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Neuroleptic Malignant Syndrome
Recognition, Prevention and Management

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Contents

Abstract

Neuroleptic malignant syndrome (NMS) is a rare but potentially lethal form of drug-induced hyperthermia characterised by mental status changes, muscle rigidity, hyperthermia and autonomic dysfunction. Increased awareness and early recognition will lead to prompt management. The diagnosis of NMS presents a challenge because several medical conditions generate similar symptoms. The presentation and course of NMS can be quite variable ranging from a stormy and potentially fatal course to a relatively benign and self-limiting course. The most important aspect of treatment is prevention. This includes reducing risk factors (e.g. dehydration, agitation and exhaustion), early recognition of suspected cases and prompt discontinuation of the offending agent. All patients with psychosis should be monitored daily for dehydration and elevated temperature, have vital signs checked and agitation should be watched for. Antipsychotics should be used conservatively with gradual titration of doses. The management of NMS should be based on a hierarchy of symptom severity.

Following an episode of NMS, the patient should be reassessed for further treatment with antipsychotics and rechallenge should not be attempted at least 2 weeks following resolution of symptoms of NMS. The patient and family should be educated about the episode and consent for further medication use obtained after a clear explanation of the risk-benefit analysis.

Neuroleptic malignant syndrome (NMS) is a rare but potentially lethal form of drug-induced hyperthermia. It was first described by Delay et al.[1] in 1960. The incidence of NMS varies considerably; results from studies have estimated an incidence ranging from 0.02 to 3.23% suggesting that it may occur on average in 1%, as originally estimated by Curoff[2] and Delay et al.[3] Increased awareness of this clinical syndrome, including an increase in published clinical data, has led to an improvement in early recognition and prompt management of this condition. This has apparently resulted in a significant reduction in the incidence of NMS and the mortality associated with this condition.[4-6]

NMS occurs in patients of all ages. Men are disproportionately represented among NMS patients in some, but not all, studies. It occurs independently of environmental heat and humidity, although antipsychotics are also known to compromise thermoregulation in heat stress as well as NMS. NMS occurs across the neuropsychiatric diagnostic spectrum and its clinical presentation usually includes severe muscle rigidity, elevated temperature and other related findings, e.g. diaphoresis, dysphagia, incontinence, change in level of consciousness ranging from confusion to coma, mutism, elevated or labile blood pressure, elevated creatine phosphokinase (CPK) level, developing in association with the use of antipsychotic medication.[7] For it to be NMS, these symptoms should not be caused by other substances or by a neurological or other general medical condition and should not be better accounted for by a mental disorder (e.g. mood disorder with catatonic features).

To a large extent, improvements in the management and outcome of NMS may come from a reduction in suspected risk factors, early recognition of developing signs, staff education, early discontinuation of antipsychotic drugs and supportive care.[8-11] Since the course of NMS can, at times, progress in a stormy fashion,[12,13] it may be critical to intervene early. In addition, early intervention may allow the prompt recognition of disorders producing the same clinical presentation that are unrelated to antipsychotic use.

Complications of NMS involve cardiac, respiratory, renal, musculoskeletal and other systems. More than one-third of patients usually require treatment in an intensive care setting.[14] Myoglobinuric renal failure, occurring as a consequence of rhabdomyolysis, is one of the most common and more serious complications of NMS.[15] Myoglobinuric renal failure may occur because of renal tubular obstruction and acute tubular necrosis which result from ischaemia. Respiratory distress is another frequent complication of NMS and this may be caused by aspiration.

NMS may occur with varying degrees of severity. It can range from a mild case that is recognised early and just requires drug discontinuation and supportive care, to a fulminant episode requiring the full battery of drug remedies and intensive care. So, it is important that healthcare providers have a flexible treatment approach to NMS involving a hierarchy of interventions that are determined by the severity of and the progression of symptoms.

