Neuroleptic Malignant Syndrome, Serotonin Syndrome & Relation to Catatonia

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Pre-Lecture Exam Question 1

1. **Which of the following statements is NOT true of NMS?**

A. Dopamine antagonists can cause it.

B. It can be lethal.

C. It occurs more frequently among catatonia patients.

D. It is not associated with elevated temperature.

E. It is associated with change in level of consciousness.

Question 2

2. **Which of the following statements is NOT true about Serotonin Syndrome?**

A. It is reported with essentially every serotonergic agent including some with serotonin antagonist effects such as mirtazapine.

B. SS is often associated with changes in level of consciousness.

C. SS is often associated with fever or sweating.

D. SS is often associated with tremor or rigidity.

E. None of the above is true.

Question 3

3. Which of the following statements is NOT true of catatonia?

A. The diagnosis of catatonia requires the presence of extreme hypoactivity.

B. Grimacing can be a feature of catatonia.

C. Hyperactivity can be a feature of catatonia.

D. Negativism can be a feature of catatonia.

E. Waxy flexibility can be a feature of catatonia.

Question 4

4. **Treatment for either NMS or SS might include all the following EXCEPT which one?**

A. Stopping the causative agent(s).

B. Supportive measures such as external cooling.

C. Hydration to limit renal toxicity.

D. Dantrolene or succinylcholine to reduce muscular rigidity.

E. Metoclopramide for NMS-associated gastroesophageal reflux.

Question 5

5. **True or False:** Neuroleptic rechallenge of an NMS patient should be delayed until the NMS episode fully resolves.

Neuroleptic Malignant Syndrome (NMS) & Serotonin Syndrome (SS) are…

- …rare, idiosyncratic reactions to dopamine antagonists or serotonin agonists.
- …capable of producing significant mortality.
- …more frequent among catatonia (Cat) patients.
- …linked with Cat through their shared relationship to mood disorders.
- …not identical to or a variant of catatonia (Cat), though shared symptoms of stupor and mutism may mislead clinicians.

NMS Historical Background

- Initially described by Delay, a French psychiatrist who pioneered the use of neuroleptics.
- Brought to US attention by Caroff and Levenson.
- Reported with essentially every D_1 or D_2 antagonist including non-psychotropics such as metoclopramide.

SS Historical Background

- First described by Insel.
- Diagnostic criteria devised by Sternbach.
- Reported with essentially every serotonergic agent
  - including some with serotonin antagonism such as mirtazapine.
  - Also including some non-psychotropics, such as linezolid, an antibiotic with MAOI effects

DSM-IV NMS Research Criteria

A) Severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication.

B) Two (or more) of the following:

1) diaphoresis
2) dysphagia
3) tremor
4) incontinence
5) changes in level of consciousness ranging from confusion to coma
6) mutism
7) tachycardia
8) elevated or labile blood pressure
9) leucocytosis
10) laboratory evidence of muscle injury (e.g., elevated CK)

C) Symptoms in A and B are not due to another substance (e.g., PCP) or a neurological or other general medical condition (e.g., viral encephalitis).

D) Symptoms in A and B are not better accounted for by a mental disorder (e.g., Mood Disorder with Catatonic Features).

abridged from DSM IV, p 742

NMS: A Diagnosis of Exclusion

- Must rule out medical (e.g. infectious or neurologic) sources of fever and rigidity such as viral encephalitis.[1]
- An “additional wrinkle”: Presence of viral encephalitis in some cases may have predisposed to development of NMS following brief neuroleptic exposure.[2]

1. Adityanjee et al 1999; 2. Serrano-Dueñas 2002.

SS: Updated Diagnostic Criteria (1)

1. Co-incident with addition or increase in known serotonergic agent to an established treatment regime, & development of at least 4 major or 3 major plus 2 minor following symptoms:

	Major symptoms	Minor symptoms
I. Mental symptoms	Consciousness impairment Elevated mood Semicoma/coma	Restlessness Insomnia
II. Neurological symptoms	Myoclonus Tremor Shivering Rigidity Hyperreflexia	Uncoordination Dilated pupils Akathisia
III. Vegetative symptoms	Fever Sweating	Tachycardia Tachy/dyspnea Diarrhea Hyper/hypotension

Radomski et al. 2000

SS: Updated Diagnostic Criteria (2)

2. Clinical features described in the first criterion were not an integral part of the underlying psychiatric disorder prior to commencing the serotonergic agent.
3. Other etiologies (e.g. infectious, metabolic or endocrine, substance abuse or withdrawal) ruled out.
4. A neuroleptic drug had not been started or increased in dosage prior to onset of the signs and symptoms listed above.

5. * Note that Myoclonus, hyperreflexia, shivering, and gastrointestinal symptoms are generally more prominent in SS than in NMS.

