Pharmacologic Induced Movement & Neurologic Disorders

Section I: EPS and NMS
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Section II: Serotonin Syndrome and Seizure Disorders
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Pharmacologic Induced Movement & Neurologic Disorders

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DISCLOSURE

No potential conflict of interest
Question

Which of the following dopamine pathways is involved in medication induced movement disorders?

A. Mesocortical pathway
B. Mesolimbic pathway
C. Tuberoinfundibular pathway
D. Nigrostriatal pathway
E. None of the above
Dopaminergic Pathways
Which of the following dopamine pathways is involved in medication induced movement disorders?

A. Mesocortical pathway
B. Mesolimbic pathway
C. Tuberoinfundibular pathway
D. **Nigrostriatal pathway**
E. None of the above
Dopaminergic Pathways

Nigrostriatal DA Pathway: This pathway projects from substantia nigra to the basal ganglia and modulates fluidity of movement. Blockade of D2 receptors in this area causes Extra pyramidal symptoms (EPS).
Case

20 y.o. African American male admitted to an inpatient psych unit for disorganized thinking, paranoid delusions and auditory hallucinations.

Medical hx, past psych hx, tox screen and drug use hx were negative. Patient is administered risperidone 2 mg po.
After 3 hours, nurse calls you and reports that the patient is very agitated, he punched a glass window in his room. He complains of neck pain and inability to freely move his neck. Doc, can I please have a prn order for Olanzapine for this patient.

What should you tell the nurse?
Extra-Pyramidal Symptoms

**Dystonia:**

It is a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures.
Extra-Pyramidal Symptoms

Akathisia:

It is a syndrome characterized by unpleasant sensations of inner restlessness that manifests itself with an inability to sit still or remain motionless.
Extra-Pyramidal Symptoms

**Consequences of Untreated Akathisia:**

- Aggression
- Suicidality
- Noncompliance with medications
- Apparent worsening of underlying illness
- Substance abuse
- Increased risk of Tardive Dyskinesia
Extra-Pyramidal Symptoms

**Parkinsonism:**

It is a neurological syndrome characterized by:

- Tremor
- Bradykinesia
- Rigidity
- Postural instability
Tardive Dyskinesia (TD):

TD is a disorder resulting in involuntary, repetitive body movements.

Risk factors:
AGE
Females >Males
Early-onset Extra-Pyramidal Symptoms
Length of neuroleptic exposure
# Extra-Pyramidal Symptoms

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Decrease dose or switch the medication</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Cogentin, Benadryl</td>
</tr>
<tr>
<td>Akathisia</td>
<td>Propranolol, Cogentin</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Cogentin, Amantadine, Bromocriptine</td>
</tr>
<tr>
<td>Tardive Dyskinesia</td>
<td>Limited help from amantadine, Vit E. Switching to Clozapine</td>
</tr>
</tbody>
</table>
21 year old Caucasian M with schizophrenia is started on Haldol 5 mg po bid and titrated up to 10 mg po tid over next 3 days. On the morning of 4th hospital day, patient appears confused with a fever of 38.4 °C (101.1 F) and pulse of 115. On Physical exam, patient shows psychomotor agitation and rigidity in all four extremities.
Which of the following is the next best step in management?

A. Increase the dose of Haldol
B. Switch to 2nd generation antipsychotic like Olanzapine
C. Transfer the patient to the ICU
D. Stop the offending agent
E. Both B and C
Neuroleptic Malignant Syndrome (NMS)

It is a life-threatening neurological disorder most often caused by an adverse reaction to antipsychotic drugs.
Epidemiology

Men > Women
Young > Elderly
Mortality rate is 10% - 20%
Incidence is 0.01% - 0.02%
Pathogenesis

Relative lack of dopamine (DA)
  DA receptor antagonism
  inadequate DA production

Supportive Evidence
  DA antagonism by antipsychotics can lead to NMS
  Abrupt withdrawal of DA agonists can cause NMS
  DA depleting agents can cause NMS
  DA agonists are beneficial in treatment
# Clinical features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthermia</td>
<td>&gt;37 C to &gt; 42 C</td>
</tr>
<tr>
<td>Muscle rigidity</td>
<td>Generalized or Localized</td>
</tr>
<tr>
<td>Mental Status Changes</td>
<td>Mild confusion to Coma</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>HTN, Orthostatic hypotension, Tachydardia, tachypnea, diaphoresis, urinary incontinence</td>
</tr>
</tbody>
</table>
Onset is related to treatment with a D2 blocker

Resolves in 1 to 2 weeks in 2/3 of patients after discontinuing antipsychotics

Prolonged course in patients on long-acting injectible antipsychotics
Laboratory Findings

Leukocytosis
Elevated CK and myoglobin - Rhabdomyolysis
Low serum iron
Metabolic acidosis
Levenson’s Diagnostic Criteria

