Schizophrenia: Pharmacology

UNIVERSITY OF HAWAI‘I HILO PRE-NURSING PROGRAM
NURS 203 – GENERAL PHARMACOLOGY
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Learning Objectives

- Understand the result of dopamine binding to D2 receptors in the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways of the brain under normal circumstances.

- Understand how the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways are affected in schizophrenia.

- Know the pathophysiologic result of treating schizophrenia and the adverse effects associated with the various treatments.

- Know the difference between 1st generation (typical) and 2nd generation (atypical) antipsychotics.

- Know the characteristics of individual drugs in each class that create a niche in therapy for that medication.

- Know the general pharmacology of each class of medication.
Overview

- Brain areas involved in schizophrenia and their functions
- How we treat and the adverse effects of treating schizophrenia
- 1st generation medications
- 2nd generation medications
Under Normal Circumstances
Effects of Dopamine on D2 Receptors

**Nigrostriatal**
- **Stimulates** initiation & coordination of movement

1. Akinesia
2. Bradykinesia
3. Tremor

1. Hyperactivity
2. Hyperkinesia
3. Tardive dyskinesia

**Tuberoinfundibular**
- **Inhibits** prolactin secretion in anterior pituitary

1. Increase milk production
2. Sexual dysfunction

1. Decrease milk production
2. Sexual dysfunction
Effects of Dopamine on D2 Receptors

- **Mesolimbic Pathway**
  - **Striatum**
    - Reward
    - Anticipation
    - Affect
    - Fear
  - **1. Increased desire and motivation**
  - **2. Addiction**
  - **3. Schizophrenia**

- **Ventral Tegmental Area (VTA)**
  - **1. Increased desire and motivation**
  - **2. Addiction**
  - **3. Schizophrenia**

- **Mesocortical Pathway**
  - **Cerebral Cortex**
    - Cognition
    - Affect
  - **1. Decreased desire and motivation**
Schizophrenia - A condition of too much dopamine expression in the brain leading to:

Positive Symptoms
- Hallucinations
- Delusions
- Paranoia
- Disorganized thoughts

Negative Symptoms
- Flat affect
- Cognitive deficits

Mesolimbic Pathway
- Reward
- Anticipation
- Affect
- Fear

Mesocortical Pathway
- Cognition
- Affect
How do we treat schizophrenia?

Block (antagonize) dopamine receptors

How does this effect the mesolimbic and mesocortical pathways in the brain?
Effects of Dopamine on D2 Receptors

**Mesolimbic**
- Reward
- Anticipation
- Affect
- Fear

**Mesocortical**
- Affect
- Cognition

**Decrease**
- Hallucinations
- Paranoia
- Delusions
- Disorganized thoughts

**No change or worse**
1. Flattened affect
2. Cognitive deficits
How does this effect other dopamine pathways in the brain?

| Nigrostriatal | Tubero-infundibular |
Effects of Dopamine on D2 Receptors

**Nigrostriatal**
- **Stimulates** initiation & coordination of movement
  1. Akinesia
  2. Bradykinesia
  3. Tremor

**Tuberoinfundibular**
- **Inhibits** prolactin secretion in anterior pituitary
  1. Increase milk production
  2. Sexual dysfunction
1st Generation Antipsychotics (Typicals)

- Prochlorperazine
- Perphenazine
- Tirfluoperazine
- Fluphenazine
- Thioridazine
- Haloperidol
- Chlorpromazine
How 1st Generation Antipsychotics Work

MOA

- Antagonize the D2 receptors in the mesolimbic pathways of the brain
  - Reduction in positive symptoms
- Antagonize the D2 receptor in the mesocortical pathways of the brain
  - Increase in or no change in negative symptoms

Other receptors potentially bound (adverse effects)

- H1 (sedation)
- M1 (anticholinergic)
- Alpha1 (orthostatic hypotension)
Characteristics of 1st Generation Antipsychotics

**ADRs**
- Extrapyramidal symptoms (EPS)
  - Tremor (at rest)
  - Rigidity
  - Akathisia (restlessness)
  - Dystonia (twisting & writhing)
- Increase in prolactin
  - Milk production
  - Infertility & decreased libido
  - Weight gain
- Reward circuit stimulation
  - Increase in cravings
    - Weight gain
    - Addiction

