PARKINSON’S DISEASE
PHARMACOLOGY

University of Hawai‘i Hilo Pre-Nursing Program
NURS 203 – General Pharmacology
Danita Narciso Pharm D
LEARNING OBJECTIVES

- Understand how movement is initiated and attenuated under normal circumstances and what happens in Parkinson’s Disease
- Know which drugs belong to which class in the treatment of Parkinson’s Disease
- Understand the pharmacologic properties that give each medication used to treat Parkinson’s disease its niche in therapy
- Know the general pharmacologic characteristics of each class of medications to treat Parkinson’s and the individual characteristics of each drug that make it unique from others in the same class
OVERVIEW

- What happens with movement under normal circumstances
- What is Parkinson’s Disease
- What causes movement disorders like PD (Parkinson’s Disease)
- Drugs used to treat PD
UNDER NORMAL CIRCUMSTANCES

Dopamine
- Stimulates the initiation of movement

Acetylcholine
- Modulates the initiation of movement
A disease that is characterized by tremor due to a loss of dopaminergic neurons in the central nervous system.

WHAT IS PARKINSON’S DISEASE
WHAT THESE MOVEMENT DISORDERS LOOK LIKE

Movement disorder – Too much Da
- [https://www.youtube.com/watch?v=QORlwMeWOeU](https://www.youtube.com/watch?v=QORlwMeWOeU)
- Too much movement initiation

Movement disorder – Too little Da
- [https://www.youtube.com/watch?v=7SyTpEdhBLw](https://www.youtube.com/watch?v=7SyTpEdhBLw)
- Difficulty initiating movement
HOW DO WE TREAT PARKINSON’S DISEASE?

1. Increase dopamine

2. Decrease acetylcholine
1. Replace dopamine levels
2. Inhibit the breakdown of dopamine
3. Stimulate dopamine receptors
DRUG THERAPY OPTIONS

- Dopamine replacement
- Dopamine sensitizer
- COMT inhibitors
- MAO – B inhibitors
- Dopamine agonists
- Anticholinergics
DOPAMINE REPLACEMENT – LEVODOPA/CARBIDOPA MOA

- Levodopa
  - Precursor of dopamine (L-Dopa) that is able to cross the blood brain barrier

- Carbidopa
  - Inhibits the peripheral breakdown of levodopa
L-Dopa (alone)
- Is quickly metabolized in the periphery (before it can cross the BBB) by DOPA decarboxylase

Only 1-3% makes it to CNS 😞

Carbidopa + L-Dopa
- Carbidopa acts only in the periphery (is a hydrophilic drug) does not cross the BBB
- Is a DOPA decarboxylase inhibitor

Now 10% makes it to the CNS, but you can use a much lower dose 😊
Dosage forms
- Oral – suspension & tablet (ER, IR, & ODT)

Kinetics
- Absorption – affected by high fat/calorie/protein meal
- Distribution – Levodopa (with carbidopa) increased passage through BBB, carbidopa does not cross BBB
- Metabolism – 2 major & 2 minor pathways, carbidopa decreases the decarboxylation (major) of L-Dopa
- Bioavailability – Levodopa > carbidopa
- Half-life – 1.5 hours (increased with ER formulas)
- Time to peak – 0.5 hours (IR), 2 hours (ER/CR)
- Excretion - urine

ADRs
- Hypotension, edema, hypertension, dizziness, headache, depression, insomnia, anxiety, confusion, nausea, constipation, dyskinesia

Interactions
- Amisulpride, antipsychotics (1st & 2nd generation)
- CI – MAOI (non-selective) & narrow angled glaucoma
- High protein diets
- Pregnancy category – C
- Breast milk - excreted
DOPAMINE SENSITIZER - AMANTADINE

- MOA – DA & NE agonist, acetylcholine & glutamate (NMDA receptor) antagonist
  - Nigrostriatal pathway – increase DA synthesis, release, & receptor expression & decrease DA re-uptake

- Dosage forms
  - Oral – capsule, tablet, syrup

- Kinetics
  - Onset – can be slow (within 48 hours)
  - Absorption – well absorbed
  - Metabolism – minor
  - Half-life – dependent of renal function
    - Normal (9-31 hours)
    - Males > 60 years (20-41 hours)
    - ESRD (8 days)
  - Time to peak – 2-4 hours
  - Excretion – urine (unchanged drug)

- ADRs
  - Livedo reticularis, agitation, anxiety, insomnia, headache, confusion, hallucination, constipation, nausea, dry mouth

- Interactions
  - Antipsychotics (1st & 2nd generation), drugs that prolong QTc, mifepristone, separate from flu vaccine (48 hours before – 2 weeks after)
• L-Dopa is broken down in the periphery by COMT
• The product is 3-OMD
• 3-OMD competed for the sites where L-Dopa crossed the BBB

COMT INHIBITORS – **ENTACAPONE**, **TOLCAPONE**
Inhibiting the COMT enzyme will decrease the amounts of COMT.

