NEUROLEPTIC MALIGNANT SYNDROME

Abstract

Neuroleptic Malignant Syndrome is both rare and potentially fatal. Health clinicians need to recognize signs and symptoms and ask the right questions to make an accurate diagnosis and begin treatment. While this condition is not entirely understood, its symptoms are recognizable and typically easily resolved with little or no long-term impact to the patient when caught early. A treatment and management plan must be implemented. Pharmacotherapy has not been consistently effective in all case reports of neuroleptic malignant syndrome. In contrast, electroconvulsive therapy may be effective. A key step in the management of neuroleptic malignant syndrome is the initiation of supportive medical therapy.

Statement of Learning Need

Because NMS can be a life-threatening condition and is relatively infrequent, it requires timely and accurate diagnosis and treatment. Better recognition and monitoring of its symptoms by clinicians early on in the course of antipsychotic treatment is needed to reduce the number of severe cases of NMS and limit this significant source of morbidity and mortality among patients receiving antipsychotics.

Course Purpose

To provide clinicians with knowledge of the signs and symptoms of NMS and with the ability to distinguish NMS from other conditions that have similar signs and symptoms.
Part 1 Antipsychotics and Neuroleptic Malignant Syndrome

Introduction

Primary care physicians and psychiatric consultants may administer neuroleptics to psychiatric patients or to their patients with dementia to control agitation or psychosis. Patients who take neuroleptic medications may exhibit symptoms of physical deterioration, confusion and fever. The widespread use of neuroleptics and anti-Parkinsonian medications may accompany these same symptoms. In these cases, neuroleptic malignant syndrome (NMS) should be considered. It is important for their health clinicians to understand the early signs of the clinical presentation, differential diagnosis, and initial management of NMS.

Overview Of Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome is a rare, potentially life-threatening complication that usually appears within a clinical setting such as during antipsychotic therapy. During the first two weeks of using antipsychotic drugs or tranquilizers, symptoms associated with neuroleptic malignant syndrome (NMS) may be seen in the patient. Neuroleptic malignant syndrome has also been reported after the use of certain antidepressants, benzodiazepines, antiepileptic drugs, metoclopramide, and lithium. It is also known to occur in patients treated for Parkinson’s disease during abrupt medication cessation, dose reduction, or a switch from one dopamine agonist to another.

The definition offered by medical research for NMS may be encapsulated as follows:
Neuroleptic malignant syndrome (NMS) is a life-threatening idiosyncratic reaction to antipsychotic drugs characterized by fever, altered mental status, muscle rigidity, and autonomic dysfunction. It has been associated with virtually all neuroleptics, including newer atypical antipsychotics, as well as a variety of other medications that affect central dopaminergic neurotransmission. Although uncommon, NMS remains a critical consideration in the differential diagnosis of patients presenting with fever and mental status changes because it requires prompt recognition to prevent significant morbidity and death. Treatment includes immediately stopping the offending agent and implementing supportive measures, as well as pharmacological interventions in more severe cases. Maintaining vigilant awareness of the clinical features of NMS to diagnose and treat the disorder early, however, remains the most important strategy by which physicians can keep mortality rates low and improve patient outcomes.”

Neuroleptic malignant syndrome can be further described as a complex cascade of dysregulation in multiple neurochemical and neuroendocrine systems, potentially culminating in an end-stage hypermetabolic syndrome.\textsuperscript{21} It has been generally regarded as an idiosyncratic drug reaction, implying that it is unpredictable and dose-independent, although this view has been recently challenged in consideration of cases of NMS induced by antipsychotic withdrawal.\textsuperscript{2} However, individual vulnerability for the development of NMS might exist, related to variations in the genes for neurotransmitter receptors or metabolic activity, although evidence in this regard is still preliminary.\textsuperscript{27}

Neuroleptic malignant syndrome leads to progressive damage of the muscular tissue and multi-organ failure.\textsuperscript{21} The risk of developing NMS seems to parallel the ability of antipsychotic medication to induce extrapyramidal symptoms (EPS) and the degree of inhibition of dopamine receptor activity, particularly the D\textsubscript{2} subtype
in the nigrostriatal pathways. Reductions in the dopaminergic tone are also deemed responsible for the abrupt shifts that occur in the activity of the hypothalamic thermoregulatory system, which would in turn induce further dysregulation of the autonomic response.  

**Dopamine Receptors and NMS**

Neuroleptic malignant syndrome comes about, most likely, as a result of dopamine D2 receptor antagonism. Dopamine is a chemical substance (neurotransmitter) found in the brain and elsewhere in the central nervous system that acts to convey messages from one cell to another. In some way, a drug may block the receptor in the brain cell for dopamine with wide-ranging effects. The areas of the brain and CNS that may be affected include the hypothalamus, the corpus striatum, the basal ganglia, and spinal areas.

When the dopamine receptors in the hypothalamus or other areas are blocked, increased muscle rigidity results. The interference with the dopamine receptors in the hypothalamus affects the thermoregulatory centers in the anterior hypothalamus and this interference is probably responsible for high body temperature, as well as swings in blood pressure. As peripheral and central dopaminergic receptors are rather similar, the specificity of action of an antagonist on peripheral or central receptors depends primarily on its pharmacokinetic features. If the drug does not cross the blood-brain barrier, or if very little of the drug crosses, the peripheral effects will prevail and conversely in the case of good penetration in the brain.

Dopamine has an emetic effect and inhibits digestive motility; its antagonists have antiemetic and digestive motility stimulant effects. Dopaminergic receptors in the chemoreceptor trigger zone responsible for vomiting are accessible to
dopaminergic antagonists which do not cross the blood-brain barrier. Drugs stimulating gastrointestinal motility are called prokinetic agents and are used specially in treating gastroesophageal reflux.

The two principal peripheral antagonists of dopamine are domperidone and metoclopramide. Domperidone, chemically derived from butyrophenones, has a poor penetration into the brain and it does not induce, under usual conditions of use, central adverse effects resulting from blocking of central dopaminergic receptors. Domperidone is used in the preventive and curative treatment of nausea and vomiting and dyspepsia with motility disorder. It reinforces esophago-gastroduodenal motility without modifying digestive secretions. It is also used to reduce the peripheral effects of dopaminergic drugs such as L-DOPA.

Effects and therapeutic uses of metoclopramide, a derivative of benzamides, are the same as those of domperidone but metoclopramide crosses the blood-brain barrier more easily than domperidone and has more frequently central adverse effects similar to those of neuroleptics, in particular acute dyskinesia, especially in the child. Metoclopramide also activates serotonin receptors; it has 5HT4 agonist properties partially responsible for increase of intestinal motility. Dopamine agonists directly stimulate a subset of dopamine receptors, with the D2 receptor usually being the most important. MAO-B inhibitors decrease the metabolic degradation of dopamine inside the brain, thereby making more dopamine available for action.

**Neuroleptic Drugs**

As mentioned above, NMS has been associated with virtually all neuroleptics, including newer atypical antipsychotics, as well as a variety of other medications
that affect central dopaminergic neurotransmission. Neuroleptic drugs are widely known for their use in the treatment of severe psychosis and serious psychiatric conditions such as schizophrenia. However, the use of these drugs can also be extremely dangerous, toxic, and even life-threatening. In addition to NMS, the use of neuroleptic agents has been associated with a variety of adverse motor effects such as parkinsonism, acute dystonia, acute akathisia, tremor, and tardive dyskinesia. It is important to distinguish NMS from these other conditions and to understand which drugs may cause NMS.

Neuroleptic drugs are generally referred to as antipsychotics. The term “neuroleptic” refers to the ability of a drug to cause a syndrome known as neurolepsis. This syndrome has three main features: psychomotor slowing, emotional quieting, and affective indifference.¹ A drug was said to have antipsychotic efficacy if these features were present but the newer view is that these effects are not required for therapeutic actions. This was the case with traditional antipsychotics that were developed in the 1950s to treat serious mental disorders.