Major Manifestations
- Rigidity
- Fever
- Elevated Creatinine Phosphokinase (CPK)

Minor Manifestations
- Tachycardia
- Abnormal blood pressure
- Tachypnia
- Altered consciousness
- Diaphoresis
- Leukocytosis

All 3 Major, or 2 Major and 4 Minor, manifestations indicates a high probability of NMS.
Risk factors

Dehydration and Agitation

Underlying brain damage and Catatonia

History of prior episodes of NMS

D2 Blockers (Antipsychotics, Metoclopramide, Prochlorperazine)

Especially when more potent D2 blocker is used at a higher dose with rapid dose escalation.
Complications

Renal failure

Respiratory failure

Pulmonary Embolus

Electrolyte disturbances

Coagulopathy
## Management

### General measures
Diagnose early, discontinue antipsychotic, provide supportive care – IV hydration, cooling blankets, ice packs, oxygenation, antipyretics

### Specific interventions

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Parenteral lorazepam, 1 to 2 mg or higher for agitation or catatonia; monitor respiratory status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine agonists</td>
<td>Bromocriptine, 2.5 mg every 8 hours or amantadine, 100 mg every 8 hours; monitor psychosis, blood pressure, nausea</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>1 mg/kg/day for 8 days then continue as PO for 7 days; avoid calcium channel blockers</td>
</tr>
<tr>
<td>ECT</td>
<td>In cases refractory to adequate trial of dopamine agonist/supportive care. Catatonia. Avoid succinylcholine in patients with rhabdo.</td>
</tr>
</tbody>
</table>
Rechallenge with Antipsychotics

- Should ideally occur in the hospital
- Reduce potential risk factors
- After 2 weeks of resolution of NMS
- Low potency or atypical antipsychotics
- Low starting doses
- Slow Titration
Which of the following is the next best step in management?

A. Increase the dose of Haldol
B. Switch to 2\textsuperscript{nd} generation antipsychotic like Olanzapine
C. Transfer the patient to the ICU
D. Stop the offending agent
E. Both B and C
REFERENCES

1. www.nmsis.org
Serotonin Syndrome
Seizure Disorders

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Ozark Center. Freeman Health System.
DISCLOSURE

No potential conflict of interest
Libby Zion

- She died in a New York Hospital in 1984.
- Home meds included Phenelzine.
- In the hospital she received Meperidine to control "strange jerky movements".
- She was seen by 2 residents.
- Based on this case, residents service hours are limited to 80 hours weekly.
Serotonin Syndrome

- Serotonin syndrome can be a serious complication of treatment or overdose with selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and other serotonergic medications or agents.

- Polypharmacy/polydrug syndrome.
Serotonin Syndrome

• History
  – First described in the 1950s, by Mitchel, in a patient after administration of iproniazid (anti-TB)(MAOI) and Meperidine.

• Epidemiology
  – Incidence is unknown. Difficult to diagnose. NMS?
  – 14% to 16% in SSRIs overdose.
  – No gender differences.
Serotonin Syndrome

• Pathophysiology
  – Hyperstimulation of the brain stem and spinal cord serotonin receptors leading to the neuromuscular and autonomic symptoms.
  – Receptors
    • Hyperstimulation of the 5-HT1A and/or 5-HT2A receptors
Clinical characteristics

1. Cognitive/behavioral alterations
   - Confusion → Delirium
   - Agitation
   - Lethargy → Coma

2. Autonomic instability
   - Hyperthermia
   - Tachycardia
   - Diaphoresis
   - Dilated pupils

3. Neuromuscular abnormalities
   - Myoclonus
   - Hyperreflexia
   - Rigidity
Clinical characteristics

– There are no specific tests available for the diagnosis of serotonin syndrome.
– Blood levels of serotonin do not correlate with clinical findings.
– Nonspecific laboratory findings may include…
  • Elevated total white blood cell count, CPK levels, and transaminases,
  • Decreased serum bicarbonate level
– Severe cases can include:
  • Disseminated intravascular coagulation, rhabdomyolysis, and metabolic acidosis
  • Seizures
  • Renal failure and myoglobinuria
  • Adult respiratory distress syndrome
Sternbach’s suggested diagnostic criteria for Serotonin syndrome

1) Recent addition or increase of pro-serotonergic medication

2) At least three of the following:
   - Agitation, Ataxia, Diaphoresis, Diarrhea
   - Hyperreflexia, Hyperthermia, Mental status changes
   - Myoclonus, Shivering or Tremor.

3) Neuroleptic agent not added or dose increased before the onset of symptoms.

4) Diagnosis of infections, withdrawal, and other poisoning or metabolic disruptions excluded.
The Hunter Serotonin Toxicity Criteria, in context of serotonergic medications.