**ADRs cont.**
- Tardive dyskinesia
  - Grimacing
  - Tongue protrusion
  - Lip smacking
  - Blinking
  - All body involvement (severe)
- Neuroleptic malignant syndrome (NMS)
  - Severe muscular rigidity
  - Fever
  - Autonomic instability
  - Changes in the level of consciousness
Haloperidol (Haldol)

- **MOA** – Non-selective blockade of the D2 receptor
- **Dosage forms**
  - Oral concentrate
  - Tablet
  - IM
  - Decanoate
  - Lactate
- **Kinetics**
  - Protein binding - ~88-92%
  - Half life
    - Decanoate - 21 days
    - IM - 20 hours
    - IV - 14-26 hours
    - Oral 14-37 hours
- **Kinetics Cont.**
  - Metabolism – Hepatic
    - 50-60% glucuronidation (inactive)
    - CYP3A4 – inactive metabolites, haloperidol, toxic metabolites/CYP2D6
  - Time to peak
    - Decanoate – 6 days
    - Oral – 2-6 hours
    - IM – 20 minutes
  - Excretion
    - Urine 30% (1% - unchanged drug)
- **Very high potency**
  - High incidence of EPS
  - Low incidence of others
- **Interactions**
  - CYP3A4 & 2D6 substrates & inhibitors
  - Pregnancy category C
    - Crosses placenta but benefit outweighs risk
Chlorpromazine (Thorazine)

MOA – Antagonist of mesolimbic D2 receptors and alpha receptors (vasculature & release of anterior pituitary hormones)

Dosage forms
- IM
- Oral

Kinetics
- Onset – 15 minutes (IM) / 30-60 minutes (Oral)
- Protein bound – 92-97%
- Metabolism – Liver, active & inactive metabolites
- Bioavailability – 20%
- Half life – Initial 2 hours, terminal 30 hours
- Excretion - Urine

Low potency
- Low EPS
- High incidence of
  - Breast milk production (D2 – endocrine)
  - Weight gain (Reward circuit)
  - Sedation (H1)
  - Orthostatic hypotension (alpha 1)
  - Anticholinergic (M1)

ADRs
- Hypotension, tachycardia, sexual dysfunction, constipation, dry mouth

Interactions
- CYP2D6 substrates/inhibitors
- Many
- Pregnancy category (not listed), detected in breast milk
2\textsuperscript{nd} Generation Antipsychotics (Atypical)

- Clozapine
- Risperidone
- Aripiprazole
- Quetiapine
- Olanzapine
- Ziprasidone
- Iloperidone
- Paliperidone
How 2\textsuperscript{nd} Generation Antipsychotics Work

Serotonin involvement in schizophrenia
- More serotonin receptors in the brain of schizophrenic patients
- Serotonin agonists can cause hallucinations/worsen schizophrenia
- Some antipsychotic medications are serotonin antagonists (atypicals)

MOA – Partial agonist at D2 receptor & antagonism of the 5HT-2A receptor

2\textsuperscript{nd} generation medications bind to D2 receptors with less affinity than 1\textsuperscript{st} generation medications

2\textsuperscript{nd} generation medications are displaced from the D2 receptor more readily than 1\textsuperscript{st} generation medications
How 2\textsuperscript{nd} Generation Antipsychotics Work

2\textsuperscript{nd} generation medications bind to D2 receptors with less affinity than 1\textsuperscript{st} generation medications.

2\textsuperscript{nd} generation medications are displaced from the D2 receptor more readily than 1\textsuperscript{st} generation medications.

Other receptors potentially bound (adverse effects):
- H1 (sedation)
- M1 (anticholinergic)
- Alpha1 (orthostatic hypotension)
Characteristics of 2nd Generation Antipsychotics

Kinetics
- Vary depending on the agent

How to choose
- Atypical
- Non-adherent – long-acting injection
- Contraindications & BBW
- ADRs

ADRs
- Increased appetite, weight gain, dyslipidemia, insulin resistance, beta cell dysfunction, cardiovascular dysfunction, movement disorders, flat affect, cognition deficits, endocrine effects

Monitor
- Lipids
- Fasting glucose
- Weight
Clozapine (Clozaril)

MOA – Antagonist at the D2, 5HT-2A, H1, alpha adrenergic, & cholinergic receptors