The newer view is that neurolepsis and all its features are not required to treat serious mental disorders effectively. Second generation antipsychotics (SGAs) were introduced in the 1990s without the typical properties or effects associated with traditional antipsychotics. By example, SGAs have a low risk of drug-induced movement disorders known as extrapyramidal symptoms (EPS), and as such, SGAs are atypical antipsychotics. Traditional antipsychotics are now ascribed the name first generation antipsychotics (FGAs) or typical antipsychotics.
The main class of atypical antipsychotic drugs (APDs) in current use includes the protypical atypical APD, clozapine, as well as aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, quetiapine, risperidone, and ziprasidone. At clinically effective doses, these agents produce extensive blockade of serotonin (5-HT2A) receptors, direct or indirect stimulation of 5-HT1A receptors, and to a lesser extent, reduction in dopamine (DA-D2) receptor-mediated neurotransmission. This contrasts with typical APDs, for example haloperidol and perphenazine, which are mainly DA-D2/D3 receptor antagonists and have weaker, if any, potency as 5-HT2A receptor antagonists. Some, but not all, atypical APDs are also effective 5-HT2C receptor inverse agonists or neutral antagonists, 5-HT6 or 5-HT7 receptor antagonists. This diverse action on 5-HT receptors may contribute to significant differences in efficacy and tolerability among the atypical APDs.5

There is considerable preclinical and some clinical evidence that effects on 5-HT receptors contribute to the low risk of producing extrapyramidal side effects, which is the defining characteristic of an atypical APD, the lack of elevation in plasma prolactin levels (with risperidone and 9-hydroxyrisperidone being exceptions), antipsychotic action, and ability to improve some domains of cognition in patients with schizophrenia. The serotonergic actions of the atypical APDs, especially 5-HT2A receptor antagonism, are particularly important to the differential effects of typical and atypical APDs to overcome the effects of acute or subchronic administration of N-methyl-d-aspartate (NMDA) receptor antagonists, such as phencyclidine, ketamine, and dizocilpine (MK-801). The 5-HT1A receptor stimulation and 5-HT6 and 5-HT7 receptor antagonism may contribute to beneficial effects of these agents on cognition. 5-HT2C receptor antagonism appears to contribute to the weight gain produced by some atypical APDs and may also affect cognition and psychosis via its influence on cortical and limbic dopaminergic activity.27,29
Neuroleptic Drugs and NMS

Almost 30 years have elapsed since the first case of NMS induced by an atypical antipsychotic was reported. Despite this, the knowledge on SGA-NMS is still quite limited and few studies have been conducted with a systematic methodology. Available evidence suggests that NMS is less frequent during treatment with SGAs than with FGAs. Second generation antipsychotics-NMS was characterized by lower clinical severity, and less frequent lethal outcome than NMS induced by first-generation antipsychotics. In a direct comparison, however, SGAs were still associated with an almost threefold higher probability of incident NMS than FGAs. Extrapyramidal adverse effects still occur with SGAs such as risperidone, olanzapine and amisulpride, if the dose is increased beyond the therapeutic range. Clozapine and quetiapine rarely cause extrapyramidal adverse effects at any dose, unless the patient has Parkinson's disease. Aripiprazole causes extrapyramidal adverse effects at a comparable rate to placebo, although a small proportion of patients may experience akathisia.

However, the report of NMS induced by withdrawal of antipsychotic or induced by the use of second generation antipsychotics (SGAs) such as clozapine, aripiprazole and amisulpride have cast doubt on the primary role of D$_2$ receptors, at least on the notion that D$_2$ receptors play a predominant role in all cases of NMS. In fact, these SGAs possess only weak activity at this level, with aripiprazole even acting as a partial agonist. Not coincidentally, our case review showed that the same SGAs are associated with the highest rates of NMS with atypical features, i.e., lacking severe EPS/rigidity, high fever, or grossly elevated CK. Thus, it is now widely acknowledged, although awaiting further confirmation, that receptors other than dopaminergic (i.e., serotonergic, adrenergic, and cholinergic) might play an important role in the pathophysiology of NMS since
they are known to take substantial part in extrapyramidal motor functions, thermoregulation, muscle metabolism, and mental status.\(^2^7\)

The mortality rate seems to be much lower for SGA-NMS than previous estimates of 10–20% among cases of FGA-NMS. Lethal cases tended to occur in older individuals.\(^2^7\) Cases of NMS associated with typical versus atypical antipsychotics also differed in terms of the populations affected. The mean age of patients affected by NMS associated with typical antipsychotics was 45.1 years, and 47.2 for patients affected by NMS associated with atypical antipsychotics. Eighty-eight percent of the atypical cases and 63% of the typical cases affected male patients. Median length of exposure to an antipsychotic prior to the onset of NMS for cases associated with atypicals was 23 days, while the median length of exposure for typical-induced onset was 6 days. In this study, mortality rate was 11% for atypical-induced NMS and 12% for typical-induced.\(^1^2\) The most common causes of death include rhythm disorders, respiratory failure, and renal or cardiovascular insufficiency.\(^2^0\)

There are also anecdotal reports that describe polypharmacy as a risk factor for NMS. In particular, either treatment with more than one antipsychotic compound or concurrent administration of an antipsychotic and lithium or carbamazepine has been implicated in several cases of NMS.\(^2^3\)

**Neuroleptics or Antipsychotics as Sole Cause of NMS**

Research suggests that some in the medical field question whether or not neuroleptics or antipsychotics alone, are responsible for the onset of NMS. It is highly likely that once clinicians understand the pathophysiology behind NMS, they may be able to determine how psychotropics exert their pharmacologic function at the cellular (neuronal) level. Currently, available theories have
limitations and they do not explain all clinical manifestations of this syndrome and other complications that are precipitated, especially by antipsychotics in general.21

**Clinical Presentation And Diagnosis Of NMS**

Neuroleptic malignant syndrome typically presents within a clinical setting such as during antipsychotic therapy; however, neuroleptic malignant syndrome is not a condition that affects only people with psychotic disorders who were treated with antipsychotic drugs, as previously thought. It may appear in a variety of psychiatric or medical conditions that have experienced an increased use of antipsychotics or other psychotropic compounds. In addition, rapid dose escalation could be another cause for the onset of NMS. While NMS is reported most commonly in people with schizophrenia, schizoaffective and other forms of psychosis, it has also been observed in other psychiatric conditions, including bipolar disorder, delirium and mental retardation. It can be associated with neurological disorders, such as Parkinson’s disease, encephalitis and dementia.

Neuroleptic malignant syndrome may appear with the use of mood stabilizers, such as lithium and antiemetic agents such as metoclopramide. Symptoms consistent with NMS have been associated with carbamazepine antidepressants such as paroxetine, sertraline and amitriptyline. While these cases may have been classified as NMS, they may have actually been examples of serotonin syndrome.13

**Diagnosing NMS**

Neuroleptic malignant syndrome’s precise mechanism of action is unknown; however, as discussed above, the pathophysiology is thought to be the result of an extensive blockade of dopamine receptors or a rapid decrease in the
dopamine activity in the nigrostriatal pathways. Because of this uncertainty, NMS is difficult to identify. Generally, NMS is diagnosed when other conditions are excluded, although in limited cases it may be diagnosed from its symptoms. Recognizing the syndrome early and promptly discontinuing the neuroleptic agent can avert a medical crisis.

The symptoms of NMS are hyperthermia, muscular rigidity and tremor, impaired consciousness and autonomic dysfunction. There is no accepted sequence or pattern to NMS. The evidence suggests that NMS symptoms progress sequentially: Mental status changes, muscle rigidity, and autonomic instability may appear first; hyperthermia is seen to develop later. While hyperthermia is considered by some as a necessary condition of NMS, and is reportedly present in at least 90% of the cases, it may not be present in all cases. The importance of understanding this sequence is that a clinician should not look for hyperthermia before suspecting NMS. This means that the early or developing stages of NMS may not always be accompanied by fever so the absence of hyperthermia should not rule out NMS early on. To be sure, the temporal progression of signs and symptoms may provide important clues to diagnosis and the severity of the illness.

The mnemonic “FEVER” may be used to help identify clinical and laboratory NMS markers in patients who exhibit mental and neurologic deterioration while taking antipsychotics or dopaminergic antagonists. One example would be: Fever, Elevated enzymes, Vitals instability, Encephalopathy, Rigidity of muscles.32

Hyperthermia
Pyrexia also occurs secondary to impaired heat dissipation when dopamine receptors are blocked in the thermoregulatory centers of the preoptic nuclei of the anterior hypothalamus. In some cases, hyperpyrexia, an extremely high rise of body temperature, may occur. Hyperpyrexia is defined as a condition where a person’s body temperature rises to or exceeds 41.5 °C (106.7 °F).

_Elevated Enzymes_

Leukocytosis and elevated hepatic transaminases are reported in at least 75% of NMS cases and increased CK in >90% of cases. These signs may be present in serotonin syndrome but are less common.²²

_Autonomic Instability_

Signs of autonomic nervous system instability that frequently accompany NMS include labile blood pressure, tachypnea, tachycardia, sialorrhea, diaphoresis, flushing, skin pallor, and incontinence. Although muscle rigidity is the most frequently described motor sign, a large number of additional extrapyramidal motor findings have been reported including tremor, chorea, akinesia, and dystonic movements including opisthotonos, trismus, blepharospasm, and oculogyric crisis. Other symptoms that have been associated with NMS include dysphagia, dyspnea, abnormal reflexes, mutism, and seizures.¹ Finally, dopamine receptor blockade at the level of the spinal cord may be responsible for the autonomic disturbances seen with NMS.

