DSH PSYCHOTROPIC MEDICATION Operational Procedures

APPENDIX -- NEUROLEPTIC MALIGNANT SYNDROME (NMS):

NOTE: Directive statements and procedures described in this chapter are informational and advisory in nature.

I. GENERAL INFORMATION:

A. Physicians in all primary care specialties, as well as psychiatrists, should be familiar with NMS. Clinicians also should be familiar with differential diagnoses for NMS, including malignant hyperthermia, excited catatonia, acute CNS depressant withdrawal states, and serotonin syndrome.

1. Early detection is paramount, given the potentially lethal outcome of this rare syndrome.

2. Within the practice of psychiatry, NMS is most often seen in the context of treatment with D_2 dopamine receptor blocking (neuroleptic) medications.

    a. Some degree of D_2 dopamine receptor blockade occurs with first- generation antipsychotics, second-generation, or atypical antipsychotics, and mixed monoamine blocking antidepressants.

    b. Medications which increase synaptic serotonin (e.g., selective serotonin reuptake inhibitors) can also cause an abrupt decline in dopamine release resulting in risks of both acute neurological symptoms, such as dystonia or Parkinsonism, and (very rarely) NMS.

3. In addition, abrupt withdrawal of dopaminergic drugs (e.g., such as carbidopa/levodopa or bromocriptine) has been reported to initiate NMS.

4. However, the first-generation antipsychotics remain the class of medications most often associated with NMS.

5. The syndrome can occur at any point during treatment with dopamine blocking medications but is somewhat more likely in the first few weeks to months of treatment, especially if dopamine antagonism increases rapidly.

6. The risk of NMS appears to be independent of dosage within the typically prescribed dose ranges.

B. Characteristic physical and mental status changes seen early in the course of NMS include:

- Fever, catatonia, episodic tachycardia or hypertension, dysarthria, urinary incontinence, confusion, mild stupor or agitation, and fluctuating level of attention.

1. The evolution of NMS is typically rapid, progressing from initial symptoms to fully developed syndrome over 24-72 hours.

2. The fully evolved syndrome is characterized by muscle rigidity, rhabdomyolysis, myoglobinemia, myoglobinuria, hyperthermia (38.3°C or 100.5°F to 44°C or 108°F), febrile seizures, autonomic dysfunction, frank delirium, renal failure, and extreme diaphoresis.

3. Often, muscle rigidity and mental status changes develop more rapidly, followed by the other signs and symptoms noted.

C. Elevated labs

1. Creatinine Phosphokinase (CPK or CK) plasma levels begin rising early in the syndrome, exceeding the upper limit of normal (269 IU/L) and rapidly soaring into the thousands of international units per liter of plasma.

2. Leukocytes and hepatic enzymes also are typically elevated, though not to as extreme a degree as CK.

3. While none of these laboratory measures alone is diagnostic, they can be diagnostically helpful early in suspected cases.

D. NMS is fatal in 15-20% of fully developed well-managed cases.

1. Prompt and aggressive intervention is vital in treating this syndrome.

2. Once the individual has recovered from NMS, defined as a CPK of less than 269 IU/L and absence of clinical symptoms of NMS, for at least 2 weeks, treatment with an antipsychotic can be resumed.

3. In general, switching from a first-generation antipsychotic to a second- generation or atypical antipsychotic should be pursued.

4. The lowest rate of NMS appears to occur with clozapine.

a. NOTE: NMS, including a variant without muscle rigidity, has been reported with clozapine.

E. NMS typically persists for 10-14 days but can last up to four weeks during treatment with depot neuroleptics.

1. NMS with depot antipsychotic treatment alone has very rarely been reported, with addition of STAT or PRN doses of high-potency dopamine antagonists (e.g., haloperidol, often being identified as the trigger for the syndrome).

F. Rapid increases in the doses of dopamine blocking drugs have been associated with initiation of NMS.

G. Individuals receiving combined lithium and antipsychotic or receiving multiple dopamine receptor blocking drugs have a higher risk of developing NMS.

H. Risk of NMS also is increased among brain injured individuals and individuals suffering degenerative brain disorders, especially those involving dopaminergic nuclei and hypothalamic brain structures.

