipsychotics are implicated (Caroff and Mann, 1988).

Complications of NMS are often due to physiological consequences of severe rigidity and immobilisation, e.g. dehydration, deep vein thrombosis, pulmonary embolism, aspiration pneumonia and disseminated intravascular coagulation (Berman, 2011). Myoglobinuria, renal failure and rhabdomyolysis are serious complications of NMS. These are strong predictors of death with a mortality rate of approximately 50 per cent if renal failure is present (Chandran et al., 2003, Shalev et al., 1989). Overall mortality rates that were reported in the 19870-1980s were high: 27.7% prior to 1980, dropped to 22.6% between 1980 and 1983, and then to 11.6% between 1984 and 1987 (Shalev et al., 1989). Using data from 2004 to 2008, Nakamura *et al.* found mortality rates of 7.6% in FGA-associated NMS, and 3.3% in SGA-associated NMS (Nakamura et al., 2012). In the study by Modi *et al.* including 1346 patients from a US nationwide inpatient sample for the years 2002–2011, the NMS mortality rate was 5.6%, with a trend of decreased mortality over the years (Modi et al., 2016). This improvement in NMS outcome is probably due to better recognition of the syndrome, early intervention and the availability of intensive supportive care (Modi et al., 2016).

**Management of neuroleptic-malignant syndrome**

NMS is a medical emergency and managed in an acute hospital.

There are no published randomised controlled studies about the management of NMS, and there are no treatments specifically approved for NMS. The most important and critical intervention in the management of NMS remains the discontinuation of the antipsychotic medication (Berman, 2011).

*Immediate management in psychiatric wards (PW)*

Successful treatment of NMS depends on early clinical recognition and prompt withdrawal of the neuroleptic agents. Neuroleptics cannot be removed by dialysis, and blood concentrations decline only slowly. If NMS is suspected, all antipsychotic medication should be immediately discontinued (Friedman, 2015). This includes drugs with weak dopamine-blocking properties such as promethazine, which has been incriminated in cases of NMS and should be immediately withdrawn if NMS is suspected (Chandran et al., 2003, Velamoor, 2017).

A thorough medical work-up should be initiated. Laboratory evaluation is essential to exclude other causes of hyperthermia and detect any medical complications. Supportive care is the mainstay of treatment for NMS and it should occur in a setting where blood pressure, cardiac rhythm, and pulse-oximetry can be continuously monitored. In the United Kingdom (UK) this usually means transfer to a medical assessment unit (MAU); given psychiatric units do not have such facilities or training. In moderate to severe cases of NMS, the need for continuous monitoring makes it imperative to transfer patients to ICU setting (Berman, 2011). There is generally lack of clear guidelines for transfer to ICU or treatment options within ICU, however some recent publications have tried to classify NMS into various stages (Table 3) and also laid out treatment options (van Rensburg R, Decloedt EH 2019). A recent review of NMS treatments reported only 14 guidelines thematically related to its management, out of which 8 were in English, 6 in German, and 1 French ((Carlos Schönfeldt-Lecuona et al 2019). None of the guidelines were from the UK.

As shown in table 3, the mild forms of NMS can be treated in a psychiatric unit or medical setting (MAU) and not necessarily need ICU care unless there is further deterioration. Again, it may not be possible always to manage mild cases of NMS on psychiatric units due to the lack of the necessary facilities like access to laboratories, equipment and trained manpower (Carlos Schönfeldt-Lecuona et al 2019).