1. Aetiology of Neuroleptic Malignant Syndrome (NMS)

The specific antidopaminergic activity of antipsychotic medications appears to be the predominant cause of NMS. Central dopaminergic systems are involved in temperature regulation as well as regulation of muscle tone and movement. It has been suggested that dopamine blockade in the nigrostriatal pathway can cause rigidity.[16] Antipsychotic-induced blockade of dopamine receptors in the hypothalamus may lead to autonomic impairment and impairment of central thermoregulation, causing hyperthermia through decreased heat dissipation.[17] Alteration of dopamine neurotransmission in the brainstem reticular activating system may cause mutism and similar disturbances in arousal.[18] The hypermetabolic state in NMS may be a result of an excess of noradrenaline (norepinephrine) relative to dopamine.[19] However, the infrequent occurrence of NMS suggests that other factors are involved. These may include imbal-

ances in other neurotransmitter systems, abnormalities in second messenger systems, and the presence of specific risk factors. In the light of emerging evidence of a genetic vulnerability to adverse drug reactions, a multidimensional analysis of the interacting variables may be essential, as they are for medication-induced movement disorders, to broaden the scope of psychopharmacology to improve therapeutic objectives.[20] There are 2 case reports that suggest that predisposition to NMS may include a genetic component.[21,22] Because of this evidence, antipsychotics should be administered cautiously in patients with a family history of NMS. To date all of the currently available antipsychotic medications have been reported to cause NMS, including atypical antipsychotics such as clozapine and risperidone. NMS has also been reported with some antiemetic medications such as prochlorperazine, which is an antipsychotic and metoclopramide, which is a dopamine antagonist.[23]

2. Recognition and Diagnosis of NMS

The diagnosis of NMS requires the presence of specific historical information, physical signs and symptoms and certain exclusion criteria must be met. There must be a recent history of exposure to antipsychotic medication. Usually this exposure is short term and the syndrome occurs within 7 to 10 days of commencing antipsychotic treatment.[24,25] However, NMS can occur after long term usage.[24,25] The syndrome is characterised by mental status changes, muscle rigidity, hyperthermia and autonomic dysfunction. My colleagues and I have reported[26] that a predictable progression of symptoms can be identified in many patients with NMS and this predictable progression may provide opportunities for early intervention. Most commonly, it appears from reports in the clinical literature[26] that mental status changes and muscle rigidity precede hyperthermia and autonomic dysfunction. Temperature elevation can be mild or severe. Autonomic instability is demonstrated by labile hypertension (or less often by hypotension) and tachycardia. Mental status is always altered, typically in the form of delirium, which may progress to stupor, obtundation and coma. My colleagues and I have been specifically interested in mental status changes[26] and we have recognised confusion as an antecedent of NMS.[27] Extreme muscular rigidity has been characterised as 'lead pipe rigidity' and is present in all skeletal muscles. Diaphoresis is always present and sialorrhoea is often present, as is dysphagia. However, it is important that alternative aetiologies for these symptoms are excluded by history, physical examination and laboratory studies.

DSM-IV[7] diagnostic criteria for research into NMS are listed in table I.

Elevated temperatures in NMS range from mild elevations [e.g. 37.2°C (99°F) to 37.7°C (100°F)] to markedly hyperthermic states [e.g. 41.1°C (106°F)]. In addition, individuals with NMS can often develop other medical conditions that can worsen an already elevated temperature. These include concurrent infections and cardiac, respiratory and renal complications.

CPK levels are typically elevated, ranging from minor to extremely large increases (i.e. levels exceeding 16 000 IU/L). It should be noted that mild

Table I. Research criteria for neuroleptic malignant syndrome (reproduced from DSM-IV,[7] with permission)

A. The development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication
B. Two (or more) of the following:
(i) diaphoresis
(ii) dysphagia
(iii) tremor
(iv) incontinence
(v) changes in level of consciousness ranging from confusion to coma
(vi) mutism
(vii) tachycardia
(viii) elevated or labile blood pressure
(ix) leucocytosis
(x) laboratory evidence of muscle injury (e.g. elevated CPK levels)
C. The symptoms in criteria A and B are not caused by another substance (e.g. phencyclidine) or a neurological or other general medical condition (e.g. viral encephalitis)
D. The symptoms in criteria A and B are not better accounted for by a mental disorder (e.g. mood disorder with catatonic features)

CPK = creatine phosphokinase.

to moderate elevations in CPK levels can also be seen with muscle damage caused by other mechanisms such as administration of intramuscular injections and use of physical restraints and have also been reported in individuals with acute psychotic disorders. The increase in CPK activity with antipsychotic drug treatment may reflect the ability of these drugs to intermittently increase cell membrane permeability, especially in the skeletal muscles, in some vulnerable patients.[28]

Apart from elevated CPK levels, leucocytosis, secondary electrolyte disturbances, hypocalcemia, hypomagnesemia and hypophosphatemia may also occur. Urinalysis often reveals proteinuria and myoglobinuria from rhabdomyolysis. An electroencephalogram may show diffuse slowing. To exclude a systemic illness, it is also important to measure serum creatinine and blood-urea-nitrogen levels, to perform liver function tests, thyroid function tests and an ECG, assess blood cultures and undertake brain imaging studies. Serum iron levels may be important to measure,[29] as the level may drop below the normal range because of haemolysis.

