**Pharmacologic Therapy**

**Antipsychotic Medications**
- Alleviate symptoms of schizophrenia but cannot cure underlying psychotic processes.
- Psychotic symptoms return with medication nonadherence.
- Antipsychotic drugs are effective in:
  - Acute exacerbations of schizophrenia
  - Preventing or mitigating a relapse

**Mechanism of Action**

**First Generation Antipsychotics (FGA)**
- Dopamine antagonist (Potent D<sub>2</sub> receptor antagonists)
- Block attachment of dopamine in several areas of the brain
  - Shotgun approach – increased side effects due to more areas of the brain affected by FGA
  - Reduce dopaminergic transmission

**Second Generation Antipsychotics (SGA)**
- Less affinity for D<sub>2</sub>; D<sub>3</sub> and D<sub>4</sub> antagonism
- Has a more targeted approach
  - D<sub>3</sub> and D<sub>4</sub> receptors are located in the limbic system and frontal lobe (thus affecting dopamine transmission in areas of the brain associated with the pathology of schizophrenia)
  - Serotonin 5-HT<sub>A</sub>, 5-HT<sub>C</sub> blockade which also inhibits the release of DA
  - Block D<sub>2</sub> preferentially in the limbic system over the nigrostriatal tract leading to the basal ganglia

**Third Generation Antipsychotics**
- Subset of second generation antipsychotics
- Dopamine system stabilizer (functional selectivity)
  - Partial D<sub>2</sub> agonist
  - 5HT<sub>2A</sub> antagonist
  - May improve positive, negative symptoms and cognitive function

**Dopaminergic Effects**

<table>
<thead>
<tr>
<th>Dopamine tracts lead to different parts of the brain causing desired or adverse effects</th>
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<tbody>
<tr>
<td><strong>Mesolimbic pathway</strong> (emotional brain)</td>
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<td><strong>Nigrostriatal tract</strong></td>
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<td><strong>Mesocortical tract</strong></td>
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<td><strong>Tuberoinfundibular tract</strong></td>
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</table>

Target of antipsychotics to reduce positive symptoms: effect of SGA/TGA on negative symptoms/cognitive symptoms.

Responsible for Extrapyramidal Symptoms.

Mediates cognitive function.

Hypothalamus to anterior pituitary.

Prolactin release.

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)

Antipsychotic Medications

**High Potency**
- Low sedation/low ACh/low EPS
  - fluphenazine (Prolixin)
  - haloperidol (Haldol)
  - pimozide (Orap)
  - thiothixene (Navane)
  - trifluoperazine (generic only)

**Low Potency**
- High sedation/High ACh/low EPS
  - chlorpromazine (Thorazine)
  - thioridazine (Mellaril)
  - Mesoridazine (Serentil)

**Medium Potency**
- Low sedation/High ACh/low EPS
  - loxetine (Loxitane)
  - molidone (Moban)
  - perphenazine (Trilafon)

Decanoate Preparations = Long acting
- Aripiprazole depot (Abilify Maintena)
- Aripiprazole lauroxil (Aristada)
- Haloperidol decanoate (Haldol decanoate)
- Fluphenazine decanoate (Prolixin decanoate)
- Olanzapine (Zyprexa Relprevv)
- Paliperidone (Invega Sustenna)
- Risperidone depot (Risperdal Consta)

Second Generation Antipsychotics (atypicals)

- 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 Antipsychotics (continued)
- Paliperidone (Invega, Invega Sustenna, Invega Trinza)
- Risperidone (Risperdal, Risperdal Consta)
- Quetiapine (Seroquel)
- Olanzapine (Zyprexa, Zyprexa Relprevv)
- Iloperidone (Fanapt)
- Ziprasidone (Geodon)
- Lurasidone (Latuda)
- Asenapine (Saphris)
- Brexpiprazole (Rexulti)
- Cariprazine (Vraylar)
- Clozapine (Clozaril)
**Third-Generation Antipsychotics**

- aripiprazole (Abilify, Abilify Maintena)
- brexpiprazole (Rexulti)
- cariprazine (Vraylar)
- Dopamine system stabilizer
- Improves positive and negative symptoms and cognitive function
  - Low risk of EPS or tardive dyskinesia