*Overview of management in an intensive care facility*

Supportive care is the mainstay of treatment. Pharmacological intervention with dopamine agonists produces mixed results and there have been no prospective randomised controlled trials comparing treatment regimens in patients with NMS. Benzodiazepines, Bromocriptine (centrally acting dopamine agonist), Amantadine (dopamine agonist) and Dantrolene (muscle relaxant) can be used. Again referring to Table 3, the pharmacological management can be divided as per the severity of NMS and treatment response. Oral or intravenous benzodiazepines, are the mainstay of early treatment of catatonia, may decrease fever and rigidity in NMS, in addition to treating agitation (Chandran et al., 2003, Chung and Lee, 2018). For early or mild forms of NMS, benzodiazepines along with withdrawal of the causative agent can be initiated in a psychiatric ward prior to transfer to a medical ward and does not necessarily need ICU care. Several clinical reports suggest that Loarzepam and other benzodiazepines may reduce the recovery time and hence improve the outcome (Yacoub A, Francis A 2006, Tural U, Onder E 2010). A Lorazepam dose of 1 to 2 mg oral or intravenously 4 to 6 hourly remains the first line pharmacological intervention (Wijdicks EFM 2018). Intramuscular administration (IM) should be avoided if possible to avoid diagnostic confusion due to potential elevation in creatine kinase (CK) levels (Konikoff, F et.al 1985). NMS of moderate severity requires ICU care, and use of benzodiazepines and bromocriptine has been shown effective in improving clinical response compared to just supportive care (Rosenberg MR, Green M 1989). It is also shown reduced mortality in NMS compared to supportive care (Sakkas P 1991). Bromocriptine has to be administered orally or through a nasogastric tube as there is no parenteral preparation available. A starting dose of Bromocriptine2.5 mg, 2–3 times daily, to be increased by 2.5 mg every 24 hours until a response is obtained or until reaching a maximum dose of 45 mg/day, can be used. It is recommended that bromocriptine to be continued for 10 days after symptoms are controlled and then tapered slowly to minimize the likelihood of recurrence of NMS. (Strawn JR 2007, Bhanushali MJ, Tuite PJ 2004)

Amantadine can be used as an alternative to Bromocriptine but there is limited evidence about its efficacy compared to the rest of the medications mentioned.

Dantrolene is recommended for severe forms of NMS along with benzodiazepines and bromocriptine. There are mixed reports about its efficacy with some meta-analysis suggesting improvement in approximately 80% patients with dantrolene monotherapy (Sakkas P et al 1991, Mann SC et al 2003); however some recent reviews suggest higher mortality with monotherapy and longer recovery times in combination treatments (Reulbach U 2007). Dantrolene is administered intravenously starting with an initial bolus dose of 1–2.5 mg/kg followed by 1 mg/kg every 6 h up to a maximum dose of 10 mg/kg/day (Strawn JR 2007, Bhanushali MJ, Tuite PJ 2004, Tsutsumi Y 1998). Response is noted within minutes of administration. Due to risk of hepatotoxicity, dantrolene should be typically discontinued once symptoms begin to resolve. However, some recommend continuing for 10 days followed by a slow taper with doses of oral dantrolene that range from 50 to 200 mg daily to minimize relapse (Bhanushali MJ, Tuite PJ 2004).

As discussed symptoms of NMS sometimes return if treatment is discontinued before complete clearance of the offending medication, so, if bromocriptine, dantrolene, or both are used, treatment should continue for ten days beyond the resolution of symptoms, or for 2-3 weeks if the offending agent is an extended release depot antipsychotic.

General symptomatic treatment, such as hydration, nutrition and reduction of fever, is very essential. Secondary complications, such as hypoxia, acidosis and renal failure, must be treated aggressively. Low‐dose heparin seems to be indicated to prevent venous thrombosis in an immobilized patient. Other dopamine antagonists, such as metoclopramide, should be avoided (Berman, 2011, Velamoor, 2017).

The treatment of NMS with pharmacological agents and ECT is still debatable due to the lack of large scale randomised clinical trials and most evidence is based on case reports.