The presentation and course of NMS can be quite variable. It may take a malignant and potentially fatal course or a relatively benign and self-limiting course. There is currently no way to predict the evolution of the syndrome in any particular individual. NMS usually develops within 4 weeks of starting antipsychotic treatment and two-thirds of cases develop within the first week.[24,25,30] However, some individuals develop NMS after taking the same dosage of antipsychotic medication for many months.[24,25] In most cases, there is eventually a total resolution of symptoms. For a minority of individuals the outcome is fatal. Fatality rates in the literature range from 10 to 20%, but these rates may be artificially high as a result of reporting bias. With increasing recognition of this condition, estimates of fatality rates have decreased.[31]

3. Risk Factors

A number of investigators have addressed the question of which patients are most at risk for NMS. The risk factors that have been proposed to date include organic brain syndrome, mood disorders, dehydration, agitation, exhaustion and rapid or parenteral administration of antipsychotics.[32,33] Recently, catatonia has received serious attention as a risk factor for NMS or as an early sign heralding the onset of full-blown NMS.[34-36]

Jauss et al.[37] performed imaging studies of dopamine receptors using I^{123}-labelled iodobenzamide (IBZM) single photon emission computed tomography (SPECT). They performed follow-up examinations with IBZM in patients with NMS to display dopamine D_2 receptor availability in the acute phase of the syndrome and during the course of the syndrome. Using SPECT, the D_2 receptor occupancy in NMS could be successfully shown to correlate with extrapyramidal symptoms. Therefore, this investigation to monitor D_2 receptor occupancy in patients at risk for NMS. Prospective studies may help to confirm if patients at risk go on to manifest signs of NMS during the course of their treatment.

4. Differential Diagnosis

The differential diagnosis of NMS encompasses a broad range of disorders presenting with fever. The early signs of the full blown syndrome comprise a nonspecific set of findings that may be associated with a variety of neurological, psychiatric, systemic and drug-induced disorders.[38] It is essential to carefully consider and investigate other disorders in the differential diagnosis of NMS to avoid misdiagnosing as NMS another potentially serious medical disorder. For example, Levenson and Simpson[39] reviewed 39 reported cases of NMS and concluded that all but 14 cases could be attributed to concomitant medical disorders such as dehydration and infections. Similarly Sewell and Jeste[40] reported on 34 hospitalised patients referred for suspected NMS and, on closer scrutiny, found that 24 had NMS, but the remaining 10 had

other acute, serious medical problems that could account for the symptoms seen. They found that the frequency of symptoms experienced by patients with NMS differed significantly from those patients with other diagnoses; patients with NMS were more likely to have dehydration, disorientation, diaphoresis, cogwheel rigidity, drooling and dysphagia. Sewell and Jeste[40] suggested that it is equally important to consider NMS as a diagnosis and to rule out other acute illnesses, such as pneumonia, when a patient taking antipsychotics is referred for suspected NMS.

4.1 Catatonia

White and Robbins[34] noted that antipsychotic induced catatonia may be a harbinger of NMS if antipsychotic treatment is continued, and in a second report, White[35] concluded that rigidity and NMS represent an antipsychotic-aggravated form of a pre-existing catatonic state. The association between catatonia and NMS was similarly emphasised by Raja et al.[41] Probable or possible NMS cases reported as 'atypical',[42,43] in which the full constellation of signs and symptoms are not present, remain controversial. It is perhaps best to treat such patients as having suspected NMS, rather than waiting for the full blown syndrome to appear before initiating treatment. Data based caveats not withstanding, study findings support the consideration of a spectrum approach to classifying and diagnosing psychotropic-related neurotoxicity.[44]