_Encephalopathy_

Physicians should have a high index of suspicion of atypical NMS particularly in non-psychiatric patients who present with a change in mental state after
administration of an antipsychotic. Mental status changes may be caused by dopamine receptor blockade in the nigrostriatal and mesocortical systems.

*Muscle Rigidity*

Muscle contraction and rigidity occur when dopamine effects are blocked in the corpus striatum. Muscle rigidity in NMS is often described as “lead pipe” rigidity because of its strong resistance to passive movement. Other motor symptoms of muscle rigidity in NMS include akinesia, bradykinesia, cogwheeling, myoclonus, tremor, chorea, opisthotonos, dysarthrias, dysphagia, trismus, akathisias, and dystonias. The muscular rigidity contributes to the underlying hyperthermia of the disorder and is usually associated with varying degrees of myonecrosis and rhabdomyolysis. Subsequent muscle contraction generates a tremendous amount of heat energy peripherally and results in pyrexia.

The temporal progression of signs and symptoms may provide important clues to diagnosis and severity of illness. Retrospective analyses suggest that alteration in mental status and other neurological signs precede systemic signs in more than 80% of cases of NMS.

*Onset of Symptoms*

Once symptoms appear, progression can be rapid and can reach peak intensity in as little as 3 days. The onset of NMS occurs over a period of one to three days (24–72 hours); however, occasional cases of NMS may have a sudden onset, that is, onset may occur within hours after drug administration. About 16% of cases of NMS develop within 24 hours after initiation of antipsychotic treatment, 66% within the first week, and virtually all cases within 30 days. It would be unusual for NMS to occur beyond 1 month after initiation of treatment unless the dose was increased or an additional antipsychotic administered. Once NMS is
diagnosed and oral antipsychotic drugs are discontinued, NMS is self-limited in most cases. The mean recovery time after drug discontinuation is in the range of 7–10 days, with 63% of patients recovering within 1 week and nearly all within 30 days. However, the duration of NMS episodes may be prolonged when long-acting depot antipsychotics are implicated. In addition, there have been several reports of patients in whom residual catatonia and parkinsonism persisted for weeks after the acute metabolic symptoms of NMS resolved. Clinicians should bear in mind that although NMS is striking in its classic form, the condition is heterogeneous in onset, presentation, progression, and outcome.

Although NMS can occur any time during the course of drug treatment, it occurs more frequently during either the initial months of treatment or after a dosage change. In this regard, higher doses of antipsychotic drugs have been correlated with a greater risk of developing NMS. In addition, parenteral routes of administration, either intramuscular or intravenous, have also been associated with greater risk. Nevertheless, NMS has been reported to occur at all standard doses and all routes of administration.24,27-31

Laboratory Testing

Because NMS is usually diagnosed by exclusion, there is no one test for NMS. However, laboratory studies are used to assess severity and complications, or to rule out other conditions. In order to conduct a careful history and physical examination and to make a diagnosis, the medical clinician evaluating a patient with suspected NMS should request laboratory tests of creatine phosphokinase concentration, white blood cell count, renal function, serum lithium level, as well as an electroencephalogram (EEG), computerized tomography (CT) scan, and lumbar puncture.
It is imperative that any underlying source of infection is excluded and consequentially patients may be extensively investigated with serial blood and urine cultures, chest X ray, neuro-imaging and CSF analysis being obtained before underlying infections can confidently be excluded. Laboratory abnormalities that may be found with NMS include increased LDH, increased creatine kinase, hyperkalemia, leukocytosis, decreased serum iron or metabolic acidosis. In addition to laboratory abnormalities, a patient may exhibit physical manifestations such as oculogyric crisis, trismus, opisthotonos, and a Babinski sign may also be present.

Laboratory findings are usually significant for a nonspecific leukocytosis and an elevated serum creatine phosphokinase (CPK). Creatine phosphokinase elevation, secondary to rhabdomyolysis, is present in up to 95% of cases. In rare situations, CPK can be as high as 2,000 times normal values. In progressive cases, myoglobinuria may be present, which can lead to acute renal failure if left untreated.

Although the pathophysiology of NMS is unclear and literature is limited, some case series report iron deficiency in >95% of cases. If this finding were replicated on a larger scale, iron deficiency might be a sensitive, rapid, and inexpensive test to help diagnose atypical NMS presentations. Larger studies are needed before clinicians can rely on this laboratory finding to diagnose NMS.

*Guidelines to Diagnose NMS*

Prior to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), clinicians used the DSM IV-TR to diagnose NMS. Diagnosis of NMS involved severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication as well as 2 or more of the following:
• Diaphoresis
• Dysphagia
• Tremor
• Incontinence
• Changes in level of consciousness ranging from confusion to coma
  Mutism
• Tachycardia
• Elevated or labile blood pressure
• Leukocytosis
• Laboratory evidence of muscle injury

The symptoms observed must be related to the use of a neuroleptic medication and are not better explained by use of another substance, such as phencyclidine. The symptoms must also not be better explained by another neurological or medical conditions (i.e., viral encephalitis), or a mental disorder.

DSM-5

Under DSM-5, a diagnosis of NMS can be considered in a patient who has been administered a dopamine antagonist when the following are present: 1) severe muscle rigidity, 2) hyperthermia, and 3) autonomic dysfunction (diaphoresis, dysphagia, tremor, urinary incontinence, changes in consciousness, mutism, tachycardia, labile blood pressure, leukocytosis, and laboratory evidence of muscle injury via elevated creatinine kinase levels). In atypical cases, NMS may present without muscle rigidity or hyperthermia. These symptoms may be milder to severe, may develop over time, or may not develop at all. Patients may exhibit fewer drug-induced movement disorders and lower elevations of creatinine kinase levels.
Other Diagnostic Methods

The DSM-5 is the current standard for psychiatric and related disorders but when diagnosing NMS, other diagnostic criteria are being used. These include the Levenson criteria, the Nierenberg criteria, and the Delphi method. These criteria have similarities and they all address a recent use or exposure to a dopamine antagonist. The Nierenberg criteria and Delphi method differ from the others because they also consider withdrawal from a dopamine agonist as a precipitating cause of NMS.

Levenson and Nierenberg divide the required criteria between major and minor features that are essential for an NMS diagnosis. The table below sets forth the Levenson criteria.

<table>
<thead>
<tr>
<th>Category</th>
<th>Manifestations</th>
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<tr>
<td>Major</td>
<td>Fever, rigidity, elevated creatinine phosphokinase concentration</td>
</tr>
<tr>
<td>Minor</td>
<td>Tachycardia, abnormal arterial pressure, tachycardia, altered consciousness, diaphoresis, leukocytosis</td>
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The Delphi Method uses a point-value system. Each of the different, clinical symptoms of NMS are assigned a number and accumulated on a scale of 0 to 100. There is no set or defined point value that results in a diagnosis of NMS but the probability that a patient has NMS increases as the point value increases.

Distinguishing NMS from Serotonin Syndrome

Symptoms of serotonin syndrome and NMS are similar in that they both present with mental status changes, autonomic dysfunction, and neuromuscular
abnormalities. This makes it difficult to differentiate the syndromes. However, therapeutic interventions and the mortality rates associated with these syndromes are widely divergent. Because many medication regimens for treatment-resistant mood disorders modulate both serotonin and dopamine systems, psychiatrists must be prepared at any time to recognize either syndrome and quickly initiate appropriate treatment. For this, health clinicians rely on disease course, lab findings, vital signs, and a physical exam.

Serotonin syndrome symptoms can develop within minutes to hours after the administration of an agent that increases central serotonergic tone, such as a selective serotonin reuptake inhibitor. After rapid onset, serotonin syndrome symptoms may improve or even resolve within 24 hours. Neuroleptic malignant syndrome, on the other hand, can develop days to weeks after the administration of a dopamine antagonist, such as an antipsychotic, and may take 3 to 14 days to resolve. There are occasional cases of NMS with a sudden onset, which may occur within hours after drug administration. These cases may be more difficult to distinguish from serotonin syndrome.

Neuromuscular manifestations also can help distinguish serotonin syndrome from NMS. Clinicians often and rightly associate muscle rigidity with NMS. This finding also is present in approximately one-half of serotonin syndrome cases, however. Hyperreflexia and myoclonus, if present, may suggest serotonin syndrome.

