REVIEW ARTICLE

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Neuroleptic Malignant Syndrome

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CME

The introduction of chlorpromazine in the mid-1950s, which represented a new class of antipsychotic drugs, marked a major advance in psychiatric care. Named "neuroleptics" — from the Greek *neuron* (nerve) and *lepsis* (to seize) — these compounds were discovered incidentally as part of a search for adjuncts to general anesthetics and analgesics.[1] Neuroleptic drugs block or alter central nervous system dopamine and have become a principal form of treatment for psychosis and, in particular, for schizophrenia.[2] Drugs with dopamine-blocking properties are also used for disorders associated with delirium[3] and for anxiety disorder,[4] Tourette's syndrome,[5] and neurogastrointestinal dysfunction.[6]

Early in the course of the development of these agents, haloperidol was found to cause not only hypokinetic and hyperkinetic motor disorders but also a potentially fatal syndrome of muscle rigidity and hyperthermia, which became known as neuroleptic malignant syndrome. The psychiatrist Jean Delay, who was studying haloperidol for Janssen Pharmaceuticals, reported that the drug was associated with a risk of *dérèglements végétatifs* (vegetative disorder or dysfunction of the autonomic nervous system).[7]

High-potency, first-generation (typical) antipsychotic agents such as haloperidol, fluphenazine, and pimozide have most often been implicated in cases of neuroleptic malignant syndrome, but these agents are still used, in part because they are effective and are less expensive than newer antipsychotic drugs. In a report based on an Australian database of adverse drug reactions, the syndrome occurred with both first-generation and second-generation (atypical) drugs, and second-generation drugs were associated with a low incidence of the disorder.[8] Moreover, patients presented with less rigidity when the syndrome was associated with clozapine than when associated with other agents. There has been a clinical sense that the syndrome has been less common and less severe with second-generation agents than with first-generation agents. Other drugs that block dopamine, such as metoclopramide, droperidol, prochlorperazine, and dopamine-depleting agents such as tetrabenazine, have also been implicated but are apparently less likely to cause neuroleptic malignant syndrome. Parkinsonism–hyperpyrexia syndrome, a rare disorder resembling neuroleptic malignant syndrome, has been reported to develop after rapid withdrawal of dopaminergic agents used to treat Parkinson's disease,[9] and subthalamic nucleus stimulation for the treatment of Parkinson's disease after withdrawal of levodopa has been associated rarely with neuroleptic malignant syndrome. Moreover, deep-brain stimulation can mask muscle rigidity in these circumstances, obscuring the syndrome.[10]

Because antipsychotic drugs are widely used as part of hospital and ambulatory care practices, clinicians in many specialties other than psychiatry, including family practitioners, emergency department physicians, anesthesiologists, intensivists, emergency medical technicians, and staff in nursing homes, may encounter neuroleptic malignant syndrome. This disorder was reviewed in the *Journal* in 1985.[11]

KEY POINTS

NEUROLEPTIC MALIGNANT SYNDROME

- Neuroleptic malignant syndrome is characterized by fever, muscular rigidity, and dysautonomia after exposure to dopamine-blocking agents, especially antipsychotic drugs.
- Clinical criteria for diagnosis vary and may include an altered level of consciousness, but the syndrome is a rare and unpredictable complication of antipsychotic drugs.
- Neuroleptic malignant syndrome may lead to major medical complications, which clinicians can anticipate.
- Treatment, which is empirical, includes muscle relaxants and close monitoring, usually in an intensive care unit.
- There is a low risk of recurrence after reexposure, but some risk remains.

The current review addresses contemporary management, with an emphasis on treatment in critical care settings.