Morbidity and the use of extensive diagnostic procedures may be avoided if prompt diagnosis and appropriate treatment are provided.[45] The relationship between catatonia and NMS has been studied by several authors.[46] Catatonia is generally viewed as a peculiar and puzzling syndrome which has attracted limited attention. The previously predominant association of catatonia and schizophrenia has been eclipsed by the more frequently seen association with severe affective disorders or with general medical conditions.[47] Antipsychotics duplicate the symptoms of catatonia in the modern guise of NMS. Patients presenting with catatonic symptoms or who have a history of such symptoms are particularly vulnerable to NMS, and treatment of catatonia requires avoidance of antipsychotics and the use of benzodiazepines or electroconvulsive therapy (ECT).[47]

The extreme negativism and constriction of consciousness in catatonia suggest a primary role of the frontal lobes with secondary involvement of the extrapyramidal system.[47] Fricchione et al.[48] relate the diagnosis of the catatonic syndrome to systemic and mental disorders such as lethal (malignant) catatonia and NMS. Castillo et al.[49] attempted to differentiate between lethal catatonia and NMS. They pointed out that lethal catatonia often begins with psychotic excitement, whereas NMS begins with severe extrapyramidally induced rigidity. The treatment for lethal catatonia requires antipsychotics, whereas with NMS immediate withdrawal of antipsychotics is recommended. But Mann et al.[50] and Kellam[51] have questioned whether the two represent the same syndrome. Clinical differentiation is considered difficult because of a number of similarities exist that involve mode of onset, signs and symptoms and outcome. Recent observations emphasising similarities between the 2 disorders suggest that catatonia and NMS may not represent separate diagnostic entities.[50] Instead, it has been hypothesised that NMS is an antipsychotic-aggravated form of catatonia.[52]

4.2 The Serotonin Syndrome

The serotonin syndrome is produced most often by the concurrent use of drugs that enhance serotonin activity such as selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), alone or in combination. It is characterised by a constellation of at least 3 of the following symptoms: mental status changes, agitation, myoclonus, hyperreflexia, fever, shivering, diaphoresis, ataxia and diarrhoea. This presentation is similar to NMS and can lead to misdiagnosis. It maybe differentiated from NMS by the offending agent, which is usually a

serotonergic agent rather than an antipsychotic, and sometimes by requiring treatment with an antiserotonergic agent such as cyproheptadine and/or propranolol.[53] Also muscle rigidity may not be as pronounced as in NMS. Although the serotonin syndrome may result in death, most patients recover completely with supportive care alone. The main pathophysiological mechanism of the serotonin syndrome appears to be excessive accumulation of serotonin; studies using specific serotonin 5-HT_{1A} antagonists have implicated this receptor as being the most likely receptor subtype involved in the serotonin syndrome.[55] The occurrence of the serotonin syndrome may increase as SSRIs continue to replace TCAs in the treatment of depression.

Reports of extrapyramidal reactions (EPRs) associated with SSRI use have been accumulating in the medical literature for several years.[55] The proposed hypothesis for EPRs occurring with SSRI use involves serotonin's inhibitory actions on extrapyramidal dopamine activity. EPRs may include dystonias, dyskinesias, akathisia, parkinsonism, exacerbations of Parkinson's disease and possibly NMS. The majority of SSRI-related reactions appear to occur within the first month of treatment. Information from available case reports does not strongly support any consistent risk factor, although some worth considering may include total SSRI daily dose, rapid dose escalation strategies, increased age, female gender, concurrent pyschotropics known to also precipitate EPRs and concurrent disease states such as Parkinson's disease.

The other conditions that need to be distinguished from NMS are heatstroke, malignant hyperthermia and a similar syndrome seen following either the abrupt discontinuation of antiparkinsonian medication in a person with Parkinson's disease or treatment with dopamine depleting agents (e.g. reserpine, tetrabenazine). Heatstroke may mimic NMS but can be distinguished by the presence of hot, dry skin rather than diaphoresis, hypotension rather than fluctuating or elevated blood pressure and limb flaccidity rather than rigidity. Patients with malignant hyperthermia present with highly elevated temperatures and rigidity. This condition usually occurs in genetically susceptible individuals who have received halogenated inhalational anaesthetics and depolarising muscle relaxants. Malignant hyperthermia usually starts within minutes of receiving anaesthesia. It is also important to determine whether the elevated temperature occurred before or subsequent to the superimposed medical problems. This condition responds to treatment with intravenous dantrolene sodium.