**NMS and Malignant Hyperthermia**

Some clinicians believe that NMS may be related to malignant hyperthermia (MH).¹ Malignant hyperthermia is a genetic disorder. Malignant hyperthermia (MH) is a severe reaction to gases administered during anesthesia or in connection with a muscle relaxant that is used to temporarily paralyze a patient.
during surgery. Signs and symptoms of MH include hyperthermia, a rapid heart rate, rapid breathing, acidosis, muscle rigidity, and rhabdomyolysis (a breakdown of muscle tissue and release of muscle fiber into the bloodstream).

A common pathophysiology of NMS and malignant hyperthermia is based mainly on three points: 1) NMS and malignant hyperthermia have clinical features in common, including hyperthermia, rigidity, an elevated creatine kinase concentration and a mortality rate for both NMS and malignant hyperthermia of 10–30%; 2) sodium dantrolene, a peripheral muscle relaxant, has been used successfully in both syndromes; and 3) abnormal results have been found in *in vitro* contractility tests in patients with NMS or malignant hyperthermia. These *in vitro* halothane–caffeine tests are at present the most reliable diagnostic measure for patients susceptible to malignant hyperthermia. They determine the sensitivity of muscle fibers to halothane or caffeine added to the bathing solution.

Muscle fibers from patients susceptible to malignant hyperthermia contract in response to these drugs at a lower concentration than those from normal patients. Hence, in order to evaluate a possible association between NMS and malignant hyperthermia, several investigators have used such tests on skeletal muscle fibers removed from patients with documented NMS episodes. However, conflicting results have been reported regarding the prevalence of malignant hyperthermia susceptibility among NMS patients.

It has been reported that five of seven NMS patients are susceptible to malignant hyperthermia on the basis of a 3% halothane response. Other studies found that NMS patients were not susceptible to malignant hyperthermia or were equivocal. One possible explanation for these discrepancies is that patients diagnosed as having NMS may be a heterogeneous group with great variability in clinical presentation, response to treatment and, possibly, response to test drugs.
Patients with clinical NMS should be tested for susceptibility to malignant hyperthermia before being considered at risk of this disorder during anesthesia.

**Other Disorders Mistaken for NMS**

Disorders that can be mistaken for NMS include rhabdomyolysis from other causes, central nervous system infections, a cerebral mass, tetanus and lithium toxicity. Other specific illnesses should be considered in the differential diagnosis of NMS, including neuroleptic-related heat stroke, catatonia, drug interactions with monoamine oxidase inhibitors, the central anticholinergic syndrome and anesthetic-induced malignant hyperthermia. Importantly, neuroleptic medications can predispose patients to hyperthermia, making them prone to heat stroke, especially if contributing factors such as hot weather, dehydration, or excessive exercise or agitation are present.\(^{22}\)

Central nervous system infection must also be considered early in someone presenting with the clinical features of NMS to avoid any delay in the appropriate treatment. Central nervous system disorders can frequently be difficult to distinguish from NMS, especially when the presenting signs are behavioral in nature. In addition to fever and mental status changes, hallmarks 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 etiology is suspected, a lumbar puncture and blood, urine, and CSF cultures are mandatory, and an EEG may be required to rule out seizure activity.\(^{22}\)

The most common disorders that can produce a clinical picture that looks like NMS are tumors, abscesses, cerebral vascular accidents, traumatic brain injury, seizures, and infections (i.e., human immunodeficiency virus, post-infectious
encephalomyelitis, and viral encephalitis). In addition, the evolution of a psychotic syndrome into a state of lethal catatonia can lead to exhaustion, stupor, hyperthermia, and possibly death. Again, a careful history, physical and neurological exams, and lab studies are all indicated, along with the use of imaging studies and lumbar puncture when clinically appropriate.

Lethal catatonia is a life-threatening psychiatric disorder that can present with clinical features of fever, rigidity, akinesia, and altered mental status. Although it can be difficult to distinguish it from NMS, the motor features in lethal catatonia are typically preceded by a few weeks of behavioral changes including ambivalence, apathy, withdrawal, automatisms, extreme negativism, and psychotic agitation. As lethal catatonia typically requires neuroleptic treatment as opposed to being caused by such treatment, rapid clinical differentiation between these two disorders is extremely important.²²

**Drugs Causing Symptoms Resembling NMS**

Often complicating the diagnosis of NMS is the large number of drug-induced syndromes that can have motor and cognitive features that resemble the condition. The use of neuroleptic agents has been associated with a variety of adverse motor effects including parkinsonism, acute dystonia, acute akathisia, tremor, and tardive dyskinesia, and several other classes of drugs at toxic levels may cause symptoms resembling NMS such as serotonergic agents, anticholinergics, monoamine oxidase inhibitors, tricyclics, lithium, meperidine, and fenfluramine. Intoxication syndromes from drug use such as cocaine, amphetamine, methamphetamine, phencyclidine, and 3, 4-Methylenedioxymethamphetamine (MDMA [aka Ecstasy]) can produce hyperthermia, mental status changes, and autonomic dysfunction and can easily be confused with NMS. Abrupt withdrawal syndromes from alcohol and
benzodiazepine can also be associated with altered mental status and muscle rigidity, and there is at least one report of a case of an NMS-like syndrome resulting from withdrawal of baclofen.\textsuperscript{22}

\textbf{NMS And Serotonergic Receptors}

The serotonergic receptors, in particular, have gained increasing attention in recent years as possible contributors to the pathophysiology of NMS, especially that induced by SGAs. In part, this hypothesis spawned from the observation that important similarities exist between NMS and serotonin syndrome at the clinical level. According to this line of research, serotonin-related toxicity would be responsible for the pathogenesis of at least some symptoms of NMS, and this would be particularly evident among atypical SGA-NMS. In apparent contrast with this hypothesis, most SGAs antagonize 5-HT\textsubscript{2A} receptors, and were even suggested for use in the treatment of serotonin syndrome. However, it is noteworthy that quetiapine, aripiprazole, clozapine, and ziprasidone share agonistic actions at 5-HT\textsubscript{1A} receptors; their stimulation was thus proposed to contribute to lower degrees of hyperthermia or EPS that are observed in some cases of SGA-NMS.\textsuperscript{27}

Moreover, it was recently hypothesized that long-term treatment with SGAs might determine unbalances in serotonergic neurotransmission, leading to sensitization towards SGAs and other psychotropic agents. Lastly, the observation of cases of NMS apparently precipitated by antidepressants, lithium, or other mood stabilizers have further highlighted a possible pathogenetic role for serotonin, although these drugs are unlikely to trigger NMS alone, in the absence of previous antipsychotic use. However, it was postulated that an excess of central serotonin due to antidepressant use could determine a ‘relative hypodopaminergic state’, which might increase the risk of developing NMS. Only statistical trends have found an association between antidepressants and the
clinical picture of NMS, and further studies based on larger samples are warranted before any clear role of these drugs can be confirmed. Overall, further evidence is also needed to elucidate the role of serotonergic neurotransmission in the pathophysiology of NMS.\textsuperscript{27}

Patients on neuroleptics who develop hyperthermia, muscle rigidity and autonomic dysfunction should have all psychotropic medications withdrawn immediately until rigorous diagnostic investigation reveals a specific aetiology. Treatments including medication treatments are available but patients do not always respond. This sometimes necessitates the use of electroconvulsive therapy.

\textbf{Part 1 Summary}

Neuroleptic malignant syndrome is a rarely encountered, life threatening complication that usually appears within the first two weeks of antipsychotic therapy. Moreover, NMS cases due to certain antidepressants, benzodiazepines, antiepileptic drugs, metoclopramide, and lithium have also been reported. Although NMS is a relatively infrequent condition, it requires timely and accurate diagnosis and treatment because of its life-threatening implications. Better recognition and monitoring of its symptoms by clinicians is needed, especially early on in the course of antipsychotic treatment.

\textbf{Part 2 Neuroleptic Malignant Syndrome, Electroconvulsive Therapy and Other Treatments}

\textbf{Introduction}

It is evident that the clinical presentation of neuroleptic malignant syndrome (NMS) is not homogeneous, but rather, the clinical signs or symptoms are rather
heterogeneous, making diagnosis difficult, especially in the early phase. Neuroleptic malignant syndrome usually starts as an unexplainable collection of several symptoms, which include tremor and muscle cramps, unstable blood pressure, and disturbance of mental status, for example, anxiety, agitation, delirium, and fulminant coma (terminal stage). Once NMS has been diagnosed, a plan for treatment and management must be developed. The first step in essentially all cases consists of cessation of the suspected offending neuroleptic pharmacologic agent or reinstituting a dopaminergic medication as quickly as possible if abrupt withdrawal of the medication is the suspected cause of NMS. Neuroleptic malignant syndrome is then managed with supportive medical therapy, and possibly drug treatment. Electroconvulsive therapy (ECT) may be effective when drug treatment or supportive medical therapy fail to provide the desired results.