EPIDEMIOLOGY

In various reports, neuroleptic malignant syndrome develops in an estimated 0.02 to 3% of patients exposed to an implicated drug, depending on the population studied, the agent, the duration of use, and the manner of obtaining and classifying adverse events.[12] Mortality from neuroleptic malignant syndrome was lower with atypical antipsychotic agents than with older agents in both a Japanese study[13] and the aforementioned Australian study,[8] but this difference may have been due to improvements in care between the epoch of treatment with typical drugs and that of treatment with atypical drugs. Risk factors for neuroleptic malignant syndrome, which have been reported in studies involving a few patients each, include dehydration, use of multiple antipsychotic agents, high and escalating drug doses, a previous episode of the syndrome, and an intramuscular route of injection, but the infrequency of the disorder precludes definite associations.[14] Nevertheless, the use of a single oral drug at a standard dose has been involved in many instances of neuroleptic malignant syndrome. There may be a propensity for signs of the syndrome to occur in patients with anti–*N*-methyl-D-aspartate receptor encephalitis who are treated with a dopamine-blocking drug; such "neuroleptic intolerance" (and several probable cases of overt neuroleptic malignant syndrome) was reported in 47% of patients in one study. However, it remains a challenge for clinicians to differentiate neuroleptic side effects from some of the manifestations of this autoimmune encephalitis.[15]

Genetic polymorphisms of drug-metabolizing enzymes, drug transporters, and drug-targeting molecules may affect drug responses and increase the risk of neuroleptic malignant syndrome, but these genetic findings have been studied only in small and predominantly Japanese populations. Variants of the gene encoding cytochrome P-450 2D6 (*CYP2D6*) that cause slower hepatic metabolism of these drugs, for example, apparently do not confer an increased risk of neuroleptic malignant syndrome. One study showed an overrepresentation of the A1 allele of the gene encoding dopamine receptor D2 (*DRD2*) in patients with neuroleptic malignant syndrome.[16] However, studies of *DRD2*, serotonin receptor genes *HTR1A* and *HTR2A* (encoding hydroxytryptamine receptors 1A and 2A), and the gene encoding ryanodine receptor 1 (*RYR1*, implicated in susceptibility to malignant hyperthermia, as discussed below) showed no difference in the incidence of neuroleptic malignant syndrome between patients with these genetic features and controls.[17]

Several polymorphisms in *CYP1A2*, *CYP2D6*, *CYP3A4*, *CYP3A5*, and *ABCB1* (encoding ATP-binding cassette subfamily B member 1) and their influence on pharmacokinetics and plasma levels of olanzapine, clozapine, aripiprazole, risperidone, and quetiapine have been described, but none of these polymorphisms have been clearly associated with neuroleptic malignant syndrome.[18] One case report described a patient with schizophrenia treated with risperidone who had an "atypical" form of neuroleptic malignant syndrome, without rigidity. The patient had variants of both alleles of *CYP2D6*. Subsequent treatment with olanzapine, which is not principally metabolized by CYP2D6, had no adverse effects.[19]

CLINICAL SYNDROME

The *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, criteria for the diagnosis of neuroleptic malignant syndrome include exposure to a dopamine-blocking drug, severe muscular rigidity, fever, and at least two of the following features: diaphoresis, dysphagia, tremor, incontinence, an altered level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, or an elevated serum creatine kinase level.[20] In practice, the syndrome is easier to identify than this list of items suggests. The history, medication list, and context usually make it apparent that the patient has been exposed to a drug implicated in neuroleptic malignant syndrome, but this is not always evident, particularly with medications that are not used primarily for the treatment of psychosis or delirium.

The typical presentation of neuroleptic malignant syndrome is dysautonomia, particularly tachycardia and rapidly fluctuating hypertensive or hypotensive blood pressure; temperature elevation to 40°C or higher; delirium that in the severe form is catatonia; and increased muscle tone. Blood-pressure alterations and muscle hypertonicity are usually the first signs of the disorder, although some reports have emphasized early behavioral features. The muscular rigidity has been described in various ways, but it is essentially an extrapyramidal "lead pipe" sign that is perceived by the examiner as uniform resistance to movement through a range of passive motion of a limb and that can be haptically differentiated from spasticity, dystonia, and spasm. A cogwheel phenomenon may interrupt the rigidity, as it does in Parkinson's disease, but whether this is a parkinsonian effect of the causative drug or an essential feature of the rigidity that characterizes neuroleptic malignant syndrome is not clear. As mentioned, in the Australian review and in other series, rigidity was less prominent with second-generation drugs than with first-generation drugs.[8] Intense rigidity may result in rhabdomyolysis, greatly elevated serum creatine kinase levels, and renal failure. Leukocytosis is common. Severe rigidity in extrapyramidal disorders such as Parkinson's disease rarely causes this degree of muscle damage, presumably because the rigidity in these disorders is milder than the rigidity in neuroleptic malignant syndrome and possibly because it is not associated with hyperthermia.