NMS must be distinguished from similar syndromes resulting from the use of other psychotropic medications (e.g. MAOIs, MAOI-TCA combinations, MAOI-serotonergic agent combinations, lithium toxicity, anticholinergic delirium), all of which may present with hyperthermia, altered mental status and autonomic changes. In such cases a diagnosis of medication induced movement disorders not otherwise specified can be given.[7]

5. Prevention

The most important aspect of treatment is prevention. This includes reducing risk factors, early recognition of suspected cases and prompt discontinuation of the offending agent. Effective prevention relies on sound clinical judgement, maintaining an index of suspicion for both NMS and NMS-like disorders (e.g., meningitis, cerebrovascular disease, hepatic encephalopathy, acute intermittent porphyria, stimulant abuse, heat-stroke and malignant hyperthermia), consulting with other specialists when necessary and documenting evidence of diagnostic evaluation and alternative management strategies. We suggest the following guidelines for prevention.

All patients with acute psychosis require aggressive medical, psychiatric and nursing management. To prevent NMS, the patient should be well hydrated. Reduction in agitation and hyperactivity is essential in preventing physical exhaustion. Adjunctive use of benzodiazepines provides the best and safest means of sedation and reduces the

chances that excessive doses of antipsychotics will be employed.

Temperature and vital signs must be carefully monitored, especially if physical restraints are used. It is recommended that antipsychotics are used conservatively with gradual titration of dosages against symptom response and adverse effects. Rapid escalation of dosages and frequent parenteral injections have been identified as risk factors for NMS.

The appearance of extrapyramidal rigidity should prompt customary ameliorating measures, e.g. administering anticholinergics, reducing antipsychotic dosage or switching to a less potent antipsychotic. Similarly, the appearance of antipsychotic-induced catatonia should prompt consideration of a dosage reduction, use of a less potent agent or administration of amantadine or benzodiazepines. Should rigidity or catatonia persist or progress, or if confusion or other neurological or autonomic signs develop, clinical reassessment should occur. Reassessment of the differential diagnosis of the symptom picture should be considered and the rationale for continued antipsychotic therapy with the same or alternative drug reviewed, discussed with the patient and family and documented in the patient's chart.

6. Management

The conservative management of full-blown cases consists of fluid replacement, reduction of temperature and monitoring of cardiac, respiratory and renal functions.

With the development of a temperature of 38°C or greater, along with rigidity, mental status and autonomic changes and laboratory findings, the diagnostic criteria for NMS are fulfilled. I suggest the following guidelines for management based on a hierarchy of symptom severity.[36,40] However, it should be noted that this protocol may not apply to every patient and it may require alteration according to specific patient needs.

Intensive care should be provided on a medical ward and all antipsychotics, dopamine depleting or dopamine antagonistic drugs should be immediately discontinued. Consideration should be given to discontinuing all other psychotropic drugs.

Abnormalities in fluids/electrolyte balance, particularly hyperkalemia, acid-base balance, cardiorespiratory function, rhabdomyolysis, renal function, level of consciousness and thromboembolic phenomenon should be monitored and corrected.

The hyperthermic patient should be actively cooled by use of intravenous cold saline, surface cooling with ice and a hypothermia blanket. The patient should be monitored for over vigorous cooling which may lead to hypothermia.

Treatment with dopamine agonists should be considered. These are administered either orally or by nasogastric tube when the patient has a temperature of 38.3°C (101°F) to 40.0°C (104°F) and moderate rigidity. Treatment should start with bromocriptine 2.5mg every 8 hours or amantadine 100mg every 8 hours. Dopamine agonist treatment should be continued for 10 days after symptoms are controlled and then the dosages should be gradually tapered. Intravenous dantrolene may be considered in patients who cannot receive oral drugs and they should be switched to oral dantrolene as soon as possible. Intravenous dantrolene 2 to 3 mg/kg bodyweight may be considered in patients who develop temperatures above 40°C (104°F), extensive rhabdomyolysis, coma and cardiorespiratory or renal failure as these patients may be at increased risk of morbidity and mortality.[32,56] When symptoms are controlled this could be switched to oral dantrolene 1 mg/kg every 6 hours and continued for another 10 days and then discontinued by tapering. It would appear overall that dopamine agonists and dantrolene may be significantly beneficial in reducing the mortality associated with NMS; however, a combination of the two has not been demonstrated to have any significant advantage over either drug alone.[57,58] Treatment with benzodiazepines, e.g. lorazepam, could be considered for control of agitation.