**Side Effects**

- Class side effects
  - Seizure
  - Impotence
  - Hyperprolactinemia
  - Hepatotoxicity
- Other side effects
  - Extrapyramidal Symptoms (EPS)
  - Sedation
  - Orthostatic hypotension
  - Weight gain
  - Metabolic syndrome/diabetes
  - Anticholinergic side effects

**Adverse effects of receptor blockage of antipsychotic agents**

- Antipsychotic effect
- EPS
- Increased appetite
- Dysphoria (mood)
- Sedation
- Orthostatic
- Sexual dysfunction

- Dry mouth
- Blurred vision
- Constipation
- Tachycardia
- Failure to ejaculate

- Orthostatic hypotension
- Dizziness
- Tachycardia
- Antipsychotic effect

- Antipsychotic effect
- Dry mouth
- Urinary retention

- Histaminic Blockade
  - Sedation
  - Substantial weight gain
  - Orthostasis

- Anticholinergic Symptoms
  - Dry mouth
  - Urinary retention and hesitancy
  - Constipation
  - Blurred vision
  - Photosensitivity
  - Dry eyes
  - Inhibition of ejaculation or impotence in men
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 (few hours – 5 days)
  ◦ Torticollis
  ◦ Opisthotonos
  ◦ Oculogyric crisis
  ◦ Laryngeal spasm
• Treatment
  ◦ Responds readily to anticholinergics/antihistamines (benztropine, diphenhydramine)
  ◦ Notify MD/hold neuroleptic
  ◦ Take to quiet area
  ◦ Stay with client until resolves
  ◦ Continue benztropine

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
  • Reduce dose
  • Change to another antipsychotic
  • Disappears once agent is stopped
  • Treat with antiparkinsonian, benzodiazepine of beta blocker

EPS: Pseudoparkinsonism

• Symptoms (5 hours - 30 days) r/t dopamine blockade
  • Masklike facies (flat affect)
  • Tremor
  • General rigidity
  • Shuffling gait
• Treatment
  • Anticholinergic: benztropine, trihexphenidyl
  • Dopamine agonist: amantadine
  • Notify HCP

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”)
  ◦ Choreiform/Athetoid movements
  ◦ Rapid hip jerks
• Treatment
  • V-MAT-2 - vesicular monoamine transporter-2 inhibitor
  • Inhibits the packaging of NT into vesicles for release in synapse
  • valbenazine (Ingrezza)
  • deutetrabenazine (Austedo)
Extrapyramidal Side Effect Summary

### Acute Dystonia
- Facial grimacing
- Involuntary upward eye movement
- Muscle spasm of the tongue, face, neck, and back
- Rapid jerky movements
- Latrogenic spasms

**Treatment Options**
- Anticholinergic (benztropine)
- Antihistamine (diphenhydramine)

### Parkinsonism
- Lower antipsychotic dosage
- Switch to another antipsychotic
- Anticholinergic medication
- Benztropine - Cogentin
- Trihexyphenidyl - Artane
- Dopamine agonist
  - Amaryllidine - Symmetrel

### Akathisia
- Lower antipsychotic dosage
- Switch to another antipsychotic
- Add benzodiazepine
- Add β-adrenergic blocker

### Tardive Dyskinesia
- Acute: treatment options may include:
  - Reversible inhibitor of vesicular monoamine transporter 2 (VMAT2)
- Moderate to Severe Tardive Dyskinesia
  - Considered a medical emergency (5-20% mortality rate)
  - Supportive measures instituted

Summary - EPS Symptom Treatment

<table>
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<th>Side effect</th>
<th>Treatment options</th>
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Rare and Toxic Side Effects

- Agranulocytosis
- Cholestatic jaundice
- Anticholinergic toxicity
- Neuroleptic malignant syndrome (NMS) – see slide below

Neuroleptic Malignant Syndrome (NMS)

- Due to dopamine blockade
- Usually occurs early in therapy but can occur months after start of antipsychotic
- Haloperidol and fluphenazine 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 of some antipsychotics:
  - olanzapine (Zyprexa)
  - 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 nicotine replacement?
- What about upon discharge?

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. Glutamate activation