*Role of ECT in the management of neuroleptic-malignant syndrome*

Electroconvulsive therapy (ECT) may be a therapeutic option for NMS, even though the evidence is mostly based on case reports and case series. Clinical response to ECT is presumably by increasing the central dopaminergic transmission. ECT seems to be relatively safe in patients with NMS, with a response onset usually observed within few sessions (Nisijima K, Ishiguro T 1999). ECT is known to reduce mortality in NMS compared to supportive care alone. (Davis JM et al 1991) ECT may be considered as a second-line treatment for patients who have not improved after 48 hours of pharmacologic treatment. Besides, ECT may be the preferred first-line treatment (i) for patients where it is not clear whether the cause of the symptoms is NMS or malignant catatonia (ii) when the underlying psychiatric diagnosis is psychotic depression, or (iii) when the catatonic features are prominent in the NMS clinical picture (Trollor and Sachdev, 1999, Hashim et al., 2014).

**Prevention of neuroleptic-malignant syndrome**

Prevention of NMS is likely the most important aspect in the management of NMS. Primary prevention of NMS may entail (i) reducing unjustified prescription of antipsychotics. This is particularly important, as up to 75% of antipsychotic prescription is off-label (Carton et al., 2015). Even low dose antipsychotics used for indications other than psychiatric can still expose to the risk of NMS, hence avoiding unnecessary prescriptions may help decrease the incidence of NMS. In psychiatry, the optimization of antidepressant, anxiolytic, and mood stabilizing treatment can also help avoid augmentation with antipsychotics, or in certain cases, allow the use of lower doses of antipsychotics. (ii) Antipsychotic polypharmacy increases the risk for NMS and avoiding it is always recommended. Antipsychotic polypharmacy is a wide-spread practice worldwide that has not been associated with any better efficacy when it comes to treating psychosis. Instead, it has been linked to higher morbidity and mortality, in particular, increased risk of QTc prolongation, extrapyramidal side effects, and metabolic side effects (Gallego et al., 2012). A higher incidence of NMS is possibly one of the explanations of this reported increase in mortality. (iii) When possible, avoiding parenteral routes, rapid titration, and high doses associated with a higher risk for NMS; (iv) preferring antipsychotics that are less commonly associated with NMS, in particular, those with lower D2 blocking effects, whenever clinically possible. High-potency antipsychotics have the highest propensity to cause NMS and might be better avoided as first-line in the presence of “safer” options. Secondary prevention of NMS involves timely detection of NMS through monitoring of vitals, mental state, and extrapyramidal signs, especially in patients requiring high doses, rapid titration, or receiving parenteral antipsychotics. In addition, educating the patient and their families about the signs that may indicate NMS could help. Tertiary prevention of NMS may comprise immediate discontinuation of all antipsychotics in the case of the slightest suspicion of NMS. Antipsychotic medication could be resumed later once NMS has been ruled out (Velamoor, 2017).

**Antipsychotic rechallenge following a neuroleptic-malignant syndrome**

Patients with a history of NMS are likely to require future antipsychotic treatment, depending on the diagnosis that required antipsychotic medication in the first place. Prevention of NMS upon rechallenge awaits a better understanding of the underlying pathophysiology. Not all patients will experience a recurrence. The estimated risk of developing NMS again with repeated exposure is 30%. It is also debated whether potency and dose of a re-challenge drug are an independent predictor of recurrence. The evidence supporting recommendations for reinstituting treatment after NMS is limited (Stroup and Gray, 2018, Rosebush et al., 1989).

In practice, rechallenge should not be tried until at least two weeks after full recovery from NMS and ideally in an inpatient setting. It is indeed likely that the risk of recurrence is more linked to the washout period than to the actual antipsychotic agent that is reintroduced (Pileggi and Cook, 2016). The washout period should take into account the severity of the NMS, the presence of any sequelae, the severity of the underlying psychiatric disorder, as well as the pharmacokinetic properties of the offending agent (Pileggi and Cook, 2016).

When re-challenging after NMS, it is generally advised to use a different antipsychotic drug, even though a case series found that recurrence rates were similar regardless of whether the same or a different antipsychotic was used (Wells et al., 1988). The clinician’s caution and the patient’s preference generally favours a different antipsychotic agent. When selecting a new agent, it is prudent to choose an agent with low D2-nigrostriatal affinity (Pileggi and Cook, 2016). Given its low D2 effects, clozapine can be an option. According to a systematic review by Lally *et al.* (2019), the outcome of rechallenge using clozapine following a non-clozapine antipsychotic–associated NMS was reported to be favourable in 79% of the cases. In patients who developed NMS on clozapine, Lally *et al. (2019)* reported that the outcome of clozapine rechallenge was favourable in 92% of cases, with no death reported even in the “unfavourable outcome” group who had an NMS recurrence.