ECT has also been studied by several investigators.[59-63] As with other specific interventions, there are no controlled studies of ECT compared to

either pharmacotherapy or supportive therapy alone. However, in view of the need for patient consent and potential complications of anaesthesia in an acutely hypermetabolic patient, ECT may only be valuable in selected patients, e.g. those with NMS that is refractory to an adequate trial of pharmacotherapy or supportive care. Additionally, ECT may be indicated in patients in whom the hypermetabolic state has resolved, but who remain catatonic or show the emergence of ECT-responsive psychotic symptoms, patients with suspected acute lethal catatonia as a result of the pre-existing psychotic disorder (e.g. manic or depressive psychosis and in patients who have a schizophrenic psychosis). NMS that is refractory to treatment may be suspected in patients experiencing elevated temperatures prior to receiving antipsychotics and in the context of agitation or hyperthermia rather than stupor.[50,62]

7. Managing Patients with History of NMS

If a history of NMS is confirmed, the physician should speak with the patient and his/her family and careful documentation should be prepared. If further treatment with antipsychotics is indicated in this patient, e.g. to treat long term psychotic disorders such as schizophrenia, then it is almost always necessary to rechallenge the patient with a different class of antipsychotic. However, this rechallenge should not take place until 2 weeks after the patient as recovered from NMS.

Rechallenge with a low potency antipsychotic may be considered. If the initial episode of NMS was caused by a low potency antipsychotic, a low potency antipsychotic from a different chemical class may be considered. Depot antipsychotics should probably be avoided as they may delay recovery from any further episodes of NMS. In addition, the use of prophylactic agents, e.g. bromocriptine, dantrolene, may be considered in conjunction with antipsychotics. Atypical antipsychotics like clozapine, risperidone and olanzapine may be considered as alternatives to conventional antipsychotic therapy. Benzodiazepines may help in the management of patients with a psychosis who are hyperactive and enable the use of a lower dosage of antipsychotic. Titration of drugs should be performed slowly.

When the primary diagnosis is affective disorder, as is the case in a significant percentage of patients developing NMS, aggressive treatment of the manic or depressive illness with antidepressants, lithium carbonate, valproic acid (sodium valproate) or carbamazepine is recommended.[63]

8. Conclusion

NMS is a serious condition associated with dopamine blocking drugs. Early recognition and the treatment of NMS will minimise complications. Availability of atypical antipsychotics offers an opportunity to protect the patient from the adverse effects of conventional antipsychotics. Future research should focus on the identification of patients at risk for adverse drug effects and NMS through imaging studies of dopamine receptors. Education of mental health care givers on the early signs and symptoms of this condition will lead to prompt management.

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References

1. Delay J, Pichot P, Lemperiere T, et al. Un neuroleptique majeur non-phenothiazine et non reserpinique, l'haloperidol, dans le traitement des psychoses. Ann Med Psychol 1960; 118: 145-52
2. Caroff SN. The neuroleptic malignant syndrome. J Clin Psychiatry 1980; 41: 79-83
3. Delay J, Pichot P, Lemperiere T, et al. L'emploi des butyrophenones en psychiatrie: etude statistique et psychometrique. In: Symposium Internazionale sull'Haloperidol e Triperidol. Milan, Instituto Luso Farmaco d'Italia, 1962; 305-319
4. Keck PE, Pope HG, McElroy SL. Declining frequency of neuroleptic malignant syndrome in a hospital population. Am J Psychiatry 1991; 148: 880-2
5. Gelenberg AJ, Bellinghausen B, Wojcik JD, et al. A prospective survey of neuroleptic malignant syndrome in a short-term psychiatric hospital. Am J Psychiatry 1988; 145: 517-8
6. Keck PE, Pope HG, McElroy SL. Frequency and presentation of neuroleptic malignant syndrome: a prospective study. Am J Psychiatry 1987; 144: 1344-6