**Overview Of NMS And Treatment Options**

The diagnosis of neuroleptic malignant syndrome (NMS) is based on history and the presence of certain physical examination and laboratory findings. Patients typically develop NMS within hours or days after exposure to a causative drug, with most exhibiting symptoms within 2 weeks and nearly all within 30 days. Although NMS has classically been characterized by the presence of the triad of fever, muscle rigidity, and altered mental status, its presentation can be quite heterogeneous. The clinical course typically begins with muscle rigidity followed by a fever within several hours of onset and mental status changes that can range from mild drowsiness, agitation, or confusion to a severe delirium or coma. Once a diagnosis of NMS has been made there are a number of treatment options.
Neuroleptic malignant syndrome in hospitalized patients is considered a neurologic emergency as a delay in treatment or withholding of therapeutic measures can potentially lead to serious morbidity or death. As such, it may be prudent in some cases to treat for NMS even if there is doubt about the diagnosis. Due to its rarity, however, systematic clinical trials in NMS are difficult to perform and so no evidence-based treatment approach exists. Nevertheless, effective general guidelines have been gleaned from case reports and analyses.

Successful treatment of NMS depends on early clinical recognition and prompt withdrawal of the neuroleptic agents. Treatment of NMS is individualized and based on the clinical presentation, but the first step in essentially all cases consists of cessation of the suspected offending neuroleptic pharmacologic agent. Neuroleptics cannot be removed by dialysis, and blood concentrations decline only slowly. If the syndrome has occurred due to an abrupt withdrawal of a dopaminergic medication, the medication must be reinstituted as quickly as possible. The next key step in addressing the symptoms of NMS is the initiation of supportive medical therapy. General symptomatic treatment, such as hydration, nutrition and reduction of fever, is essential.

**Antipsychotic Use And Discontinuance**

Once a presumptive diagnostic impression is suggested by the clinical history and semiological findings, the single most critical strategy in the therapeutic management of NMS is to discontinue the suspected pharmacological compound. Even while waiting to obtain laboratory results for the CPK or other indices, one should immediately discontinue the potentially harmful compound upon suspicion of NMS. If, however, the syndrome has occurred in the setting of an abrupt withdrawal of a dopaminergic medication, then this medication is reinstituted as quickly as possible.
Additional research has supported the medical opinion that all neuroleptics or antipsychotics be stopped immediately when there is any possible suggestion of NMS, and the patient should be admitted to hospital for close observation to evaluate the clinical signs and to perform the relevant laboratory investigations. This should be done in an Intensive Care Unit (ICU), especially for patients who have significant hyperpyrexia and rigidity. This is because these individuals need aggressive supportive care. One should evaluate biological treatment with dantrolene, bromocriptine, and/or amantadine in patients who have significantly elevated CK values or hyperpyrexia on the first presentation, and in those who are irresponsive to withdrawal of a psychotropic drug (or the offending drug) within the first 48 hours of admission.

**Pharmacologic Therapy For NMS**

In more severe cases of NMS, empiric pharmacologic therapy is typically tried. The three main drug options for treating NMS are dantrolene, bromocriptine, and biperiden; however, the use of these drugs to treat NMS is a controversial topic. In the case of biperiden, it has been suspected as a cause of NMS. Dantrolene and bromocriptine are discussed in more detail below.

The use of drugs to treat NMS is a controversial topic because randomized controlled trials are lacking and recommendations are based on consensus and expert opinion. In this regard, one group of researchers would be more inclined to treat NMS with just supportive treatment and they would not add specific drugs as a first-line treatment. On the other hand, there are others that strongly emphasize the need of starting specific pharmacologic treatment as soon as possible. The evidence available supporting the use of different treatment regimes is based on case series, expert opinion and consensus. In other words, anecdotal reports and meta-analyses suggest these agents may shorten the
course of the syndrome and possibly reduce mortality when used alone or in combination.

**Dantrolene**

Because of its efficacy in anesthetic-induced malignant hyperthermia, the muscle relaxant dantrolene has been used in the treatment of NMS but its use is not well-defined. Dantrolene may be useful only in cases of NMS with extreme temperature elevations, rigidity, and true hypermetabolism. Dantrolene can be combined with benzodiazepines or dopamine agonists, but it should not be co-administered with calcium channel blockers, as cardiovascular collapse can occur.

Sodium dantrolene inhibits calcium release from the sarcoplasmic reticulum, decreasing available calcium for ongoing muscle contracture. The drug is a non-specific, directly acting muscle relaxant and a decrease in body temperature coincides with muscle relaxation. Oxygen consumption diminishes and heart rate and respiratory rate decrease correspondingly.

Generally, rapid reversal of the hyperthermia and rigidity is observed in patients treated with dantrolene, but symptoms may return if treatment is discontinued prematurely. Notwithstanding the foregoing, the effectiveness of dantrolene to treat NMS is anecdotal and there are no conclusive studies. This is due in part to the low incidence of NMS. Because of its low incidence, large prospective studies of the use of dantrolene are difficult to conduct. Investigation into dantrolene relies on case reports. Single-case reports seem to say that dantrolene is not the treatment of choice in cases of NMS. Nevertheless, there is also no evidence to categorically deny the benefits of dantrolene therapy.

In some cases, dantrolene was successfully used to treat NMS after other treatment trials failed. It was useful to treat patients who received only supportive treatment for a period of time, followed by dantrolene treatment.
Further investigations are still needed to understand the etiopathology of NMS and its causal treatment. A promising approach might be the further exploration of possible central effects of dantrolene apart from its role as a muscle relaxant; however, the success of such analyses most likely will depend on the accuracy, uniformity, and completeness of these reports.

Typical dosing of intravenous dantrolene in the treatment of NMS is 1–2.5 mg/kg body weight administered initially, followed by 1 mg/kg every 6 hours if rapid resolution of the fever and rigidity is observed, with tapering or switching to oral dantrolene after the first few days. On the other hand, it has been suggested that the initial dosage should be 2 mg/kg given intravenously. This dose may be repeated every 10 min, up to a total dose of 10 mg/kg/day. Oral dantrolene is used in less severe cases or to taper down from the intravenous form after a few days with doses that range from 50 to 200 mg/day. Hepatic toxicity may occur with doses of >10 mg kg/day. Due to a risk of hepatotoxicity, dantrolene is typically discontinued once symptoms begin to resolve.

As stated, the side effects of dantrolene may include impairment of respiratory or hepatic function. In some meta-analyses, improvement has been reported in approximately 80% of NMS patients treated with dantrolene monotherapy. In addition, recovery time may be shortened, and mortality is decreased by nearly half compared with supportive care, whether dantrolene is used alone or in combination with other agents. However, other anecdotal reports and a recent meta-analysis of published cases did not support the efficacy of dantrolene in NMS.

**Bromocriptine**

Bromocriptine mesylate, a dopamine agonist, is also used to treat NMS. Bromocriptine is given to reverse the hypodopaminergic state and is
administered orally (or via nasogastric tube), starting with 2.5 mg given 2 to 3 times daily and increasing doses by 2.5 mg every 24 hours until a response or until reaching a maximum dose of 45 mg/day. Bromocriptine, however, is generally maintained for at least 10 days for NMS related to oral neuroleptics and 2 to 3 weeks for depot neuroleptics.\(^1\) Depot preparations are special preparations of a medication that is administered by injection. The medication is typically released into the body over a period of time, such as over a number of weeks.

Hypotension is the most limiting side-effect. The drug seems to be well tolerated by psychotic patients even though it is a strong central dopamine agonist. Rigidity may begin to decrease during the first few hours followed by a decrease in temperature, along with normalization of arterial pressure. This effect on rigidity and tremor strengthens the hypothesis of a dopamine-receptor blockade in NMS. Bromocriptine and dantrolene have been used together without complications.

**Lorazepam**

Treatment for NMS is generally supportive and pharmacological depending on the clinical presentation of illness stage or severity. Hyperthermia may improve with high-dose lorazepam and diazepam administration. Lorazepam and other benzodiazepines are administered to treat NMS symptoms; these drugs may reduce recovery time in NMS. Diazepam is effective in the treatment of NMS by enhancement of the GABAergic system. The cerebrospinal fluid (CSF) level of gamma-aminobutyric acid (GABA) is significantly decreased in the active phase and the GABAergic system is considered hypofunctioning in NMS.\(^2\)

Reducing the recovery time with benzodiazepine treatment may be related to the effects of these drugs on GABAergic hypofunction. In a patient with severe NMS and rhabdomyolysis, high-dose lorazepam and diazepam may be prescribed for
treatment. In addition, a clinician may administer the antipsychotic olanzapine 5 days after NMS resolution, which is quicker than some reports delaying antipsychotic treatment until approximately 2 weeks following the NMS resolution.