I. NMS can occur at any age, but shows a peak incidence between 21 and 30 years of age.

J. Males are twice as likely as females to develop NMS.

K. Additional factors associated with an increased risk of NMS are reported to include dehydration, increased heat load, exhaustion, and prior history of NMS.

II. PATHOGENESIS:

A. The severe muscle rigidity and consequent extreme heat production, rhabdomyolysis, and myoglobinuria appear to result from blockade of D_2 dopamine receptors receiving axonal projections from dopamine neurons in the pars compacta of the substantia nigra.

Additionally, the presence of temperature dysregulation and dysautonomia indicate that hypothalamic nuclei, which are modulated by dopaminergic tracts, are likely involved in NMS.

III. Because of the similarity of NMS, in some respects, to malignant hyperthermia another possible feature of pathogenesis might involve central and/or peripheral abnormalities in cell membrane ion transport, in addition to the cited role of dopamine blockade.

IV. DIAGNOSTIC CRITERIA FOR NMS:

International NMS Consensus Criteria [J Clin Psychiatry Sept 2011; 72(9): 1222-28]

DIAGNOSTIC CRITERIA	PRIORITY SCORE
Exposure to dopamine antagonist or dopamine agonist withdrawal within past 72 hours	20
Hyperthermia (>100.4°F or >38.0°C) on at least 2 occasions, measured orally	18
Rigidity	17
Mental Status Alteration (reduced or fluctuating level of consciousness)	13
Creatine Kinase elevation (at least 4 times upper limit of normal)	10
Sympathetic nervous system lability, defined as at least 2 of the following: • Blood pressure elevation (Systolic or Diastolic ≥ 25% above baseline) • Blood pressure fluctuation (≥ 20 mm Hg diastolic change or ≥ 25 mm Hg systolic change within 24 hours) • Diaphoresis • Urinary incontinence	10
Hypermetabolism, defined as: • Heart rate increase (≥ 25% above baseline) AND • Respiratory rate increase (≥ 50% above baseline)	5
Negative workup for infectious, toxic, metabolic or neurologic cases	7

A. In a 2017 validation study of the above NMS criteria, data were extracted from 221 clinician-initiated consultations for suspected NMS from 1997 to 2009, and each case given a total priority point score on the basis of the consensus criteria.

B. Agreement was best between International NMS Consensus Criteria with a **cutoff score of 74** and modified DSM-IV-TR Research NMS Diagnostic Criteria (sensitivity, 69.6%; specificity, 90.7%.)

C. The cutoff score of 74 demonstrated the highest agreement in all comparisons.

Modified DSM-IV-TR Research NMS Diagnostic Criteria [Gurrera J Clin Psychopharm 2017;37: 67–71]

A. The development of severe muscle rigidity (modified to any amount of rigidity) and elevated temperature associated with the use of neuroleptic medication.

B. 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
- Leucocytosis (above 11.5)
- Laboratory evidence of muscle injury (eg, elevated creatine phosphokinase)

C. The symptoms in criteria A and B are not due to another substance (eg, phencyclidine) or a neurological or other general medical condition (eg, 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).

V. DIFFERENTIAL DIAGNOSES:

A. Diagnosis of NMS is complicated by its similarity to other syndromes, including:

- malignant hyperthermia
- central nervous system infections
- anticholinergic delirium
- hyperthyroidism (thyroid storm)
- neuroleptic induced catatonia
- toxic or metabolic encephalitis
- Stauder catatonia
- heat stroke

B. Published case reports describing NMS have varied widely, making differential diagnosis more difficult. For example, Bernstein has suggested that the toxic syndrome attributed to combined lithium and haloperidol use by Cohen and Cohen may have actually been NMS.

C. Of note, neuroleptic induced catatonia may closely resemble NMS, but usually has additional Parkinsonian features and responds to anticholinergic treatment.

D. Malignant hyperthermia is a pharmacogenic syndrome which resembles NMS closely, but which results from halothane anesthesia and succinylcholine paralysis.

E. Stauder's syndrome is characterized by bizarre behavior, hyperpyrexia, muscle hypertonicity, and autonomic dysfunction.

1. It occurs in the context of schizophrenia and catatonic excitement and has been associated with dehydration and exhaustion.

2. Importantly, this condition is treated with antipsychotic medications, while NMS calls for the immediate discontinuation of antipsychotics.

3. In uncertain cases, measurement of CK or CPK to clarify the diagnosis and initial control of agitation with benzodiazepines alone may be prudent.