7. DSM IV. Diagnostic and statistical manual of metal disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994: 741-2
8. Konikoff F, Kuritzky A, Jerushalmi Y, et al. Neuroleptic malignant syndrome induced by a single injection of haloperidol. BMJ 1984; 289: 1228-9
9. Susman VL, Addonizio G. Reinduction of neuroleptic malignant syndrome by lithium. J Clin Psychopharmacol 1987; 7: 339-41
10. Goulon M, Rohan-Chabot P, De Elkhaart D, et al. Beneficial effects of dantrolene in the treatment of neuroleptic malignant syndrome: a report of two cases. Neurology 1983; 33: 516-8
11. Weinberg SE, Twerski RS. Neuroleptic malignant syndrome. Anesth Analg 1983; 62: 848-50
12. Henderson A, Longdon P. Fulminant metoclopramide-induced neuroleptic malignant syndrome rapidly responsive to intravenous dantrolene. Aust NZ J Med 1991; 21: 742-3
13. Lenler-Peterson P, Hansen BD, Hasselstrom L. A rapidly progressing lethal case of neuroleptic malignant syndrome. Intensive Care Med 1990; 16: 267-8
14. Lavie CJ, Ventura HO, Walker G. Neuroleptic malignant syndrome: three episodes with different drugs. South Med J 1986; 79: 1571-3
15. Eiser AR, Neff MS, Slifkin RF. Acute myoglobinuric renal failure. Arch Intern Med 1982; 142: 601-3
16. Marsden CD, Jenner P. The pathophysiology of extrapyramidal side-effects of neuroleptic drugs. Psychol Med 1980; 10: 55-72
17. Henderson VW, Wooten GF. Neuroleptic malignant syndrome; a pathogenetic role for dopamine receptor blockade? Neurology 1981; 31: 132-7
18. Behman S. Mutism induced by phenothiazines. Br J Psychiatry 1972; 121: 599-604
19. Ansseau M, Diricq ST, Grisar TH, et al. Biochemical and neuroendocrine approaches to a malignant syndrome of neuroleptics. Acta Psychiatr Belg 1980; 80: 600-6
20. Tu JB. Psychopharmacogenetic basis of medication-induced movement disorders. Int Clin Psychopharmacol 1997 Jan; 12 (1): 1-12
21. Deuschal G, Oepen G, Hermle L, et al. Neuroleptic malignant syndrome: observations on altered consciousness. Pharmacopsychiatry 1987; 20: 168-79
22. Otani K, Horiuchi M, Kondo T, et al. Is the predisposition to neuroleptic malignant syndrome genetically transmitted? Br J Psychiatry 1991; 158: 850-3
23. Caroff SN, Mann SC. Neuroleptic malignant syndrome (review). Med Clin North Am 1993; 77: 185-202
24. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Psychopharmacol Bull 1988; 24: 25-9
25. Addonizio G, Susman VL, Roth SD. Neuroleptic malignant syndrome: review and analysis of 115 cases. Biol Psychiatry 1987; 22 : 1004-20
26. Velamoor VR, Norman R, Caroff SN, et al. Progression of symptoms in neuroleptic malignant syndrome. J Nerv Ment Dis 1994; 182: 168-73
27. Velamoor VR, Fernando MLD, Williamson P. Incipient neuroleptic malignant syndrome? Br J Psychiatry 1990; 156: 581-4
28. Meltzer HY, Cola PA, Parsa M. Marked elevations of serum creatine kinase activity associated with antipsychotic drug treatment. Neuropsychopharmacology 1996 Oct; 15 (4): 395-405
29. Rosebush P, Stewart T. A prospective analysis of 24 episodes of neuroleptic malignant syndrome. Am J Psychiatry 1989 Jun; 146 (6): 295-8
30. Shalev A, Munitz H. The neuroleptic malignant syndrome: agent and host interaction. Acta Psychiatr Scand 1986; 73: 337-47
31. Yamawaki S, Yano E, Uchitomi Y. Analysis of 497 cases of neuroleptic malignant syndrome in Japan. Hiroshima J Anesth 1990; 26: 35-44
32. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Med Clin North Am 1993; 77: 185-202
33. Keck PE, Pope HG, McElroy SL. Frequency and presentation of neuroleptic malignant syndrome: a prospective study. Am J Psychiatry 1987; 144: 1344-6
34. White DAC, Robins AH. Catatonia: harbinger of the neuroleptic malignant syndrome. Br J Psychiatry 1991; 158: 419-21
35. White DAC. Catatonia and the neuroleptic malignant syndrome: a single entity? Br J Psychiatry 1992; 161: 558-60
36. Woodbury MM, Woodbury MA. Neuroleptic-induced catatonia as a stage in the progression toward neuroleptic malignant syndrome. J Am Acad Child Adolesc Psychiatry 1992; 31: 1161-4
37. Jauss M, Krack P, Franz M, et al. Imaging of Dopamine receptors with [1-123] iodobenzamide single-photon emission-computed tomography in neuroleptic malignant syndrome. Mov Disord 1996 Nov; 11 (6): 726-8
38. Velamoor VR, Swamy MB, Parmar MB, et al. Management of suspected neuroleptic malignant syndrome. Can J Psychiatry 1995; 40: 545-8
39. Levenson DF, Simpson GM. Neuroleptic-induced extrapyramidal symptoms with fever: heterogeneity of the neuroleptic malignant syndrome. Arch Gen Psychiatry 1986; 43: 839-48
40. Sewell D, Jeste DV. Distinguishing neuroleptic malignant syndrome (NMS) from NMS-like acute medical illnesses: a study of 34 cases. J Neuropsychiatry 1992; 4 (3): 265-9
41. Raja M, Altavista MC, Cavallari S, et al. Neuroleptic malignant syndrome and catatonia. Eur Arch Psychiatry Clin Neurosci 1994; 243: 299-303
42. Bernstein RA. Malignant neuroleptic syndrome: an atypical case. Psychosomatics 1979; 20: 840-6
43. Misiaszek JJ, Potter RL. Atypical neuroleptic malignant syndrome responsive to conservative management. Psychosomatics 1985; 26: 62-6
44. Goldman SA. FDA medwatch report – lithium and neuroleptics in combination – the spectrum of neurotoxicity. Psychopharmacol Bull 1996; 32 (3): 299-309
45. Martin TG. Serotonin syndrome. Ann Emerg Med 1996; 28 (5): 520-6
46. Northoff G. Neuroleptic malignant syndrome and catatonia – one entity or two. Biol Psychiatry 1996 Sep; 40 (5): 431-2
47. Blumer D. Catatonia and the neuroleptics – psychobiologic significance of remote and recent findings. Compr Psychiatry 1997 Jul-Aug; 38 (4): 193-201
48. Fricchione G, Bush G, Fozdar M, et al. Recognition and treatment of the catatonic syndrome [review]. J Intens Care Med 1997 May-Jun; 12 (3): 135-47
49. Castillo E, Rubin RT, Holsboer-Trachsler E. Clinical differentiation between lethal catatonia and neuroleptic malignant syndrome. Am J Psychiatry 1989 Mar; 146 (3): 324-8
50. Mann SC, Caroff SN, Bleier HR, et al. Lethal catatonia. Am J Psychiatry 1986; 143: 1374-81
51. Kellam AMP. The neuroleptic malignant syndrome, so called: a survey of the world literature. Br J Psychiatry 1987; 150: 752-9