ADRs
- Tachycardia, drowsiness, dizziness, insomnia, drooling, weight gain, constipation, nausea/vomiting, abdominal pain/heartburn

Black Boxed Warning (BBW)
- Orthostatic hypotension, bradycardia, syncope, & cardiac arrest
- Fatality due to myocarditis & cardiomyopathy
- Severe neutropenia (ANC < 500 mcL) agranulocytosis
- Seizures
- Dementia

Interactions
- CYP1A2 (major) others (minor), dopamine agonists, medication that prolong QT interval, anticholinergic, metoclopramide, mifepristone, potassium chloride, St. John’s Wort, other antipsychotic medications
- Pregnancy category B (can affect the fetus)

REMS program medication – Program to help protect patients against serious adverse effects

Used for refractory schizophrenia
Onlanzapine (Zyprexa)

Receptor binding similar to clozapine – Binds to:
- D1-4
- 5HT2A, 2C, & 3
- H1
- M1-5
- Weak
  - GABA A, BZD, beta adrenergic

Dosage forms
- Oral, IM, & ODT

ADRs – Similar to clozapine (no agranulocytosis)
- Causes the most weight gain

Interactions
- Similar to clozapine
- CYP1A2

BBW
- Sedation
- Dementia

Pregnancy category C
- Excreted in breast milk
Quetiapine (Seroquel)

Receptor binding
- D2 & D1
- 5HT-2, 1A
- H1
- Alpha 1 & 2
- BDZ
- Muscarinic

Dosage form
- Tablet

Half life
- Short, 6 hours

ADRs
- Similar to clozapine
- **Higher incidence of drowsiness**

Interactions
- Similar to clozapine
- CYP3A4

BBW
- Increase suicide risk w/MDD
- Dementia

**Not indicated for use in children less than 10 years of age**

Pregnancy category C
- Excreted in breast milk
Risperidone (Risperdal)

Receptor binding (highest to lowest affinity)
- 5HT2
- H1 & alpha 1&2
- D2
- Others

Dosage forms
- Oral, IM, ODT

ADRs – Similar to other atypicals
- Less hypotension & tachycardia, weight gain, & sedation
- More endocrine (galactorrhea & sexual dysfunction)

Interactions – Similar to other atypicals
- CYP2D6 substrates/inhibitors

BBW
- Dementia

Pregnancy category C
- Excreted in breast milk
Aripiprazole (Abilify)

Receptor binding (highest to lowest affinity)
- D2 & 3, 5HT-1A (partial agonist) / 5HT-2A (antagonist)
- NO affinity for M

Dosage forms
- IM, oral, ODT

Uses
- BP1
- Autistic irritability
- MDD
- Schizophrenia
- Tourette's
- Agitation - IM

Half life
- Very long, 75 hours

ADRs – Similar to other atypicals
- Moderate effects on weight gain

Interactions – Similar to other atypicals
- CYP2D6

BBW
- Increased risk suicide in children
- Dementia

Pregnancy category C
- Excreted in breast milk
Long-acting Injectables

Fluphenazine
Haldol
Risperdal
Olanzapine
Paliperidone
Haldol Decanoate

Must overlap therapy with oral medications
  • 2 weeks

Z-track administration

Dosed every 4 weeks
Fluphenazine Decanoate

Must overlap therapy with oral medications
  ◦ 1 week

Z-track administration

Dosed every 3-4 weeks
Risperdal Consta

Must overlap therapy with oral medications
  ◦ 4-6 weeks

Reconstitute and inject immediately

NO Z-track administration

Dosed every 2 weeks
Invega Sustenna

No overlap with oral therapy
No Z-track administration
Dosed every 4 weeks
Complicated dosing schedule
Zypadhera (Olanzapine)

Specific dosing conversion from PO to injection

No overlap with oral medications

REMS program
- Certification (renewed every 3 years)
  - Prescriber
  - Dispenser
  - Facility where given

Pre administration
- Patient must have transportation

Post administration
- Patient must wait in office for 3 hours
- Must be alert and oriented with no signs of symptoms
Treating adverse effects

Movement disorders
- Anticholinergics
- Antihistamines
- Dopaminergic

Restlessness
- Beta blockers
- Benzodiazepines
Questions