Supportive treatment, including antipyretic medications such as non-steroidal anti-inflammatory drugs or acetaminophen, and external cooling are frequently administered. Endovascular cooling has been reported in an NMS patient.

Case Study 2: Male Patient, Age 34

A male patient with history of Type 2 diabetes mellitus on oral hypoglycemic agents was hospitalized twice with symptoms of ketosis. He was treated with Insulin, intravenous fluids, and supportive therapy. He was discharged on twice daily dosing of insulin. Poor drug compliance, poor motivation regarding diabetes care, and psychomotor agitation were noted during hospitalization. Psychiatry consultation was sought for behavioral abnormalities. On psychiatry evaluation, the patient was diagnosed to have mental retardation with psychotic features. He was started on the antipsychotic risperidone, at a dose of 1 mg twice daily.

One week after starting on antipsychotics, he presented with extrapyramidal symptoms of dystonia, parkinsonian gait, fine tremors, high spiking fever, altered sensorium, and muscle rigidity. He was hospitalized and started on supportive therapy. Blood counts, urine microscopy, and renal function were normal except for low sodium. Creatine phosphokinase (CPK) was ordered in view of muscle rigidity that was very high (1543). A diagnosis of NMS was made and imaging and lumbar puncture were deferred as the initial reports were suggestive of NMS.

Risperidone was stopped immediately, and he was treated with lorazepam, trihexyphenidyl, paracetamol, and intravenous fluids in consultation with psychiatrist. Within 48 h of hospitalization, his symptoms improved and CPK level gradually came down. The patient was afebrile on the 3rd day and his glycemtic control improved. Family was informed of the diagnosis and the need for close monitoring of his glycemic control. Psychiatrists decided not to restart antipsychotic drugs. His behavioral abnormalities were to be managed with counseling sessions. He was discharged without further complications.

Treatment depends on the severity of symptoms. Patients who are hemodynamically unstable are to be transferred to higher centers for intensive monitoring. Mild cases can be managed at the secondary care setting in consultation with a psychiatrist.

Supportive therapy involves discontinuation of antipsychotic agents, correction of
electrolyte imbalances, nutritional deficiencies and monitoring of airway, breathing, and circulation. Specific dopaminergic agents such as bromocriptine, dantrolene, and electroconvulsive therapy as an option are considered for more severe cases by psychiatrists. Iron deficiency should be corrected as low iron levels may aggravate movement disorders.

Complete resolution of symptoms takes around 2 days to 2 weeks. Symptoms may last for a month in patients being administered depot preparations. Restarting antipsychotics in patients with history of NMS if needed is done on consultation with psychiatry. Depot preparations are generally not recommended, however, a 2-week interval is to be considered between recovery and restarting antipsychotic agents. No complications with anesthesia have been reported in post-NMS patients.\textsuperscript{31}

**Other Pharmacologic Approaches**

Amantadine may be used due to its dopaminergic and anticholinergic pharmacologic effects. It has been used successfully in some NMS cases. Apomorphine is being considered but it is still not an optimal choice because it is not supported by major evidence.

Levodopa, combined with the carbidopa (dopadecarboxylase inhibitor), has also been reported to be effective in reversing hyperthermia.\textsuperscript{18} Treatment may have to be continued for several days. Minor tranquilizers such as benzodiazepines are a good choice for treating agitation and catatonia.
Anticholinergic drugs, such as benztropine, usually do not reduce the rigidity of NMS and do not affect hyperthermia. Benzodiazepine derivatives, which enhance GABA-ergic function, have caused transient decreases in symptoms. In every case, these drugs are recommended to control agitated patients being treated for NMS. Carbamazepine has reportedly been used successfully, and NMS completely resolved within 8 hours.

The mechanism of interaction between benzodiazepines and hyperthermia is still unknown. Low serum iron levels in NMS have been associated with poor responses to benzodiazepines and patients with normal iron serum levels show good responses to benzodiazepines. However, the relationship between low serum iron and treatment resistance to benzodiazepines is still unknown.

The benefits achieved by the above-mentioned drugs are claimed to be uncertain, at least by some research groups. The evidence that supports the use of the above-mentioned agents is limited because 1) these agents are frequently used anecdotally because they lack scientific evidence regarding efficiency, 2) absence of evidence-based optimal pharmacologic treatment, and 3) high morbidity and mortality rates in this syndrome.

**Hypothermia and Regulation of Body Temperature**

In NMS, controlling of fever is a significant matter. There are non-pharmacological maneuvers to consider, which can target the environmental conditions that might predispose or worsen the condition. Specifically, a comfortable ambient temperature not higher than 21-23º C will allow better heat dissipation. In this regard, physical measures to control temperature such as application of wet cold cataplasms have not been systematically evaluated, but are a low-cost and very low-risk measure to apply.
Hyperthermia should be treated with cooling blankets, ice packs, cooled intravenous (IV) fluids, and antipyretics, although some researchers believe antipyretics are ineffective because hyperthermia in NMS is not mediated by pyrogens. In addition, IV fluids and parenteral nutrition are recommended for patients in respiratory distress or those unable to tolerate oral intake.\(^4\)

Maintaining cardiorespiratory stability via mechanical ventilation, antiarrhythmic agents, or pacemakers may be required. Other complications including cardiorespiratory failure, thrombocytopenia, renal or hepatic failure, and sepsis also need to be corrected immediately before they become fatal.\(^{24}\)

**Electroconvulsive Therapy**

Pharmacotherapy has not been consistently effective in all case reports of NMS. Moreover, drug effects are usually observed early and are unlikely to occur after the first few days of treatment. In contrast, electroconvulsive therapy (ECT) may be effective if symptoms are refractory to supportive care and pharmacotherapy even late in the course of NMS. The reason for its use in NMS is attributed to its efficacy in treating malignant catatonia and Parkinsonism. ECT is used if idiopathic malignant catatonia due to an underlying psychotic disorder cannot be excluded, or if the patient has persistent residual catatonia and parkinsonism after resolution of the acute metabolic symptoms of NMS.

Electroconvulsive therapy has improved some of the syndrome’s components, notably fever, sweating and level of consciousness. However, ECT has been suggested by certain groups to have no proven empirical benefits.\(^{21}\) While some researchers have found that ECT was consistently effective even after failed pharmacotherapy and that clinical response often occurred over the course of the first several treatments.\(^{21}\) Treatment response to ECT was not predicted by age, sex, psychiatric diagnosis, or any particular features of NMS.\(^{20,25,26}\)
A typical ECT regimen for acute NMS would include 6 to 10 treatments with bilateral electrode placement. ECT is a relatively safe treatment in NMS, although use of succinylcholine during anesthesia should be carefully considered in patients with severe rhabdomyolysis to avoid the risk of hyperkalemia and cardiovascular complications.

Since a common pathophysiology has been suggested between NMS and malignant hyperthermia, the possibility that patients with a history of NMS may be vulnerable to developing malignant hyperthermia is an important factor when considering general anaesthesia, especially succinylcholine administration immediately before electrical stimulation for ECT. Currently, ECT with the use of succinylcholine, which is an effective and rapid mode of treatment for cases of NMS unresponsive to supportive medical therapy, is not contraindicated. Researchers have reviewed anesthesia case outcomes with IV administration of succinylcholine in dose ranges of 15–30 mg without any complication reported complication. Nonetheless, until the association between NMS and malignant hyperthermia is conclusively disproved, careful metabolic monitoring of general anesthesia is necessary.25,31

If a patient should fall into a coma or become catatonic, there is research to suggest that ECT can be helpful in a high percentage of cases. It can also be helpful if a patient with NMS also has Malignant Catatonia (MC). Retrospective observational studies report a response rate to ECT in catatonic patients ranging from 80% to 100%. Hawkins, et al., as early as 1995 reviewed the treatments of catatonia in clinical records of 178 patients in 270 episodes. ECT alone was employed in 55 (about 30%) patients, obtaining the resolution of catatonic symptoms in 85% of the cases. When the presence of MC was suspected, the response to ECT was 89% (9 of 11). In another study, 50 catatonic patients where reviewed where ECT or drug treatment were administered. Response
rates, defined as the number of patients who respond completely to ECT divided by the total (cumulative) number of patients, were equal to 100%. In such studies, researchers reported that ECT should be the first choice treatment for catatonic symptoms, especially when doses of benzodiazepines above the upper limits cannot be applied. In a recent observational study by Medda, et al., a favorable response to ECT was observed in 21 (81%) out of 26 catatonic inpatients resistant to benzodiazepines.\textsuperscript{25}

Another recent review of ECT in a large Dutch teaching hospital involved 27 cases of catatonia among 285 ECT-treated patients over an 18-year period. Of the entire sample 48% presented mood disorders and 44% psychotic disorders. Although pharmacotherapy had failed in 85% of the patients, ECT was effective in improving 59% of the cases. The reduced treatment response in this study, compared with other reports (59% versus 85%-100%), may be related to the high prevalence of psychotic disorders, the delayed use of ECT (after two months of pharmacotherapy) and the previous use of antipsychotics in many of these patients. Finally, one-third of the patients suffered from neurological comorbidity. The same study reported the benefit of daily ECT in catatonic patients with autonomic disturbances (that can be considered mild cases of MC).

