Sometime it *is* a **Zebra**: Neuroleptic Malignant Syndrome in Palliative Care

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What are Extrapyramidal Symptoms

- Antipsychotic medications (neuroleptic agents) commonly produce extrapyramidal symptoms as side effects. **The extrapyramidal symptoms include acute dyskinesias and dystonic reactions, tardive dyskinesia, Parkinsonism, akinesia, akathisia, and neuroleptic malignant syndrome.**

Recap of Terminology

- Akathisia: an inability to remain still. It is a neuropsychiatric syndrome that is associated with **psychomotor restlessness.** The individual with akathisia will generally experience an intense sensation of unease or an inner restlessness that usually involves the lower extremities. This results in a compulsion to move. In most cases the movement is repetitive. The individual may cross, uncross, swing, or shift from one foot to the other. To the observer, this may appear as a persistent fidget.

- Acute Dystonia: **reaction is characterized by involuntary contractions of muscles of the extremities, face, neck, abdomen, pelvis, or larynx in either sustained or intermittent patterns that lead to abnormal movements or postures.** The symptoms may be reversible or irreversible and can occur after taking any dopamine receptor-blocking agents.

Tardive Dyskinesia

- Tardive Dyskinesia: caused due to **long-term exposure to first and second-generation neuroleptics, certain antidepressants, lithium, and some antiemetic medications.**

Neuroleptic Malignant Syndrome

- Symptoms of NMS develop over one to three days, characterized by the following: **High fever, muscle rigidity, autonomic dysfunction and altered mental status,**
- 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.

Risk Factors-Neuroleptics

- The main risk factors for developing NMS are the initiation or increase in dose of a neuroleptic medication and the potency and administration form of that drug.
- -The use of high-dosed, high-potency and long-acting or intramuscular depot forms of neuroleptics, as well as a rapid increase in dosage of neuroleptics, both increase the risk of developing NMS. The concurrent use of multiple neuroleptics, or concomitant taking of predisposing drugs such as lithium, also appear to confer an increased risk.

Other risk Factors

- dehydration,
- physical exhaustion,
- exposure to heat, h
- yponatremia,
- iron deficiency,
- malnutrition, t
- trauma, thyrotoxicosis,
- alcohol, psychoactive substances,
- resence of a structural or functional brain disorder such as encephalitis, tumor, delirium, or dementia.

TIMING?

- Although NMS can occur at anytime during neuroleptic treatment and no definite correlation between the duration of exposure to a neuroleptic and risk of developing the condition has been found, it is less likely to occur if a patient has been on a stable dose of their antipsychotics for a long period of time and there are no issues of noncompliance.[3,13]

For contrast: Neuroleptic Malignant Syndrome (NMS)

"Can't Bend(er)"

