Drugs used in parkinsonism

- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

- Recognize the symptoms and pathophysiology of parkinsonism
- Understand the pharmacology of drugs used for treatment of parkinsonism.
- Define pharmacokinetics, pharmacodynamics and side effects of different drugs used for the treatment of parkinsonism.

Dr.Foda

Osmosis

Parkinson's Disease

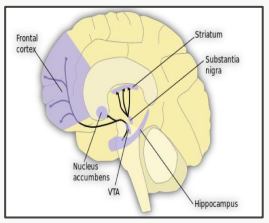
Definition

- A **Progressive neurodegenerative** brain disorder that was first described by Dr. James Parkinson in 1817.
- PD is a common disease that affects movement and muscle control. It occurs mainly in the elderly (> 65) and can lead to disability unless effective treatment is provided.

There is no cure, Drugs are given only to improve the patient's lifestyle

Pathophysiology

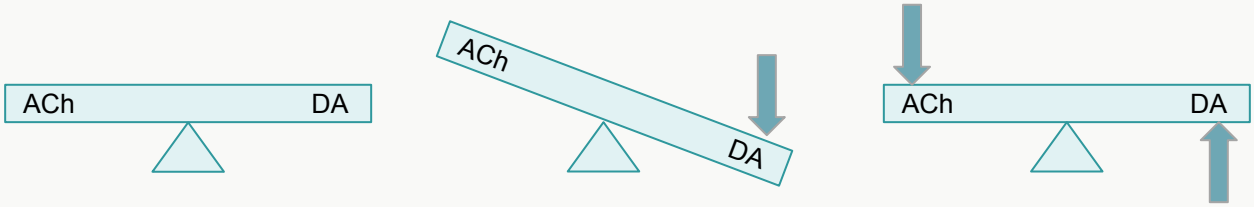
- This movement disorder occurs mainly due to **dopamine/acetylcholine imbalance** in basal ganglia (caudate nucleus, substantia nigra & corpus striatum) that is involved in motor control.
- PD affects the **extrapyramidal system at the level of the corpus striatum & substantia nigra** (parts of the brain "basal ganglia").



Dopamine Pathways

Motor Pathway:
Cell bodies in the **substantia nigra** that manufacture and release dopamine into the striatum.

Reward Pathway:
Dopamine is manufactured in nerve cell bodies located within the **ventral tegmental area** (VTA) and is released in the nucleus accumbens and the prefrontal cortex.



Normal

Parkinson's
Deficiency of dopamine
Predominance of ACh

Treatment

ACh: Acetylcholine / DA: Dopamine

Causes and Characters of the Disease

Causes

It is an **idiopathic** disease but some causes may be:

- Genetic.
- Toxins (MPTP= methyl phenyl tetrahydropyridine) An agent that targets substantia nigra
- Head trauma
- Cerebral anoxia.(severe hypoxia)
- Oxidative stress.
- **Drug-induced parkinson's disease (Dopamine antagonist)** Any medication that lowers Dopamine levels ex:

1- Antipsychotics e.g. haloperidol.
2- Antiemetics e.g. metoclopramide

Characters

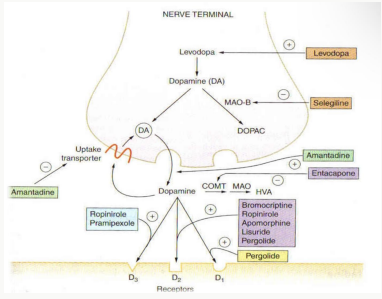
Simplified by the acronym **"TRAP"**

- **T**remors at rest.
- **R**igidity of muscles.
- **A**kinesia or Bradykinesia: (Slowness in initiating and carrying out voluntary movements)
- **P**ostural and gait abnormalities.
- Anxiety or depression.

Drugs Used For the Treatment

Drugs Used For the Treatment

Major Approach:
Drugs to **increase** dopaminergic activity



- **Dopamine precursor :** L-dopa+Carbidopa
- **Dopamine Agonist:** **1-Ergot** derivatives: Bromocriptine & Pergolide. **2-Non-ergot derivatives :** Pramipexole
- **Dopamine releaser:** Amantadine
- **MAO-B inhibitors:** Selegiline
- **COMT inhibitors:** Entacapone

Minor Approach:
Drugs to **block** cholinergic activity

- **Muscarinic Antagonist:** Benz**tropine** Trihexyphenidyl

1.Dopamine Precursor

Drug	Levodopa (L-Dopa) First line
Overview	• is the first line treatment of Parkinsonism. • Dopamine is a polar molecule →can't cross BBB, therefore we use L-dopa because it can cross the BBB • It is a precursor of dopamine **Is converted into dopamine peripherally and centrally by dopa decarboxylase (DC).** • 95/99% L-dopa is decarboxylated to give dopamine in gut and liver peripherally, therefore only 1% crosses BBB to form dopamine centrally. • Dopamine formed peripherally is metabolized by **MAO** (monoamine oxidase) & **COMT** (catechol-o-methyltransferase) enzymes. • L-dopa is usually given combined with **DC inhibitors (Carbidopa or benserazide)** to **prevent peripheral conversion of L-dopa to dopamine.**
DC Inhibitors:	• E.g: **Carbidopa** , Benserazide (car→ it delivers L-dopa to the brain) • Are peripheral DOPA decarbox inhibitors • They inhibit peripheral conversion of L-dopa to dopamine in GIT and other peripheral tissues, thus increasing T1\2. • Why do DC inhibitors act only Peripherally? ➔ DC inhibitors do not cross the BBB, that's an advantage because they won't work in the CNS. Thus L-dopa is converted to dopamine only in the CNS. • **Benefits of L-dopa+carbidopa combination:** 1. Inhibit peripheral conversion of L-dopa to dopamine in GIT and other peripheral tissues. 2. Increases the availability of levodopa to the CNS. 3. Lowers the effective levodopa dose "it won't be converted to dopamine peripherally thus decreasing its peripheral ADRs" 4. Reduce dose of levodopa and side effects