1) If patient has spontaneous clonus, serotonin toxicity present
2) If no spontaneous clonus, one of the following needed for a diagnosis of serotonin toxicity:
   - Inducible clonus and agitation or diaphoresis
   - Ocular clonus and agitation or diaphoresis
   - Tremor and hyperreflexia
   - Temperature >38°C and ocular clonus or inducible clonus
Serootonin Syndrome

- Risk factors
  - Administration of 2 or more serotonergic medications
  - Rarely with monotherapy
- Prevention
  - Awareness of risk when prescribing medications that may lead to increased levels of serotonin in the CNS
    - Pharmacodynamic interactions
    - Pharmacokinetic interactions
  - Avoidance of these interactions whenever possible
Differential Diagnosis

- Neuroleptic malignant syndrome (NMS), substance abuse (e.g., cocaine, amphetamines), anticholinergic toxicity, thyroid storm, infection (e.g., meningitis, encephalitis), alcohol and opioid withdrawal.
- Carcinoid and small cell carcinoma.
Serotonin Syndrome

• Clinical course and outcome
  – Rapid onset
  – Serotonin syndrome is usually self-limited, with an uneventful resolution, once the offending agent has been discontinued.
Serotonin Syndrome

• Treatment
  • No standardized treatment of serotonin syndrome.
  • Management starts with early recognition of the syndrome, and supportive care.
  • The basic treatment of serotonin syndrome consists of
    – Discontinuation of the causative drugs
    – Supportive therapy
      » Hydration
      » Cooling
    – Medications
Treatment

• Pharmacologic Treatment
  – Several drugs have been used to treat serotonin syndrome.
    • Cyproheptadine
    • Propranolol
    • Chlorpromazine
Treatment

• Pharmacologic Treatment
  – Benzodiazepines
    • Control of agitation
    • May blunt the hyper adrenergic component of the syndrome
Pharmacologic Treatment

- **Cyproheptadine**
  - First-generation antihistamine
  - Shown in animal studies to prevent the onset of experimentally induced serotonin syndrome.
  - No randomized control trials have been conducted to evaluate fully the efficacy of cyproheptadine, its use in the treatment of serotonin syndrome has been documented.
- **Mechanism**
  - 5-HT1A and 5-HT2 receptor antagonists
- **Dose**
  - May consider an initial dose of 12mg followed by 2mg every 2 hours if symptoms continue. (up to 32 mg/day).
  - Maintenance dosage is 8mg every 6 hours
Treatment

– Atypical antipsychotic agents with serotonin antagonist properties (e.g., olanzapine 10 mg SL) have been tried with some success.
Treatment

- Patients who are severely hyperthermic with temperatures greater than 41° C (106° F) should be given IV sedation, paralyzed, and intubated. Cooling blankets can be used for patients with mild to moderate hyperthermia. There is no role for acetaminophen here.

- Intubation is recommended for patients unable to protect their airways as a result of mental status changes or seizures.
Question

• Which of the following can contribute to cause a Serotonin Syndrome?

A) Cocaine
B) Lithium
C) Linezolid
D) Dextromethorphan

• 1) None
• 2) A+B
• 3) C+D
• 4) All
Drugs that potentiate Serotonin

• Enhance Serotonin Synthesis:
  L-Triptophan

• Increase Serotonin Release:
  Cocaine, Amphetamine, Sibutramine, Dextromethorphan, Meperidine, Fentanyl, MDMA, Lithium.

• Stimulate Serotonin Receptor:
  Buspirone, Triptans, Ergot Alkaloids, Trazodone.
Drugs that potentiate Serotonin

• Inhibit Serotonin catabolism:
  MAOIS, Moclobemine, Selegine, Linezolid, Isoniazid, Procarbazine.

• Inhibit Serotonin reuptake:
  SSRIs, Mirtazapine, Trazodone, SNRIs, TCAs, Dextromethorphan, Meperidine, Tramadol.

• Opioids:
  Methadone, propoxyphene.
Case

- 34 yo female, with history of migraines, HTN, DM II, depression and back pain. Serotonergic medications included: Fluoxetine and Sumatriptan prn and Methadone.
- Patient recently got married and visited her psychiatrist c/o sexual side effects, her psychiatrist decided to stop fluoxetine and start Venlafaxine 1 week after stopping fluoxetine.
- 2 days after starting Venlafaxine pt is admitted to a hospital for serotonin syndrome.
- What happened?
Case