Mental status changes

Autonomic instability

Lead pipe rigidity
- *can't bend 'er limbs*

High fever

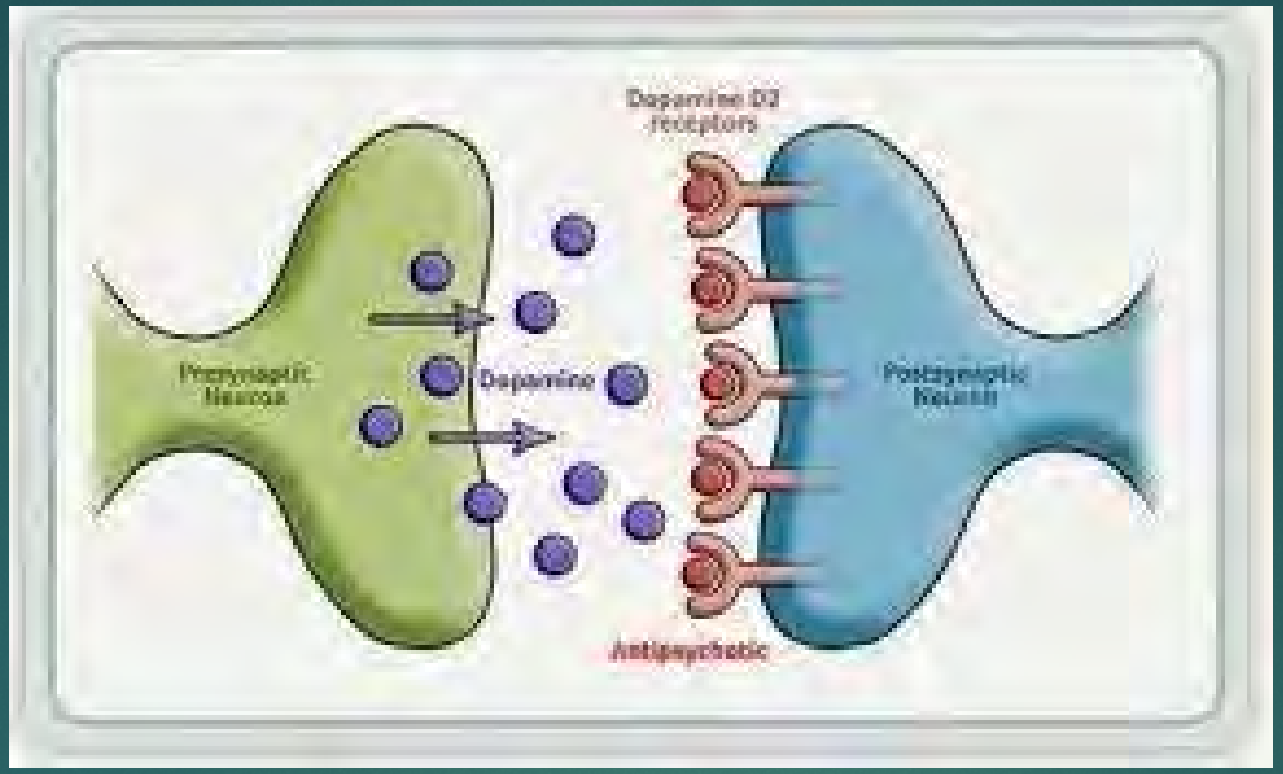
Sweating

Neuroleptic, a synonym of antipsychotic, refers to something that "grabs ahold of nerves". Idiopathic NMS (with no identifiable culprit drug) is called malignant catatonia.

Etiology of NMS

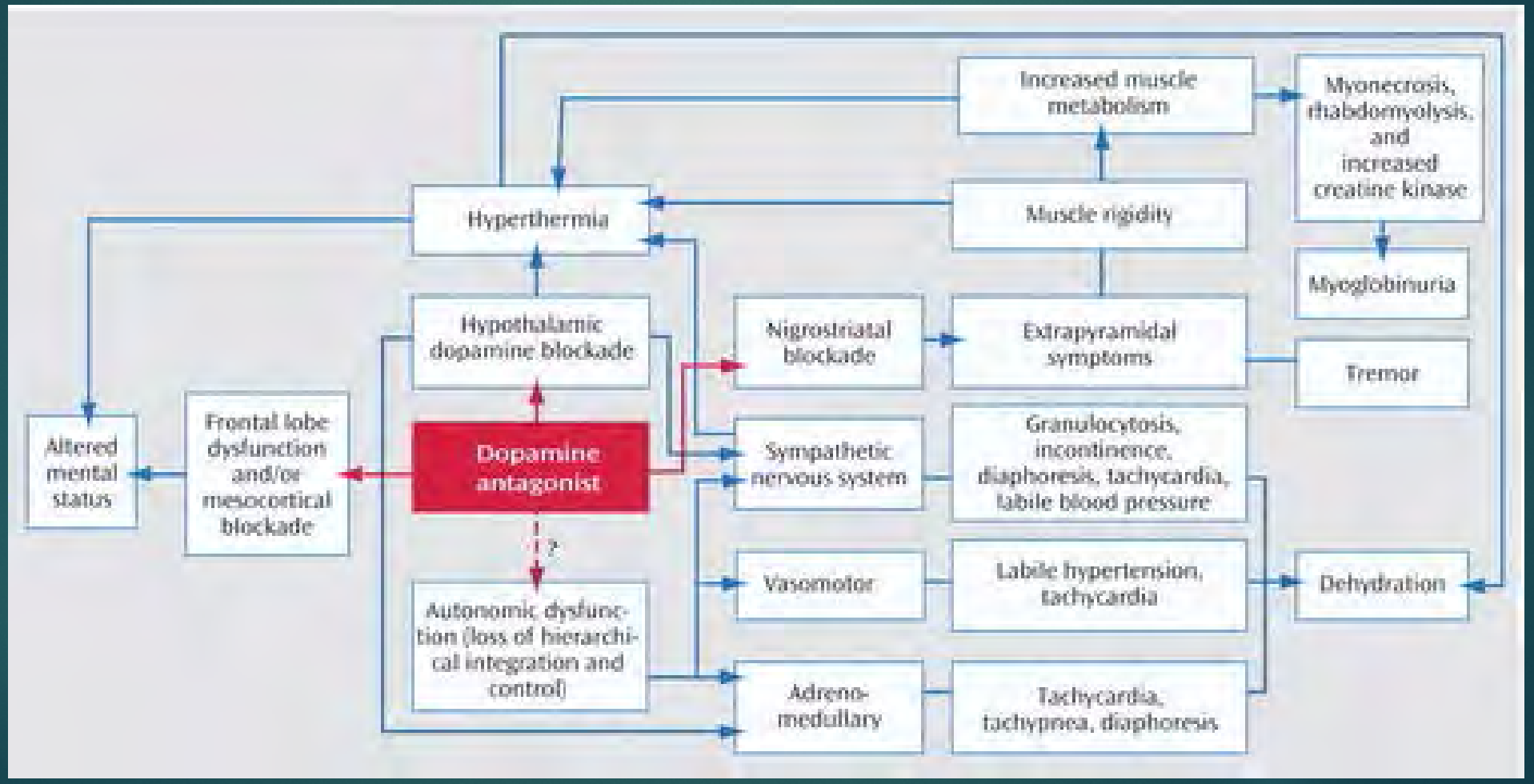
- **The main risk factor for developing NMS is the initiation or increase in the dosage of neuroleptic medication.** High-potency and long-aging neuromuscular depot forms carry the greatest risk but also may be caused by low-potency and atypical antipsychotic agents, antiemetics, tricyclic antidepressants, and lithium. The concurrent use of multiple neuroleptic agents or lithium also increases the risk. Abrupt withdrawal of dopaminergic agents is a less common but important cause of NMS. Rapid withdrawal of dopaminergic drugs, most often used to manage parkinsonian diseases, such as levodopa and amantadine, also may cause this syndrome. The rapid switching of one Parkinson medication to another also is associated with the development of NMS. [