The median interval between drug exposure and the appearance of symptoms in a collection of published cases was 4 days, and the median duration of illness was 9 days, but some cases occurred within a day after exposure to the drug, and others occurred more than 30 days later. Most patients in that case series had been exposed to a single drug.[21] The entire syndrome, or any one of its components, persists for several days or more and typically peaks in intensity on the second or third day after the onset.

Clinicians encounter neuroleptic malignant syndrome much less frequently than neuroleptic-induced parkinsonism. It has been estimated that parkinsonian features with rigidity or dystonia develop in 30% of patients exposed to antipsychotic agents,[22] and these findings may be mistaken for incipient neuroleptic malignant syndrome.

PATHOGENESIS

The biologic basis of neuroleptic malignant syndrome is not known, but neuroleptic antipsychotic agents block dopamine D2 receptors, a family of G protein–coupled receptors that bind extracellular dopamine, and this blockade is inferentially implicated in the disorder. These receptors are inhibitory and are presumed to be the main therapeutic targets of neuroleptic drugs used for the treatment of schizophrenia and other neuropsychiatric disorders.[22] The dopamine D4 receptor has also been associated with the effects of this class of drugs, but it is uncertain whether neuroleptic agents other than the atypical antipsychotic agents target this receptor to any great degree.[23] Recordings from dopaminergic neurons in the brains of rats showed that several weeks of treatment with haloperidol led to inactivation of neuron firing, an effect known as depolarization blockade.[24] Repeated antipsychotic drug–induced depolarization blockade of dopamine pathways has been associated with an increase in the clinical efficacy of the drug, and depolarization blockade of the nigrostriatal system has been associated with extrapyramidal side effects.[25] These findings would seem to have some bearing on neuroleptic malignant syndrome, but they have not been extensively explored.

Table 1. Disorders That Simulate Neuroleptic Malignant Syndrome (NMS).*

Feature	NMS	Serotonin Syndrome	Malignant Hyperthermia	Withdrawal Syndromes†	Catatonia	Anti-NMDAR Syndrome
Fever	+++	++	+++	+	—	+
Muscle rigidity	+++	+	++++	—	++	+
Hyperreflexia	—	+++‡	—	++	—	—
Tachycardia	++	++	+	++	—	++
Hypersalivation	+++	++	—	—	—	+++
Hypertension	+++§	++	+	+	—	+
Diaphoresis	++		+	+++	—	+
Dilated pupils	—	++	—	+++	—	+++
Delirium or coma	++	+	—	+++	+++	+++
Elevated CK level	+++	+	++++	—	+	++

* The number of plus signs indicates the relative frequency and intensity of each feature in typical cases, from minimal or infrequent (—) to severe and frequent (++++), on the basis of articles cited in the text and personal experience in a neurologic intensive care unit. A dash indicates that the feature appears in only a few patients with the syndrome. CK denotes creatine kinase, and NMDAR *N*-methyl-D-aspartate receptor.
† These syndromes involve withdrawal from ethanol, opioids, cocaine, amphetamine, MDMA (3,4-methylenedioxymethamphetamine), and other substances.
‡ Clonus and myoclonus are also prominent in serotonin syndrome and are not typically as severe in the other syndromes.
§ Some patients with NMS have hypotension, which is uncommon in the other syndromes unless dehydration is present.

Another hypothesis, based on studies from the early 1990s, presumes that the autonomic symptoms in neuroleptic malignant syndrome are due to hyperactivity of the sympathoadrenergic system, which leads to increased concentrations of intracellular calcium ions in muscles and contributes to increased muscle tone. According to this hypothesis, blockade of dopamine receptors in the hypothalamus causes impaired heat dissipation, and blockade of dopamine receptors in the caudate nucleus, putamen, and ventral striatum causes muscular rigidity. The excess heat production in association with decreased heat dissipation results in hyperthermia, a main sign of the syndrome.[26] In this model, the changes in mental status purportedly result from dopamine depletion in the midbrain–cortex–limbic system pathways.