Increase the concentrations of L-Dopa crossing the BBB.

COMT INHIBITORS – **ENTACAPONE**, TOLCAPONE
- MOA – Reversible & selective inhibitor of catechol-O-methyltransferase, increases the concentration of levodopa available for transfer through the BBB by inhibiting the conversion of L-Dopa to 3-OMD

- Dosage forms
  - Oral – tablet
    - Combination - Entacapone+L-Dopa+Carbidopa (Stalevo)

- Kinetics
  - Onset – rapid
  - Absorption – rapid
  - Protein bound – 98% albumin
  - Metabolism – liver, not CYP
  - Half-life – phases
  - Time to peak – 1 hour
  - Excretion – mostly feces

- ADRs
  - Nausea, dizziness, dyskinesia, diarrhea, abdominal pain, urine discoloration (orange brown), hyper & hypokinesia

- Interactions
  - CNS depressants, zolpidem, hydrocodone, bupenorphine, MAOI
  - Pregnancy category – C
  - Breast milk – not known
Most MAO-B is in the CNS

A

EPI
NE
DA
Tyramine

B

DA only

Non selective MAOI

Selective MAO-B inhibitor

May alter PK’s disease progression

- It has been shown that the breakdown of DA by MAOB leads to a reactive oxygen species
- Reactive oxygen species can cause the death of dopaminergic neurons
- MAO-B inhibitors decrease this process

MAO – B INHIBITOR – SELEGILINE, RASAGILINE
- MOA – stimulates dopamine activity by binding to dopamine receptors
- Dosage forms
  - Oral – tablet (IR/ER)
- Kinetics
  - Absorption – rapid
  - Distribution – well, Vd 500L
  - Metabolism – less than 10%
  - Half-life – 8.5 hours, 12 hours (elderly)
  - Time to peak – 2 hours/6 hours
  - Excretion – urine, mostly unchanged drug

- ADRs
  - Hypotension (orthostatic), drowsiness, EPS, dizziness, hallucinations, nausea, constipation, dyskinesia, weakness

- Interactions
  - Antipsychotic (1\textsuperscript{st} & 2\textsuperscript{nd} generation)
  - Pregnancy category – C
  - Breast milk – not known

**DOPAMINE AGONISTS - PRAMIPEXOLE**
- MOA – Agonist at the post synaptic D2 receptor in the brain
- Dosage forms
  - Oral – tablet (IR/ER)
- Kinetics
  - Absorption – rapid
  - Metabolism – high first pass effect, CYP1A2, inactive metabolites
  - Half-life – 6 hours
  - Time to peak – 1-2 hours (IR), 6-10 hours (ER), Tmax extended by ~3 hours when taken with a high fat meal
  - Excretion – urine, mostly metabolites
- ADRs
  - Orthostatic hypotension, dizziness, drowsiness, fatigue, nausea, vomiting, viral infection, edema, pain, confusion
- Interactions
  - Antipsychotic agents (1\textsuperscript{st} & 2\textsuperscript{nd} generation), inducers/inhibitors of CYP1A2
  - Pregnancy category – C
  - Breast milk – not known

DOPAMINE AGONISTS - ROPINIROLE
ANTICHOLINERGICS
MOA – Anticholinergic & antihistaminic

Dosage forms
- Oral
- Injection

Kinetics
- Onset – IV & IM, within minutes
- Metabolism – hepatic
- Time to peak – 7 hours

ADRs
- Tachycardia, confusion, depression, rash, constipation, nausea, urinary retention, blurry vision

Interactions
- Other agents with anticholinergic actions, tiotropium
- Pregnancy category – Not conducted
- Breast milk – not known
- MOA – inhibition of the PNS
- Dosage forms
  - Oral
- Kinetics
  - Metabolism – hydroxylation (liver)
  - Half-life - 33 hours
  - Time to peak – 1.3 hours
  - Excretion – urine & bile
- ADRs
  - Tachycardia, confusion, depression, rash, constipation, nausea, urinary retention, blurry vision
QUESTIONS