Physiology



- The pathophysiology of NMS is complex and incompletely understood. **Most symptoms are attributed to the sudden reduction in central dopaminergic activity due to a D2 receptor blockade or abrupt withdrawal of D2 receptor stimulation.**

PathoPhys


Increased muscle metabolism
Myonecrosis, rhabdomyolysis, and increased creatine kinase
Hyperthermia
Muscle rigidity
Myoglobinuria
Hypothalamic dopamine blockade
Nigrostriatal blockade
Extrapyramidal symptoms
Tremor
Altered mental status
Frontal lobe dysfunction and/or mesocortical blockade
Dopamine antagonist
Sympathetic nervous system
Granulocytosis, incontinence, diaphoresis, tachycardia, labile blood pressure
?
Vasomotor
Labile hypertension, tachycardia
Dehydration
Autonomic dysfunction (loss of hierarchical integration and control)
Adrenomedullary
Tachycardia, tachypnea, diaphoresis

Epidemiology

- The incidence decreasing due to newer agents, which are less likely to cause NMS, and increased awareness of the condition.
- NMS range from 0.01 to 3.2 percent among patients taking antipsychotic agents.

- THIS IS RARE!!!!!!!!!

TABLE 1. Differential Diagnosis of Neuroleptic Malignant Syndrome

Infectious
Meningitis or encephalitis
Postinfectious encephalomyelitis syndrome
Brain abscess
Sepsis
Psychiatric or neurological
Idiopathic malignant catatonia
Agitated delirium
Benign extrapyramidal side effects
Nonconvulsive status epilepticus
Structural lesions, particularly involving the midbrain
Toxic or pharmacological
Anticholinergic delirium
Salicylate poisoning
Malignant hyperthermia (inhalational anesthetics, succinylcholine)
Serotonin syndrome (monoamine oxidase inhibitors, triptans, linezolid)
Substances of abuse (amphetamines, hallucinogens)
Withdrawal from dopamine agonists, baclofen, sedative-hypnotics, and alcohol
Endocrine
Thyrotoxicosis
Pheochromocytoma
Environmental
Heatstroke