When re-challenging after NMS, it is recommended to begin with a low dose, and to advance slowly toward the target dose. Careful monitoring for fever, autonomic instability, mental status change, extrapyramidal symptoms, and dehydration is indicated. Neuroleptics should be discontinued if fever, muscular rigidity and/or labile blood pressure are noted **(Box 2)**. Serial measurements of white blood cell count and CK are also warranted. Agitation should be treated aggressively with benzodiazepines, since agitation increases the risk for NMS. Adjunctive treatment with a mood stabilizer, antidepressant, or both for the affective symptoms may minimize the required dose of antipsychotic (Velamoor, 1998).

**Conclusion**

NMS is rare idiosyncratic reaction to antipsychotics, which is associated with substantially high morbidity and mortality. Early recognition remains paramount to avoid complications and mortality, with careful monitoring of vitals and mental state. Prompt discontinuation of antipsychotics is essential with any suspicion of NMS. Management requires admission to an acute medical unit, for supportive care. One of the main difficulties with treating NMS is that it is very hard to predict who will develop it and when. Further studies may help provide a deeper insight into the pathophysiology of NMS and help clinicians to predict it better. In the meantime, emphasising conservative prescribing guidelines, and providing proper education to the patient and family are vital in early recognition and management of NMS.

**Table 1: Diagnostic criteria for neuroleptic malignant syndrome**

|  |  |
| --- | --- |
| **DSM-5 criteria** | **Levenson’s criteria** |
| The clinical features described below are those considered most important in making the diagnosis of neuroleptic malignant syndrome based on DSM-5 consensus recommendations.  **Hyperthermia** (>100.4°F or >38.0°C on at least two occasions, measured orally). Extreme elevations in temperature, reflecting a breakdown in central thermoregulation, are more likely to support the diagnosis.  **Mental state changes** characterized by delirium or altered consciousness ranging from stupor to coma, are often an early sign. Patients may appear alert but dazed and unresponsive, consistent with catatonic stupor.  **Autonomic activation and instability** manifested by tachycardia (rate >25% above baseline), diaphoresis, blood pressure elevation (systolic or diastolic >25% above baseline) or fluctuation (>20 mmHg diastolic change or >25 mmHg systolic change within 24 hours), urinary incontinence, and pallor—may be seen at any time but provide an early clue to the diagnosis. Tachypnea (rate >50% above baseline) is common, and respiratory distress—resulting from metabolic acidosis, hypermetabolism, chest wall restriction, aspiration pneumonia, or pulmonary emboli—can occur and lead to sudden respiratory arrest.  **Muscle rigidity**- Generalized rigidity, described as "lead pipe" in its most severe form and usually unresponsive to antiparkinsonian agents, is a cardinal feature of the disorder and may be associated with other neurological symptoms (e.g., tremor, sialorrhea, akinesia, dystonia, trismus, myoclonus, dysarthria, dysphagia, rhabdomyolysis). | The presence of all three major, or two major and four minor, manifestations indicates a high probability of the presence of neuroleptic malignant syndrome, if supported by clinical history.  **Major criteria**  Fever  Rigidity  Elevated creatine kinase (CK)  **Minor criteria**  Tachycardia  Abnormal blood pressure  Altered consciousness  Diaphoresis  Leucocytosis |

