ANTIPSYCHOTICS/NEUROLEPTICS

Pharmacological Interventions

• Antipsychotic medications
  • First Generation (Typicals)
    • Includes phenothiazines, thioxanthenes, butyrophenones
  • Second Generation (Atypicals)
  • Third Generation

Mechanism of Action

• First Generation (Typical) antipsychotics
  • Dopamine antatonist (D₂ receptor antagonists)
  • Block attachment of dopamine in several areas of the brain
  • Reduce dopaminergic transmission
• Second Generation (Atypical) Antipsychotics
  • Serotonin (5-HT₂) & Dopamine (D₂) receptor antagonists
  • Block D₂ preferentially in the limbic system over the nigrostriatal tract leading to the basal ganglia
  • Third Generation Antipsychotics
  • Dopamine system stabilizer

Dopaminergic Effects

• Dopamine tracts lead to different parts of the brain causing desired or adverse effects
  • DA tracts that lead to the basal ganglia (nigrostriatal tract) are responsible for movement disorders (the blockade of DA in this tract leads to an increase of ACh = EPS)
  • DA tracts that lead to the mesolimbic system (emotional brain) are responsible for the desired effect reduction of schizophrenic symptoms (positive/negative).
  • DA tracts that lead to the anterior pituitary cause increased prolactin levels (gynecomastia, galactorrhea)
  • DA tracts leading to the mesocortical area of the brain = further cognitive dysfunction

First Generation (Typical) Antipsychotic Drugs

• Target positive symptoms of schizophrenia (delusions/hallucinations)
• Advantage
  • Less expensive than atypical antipsychotics
• Disadvantages
  • Do not treat negative symptoms
  • Higher incidence of extrapyramidal side effects (EPS)
  • Tardive dyskinesia
  • Lower seizure threshold

Antipsychotic Medications: Traditional

• High potency = low sedation + low ACH + high EPSs
  • Haloperidol (Haldol)
  • Trifluoperazine (Stelazine)
  • Fluphenazine (Prolixin)
  • Thiothixene (Navane)
  • Pimozide (Orap)
• Medium potency
  • Loxapine (Loxitane)
  • Molindone (Moban)
  • Perphenazine (Trilafon)
Antipsychotic Medications: First Generation
Continued

- Low potency = high sedation + high ACH + low EPSs
  - Chlorpromazine (Thorazine)
  - Thioridazine (Mellaril)
  - Mesoridazine (Serentil)

Decanoate Preparations = Long acting

- Aripiprazole depot (Abilify Maintena)
- Haloperidol decanoate (Haldol decanoate)
- Fluphenazine decanoate (Prolixin decanoate)
- Olanzapine (Zyprexa Relprevv)
- Paliperidone (Invega Sustenna)
- Risperidone depot (Risperdal Consta)

Second Generation (Atypical) Antipsychotics
Serotonergic Effects (5HT₂a)

- Attaches to the presynaptic DA neuron and fine tunes the release of DA
- Can both increase and decrease release of DA depending on the area of the brain
  - Positive symptoms
  - Mesolimbic pathway – DA blockade predominates → therapeutic effect
  - Negative symptoms (mild improvement)
    - Frontal Cortex – 5HT₂a blockade predominates and releases DA “brake” → DA = improved cortical function (memory, problem-solving, etc.) and mood
- Extrapyramidal Side Effects
  - Nigrostriatal tract (basal ganglia) – 5HT₂a blockade predominates and releases DA “brake” → therefore less chance of EPS due to incomplete blockade of DA

Atypical Antipsychotics
Continued

- Advantages
  - Diminishes negative as well as positive symptoms of schizophrenia (avolition, anhedonia, affective blunting)
  - Less side effects encourages medication compliance
  - Improves symptoms of depression and anxiety
  - Decreases suicidal behavior
- Disadvantages
  - Weight gain
  - Metabolic abnormalities – Metabolic Syndrome

Second Generation (Atypical) Antipsychotics
Continued

- Paliperidone (Invega, Invega Sustenna)
- Risperidone (Risperdal, Risperdal Consta)
- Quetiapine (Seroquel)
- Olanzapine (Zyprexa, Zyprexa Relprevv)
- Iloperidone (Fanapt)
- Ziprasidone (Geodon)
- Lurasidone (Latuda)
- Asenapine (Saphris)
- Clozapine (Clozaril)

Third-Generation Antipsychotic

- Aripiprazole (Abilify, Abilify Maintena)
- Dopamine system stabilizer
- Improves positive and negative symptoms and cognitive function
- Low risk of EPS or tardive dyskinesia
Antipsychotic Side Effects