DSM 5 Criteria for Diagnosis

- **Major Criteria (all required)**
- **Exposure to dopamine-blocking agent**
- **Severe muscle rigidity**
- **Fever**

- **Other Criteria (at least two required)**
- Diaphoresis
- Dysphagia
- Tremor
- Incontinence
- Altered level of consciousness
- Mutism
- Tachycardia
- Elevated or labile blood pressure
- Leukocytosis
- Elevated creatine phosphokinase

Classic Differentials: Serotonin Syndrome & Malignant Hyperthermia

- Serotonin syndrome has similar features to NMS and is most easily distinguished by the causative agent, most frequently the serotonin-specific reuptake inhibitors. Hyperthermia and muscle rigidity are usually less severe with serotonin syndrome than with NMS; additionally, **serotonin syndrome is more commonly associated with gastrointestinal symptoms, hyperreflexia, and myoclonus**.
- **Malignant hyperthermia is almost clinically indistinguishable from NMS, but the history of exposure to depolarizing muscle relaxants, most commonly succinylcholine, or inhaled anesthetic agents** make the distinction clear in most cases.

Medications Associated with Neuroleptic Malignant Syndrome

- **Typical Neuroleptics**
- Haloperidol
- Chlorpromazine
- Fluphenazine
- Thioridazine
- Trifluordazine
- Thiothixene
- Loxapine
- Bromperidol
- Promazine
- Clopenthixol

Atypical Neuroleptics

Olanzapine
Clozapine
Risperidone
Quetiapine
Ziprasidone
Aripiprazole
Zotepine
Amisulpride

Antiemetics

Droperidol
Domperidone
Metoclopramide
Promethazine
Prochlorperazine

Others

Tetrabenazine
Reserpine
Amoxapine
Diatrizoate
Lithium
Phenelzine
Dosulepin
Trimipramine
Desipramine

Second- versus first-generation antipsychotics

- NMS was originally described with first-generation ('conventional' or 'typical') antipsychotics. Although second-generation ('atypical') antipsychotics are overall less likely to induce severe hyperthermia or rigidity, NMS has been reported with virtually all SGAs

- Yet, apart from possibly blonanserin and perospirone, SGAs appear to be significantly less associated with NMS than haloperidol, with clozapine being possibly the safest in this regard, followed by quetiapine (Anzai Reference Anzai, Takahashi and Watanabe2019).

THE CASE

- 80 yo m w/ hx of disseminated cutaneous mycobacterium, a fib, HFmrEF w/ right side heart failure, ASD, SSS s/p pacer, RCC s/p nephrectomy, chronic skin wounds, admitted on for dyspnea, course complicated by transfer to ICU for management of undifferentiated shock, found to be in acute decompensated right heart failure w/ AKI, in light of extensive and progressing cardiac disease and other comorbidities patient elected to shift focus of care to comfort measures, transferred to palliative unit.

“Overnight pt noted to be restless and anxious”

- Initial Treatment Regimen
- Scheduled:
- > Olanzapine 5mg at night
- PRN > Haloperidol 1 mg IV q1h prn (initial therapy) > Haloperidol 2 mg IV q1h prn (refractory to initial) > Thorazine 25 mg IV q6h prn (2nd line, refractory to haldol)

Haldol Dose Equivalents?! Hui Knew?!

- **"Neuroleptic dose in the management of delirium in patients with advanced cancer**
- D Hui 2010

- **HEDD using concept of daily defined dose**
- **DDD for Haldol (oral/IV)-8mg**
- **Thorazine(IV) 100 mg**
- **Olanzapine (oral) 10 mg**

Back to our patient

- Overnight pt received PRNS as above for non-verbal pain assessment as well as agitation. Around 0400 pt was noted by nursing to have **myoclonic jerks concerning for possible seizure activity. As a result provider was notified and pt received IV ativan**. This AM pt was evaluated at bedside with wife present. Pt was noted to have slow resting tremor in the upper and lower extremities with belly breathing. During assessment pt had an episode of worsening similar to event overnight. Tremors in upper and lower extremities became more profound and pt began turning head towards the left. Given unclear etiology with possible seizure focal vs medication induced on ddx additional ativan was administered. During event pt was arousable but unable to follow commands. Pts wife reports that during episode earlier in the night she was able to interact with patient.