There is no evidence of a primary skeletal muscle defect or a direct toxic effect of dopamine-blocking drugs on skeletal muscle. However, an animal model showed that increasing ambient temperature after intramuscular administration of haloperidol increased electromyographic activity (interpreted as rigidity) and elevated serum creatine kinase levels, which could be mitigated with dantrolene.[27]

OTHER SYNDROMES OF ACUTE HYPERTHERMIA AND RIGIDITY

Distinguishing neuroleptic malignant syndrome from other states of rigidity and hyperthermia may be difficult, but the context in which each disorder occurs usually directs attention to the appropriate diagnosis (Table 1). Malignant hyperthermia from anesthetic agents shares features of neuroleptic malignant syndrome — elevated temperature and muscular rigidity — but the contexts of the two disorders and the timing in relation to drug exposure differ. However, if neuroleptic agents have been used for anesthesia induction or were recently introduced as treatment for a psychiatric or other disorder, the distinction may be challenging. Heat stroke, withdrawal syndromes, and acute intoxication with recreational drugs of abuse, such as amphetamines, cocaine, MDMA (3,4-methylenedioxymethamphetamine), and phencyclidine, superficially mimic neuroleptic malignant syndrome. Abrupt discontinuation of muscle relaxants such as baclofen may cause muscular rigidity and mental changes that simulate features of neuroleptic malignant syndrome.

With respect to the differential diagnosis of neuroleptic malignant syndrome, pedagogic exer-

cises emphasize consideration of acute serotonin syndrome, since it may cause acute dysautonomia, but hyperreflexia, clonus, myoclonus, and shivering, which characterize serotonin syndrome, are not components of neuroleptic malignant syndrome. The muscular salience in serotonin syndrome is closer to spasticity than to the lead-pipe rigidity of neuroleptic malignant syndrome, and hyperreflexia is characteristic of serotonin syndrome, in contrast to the diminished or normal tendon reflexes in neuroleptic malignant syndrome. Another distinctive feature of the serotonin toxidrome is leg myoclonus, which may spread to the chest, abdomen, and arms and may even involve eye motility as summarized in a review in the *Journal*.[28] Sialorrhea occurs in both syndromes. Curiously, metoclopramide, which can cause neuroleptic malignant syndrome, can also exacerbate serotonin syndrome. The simultaneous presence of the two syndromes has been described in case reports, with the implicated drug (e.g., tefludazine) having both antidopaminergic and serotonergic activity.

Extreme catatonia, so-called lethal catatonia, may mimic neuroleptic malignant syndrome, particularly when encountered in the emergency department in the absence of the recent medical history, and may cause diagnostic confusion because it is associated with an elevated serum creatine kinase level, as noted in a review on catatonia in the *Journal*.[29] The distinction between these disorders is clouded when neuroleptic malignant syndrome causes a catatonia-like state. Features such as stereotypy, cataplexy, and mannerisms help differentiate catatonia from neuroleptic malignant syndrome.

Finally, neuroleptic malignant syndrome has been invoked as a cause of fever of unknown origin,[30] given that leukocytosis is a feature of both. Thus, neuroleptic malignant syndrome may be mistaken for infection, but the distinction should be straightforward because fever and infection, in isolation, are not similar to neuroleptic malignant syndrome.

TREATMENT

Management of neuroleptic malignant syndrome, like the management of any other critical illness, requires close clinical attention and a focus on risk factors for complications and death. In addition to withdrawal of the offending agent when possible, treatment involves a tiered approach to the main features of the syndrome: blood-pressure instability, hyperthermia and rhabdomyolysis from severe rigidity, and the potential for respiratory compromise.[31] Data from prospective trials of the currently used interventions are lacking, and there may be several effective approaches.