**Table 2: Differential diagnoses for neuroleptic-malignant syndrome**

|  |  |  |
| --- | --- | --- |
| **Diagnosis** | **Suggestive Clinical Features** | **Indicated Lab Testing** |
| **CNS infection, sepsis** | Hallmark of a CNS infection include a history of prodromal illness, headaches, meningeal signs, focal neurological signs, seizures, and frequently positive CSF and neuroimaging studies. | If an infectious aetiology is suspected, a lumbar puncture and blood, urine, and CSF cultures are mandatory, and an EEG may be required to rule out seizure activity. |
| **Endocrine disorders: thyrotoxicosis,**  **Pheochromocytoma** |  | Check TSH, FT4, FT3.  Check urine catecholamines and metanephrines. |
| **Epilepsy: nonconvulsive**  **status epilepticus, postictal**  **state** |  | EEG. |
| **Drug intoxications : MDMA,**  **Cocaine, Amphetamines** |  | Urine toxicology. |
| **Serotonin syndrome** | Can usually be distinguished by the drug history.  Usually milder, quick in onset (minutes or hours) and is transient.  Associated with gastrointestinal signs and symptoms (hyperactive bowel sounds, diarrhoea, vomiting), myoclonus,  Hyperreflexia. | Absence of leucocytosis and CK elevation. |
| **Monoamine Oxidase Inhibitors (MAOIs) toxicity** | Monoamine Oxidase Inhibitors (MAOIs) produce a similar reaction to NMS when used in combination with TCAs, which may consist of agitation, delirium, hyperthermia and even death. | If patients are taking a combination of an MAOI and an antipsychotic, MAOI toxicity will need to be ruled out before NMS is diagnosed. |
| **Lithium toxicity** | Myoclonus, hyperreflexia, tremor | Check lithium level. |
| **Central anticholinergic**  **syndrome** | Dry flushed skin, diminished sweating, urinary retention, dilated pupils.  The patient is usually confused and disorientated (anticholinergic delirium) and the temperature is often elevated. | Peripheral signs of atropine poisoning characterize the syndrome. |
| **Malignant hyperthermia** | Exposure to halogenated anaesthetics can present in an identical manner to NMS; the setting and history of drug exposure usually distinguish it from NMS. |  |
| **Malignant catatonia** | The diagnosis requires careful detailing of the patient’s condition in the preceding 2–3 weeks. May be preceded by emotional withdrawal, anxiety, agitation, stereotypies, posturing, waxy flexibility, and mutism.  Associated with hyperpyrexia, rigidity, and akinesia. | Indistinguishable from neuroleptic malignant syndrome. Some investigators consider neuroleptic malignant syndrome to be a drug-induced form of malignant catatonia. |
| **Neuroleptic-induced heat**  **stroke** | Neuroleptic‐induced heat stroke can be differentiated from NMS by abrupt onset, often with seizures, the absence of extrapyramidal signs, absence of sweating, and a history of physical exercise or exposure to high ambient temperature. | NMS occurs at normal ambient temperatures. |
| **Withdrawal of Dopamine agonist** | A number of case reports appear in the literature of an NMS-like syndrome (NMLS) following withdrawal of levodopa preparations. Withdrawal of dopamine agonists mimics the dopamine antagonist action of antipsychotics and reduces the amount of usable dopamine in the brain, which is thought to be part of the pathogenesis of NMS. |  |
| Adapted from Table 3 in the review by Guzofski *et al.* (Guzofski and Peralta, 2006) | | |

**Table 3 NMS stages and treatment recommendations**

|  |  |  |  |
| --- | --- | --- | --- |
| **NMS Stage** | **Clinical presentation** | **Proposed treatment** | **Treatment Setting** |
| I: Drug-induced parkinsonism | Rigidity, tremor | Reduce or switch antipsychotics Anticholinergic agents | PW |
| II: Drug-induced catatonia | Rigidity; mutism; stupor | Discontinue, reduce, or switch antipsychotics  Use Lorazepam (up to 8 mg/day) | PW/MAU |
| III: Mild, early NMS | Mild rigidity; catatonia or confusion; temperature≤38°C (100.4°F); heart rate≤100 bpm | Discontinue antipsychotics  Use Lorazepam (up to 8 mg/day) | MAU |
| IV: Moderate NMS | Moderate rigidity; catatonia or confusion; temperature 38–40°C (100.4–104°F); heart rate 100–120 bpm | Discontinue antipsychotics  Intensive care  Lorazepam (up to 8 mg/day), bromocriptine (up to 15 mg/day), or amantadine (up to 300 mg/day) ECT as second line therapy | ICU |
| V: Severe NMS | Severe rigidity; catatonia or coma; temperature≥40°C (104°F); heart rate≥120 bpm | Discontinue antipsychotics  Intensive care  Dantrolene (up to 10 mg/day), bromocriptine (up to 15 mg/day), or amantadine (up to 300 mg/day) ECT as second line therapy | ICU |