Timeline of symptoms and treatment

- Day Shift:
- Administered haldol IV haldol 2 mg x4 for restlessness, haldol 1mg IV x1 and agitation. Thorazine 25 mg given IV x2
- HEDD: 13
- Overnight:
- Administered IV haldol 2 mg x1, 25mg thorazine x1
- HEDD:? Total to date:17

Delirium Cont.

- Waxing and Waning:
- Suspect worsening due to receipt of ativan overnight for myoclonus as above.
- > **Hold olanzapine at night - PRN**
- > **Hold haldol and thorazine given concern for myoclonus > Begin Ativan 0.5mg IV q4h (1st line)**

- **Noted to have progression of symptoms with development of fever (102.7)**in the evening raising concern for possible neuroleptic malignant syndrome - pt treated with one dose of dantrolene and myoclous treated with Benzos
- - Discontinue haldol and thorazine
- **Begin dantrolene IV 1mg/kg q6h - Continue benzodiazepines as below - PRN > Midazolam 1mg IV q15 minutes (1st line) > Midazolam 2mg IV q1 hours (refractory to initial)**

Treatment for NMS

- 1)STOP Offending Agent
- 2) Supportive Therapy for complications(Fluids etc)
- 3) Pharmacotherapy

Box 4: Complications associated with NMS

- Rhabdomyolysis
- Acute renal failure
- Acute respiratory failure (pulmonary embolism, aspiration pneumonia)
- Seizures
- Brain damage
- Myocardial infarction
- Disseminated intravascular coagulation
- Hepatic failure
- *Escherichia coli* fasciitis
- Sepsis

Pharmacotherapy

- ●Lorazepam, a benzodiazepine, is used 1 to 2 mg IM or IV every four to six hours.Diazepam is dosed as 10 mg IV every eight hours.In addition to mitigating agitation, benzodiazepines, particularly diazepam, may alsohave a muscle relaxant effect [18,47,69].

- **●Dantrolene is a direct-acting skeletal muscle relaxant and is effective in treatingmalignant hyperthermia (MH). Doses of 1 to 2.5 mg/kg IV are typically used in adults and can be repeated to a maximum dose of 10 mg/kg/day** [70,71]. Efficacy includesreduction of heat production as well as rigidity, and effects are reported within minutesof administration. There is associated risk of hepatotoxicity, and dantrolene shouldprobably be avoided if liver function tests are very abnormal. While some recommenddiscontinuing it after a few days, others suggest continuing for 10 to 14 days followedby a slow taper to minimize risk of relapse [72].
- **●Bromocriptine**, a dopamine agonist, is prescribed to restore lost dopaminergic tone[68]. It is well tolerated in psychotic patients. **Doses of 2.5 mg (through nasogastrictube) every six to eight hours are titrated up to a maximum dose of 40 mg/day**. It issuggested that this be continued for 7 to 14 days after NMS is controlled and thentapered slowly.
- ●**Amantadine** has dopaminergic and anticholinergic effects and is used as analternative to bromocriptine [21,73-76]. **An initial dose is 100 mg orally or via gastrictube and is titrated upward as needed to a maximum dose of 200 mg every 12 hours**.●Other medications used with anecdotal success include levodopa (particularly inpatients with NMS related to antiparkinson medication withdrawal) [25,34,77-80],apomorphine [81], carbamazepine [82], bupropion [83], and dexmedetomidine [84-86].

Recurrence?!

- Recurrences of NMS do occur, especially when a patient is restarted on a neuroleptic with high potency or too quickly after their initial episode.[1] Most patients who require continued antipsychotic treatment, though, are able to have a neuroleptic safely reintroduced with proper precautions including very slow titration and careful monitoring after a waiting period of about 2 weeks for an oral neuroleptic and at least 6 weeks for a depot form.

Prognosis

- Early mortality reports were greater than 30% for NMS; however, increased awareness, earlier detection, and better supportive care have reduced mortality to less than 10%. With early recognition and aggressive treatment, most patients will fully recover in 2 to 14 days. Delayed treatment may result in significant morbidity such as residual catatonia, parkinsonism, renal, or cardiopulmonary complications. When fatal, deaths are usually due to cardiac arrhythmias, disseminated intravascular coagulation, respiratory failure, or renal failure.

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THANK YOU