52. Topka H, Buchkremer G. Lethal catatonia, malignant neuroleptic malignant syndrome and myositis ossificans. Nervenarzt 1996 May; 67 (5): 413-7
53. Lane R, Baldwin D. Selective serotonin reuptake inhibitor-induced serotonin syndrome: review. J Clin Psychopharmacol 1997; 17 (3); 208-21
54. Sporer KA. The serotonin syndrome: implicated drugs, pathophysiology and management. Drug Saf 1995; 13: 94-104
55. Caley CF. Extrapyramidal reactions and the selective serotonin-reuptake inhibitors. Ann Pharmacother 1997; 31: 1481-9
56. Shalev A, Hermesh H, Munitz H. Mortality from neuroleptic malignant syndrome. J Clin Psychiatry 1989; 50: 18-25
57. Sakkas P, Davis JM, Hua J, et al. Pharmacotherapy of neuroleptic malignant syndrome. Psychiatr Ann 1991; 21: 157-64
58. Sakkas P, Davis JM, Janucak PG, et al. Drug treatment of the neuroleptic malignant syndrome. Psychopharmacol Bull 1991; 27: 381-4
59. Scheftner WA, Shulman RB. Treatment choice in neuroleptic malignant syndrome. Convuls Ther 1992; 8 (4): 267-79
60. Davis JM, Janicak PG, Sakkas P, et al. Electroconvulsive therapy in the treatment of the neuroleptic malignant syndrome. Convuls Ther 1991; 7: 111-20
61. Mann SC, Caroff SN, Bleier HR, et al. Electroconvulsive therapy of the lethal catatonia syndrome: case report and review. Convuls Ther 1990; 6: 239-47
62. Lazarus A, Mann SC, Caroff SN. The neuroleptic malignant syndrome and related conditions. Washington, DC: American Psychiatric Press Inc., 1989
63. Jacobson JL, Jacobson AM. Psychiatric secrets. Philadelphia: Hanley and Belfus Inc., 1996: 466

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