A suggested approach to critical care management is shown in Figure 1. Patients may present in acute respiratory distress from rigidity of the upper-airway muscles, respiratory musculature, and diaphragm. In addition, patients may aspirate secretions or gastric contents because of an ineffective cough. Intubation and mechanical ventilation are then warranted. There may be marked sialorrhea, which can be managed with mucolytic agents or an anticholinergic agent such as glycopyrrolate.[32]

Most patients have tachycardia with fluctuating blood pressure, which may be an acceptable adverse event in younger persons but can induce demand ischemia (type 2 myocardial infarction) and increased serum troponin levels in patients with coronary artery disease. Whether neuroleptic agents can directly damage cardiac muscle is uncertain.[33] Patients may be stuporous and mute or become agitated and delirious, clinical features that can be managed with dexmedetomidine, a selective, short-acting α_2-adrenergic agonist with sedative–hypnotic and anxiolytic effects, in order to avoid reintroducing an antipsychotic agent.

Severe cases of neuroleptic malignant syndrome cause hypocalcemia, hypomagnesemia, hyponatremia and hypernatremia, hyperkalemia, and metabolic acidosis, all of which require correction. Abnormal levels of serum lactate dehydrogenase, alkaline phosphatase, and liver aminotransferase are common but transient. Most patients with fever become dehydrated, and rigidity breaks down muscle, allowing levels of serum creatine kinase to increase to 10,000 U per liter or higher, often days into the illness. In contrast, normal values may be present at the outset and give false assurance that the condition is not serious.

Substantial amounts of intravenous fluids may be needed to maintain euvolemia and to manage

rhabdomyolysis, with a target urine output of approximately 200 to 300 ml per hour.[34] Dialysis can be considered for patients with severe hyperkalemia, hypocalcemia, azotemia, or volume overload from treatment. Hypocalcemia, a common complication of rhabdomyolysis, results from calcium entering damaged muscle cells and from the precipitation of calcium phosphate within necrotic muscle. In exceptional cases, severe local rhabdomyolysis causes compartment syndrome, which is treated with fasciotomy. Hyperthermia is treated with an antipyretic agent such as oral acetaminophen, at a suggested dose of 1000 mg every 6 hours, and evaporative cooling with mists and fans or, more efficiently, with surface thermoregulation. In severe cases, high temperature, tachycardia, and severe blood-pressure instability have been treated with clonidine, an agonist of α_1-adrenoceptors, or calcium-channel blockers such as clevidipine or nicardipine.[35]

Rigidity is monitored by clinical examination. Lorazepam causes muscle relaxation in mild cases. However, if muscular signs of neuroleptic malignant syndrome persist or worsen, dantrolene, a direct-acting skeletal-muscle relaxant that inhibits the release of calcium at the sarcoplasmic reticulum, can be administered. By reducing rigidity and through ostensible effects on central thermoregulatory areas, dantrolene mitigates hyperthermia and reduces elevated levels of serum creatine kinase.[36] There is a risk of hepatotoxic effects with high doses of the drug, and liver function is generally monitored. Bromocriptine or amantadine has been suggested as an alternative agent; both are dopamine agonists that displace antipsychotic dopamine antagonists and are associated with few short-term side effects.[37]

These specific dopaminergic interventions are usually justified when the core temperature reaches 38 to 40°C and rigidity is moderate or severe,