• A) Patient was having more frequent headaches, hence more *Sumatriptan* prn.
• B) She was abusing Methadone from the street.
• C) She forgot to stop taking Fluoxetine.
• D) Fluoxetine and its metabolite norfluoxetine, can have an elimination half-life of 4 to 16 days.
<table>
<thead>
<tr>
<th>Causative drugs</th>
<th>SSRIs, TCAs, MAOIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>5-HT receptor overstimulation</td>
</tr>
<tr>
<td>Onset of symptoms</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Autonomic, mental, neurological</td>
</tr>
<tr>
<td>Differentiating symptoms</td>
<td>Myoclonus, diarrhoea, nausea, shivering</td>
</tr>
<tr>
<td>Signs</td>
<td>Dilated pupils, myoclonus, hyperreflexia</td>
</tr>
<tr>
<td>Laboratory results</td>
<td>↑ WCC, ↑ CK</td>
</tr>
<tr>
<td>Disease severity</td>
<td>Wide spectrum mild to severe</td>
</tr>
<tr>
<td>Serious complications</td>
<td>DIC, leucopenia, thrombocytopenia, seizures, multi-organ failure, rhabdomyolysis</td>
</tr>
<tr>
<td>Main treatment</td>
<td>Discontinue causative drug(s); supportive</td>
</tr>
<tr>
<td>Specific treatments</td>
<td>Benzodiazepines, cyproheptadine, chlorpromazine</td>
</tr>
<tr>
<td>Recovery</td>
<td>70% within 24 hours</td>
</tr>
<tr>
<td>Mortality</td>
<td>Total of 23 deaths reported up to 1999</td>
</tr>
</tbody>
</table>
### Neuroleptic Malignant Syndrome vs. Serotonin Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Neuroleptic Malignant Syndrome</th>
<th>Serotonin Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Precipitated by</strong></td>
<td>Dopamine antagonists</td>
<td>Serotoninergic agents</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Variable (1-3 days)</td>
<td>Variable (&lt;1d)</td>
</tr>
<tr>
<td><strong>Vital Signs</strong></td>
<td>Hypertension, tachycardia, tachypnea</td>
<td>Hypertension, tachycardia, tachypnea</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>Hyperthermia</td>
<td>Hyperthermia</td>
</tr>
<tr>
<td><strong>Mucosa</strong></td>
<td>Sialorrhea</td>
<td>Sialorrhea</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Diaphoresis</td>
<td>Diaphoresis</td>
</tr>
<tr>
<td><strong>Mental Status</strong></td>
<td>Delirium</td>
<td>Delirium</td>
</tr>
<tr>
<td><strong>Muscles</strong></td>
<td>“Lead pipe” rigidity</td>
<td>Increased tone</td>
</tr>
<tr>
<td><strong>Reflexes</strong></td>
<td>Hyporeflexia</td>
<td>Hyperreflexia, clonus</td>
</tr>
<tr>
<td><strong>Pupils</strong></td>
<td>Normal</td>
<td>Dilated</td>
</tr>
</tbody>
</table>
SEIZURE DISORDERS
Case

• 45 yo male, with history of Schizophrenia, HTN, COPD (smoker) and DM II. He lives in a group home. Home psychotropic medications include: Xanax 0.25 mg HS, Clozaril 450 mg daily. Patient admitted to a Medical Floor for COPD exacerbation/Pneumonia. On day 4 of admission, he starts seizing.

• What happened?
Case

A) Withdrawal Seizure (Likely he was abusing Xanax at home).
B) CNS infection needs to be ruled out.
C) Due to an error in Med reconciliation, an AED was not re-started.
D) An interaction related to the P450 system
SEIZURE DISORDERS

• Lower seizure threshold
  - Non-steroidal anti-inflammatory drugs, tramadol, diamorphine, meperidine.
  - Penicillins, cephalosporins, quinolones
  - Clozapine, TCAs, and lithium
  - Bupropion, provokes seizures in 1 in 1000 patients.
SEIZURE DISORDERS

• Lower seizure threshold (continued)

-Antidepressants, anticholinergics, antiemetics, antihistamines, antimalarials, antipsychotics, antispasmodics, amphetamines, baclofen, bupropion, chemotherapy (vincristine), cholinesterase inhibitors, cyclosporine, isotretinoin, oral contraceptives, and theophyllines.
SEIZURE DISORDERS

• Withdrawal seizures:
  - barbiturates, benzodiazepines, baclofen

• Drug interactions:
  - AEDs are susceptible to drug interactions as many are both substrates and inhibitors of cytochrome P450 (CYP450) isoenzymes.
References

• Neuro Malignant Syndrome and Serotonin Syndrome. Thomas W. Heinrich, M.D. Academy of Psychosomatic Medicine-Educational Slides.

• Grosset KA, Grosset DG. Prescribed drugs and neurological Complications. J Neuro Neurosurg Psychiatry 2004, 75 (Suppl 3)

References

• Serotonin Syndrome and Opioids—What’s the Deal? Annals of Emergency Medicine. 2015
• Ferri's Clinical Advisor .2015.