Chapter 161 – Antipsychotics

Episode Overview

- Extrapyramidal syndromes are a common complication of antipsychotic medications. First line treatment is benztropine or diphenhydramine. Lorazepam is used in refractory cases.
- The most common finding in antipsychotic overdose is CNS depression. Treatment centers around supportive care, airway management, and cardiac monitoring.
- QT prolongation and Torsades de Pointes are potential complications of many antipsychotic medications in overdose. These arrhythmias can also occur with therapeutic doses.
- Clozapine is associated with potentially life-threatening agranulocytosis. Treatment includes stopping the drug, treating infections, and supportive care.
- Neuroleptic Malignant Syndrome (NMS) is characterized by altered mental status, hyperthermia, muscle rigidity, and autonomic instability. Supportive care includes airway management, benzodiazepines, treatment of muscular rigidity, and evaporative cooling.

Core Questions

1. List 8 adverse effects of antipsychotics
2. List 4 physiological effects of antipsychotics in acute overdose
3. Compare typical and atypical antipsychotic adverse effect profile
4. Describe 4 common extrapyramidal reactions associated with antipsychotic use other than NMS
5. Describe the management of acute extrapyramidal symptoms (EPS)
6. Describe the diagnostic criteria for NMS
    a. List 3 other most likely DDx
7. Describe the management of NMS

Rosen's In Perspective

A brief history of antipsychotics:

- In 1950, promethazine was synthesized. Soon after, chlorpromazine was synthesized.
    - ❏ These drugs brought about sedation and apathy in patients (i.e.neuroleptic effects)
    - ❏ The term neuroleptic has since been replaced with antipsychotic, because newer agents are less sedating
- In 1956, clozapine was synthesized
    - ❏ Significant extrapyramidal effects at therapeutic doses were found to be one of the most common adverse reactions
    - ❏ Agranulocytosis led to clozapine's withdrawal from the market in 1974

- Antipsychotic medications are used to treat schizophrenia, schizoaffective disorder, mania, anxiety disorders, and psychoses (including psychosis associated with substance use and withdrawal)
- All antipsychotics are dopamine receptor antagonists
- Divided into typical, or first-generation antipsychotics (FGAs), and atypical, or second-generation antipsychotics (SGAs).
    - ❏ SGAs exhibit less extrapyramidal symptoms, treat negative symptoms of thought disorders, and typically have 5-hydroxytryptamine-type 2A (5-HT2A) serotonin receptor antagonism in addition to dopamine receptor antagonism
        - ❏ Movement disorders also occur with SGAs but with lower frequency
    - ❏ FGAs are sometimes also classified as low-potency or high-potency on the basis of their affinity for the dopamine D2 receptor subtype
        - ❏ In general, low-potency FGAs are the most sedating. Movement disorders are one of the most prominent adverse side effects of FGAs.
- Although neuroleptic malignant syndrome (NMS) can occur with all antipsychotic agents, it occurs with much less frequency with SGAs.

[1] List 8 adverse effects of antipsychotics

ANSWER:

- Blockade of dopamine
- Dopamine-mediated meningeal artery vasodilation
- Weight gain
- Dyslipidemia
- Glucose intolerance
- New-onset diabetes
- Metabolic syndrome

NOTE:

Toxicity of antipsychotic drugs can be broadly divided into three categories:

- Exaggeration of pharmacologic effects (as occurs in acute overdose)
    - ❏ Undesired clinical effects occurring in therapeutic use such as extrapyramidal syndromes
    - ❏ Idiosyncratic effects such as NMS
- D2 receptor antagonism
    - ❏ Reducing positive symptoms of schizophrenia
    - ❏ EPS symptoms
    - ❏ NMS
- Common “off- target” effects include:

- ❑ Alpha-1 adrenergic receptor antagonism
  - ❑ Orthostatic hypotension
- ❑ Muscarinic acetylcholine receptor antagonism
  - ❑ Anticholinergic toxicity
- ❑ Histamine H1 receptor antagonism
  - ❑ Sedation
- ❑ Fast voltage-gated sodium channel blockade
  - ❑ Wide complex dysrhythmias
- ❑ Delayed potassium rectifier channel blockade
  - ❑ QT prolongation and, potentially, Torsade's de Pointes
- ❑ EPS: High potency (Haldol, Droperidol, Loxapine)
- ❑ NMS: High potency
- ❑ Seizures: Clozapine
- ❑ Long QTc: Phenothiazines (low potency)
- ❑ Agranulocytosis: Clozapine
- ❑ Metabolic syndrome: Atypicals

[2] List 4 physiological effects of antipsychotics in acute overdose

- CNS depression is common
  - ❑ Mild sedation to coma.
- Anticholinergic delirium and agitation
- Airway reflexes can be impaired and respiratory depression can occur after overdose.
- Pupils may be of variable size
  - ❑ Anticholinergic effects promote mydriasis, whereas miosis, resulting from alpha-antagonism, may mimic opioid toxicity.
- Mild orthostatic hypotension is also a common finding from alpha-adrenergic blockade
- Seizures
- EPS symptoms

[3] Compare typical and atypical antipsychotic adverse effect profile

Please refer to Box 155.1 in Rosen's 9th Edition for a comprehensive table outlining the various classifications of low/medium potency antipsychotics and atypical antipsychotics.