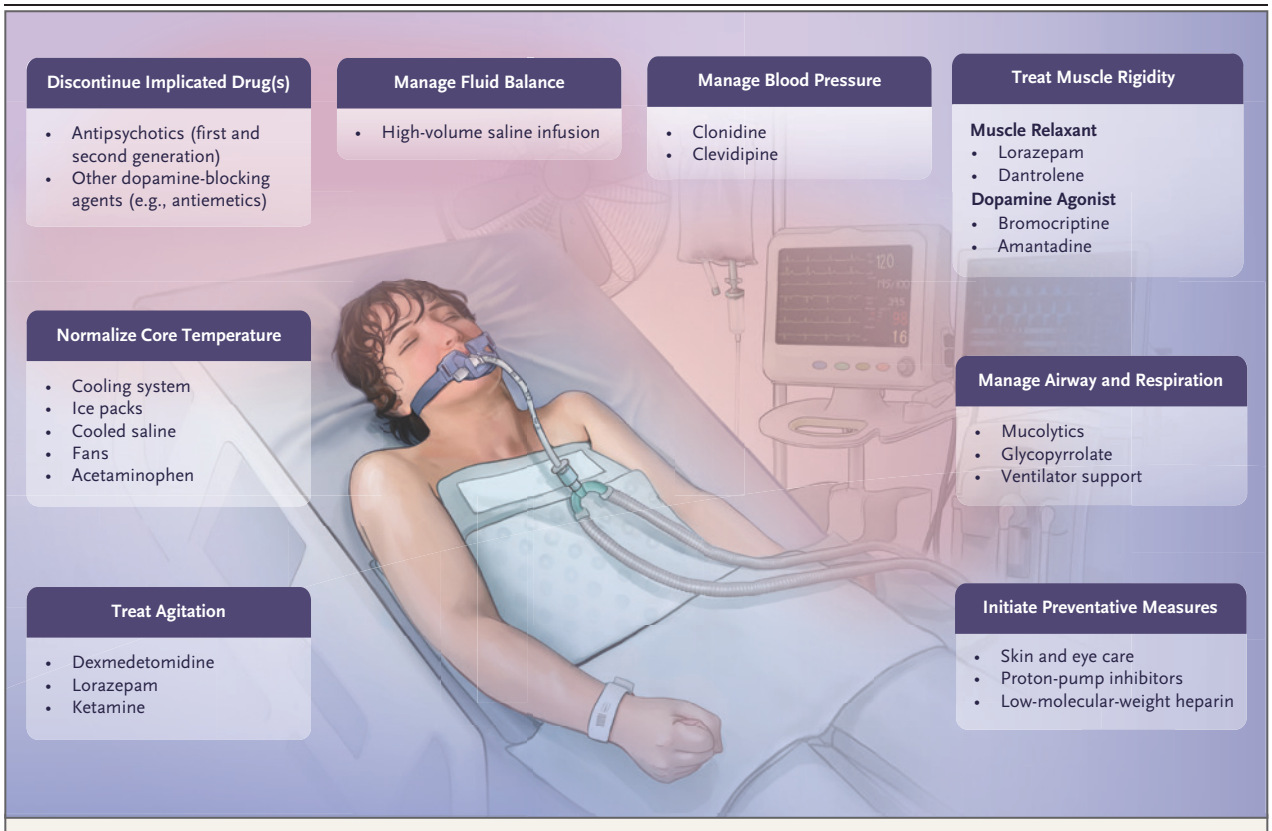

Figure 1. Management of Neuroleptic Malignant Syndrome in the Intensive Care Unit.

The illustration shows a patient with sweaty hair, extreme rigidity, and clenched fists undergoing mechanical ventilation. High fever is managed with cooling devices.

as marked by a transition from palpably mild rigidity with cogwheeling to sustained rigidity. In life-threatening cases, electroconvulsive therapy (ECT) has been reported to be rapidly effective, but it has been reserved for patients who do not have a response to other treatments.[38] The mechanism underlying the effect of ECT on neuroleptic malignant syndrome is not known, which is also true for the effect of ECT on depression and catatonia.

The appropriate duration of each of these interventions and how to calibrate or discontinue them have not been established, and practices vary among intensive care units; pharmaceutical intervention has been continued for days in some units and for weeks in others, particularly if the offending drug has a long duration of action. The general principles of critical care are followed, including stress ulcer prophylaxis in patients undergoing mechanical ventilation[39] and prophylaxis for deep venous thrombosis with subcutaneous heparin or enoxaparin.[40]

After the offending agent (or agents) is discontinued, it is typically not reintroduced. This may make it difficult to control the underlying disorder for which the agent was used. Other psychotropic agents, such as lithium, anticholinergic therapy, and serotonergic agents, are also usually withheld, if possible, to avoid the occurrence of signs that confound assessment of the signs of neuroleptic malignant syndrome. Immediate removal of the effects of the antipsychotic drug is not possible in the case of long-acting injectable agents because of their prolonged release. For some antipsychotic drugs, an interval of up to 60 days is required for blood levels of the drug to become undetectable. In the case of shorter-acting oral antipsychotic drugs, spontaneous reduction to low serum levels generally occurs within 3 to 5 days.