- Related to antagonist effects of these receptors:
  - Dopamine
  - Serotonin (atypicals)
  - Acetylcholine (muscarinic blockade)
  - Norepinephrine (adrenergic blockade)
  - Histamine
  - GABA

Side Effects: Antiandrenergic Effects (norepinephrine)

- α-1 blockade
  - Orthostatic hypotension
  - Dizziness
  - Tachycardia
  - Failure to ejaculate
  - Antipsychotic effect
- α-2 blockade
  - Sexual dysfunction
  - Priapism

Anticholinergic Symptoms (muscarinic blockade)

- Dry mouth
- Urinary retention and hesitancy
- Constipation
- Blurred vision
- Photosensitivity
- Dry eyes
  - Inhibition of ejaculation or impotence in men

Histaminic Blockade

- Sedation
- Substantial weight gain
- Orthostasis

GABA Blockade

- Lowers seizure threshold

Extrapyramidal Side Effects (imbalance of dopamine/acetylcholine)

- Acute dystonic reactions
- Pseudoparkinsonism
- Akathisia
- Tardive dyskinesia
  - Abnormal Involuntary Movement Scale (AIMS test)
EPS: Acute Dystonia
- Symptoms (1 – 5 days)
  - Torticollis
  - Opisthotonos
  - Oculogyric crisis
  - Laryngeal spasm
- Treatment
  - Responds readily to anticholinergics/antihistamines (Cogentin, Benadryl)
  - Notify MD/ hold neuroleptic

EPS: Akathisia
- Symptoms (2 hours – 60 days)
  - Motor restlessness, urge to pace, shift weight
  - Cannot sit or stand still
  - Always moving some body part
- Treatment
  - Disappears once agent is stopped
  - Change to another antipsychotic
  - May add antiparkinsonian agent

EPS: Pseudoparkinsonism
- Symptoms (5 hours -30 days) r/t dopamine blockade
  - Masklike facies (flat affect)
  - Tremor
  - General rigidity
  - Shuffling gait
- Treatment
  - Symmetrel, Cogentin, Artane, Benadryl
  - Notify MD

EPS: Tardive Dyskinesia
- Symptoms (months to years)
  - Involuntary movement of the face, jaw, tongue
  - Bizarre grimaces, lip smacking/pursing, tongue protrusion, excessive eye blinking
  - Rapid movements of the limbs, torso and fingers (“piano playing”)
  - Choreaform/Athetoid movements
  - Rapid hip jerks
- Treatment
  - Y-MAT-2: vesicular monoamine transporter-2
  - Packages NT into vesicles for release in synapse
  - 2008 – best treatment
    - tetrabenazine (Austedo)
  - New agent approved in 2017 for treatment
    - valbenazine (Ingrezza)

Rare and Toxic Side Effects
- Agranulocytosis
- Cholestatic jaundice
- Anticholinergic toxicity (next slide)
- Neuroleptic malignant syndrome (NMS) – see slide below

Anticholinergic Toxicity
Neuroleptic Malignant Syndrome (NMS)

- Due to dopamine blockade
- Usually occurs early in therapy but can occur months after start of antipsychotic
- Haldol and Prolixin are most likely to cause NMS
- Symptoms: extreme muscle rigidity, hyperpyrexia, altered consciousness, autonomic disturbance
- Considered a medical emergency (5-20% mortality rate)
- Needs immediate transfer (including 911) to emergency room
- Notify MD
- No specific treatment - supportive measures instituted

Smoking and Antipsychotics

- Smoking induces the metabolism some antipsychotics
  - olanzapine (Zypreza)
  - fluphenazine (Prolixin)
  - clozapine (Clozaril)
  - chlorpromazine (Thorazine)
  - haloperidol (Haldol)
  - perphenazine (Trilafon)
  - thioridazine (Mellaril)
- What happens when a patient who smokes 2 packs/day is admitted to the hospital with limited smoke breaks and is on one of these agents?
- What about upon discharge?
- Will inpatient nicotine replacement help?

Adjunct Treatments

- Antidepressants
- Mood stabilizers
- Benzodiazepines
- Electroconvulsive therapy (ECT)
  - Suicidal, violent, self-starvation, psychotic depression
  - Lifestyle changes when taking antipsychotics
    - Stop smoking
    - Avoid alcohol, street drugs, marijuana
    - Low calorie, high fiber diet
    - Increase fluids
    - Exercise
    - Avoid excess exposure to sunlight

Quick Question

EPS are the result of which one of the following?

- a. Too much serotonin
- b. Dopamine blocking
- c. Too little serotonin
- d. Genetic variations