This is some spaced repetition from earlier segments.

Remember:

- Divided into typical, or first-generation antipsychotics (FGAs), and atypical, or second-generation antipsychotics (SGAs).
    - ❑ SGAs exhibit less extrapyramidal symptoms, treat negative symptoms of thought disorders, and typically have 5-hydroxytryptamine-type 2A (5-HT2A) serotonin receptor antagonism in addition to dopamine receptor antagonism.
        - ❑ Disorders of metabolism occur more with atypical antipsychotics:
            - ❑ Impaired glucose tolerance
            - ❑ Weight gain
            - ❑ Dyslipidemias
            - ❑ Metabolic syndrome
        - ❑ Movement disorders also occur with SGAs but with lower frequency
    - ❑ FGAs are sometimes also classified as low-potency or high-potency on the basis of their affinity for the dopamine D2 receptor subtype
        - ❑ In general, low-potency FGAs are the most sedating
        - ❑ First generation or typical antipsychotics typically produce more extrapyramidal symptoms (e.g., tardive dyskinesia, Parkinsonian syndrome, akathisia)

Low Potency (First Generation Antipsychotics)	Chlorpromazine, fluphenazine, perphenazine, promethazine, thiordazine
High Potency (First Generation Antipsychotics)	Droperidol, haloperidol, loxapine, pimozide, thiothixene, trifluoperazine
Atypical Antipsychotics (Second Generation Antipsychotics)	Aripiprazole, asenapine, clozapine, iloperidone, lutasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone

[4] Describe 4 common extrapyramidal reactions in antipsychotic use other than NMS

- Dystonic Reaction
    - ❑ Oculogyric crisis (eyes rolling back in head)
    - ❑ Opisthotonos (severe hyperextension spasm of head, neck, spine)
    - ❑ Torticollis
- Akathisias
    - ❑ Feeling of motor restlessness
- Parkinsonism Trap
    - ❑ Tremor
    - ❑ Rigidity

- ❏ Akinesia / bradykinesia
- ❏ Postural instability

- Tardive Dyskinesia
  - ❏ Choreiform movements
  - ❏ Lip smacking
  - ❏ Chronic/difficult to treat

NOTE:

Acute = Dystonic reactions / Akathisias / Parkinsonism Trap

Chronic = Tardive Dyskinesia

[5] Describe the management of acute EPS

Remember the 3 B's of acute EPS management:

- Benadryl 50mg PO/IV
- Benztropine 2mg PO/IV
- Benzodiazepines

[6] Describe the diagnostic criteria for NMS

Please refer to Table 155.1 in Rosen's 9th Edition for a comprehensive table outlining the diagnostic criteria for NMS

Criterion for Neuroleptic Malignant Syndrome
• Exposure to a dopamine antagonist or withdrawal of a dopamine agonist within 72 hours • Hyperthermia (>38 degrees Celsius) on at least two occasions, measured orally • Rigidity • Mental status alteration • Creatinine kinase elevation (at least four times the upper level of normal) • Sympathetic nervous system lability, defined as at least two of the following: 1. Blood pressure fluctuation (>/20% DBP change or >/25% SBP change in 24 hours) 2. Diaphoresis 3. Urinary incontinence 4. Hypermetabolic state (heart rate >/25% and respiratory rate >/50% above baseline) **5.** Negative evaluation for other toxic, metabolic, infectious, or neurologic causes

Please refer to Table 155.2 in Rosen's 9th Edition for a comprehensive table outlining the differential diagnosis for malignant hyperthermia

- List 3 other most likely DDx
    - ❏ Serotonin Syndrome
    - ❏ Malignant or Lethal Catatonia
    - ❏ Sympathomimetic Toxicity
    - ❏ Malignant hyperthermia
    - ❏ Heatstroke

[7] Describe the management of NMS

- Stop offending medication
- Hydration
- Active cooling
- IV benzodiazepines
- Non-depolarizing neuromuscular blockade
- Limited evidence: Dantrolene
- Dopamine agonists (e.g., bromocriptine)
- Consider ECT for refractory cases