Woodbury and Woodbury devised a three-stage system for classifying the severity of neuroleptic malignant syndrome, with a focus on catatonia in adolescents.[41] This classification system is often referred to in the literature and applied to adult patients. The severe stage includes marked rigidity, catatonia or confusion, a temperature of 40°C or higher, and a heart rate of 120 beats per minute or higher. Uniformly accepted treatment guidelines from academic societies are lacking, but the Malignant Hyperthermia Association of the United States offers assistance with treatment-related questions (https://my.mhaus.org/page/contactmhaus).

OUTCOME

Recovery times vary but generally range from 7 to 11 days and may be roughly predicted from the half-life of the implicated neuroleptic drug.[42,43] The relative effects of different treatments on outcome have been estimated by comparing the amount of time required for complete recovery — for example, a mean of 15 days with supportive care as compared with 9 days with dantrolene and 10 days with bromocriptine. In a case–control analysis based on published reports, mortality appeared to be lower among patients treated with dopaminergic drugs than among those who were not treated with these agents.[44]

Rare cases in which the syndrome persists for months, with residual catatonia and motor signs, have been reported. Mortality, which in the past ranged from 20 to 30%, has ranged from 4.7% at 30 days to 9.9% at 90 days and up to 15.1% at 1 year in more recent studies, which suggests that there are late complications that may be fatal,[44] such as aspiration pneumonia or renal failure. A prolonged period of recovery increases the risk of ventilator-associated pneumonia and sepsis. However, the patient can be weaned from the ventilator if pulmonary mechanics have returned to safe levels, the secretion burden has been reduced, and axial rigidity that impedes breathing has lessened. Rhabdomyolysis and acute kidney injury occurred in up to 30% of cases in a nationwide sample of inpatients with an unvetted diagnosis of neuroleptic malignant syndrome.[45] Acute respiratory failure, sepsis, and coexisting congestive heart failure were (surprisingly) not found to be independent predictors of death but are nevertheless potentially modifiable risk factors for a poor outcome.

Resumption of treatment with antipsychotic drugs may hypothetically result in a recurrence of neuroleptic malignant syndrome, reportedly even up to 2 years after the first exposure.[46] However, an underlying psychiatric condition may necessitate treatment, and some expert groups have suggested waiting approximately 2 weeks or longer before resuming therapy if any features of neuroleptic malignant syndrome persist, and then instituting treatment with low-potency agents.[47]

Another suggestion for preventing a recurrence is to administer low initial doses of antipsychotic drugs, with slow upward adjustment. Switching to atypical neuroleptic agents, includ-

ing clozapine, may not necessarily prevent a recurrence of neuroleptic malignant syndrome but may be associated with a low risk of a severe or fatal recurrence. Despite the apparent risk of reintroducing antipsychotic agents, in a nationwide study, only 5 of 119 patients with schizophrenia who underwent a rechallenge with these drugs had a recurrence; nevertheless, a low level of risk remains.[48] In a systematic review addressing the risks of clozapine treatment for various disorders, a rechallenge was successful in all 7 patients with clozapine-associated neuroleptic malignant syndrome but did not prevent the recurrence of agranulocytosis or myocarditis attributed to the drug.[49] It is advisable to list neuroleptic malignant syndrome as a serious adverse drug reaction in the patient's medical record.

CONCLUSIONS

Neuroleptic malignant syndrome is a distinctive and alarming syndrome that occurs in some persons who have been exposed to dopamine-blocking agents, particularly (but not exclusively) antipsychotic drugs. It is unclear which clinical features carry the greatest weight for the diagnosis of the syndrome and whether the entity is underdiagnosed or overdiagnosed. The causes of most of the features of the syndrome are not understood, and the apparently low likelihood of relapse with reexposure argues against a simple explanation. Intensive care is directed at the cardinal features of fever, dysautonomia, and muscular rigidity and is supplemented with drugs that enhance dopamine activity or with ECT. Treatments have been supportive and empirical. The prevalence of genomic variants, the risk of the occurrence and recurrence of the disorder, and intensive care management require further study in diverse populations of patients with neuroleptic malignant syndrome.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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