Radomski et al. 2000

Catatonia: Diagnostic Criteria

Presence or absence of these 14 items are used for screening	
Excitement	Extreme hyperactivity, apparently non-purposeful. Not attributed to goal-directed agitation
Immobility/stupor	Extreme hypoactivity, immobile, minimally responsive to stimuli.
Mutism	Verbally unresponsive or minimally responsive.
Staring	Fixed gaze, little or no visual scanning of environment, decreased blinking.
Posturing/catalepsy	Spontaneous maintenance of posture(s) (e.g. sitting or standing for long periods without reacting).
Grimacing	Maintenance of odd facial expressions.
Echopraxia/echolalia	Mimicking of examiner's movements/speech.
Stereotypy	Repetitive, non-goal-directed motor activity.
Mannerisims	Odd, purposeful movements.
Verbigeration	Repetition of phrases or sentences.
Rigidity	Maintenance of a rigid position despite efforts to be moved.
Negativism	Apparently motiveless resistance to instructions or attempts to move/examine patient.
Waxy flexibility	During reposturing of patient, patient offers initial resistance similar to that of a bending candle.
Withdrawal	Refusal to eat, drink and/or make eye contact.

Bush et al 1996

NMS Risk Factors

- These risk factors are of limited value in individual cases, representing statistical description of a population.
- Suggested risk factors for NMS:
    - Neuroleptic dose (but there is not evidence of greater safety of atypicals because sample would need to be very large)
    - Dose increase
    - Baseline serum creatinine kinase
    - Cytochrome interactions
    - Co-morbid conditions
    - Age
    - Gender

Serotonin Syndrome

- Some persons are highly sensitive to serotonergic effects, but this was not apparent in more severe cases of SS.

- Use of SSRI with MAOI has been lethal, but uncomplicated cases were more frequent, similar to use of meperidine with MAOI.

Incidence: NMS, SS, & Cat

- Incidence of NMS in schizophrenics: 0.02-0.1%
- Incidence is significantly higher in mood disorder patients
- Incidence of SS is not known
- Occurrence of SS in Cat populations is rare, exact frequeny is unknown.

NMS and SS: Proposed Mechanisms

- Idiosyncratic reactions likely involve unknown genetic variants.
- Current research includes a report of higher incidence of *Taq*1 A polymorphism of the dopamine D_2 receptor gene in a group of patients with a history of NMS compared to a similar group without it by Suzuki et al.
- Gurrera has suggested possible alterations in sympathetic neuronal calcium metabolism.
- Efforts to understand NMS and SS by physiologic mechanisms have limited utility.

Treatment of NMS and SS (1)

- Stopping dopamine antagonists and serotonin agonists.
- Response of some Cat patients to benzodiazpines suggests a trial in cases with Cat symptoms ascribed to NMS or SS.
- Serotonin antagonism by cyproheptadine has been helpful in SS as reviewed by Gillman.
- Hydration to limit renal toxicity due to rhabdomyolysis
- Reduction of hyperthermia by external cooling
- Dantrolene or succinylcholine with intubation to abolish musular rigidity
  - Dantrolene is easier to use and has rarely caused hepatotoxicity, but some facilities prefer succinylcholine/intubation.
  - These treatments are especially useful for fever >103° F when excitation-contraction uncoupling may prevent muscular relaxation and cause further hyperthermia. Clinically significant alterations in blood pressure, heart rate, and oxygenation also require standard management.

Treatment of NMS and SS (2)

- Improvement and reduced mortality compared to supportive care in NMS has been reported with dopamine agonists, mainly bromocriptine, but they may aggravate psychosis or mania, and fatal increased hyperthermia occurred in a case of SS. Failure to respond to the above interventions within a few days increases the likelihood of Cat requiring ECT.
- Although muscle biopsy in some NMS cases showed susceptibility to malignant hyperthermia, it has not occurred with succinylcholine for ECT. Due to severity of the condition, some have used daily or multiple (two seizures during one session) ECT, but there is no evidence of superior efficacy to conventional twice-weekly ECT with bitemporal electrode placement.

NMS Managment

- Occurrence of NMS increases recurrence risk but does not indicate predictable risk of recurrence with neuroleptic rechallenge
- Low potency medication preferred in re-challenge
- Waiting for episode to fully resolve (~2 weeks) associated with lack of recurrence
- If atypical implicated, re-challenge should use a difference class of medication

Additional NMS Resource

- For Additional information on NMS or SS, use NMSIS Information Service.
- NMSIS Hotline 1(888) 667-8367 provides immediate access to an experienced consultant.

References

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Post Lecture Exam Question 1

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Answers to Pre & Post Competency Exams

1. D
2. E
3. A
4. E
5. True