F. Heat stroke differs from NMS in that muscle rigidity is absent and the skin is dry.

*****Please see table on NMS differential diagnoses on next page.*****

Table: Differential Diagnosis of NMS

SYMPTOM	NMS	MALIGNANT HYPERTHERMIA	HEATSTROKE	LETHAL CATATONIA (functional origin)
Hyperthermia	Yes	Yes	Yes	Yes
Muscle Rigidity	Yes	Yes	Not Typical	Yes
Diaphoresis	Yes	Yes	Not Typical	Yes
Tachycardia	Yes	Yes	Yes	Yes
Respiration	Rapid	Rapid	Rapid	N/A
Blood Pressure	Increased or Decreased	Increased	Increased	N/A
Acidosis	Yes	Yes	Yes	?
Coagulopathy	Yes	Yes	Yes	?
Myoglobinuria	Yes	Yes	Yes	?
Mental Status	Impaired	Impaired	Impaired	Impaired
Genetic Predisposition	No	Often	No	No
Precipitant	Antipsychotics	Halothane Anectine ?Stress	Exposure or Exercise	?
Elevated CPK	Yes	Yes	N/A	N/A

Elevated LFTs	Yes	Yes	N/A	N/A
Leukocytosis	Yes	N/A	Yes	N/A
Onset	Hours-Days	Minutes-Hours	Min.-Hrs.	Days-Weeks
Mortality	10%-20%	30%	20%-50%	75%-100%
Therapy	Dantrolene Dopaminergic Agonists	Dantrolene	?Dantrolene	ECT Cortico-steroids

N/A = Lack of literature documentation.

VI. LABORATORY EVALUATION:

A. Laboratory evaluation of suspected NMS cases is vital.

B. Recommended laboratory measures include:

1. Complete blood count with differential analysis; plasma electrolytes; urinalysis; creatinine phosphokinase; and liver function tests.

2. Serial measures of blood urea nitrogen and creatinine also should be obtained.

3. If a drug induced encephalopathy is suspected, a urine toxicology screen should be obtained.

C. If the individual is taking lithium, it should be discontinued and serial measures of lithium plasma concentrations should be made.

VII. TREATMENT:

A. The first step in treatment after the diagnosis of NMS is made is removal of the offending agent and avoidance of any other medications which block dopamine transmission or lower dopamine transmission until the syndrome has clinically been resolved for ≥ 2 weeks and/or plasma CK or CPK concentrations have consistently declined to within the normal range.

B. If the individual is not already receiving an anticholinergic medication, such medication should be begun.

C. Additional measures should include cooling measures, intravenous hydration, and correction of any electrolyte abnormalities.

D. Additionally, secondary complications, such as hypoxia, renal failure, febrile seizures, and metabolic acidosis should be vigorously treated.

E. Specific medications which have been reported to be beneficial in treating NMS include the dopaminergic agonist, bromocriptine, and the neuromuscular blocking agent, dantrolene. Other dopaminergic agents also would be likely to be beneficial but have not been studied in NMS extensively.

1. Bromocriptine is usually started at 2.5 mg. every eight hours and has been titrated to as much as 65 mg. per day in some cases of NMS.

2. Dantrolene dosing varies from 0.8-2.5 mg/kg of body weight per day. Dantrolene 60 mg orally or intravenously every 6-8 hours is a commonly employed treatment strategy.

F. Amantadine 200 mg per day also has been used in some individuals suffering from NMS.

G. Resumption of antipsychotic treatment should not commence until the syndrome has been clinically absent for 2 weeks and/or plasma CK or CPK concentrations have stably returned to normal.

1. Several studies indicate that following recovery from NMS most individuals can tolerate re-exposure to traditional antipsychotics without recurrence of NMS.

2. Presently, however, it may be prudent to choose an antipsychotic with lesser dopamine blockade (i.e., an atypical or second-generation antipsychotic).

3. If a first-generation antipsychotic is resumed, high-potency drugs should be avoided.

4. Some studies have suggested that among the first-generation antipsychotics, thioridazine (Mellaril) may pose the least risk, though is an unlikely choice, due to its propensity to prolong the QT interval.

5. Concurrent use of antipsychotic and benzodiazepine medications may reduce the antipsychotic dose.

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