(Adapted and modified from the current version of the update of the DGPPN S3-schizophrenia guideline (Carlos Schönfeldt-Lecuona et al 2019) ( PW- Psychiatric ward, MAU- Medical Assessment unit, ICU- Intensive care unit)

**Box 1: Royal College of Psychiatrists - Position Statement PS03/2014 - December 2014**

The Colleges make the following joint recommendations for the diagnosis and management of neuroleptic malignant syndrome (NMS):

1. NMS is a rare and serious complication of antipsychotic therapy about which there is much uncertainty over definitions, cause, course and outcome. Nonetheless, all psychiatrists practising without immediate on-site supervision should be able to diagnose NMS.

2. NMS is best considered a medical emergency and is properly managed in an acute hospital. All medical staff in acute hospitals with responsibility for taking emergency referrals should know this and act accordingly. Acute clinicians should be prepared to accept cases of diagnosed NMS without reference to the current clinical state of the patient. Any debate over whether a patient should be transferred to the acute hospital should be about the issue of the diagnosis only. Liaison psychiatry services within acute hospitals can manage the mental health needs of such patients, so these needs should never influence the decision to transfer.

**Box 2: Reinstituting antipsychotic treatment- Checklist**

Recheck the accuracy of the diagnosis of a previous NMS episode.

Document indications for antipsychotic medications.

Consider alternate pharmacologic agents.

Discuss risks and benefits, including the risk of recurrence, with patient and family.

Minimize risk factors.

Prescribe an initial test dose.

Monitor vital signs and neurologic status.

Titrate doses gradually.

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**MCQs**

Select the single best option for each question stem.

**1. Which of the following is required to diagnose neuroleptic-malignant syndrome?**

a severe hyperthermia.

b tachycardia and hypotension.

c elevated creatine kinase (CK).

d myoglobinuria.

e none of the above. (T)

**2. Which of the following symptoms and signs can help you disentangle neuroleptic-malignant syndrome from serotoninergic syndrome?**

a hyperthermia.

b tachycardia and hypertension.

c muscle rigidity.

d the absence of gastrointestinal symptoms. (T)

e delirium.

**3. Which of the following factors has been associated with a higher risk for neuroleptic-malignant syndrome?**

a young age.

b male gender.

c the use of electroconvulsive therapy (ECT).

d antipsychotic polypharmacy (T).

e combination of benzodiazepines with antipsychotics.

**4. Which is the single most important therapeutic intervention for neuroleptic-malignant syndrome?**

a rehydration.

b discontinuing all antipsychotic drugs (T).

c timely administration of dopamine agonists, e.g. bromocriptine.

d use of benzodiazepines and anticholinergics.

e electroconvulsive therapy (ECT).

**5. Which is of the following is true regarding antipsychotic rechallenge following a neuroleptic-malignant syndrome?**

a antipsychotic rechallenge should occur as soon as possible following a neuroleptic-malignant syndrome, especially when the patient is agitated.

b the use of depot antipsychotics following a neuroleptic-malignant syndrome can be a good option, thanks to more regular pharmacokinetics.

c alternatives to antipsychotics, whenever possible, can be warranted (T).

d creatine kinase (CK) monitoring following rechallenge is useless.

e If the patient does not develop neuroleptic-malignant syndrome within one month of the antipsychotic rechallenge, then there is no longer any risk of neuroleptic-malignant syndrome recurrence.