The need for daily ECT was already suggested in 1952 when a classic study by Arnold and Stepan reported that this procedure seems to avoid fatalities in MC. In a review of the most recent literature of 46 published reports describing ECT experience with 55 patients, ECT was effective in 40 (73%) patients with NMS. Complete recovery of symptoms was reported in 25 (63%) of the cases, and partial recovery was noted in 11 (28%).\textsuperscript{25}
Case Study 1: Female (Age 42)

A 42-year-old female with paranoid schizophrenia was treated with perphenazine at 16 mg daily, initially started at 2mg daily and gradually increased. Additionally, she was administered risperidone 6mg daily.

Patient developed clinical signs and symptoms of neuroleptic malignant syndrome (NMS), including an elevated creatinine kinase level to 3766/L, tachycardia, increased muscle tone, diaphoresis, dysphagia, incontinence, labile blood pressure, and severe confusion. Initially, she was treated with intravenous fluids and supportive care while her risperidone and perphenazine were discontinued. After her medications were discontinued, she developed paranoid persecutory delusions with loss of concentration. She also was discovered to have bilateral pulmonary embolism. She was started on enoxaparin and warfarin.

The patient's NMS showed a progressive increase in symptoms in spite of discontinuing her medications, so ECT was tried. Bitemporal ECT with a MECTA-type device using 1.0 milliseconds pulse width and 30 to 50 joule was applied three times a week for a total of eight sessions. Sodium thiopental and succinylcholine were used as anesthesia. After the second session of ECT, the patient’s tachycardia decreased and she started to communicate. Following the fourth ECT, she was able to spend half of the day out of bed. The symptoms of NMS were resolved totally by the eighth session. No serious adverse event was observed with ECT and the acute postictal confusional states that did occur subsided within 20 to 30 minutes. Electrocardiogram, blood pressure, and pulse rates stayed within normal limits during the ECT sessions. After the last ECT application, the CK level was measured as 98U/L. Along with the improvement in NMS, we observed significant reductions in her psychotic symptoms.

The choice of ECT in this case was made to provide an emergent intervention to a complicated case of severe NMS and pulmonary embolism. The reported mortality rate of NMS is broadly reported to be 4 to 20%. ECT was selected in this case for a rapid treatment rather than reliance upon pharmacology.

Electroconvulsive therapy may be considered for treatment of neuroleptic malignant syndrome (NMS) when autonomic stability has been re-established, and there is inadequate response to pharmaceutical measures or nonpharmacological treatment is required for continuing comorbid psychiatric illness. The efficacy of ECT in neuroleptic malignant syndrome is well recognised despite the absence of randomised controlled data. ECT reduces the mortality of NMS by approximately half. This same effect has been achieved by treatment with dantrolene, amantadine, L-DOPA and bromocriptine. When
pharmacological treatments fail to control the NMS disorder, ECT can be potentially lifesaving in severe cases. However, ECT for NMS is not without hazard and has been associated with ventricular fibrillation, cardiac arrest and uncontrolled spontaneous seizures. ECT is sometimes used to control psychiatric symptoms while neuroleptics may be contraindicated. Additionally, care must be taken in the anesthetic management of patients with NMS, particularly when autonomic instability is a key feature.  

Because ECT effectively treats acute lethal catatonia (ALC), it stands to reason that ECT might effectively reverse skeletal muscle rigidity in NMS. Mann, et al. found ECT effective in 20 of 27 cases and partially effective in 3 cases of ALC. Two patients in this series developed serious cardiovascular complications during ECT, including cardiac arrest in one patient and ventricular fibrillation in the other. It has been found that the majority of patients improve with ECT. Of the cases in which ECT was the primary treatment, the complete recovery rate was more than half and the partial recovery rate was approximately one-fourth of patients treated. In ECT for severe NMS cases in which there is a high risk of complications, dysphoria with psychotic features is the primary disorder, and catatonia (muscle rigidity) is the major symptom. Although controversial, the use of anesthetic agents in NMS patients is feasible. Usually succinylcholine, was used in 50% of cases. The use of succinylcholine did not result in MH or any laboratory abnormalities, although other case reports have reported these occurrences. 

Clinical Management Of NMS

Management of NMS focuses on withdrawal of the neuroleptic medication and meticulous supportive care, which includes aggressive hydration. Because renal failure is a common complication in NMS, strategies must be directed at
managing the elevations of creatinine kinase (CK), with its resulting myoglobin load to the kidneys. Fluid input and output must be monitored carefully. Autonomic instability results in increased insensible water losses as body temperature rises. The use of cooling blankets is essential to decrease body temperature; antipyretic agents can be helpful if an infection is a comorbid factor.

Patients with NMS should be admitted to an intensive care setting. In addition to aggressive supportive measures, several specific treatments mentioned in the literature have been previously mentioned: 1) Dantrolene sodium, 3 to 5 mg/kg IV given 3 to 4 times per day has been recommended to treat skeletal muscular rigidity, and 2) Bromocriptine, 5 mg by nasogastric tube, which can be increased to a maximum of 40 mg/day. Dantrolene sodium exerts its therapeutic effect by means of the blockade of calcium release from the muscle fiber's sarcoplasmic reticulum; and, the therapeutic effect of bromocriptine is related to its dopamine agonism, resulting in enhancement of dopaminergic transmission.\textsuperscript{1,3,20}

Other proposed treatments of NMS include pancuronium, "G carbamazepine," amantadine, anesthesia and plasmapheresis. ECT as a successful mode of therapy for NMS has been reviewed above. Its mechanism of action is not completely elucidated, but reports of its efficacy are encouraging, including in the treatment of most types of catatonia. Although the various specific treatments presented raise interesting questions regarding various aspects of the pathophysiology of NMS, these treatment approaches have not been studied using well-designed methodologies. In fact, most of the proposed therapies are supported by single case reports only.
In Caroff’s review of 60 cases, supportive therapy was the predominant treatment modality. The benefit of adding specific therapies to supportive measures is still debated. Insufficient data are available to evaluate the efficacy of specific treatments reported in the literature, however, potential benefits from their use cannot be excluded. However, efficacy of the varied approaches to therapy have been evaluated in terms of the clinical response and time to complete recovery. Therapy with bromocriptine has been shown to be significantly more rapid than that achieved by supportive therapy alone. Complete resolution was achieved more quickly with bromocriptine or dantrolene than with supportive therapy. Patients who do not respond to medical therapy during the first 7 days, especially those with persistent catatonia after the resolution of other symptoms, lethal catatonia should be regarded as an alternative diagnosis or as a concomitant sequel, and ECT should be seriously considered.\textsuperscript{23-27}

Should the patient need antipsychotic therapy after NMS has subsided, risk of the syndrome will still be there although it may be minimized if the following guidelines are followed:\textsuperscript{21}

- Therapy should be postponed for at least 14 days or more, until all the residual symptoms have subsided (especially those of EPS).
- An agent of lower potency should be chosen where the possibility of NMS relapse is minimal (or less likely).
- The initial start dose should be the lowest possible (\textit{i.e.}, lowest recommended), where the clinician can increase the dose gradually by titration in order to establish the lowest possible therapeutic level that clinically controls psychosis.
An important study by Rosebush, et al., raises serious questions not only about the efficacy of these treatment measures but also about the suggestion that in some cases, the various specific therapies can result in a prolongation of the syndrome. As a result, it is not possible to make clear treatment recommendations; management of NMS centers primarily on supportive care, with the role of specific treatment modalities remaining uncertain.

**Secondary Complications for NMS Patients**

Patients with NMS may be at increased risk of morbidity due to renal failure, disseminated intravascular coagulation (DIC) secondary to rhabdomyolysis, deep venous thrombosis and pulmonary embolism resulting from dehydration and immobilization, aspiration pneumonia because of difficulty swallowing combined with an altered mental status, as well as other medical complications including cardiopulmonary failure, seizures, arrhythmias, myocardial infarction, and sepsis, and so many cases require intensive care monitoring and support.¹

Management should be started actively once the syndrome is suspected, that is, when the individual has the criteria mentioned above. After the patient has been admitted to a well-equipped ICU, active treatment should commence immediately after removal of the offending agent and the effects of its active metabolites and cooling down the patient has commenced.

Importantly, aggressive hydration is often required, especially if highly elevated CPK levels threaten to damage the kidneys. Metabolic abnormalities may need to be corrected, and bicarbonate loading should be considered in some cases as it may be beneficial in preventing renal failure.
The optimal pharmacologic treatment, as indicated above, is still to be elucidated and there is no general agreement among clinicians concerning the therapeutic significance of currently used drugs to treat NMS. In fact, all these drugs are administered for symptomatic treatment of the complications, not the syndrome itself. Being a rare condition, there are two basic lines of treatment, one being a biological approach and the other parallel supportive therapy.¹⁸

Some of the immediate treatment guidelines are considered to be the following: Creatinine kinase (CK) is typically elevated and when significant muscle breakdown is present and CK is >10,000 IU/L, patients are at risk for rhabdomyolysis induced acute renal failure. CK should be trended at least initially on a daily basis to ensure a downward trend.

Basic metabolic panel with magnesium, calcium, phosphate should initially should be checked at least twice a day as patients are at risk for renal failure and electrolyte derangement. Renal failure should be treated with intravenous hydration and electrolytes should be closely monitored and replenished as needed.

Liver function testing includes the liver transaminases, lactate dehydrogenase, and alkaline phosphatase, which may be slightly elevated in NMS. If a patient is being treated with dantrolene, liver function tests should be reviewed every day or every 2 days to ensure there is no upward trend which could suggest dantrolene induced hepatotoxicity. Given the typical rapid resolution of NMS, there is no long-term management of the disorder. However, one of the long-term issues is when and how to restart neuroleptics.

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.

Other non-pharmacological maneuvers to consider are those related to the risk factors discussed above, which should target the environmental conditions that might predispose or worsen the condition. Specifically, a comfortable ambient temperature not higher than 21-23º C will allow better heat dissipation. In this regard, physical measures to control temperature such as application of wet cold cataplasms have not been systematically evaluated, but are a low-cost and very low-risk measure to apply. Another important general consideration is to assess the general nutritional and hydration state so that appropriate corrective procedures can be applied.

Another important general consideration is to assess the general nutritional and hydration state so that appropriate corrective procedures can be applied. Also, it is very important to keep in mind that fluctuation in the level of consciousness is accompanied with an impaired deglutory reflex, and therefore, increased risk for aspiration pneumonia, which is associated with a significant mortality rate.\textsuperscript{2} In this regard, it has been demonstrated that a low-cost and low-risk measure that significantly reduces the risk of aspiration pneumonia is to adopt a semi-recumbent positioning (defined as elevation of the head of the bed to 45 degrees). Physical restraint may be necessary but should be used discreetly since it has been associated with increased risk for NMS as mentioned above.\textsuperscript{23}

**Prognosis And Recovery From NMS**

Initial reports of mortality rates from NMS were over 30%, but increased physician awareness and introduction of newer neuroleptic medications over the last few decades have helped reduce them closer to 10%. When recognized early
and treated aggressively, NMS is usually not fatal and a majority of patients will recover completely between 2 and 14 days. But if diagnosis and treatment are delayed, resolution can require several weeks or longer, and surviving patients may have residual catatonia or Parkinsonism, or significant morbidity secondary to renal or cardiopulmonary complications. When death does occur, it is usually attributable to arrhythmias, DIC, or cardiovascular, respiratory, or renal failure. Thus, early recognition and initiation of therapeutic measures by physicians remain paramount to reducing the number of severe cases of NMS and limiting this significant source of morbidity and mortality among patients receiving antipsychotics.¹

Concerning the prognosis of this syndrome, this is mainly dependent on early diagnosis and active intervention without delay in a well-equipped ICU. Although the majority of cases can be successfully managed, approximately 10% of cases can be fatal, regardless of early diagnosis and treatment. Hyperpyrexia, rhabdomyolysis, and neuronal damage can lead to amnesia (memory impairment), which could be temporary or persistent in certain cases. Among the elderly, acute respiratory failure, acute renal shutdown, infections (septic shock), and coexisting congestive heart failure are significant predictors of mortality in this rare syndrome. Acute respiratory insufficiency is the strongest independent mortality prognosticator. The majority of psychiatric centers recommend a drug from the atypical group (second-generation or nonconventional) of a low-potency type should one be needed.³

The majority of psychiatric centers recommend a drug from the atypical group (second-generation or nonconventional) of a low-potency type.²¹ As the majority of NMS cases have been attributed to the use of antipsychotic agents, especially first-generation (conventional or typical) drugs, one should be careful when prescribing such agents to psychotic patients. The current trend in many psychiatric centers of the developed world is the use of second-generation (atypical) agents. NMS, however, has not been totally abolished. In other words, the syndrome can still be encountered even with the availability of the second-
generation of newly designed agents, although the clinical picture might be milder than what is encountered in NMS with typical antipsychotics.\(^{21}\)

Amisulpride, a relatively newly designed atypical antipsychotic, has also been shown to be associated with the occurrence of NMS. This has to be attributed to the fact that the nature of the exact biological changes that occur in the neurons of psychotic patients is not known. Once this dilemma is understood, better agents with least possible side effects may be developed. It is also necessary to remember that the use of drugs other than antipsychotic agents can lead to NMS, for example, drugs such as metoclopramide (antiemetic), amoxapine (tetracyclic antidepressant), and lithium (mood stabilizer) have been recognized as being perpetrators of NMS.\(^{21}\)

It is not only antipsychotics alone that should be blamed for being behind the occurrence of NMS. A retrospective survey on patients in a study showed that citalopram (an SSRI antidepressant) can trigger acute dystonia which could be the prodromal stage of NMS. The same thing is also true for metoclopramide, and, as stated before, this indeed makes the prediction of NMS almost impossible. It is likely that the number of agents that can precipitate NMS will most probably increase year by year.

Because there is no pathognomonic laboratory test to pinpoint the diagnosis of this idiosyncratic syndrome, careful periodic clinical observation of psychotic patients is warranted, especially those who have recently started taking antipsychotics (particularly those being treated with oily depot injections of long-acting potent first-generation drugs in outpatient clinics of psychiatric centers). This action may help the early diagnosis of NMS and thus ensure an early start of treatment intervention with the hope of minimum negative consequences.
It is clear that the majority of drugs that are associated with the induction of NMS are either antipsychotics or antidepressants. These groups of drugs are cornerstones as biological treatment tools in contemporary clinical psychiatry. It is evident that these drugs have no selective actions when prescribed as monotherapy and the optimal therapy may require polypharmacy, a fact that increases the spectrum of anticipated side effects, including NMS.\textsuperscript{21}

**Part 2 Summary**

Neuroleptic malignant syndrome in hospitalized patients is considered a neurologic emergency as a delay in treatment or withholding of therapeutic measures can potentially lead to serious morbidity or death. Treatment of NMS is individualized and based on the clinical presentation, but the first step in essentially all cases consists of cessation of the suspected offending neuroleptic pharmacologic agent. If the syndrome has occurred in the setting of an abrupt withdrawal of a dopaminergic medication, then this medication is reinstituted as quickly as possible. The next key step in the management of NMS is the initiation of supportive medical therapy. Patients with NMS may be at increased risk of morbidity and frequently cases of NMS require intensive care monitoring and support.

Management should be started actively once the syndrome is suspected, and active treatment should commence immediately, such as removal of the offending agent and initiation of cooling measures. The efficacy of ECT in neuroleptic malignant syndrome is well recognized despite the absence of randomized controlled data. ECT reduces the mortality of NMS by approximately half. This same effect has been achieved by treatment with dantrolene,
amantadine, L-DOPA and bromocriptine. When pharmacological treatments fail to control the NMS disorder, ECT can be potentially lifesaving in severe cases.

When diagnosis and treatment of NMS are delayed, resolution can require several weeks or longer, and surviving patients may have residual symptoms; and death may occur due to major organ failure, such as to the heart and kidneys. Therefore, early recognition and initiation of therapeutic measures by clinicians remain paramount to reducing the number of severe cases of NMS and limiting this significant source of morbidity and mortality among patients receiving antipsychotics.

Initial reports of mortality rates from NMS were higher in previous years but increased physician awareness and introduction of newer neuroleptic medications over the last few decades have helped reduce mortality. When recognized early and treated aggressively, NMS is usually not fatal and a majority of patients will recover completely.

**Reference Section**


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