1.Dopamine Precursor

Levodopa (L-Dopa) First line

PK

- Given orally **(should be taken on empty stomach).** Dietary amino acids compete for absorption
- Absorbed from the small intestine and taken up to CNS by **active transport system.**
- High protein meal interferes with its absorption and transport into CNS.
- **Short duration of action** (t1/2 =2 h) (fluctuation of plasma concentration).

MOA

Dopamine acts on dopaminergic receptors D1-D5 (G-protein linked receptors):

- D1, D5 → Excitatory
- D2, D3, D4 → inhibitory

Uses

- The **most efficacious therapy**.
- The best results of levodopa are obtained in the first few years of treatment.
- L-dopa ameliorates all signs of parkinsonism particularly bradykinesia & rigidity but does not cure the disease.
- Should not be used in parkinsonism associated with antipsychotic drug therapy. They block dopamine receptors

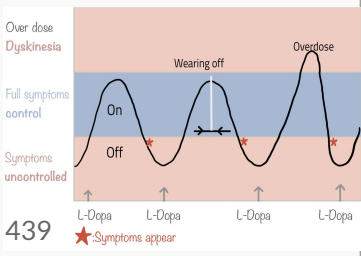
ADR's

- **Peripheral effects:**
  - Anorexia, nausea,vomiting (due to **stimulation of Chemoreceptor trigger zone CTZ**)
  - Cardiac arrhythmias
  - ★Mydriasis # in glaucoma
  - Orthostatic hypotension
- **CNS effects:**(Psychological disorders)

Mainly depression,hallucinations, delusions, confusion, sleep disturbances (insomnia).

Limitations

- Dyskinesia (involuntary movements occurs in 40 to 90% of patients), due to fluctuating plasma levels of levodopa. "seen In overdose"
- The dyskinesia can be reduced by lowering the dosage; however the symptoms of parkinsonism may then reappear.
- **Wearing-off effect** (duration of "on" states becomes shorter)
- **On-off phenomenon** (On= improved mobility & Off=Akinesia or hypomobility)
- **Wearing off effect and on-off phenomena occur due to progression of the disease and the loss of striatal dopamine nerve terminals.**



Drug inter-actions

- High protein meals.
- Pyridoxine (Vitamin B6) —>Diminished effect due to Increases peripheral metabolism
- Non-Selective MAO inhibitors (Phenelzine)—> increase catecholamines —> Hypertensive crisis

C.I

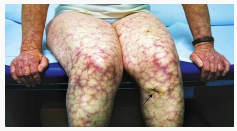
- Psychotic patients.
- Glaucoma (due to mydriatic effect).
- Patients with history of melanoma, Why? **L-dopa is a precursor of melanin**

2.Dopamine receptor agonist

Drugs	Bromocriptine An ergot derivative	Pramipexole A non-ergot derivative
Overview	• Have **longer** duration of action than L-dopa **(less likely to cause dyskinesia than levodopa).**	
Clinical Use	• As **monotherapy,** the dopamine agonists are less effective than levodopa. • In **advanced stages,** dopamine agonists are used as an **adjunct** to levodopa, they may contribute to clinical improvement and reduce levodopa dosage needs.	
P.K	• D2 agonist • Is given orally • T1/2= 6-8h. long	• D3 agonist • Is given orally • Has the advantage of being free radicals scavenger.
Uses	• Parkinson's disease. • Hyperprolactinemia (Galactorrhea). • Infertility in women.	• Used alone as Initial therapy or in combination with L-dopa
ADRs	Similar to L-dopa: • Nausea, vomiting, cardiac arrhythmias. • Confusions, hallucination, delusions. • Dyskinesias (**less prominent**).	
C.I	• Psychosis. • **Patients with peripheral vascular disease (Ergot derivatives only).** • Recent myocardial infarction.	

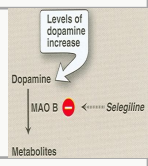
3.Dopamine releaser

Amantadine

M.O.A	• Originally introduced as an **antiviral**. • **Inhibits dopamine reuptake, and increases its release.** • Acts as an antagonist at muscarinic & NMDA receptors(N-methyl-D-aspartate).
P.K	• Given orally with **short half life**. • Most of the drugs is excreted unchanged in urine. • Less efficacious than L-dopa. • Tolerance develops to its therapeutic effect after 6-8 months.
Uses	• It's benefits last only for short period and only used for L-dopa resistance. • Useful in the **early** stages of Parkinsonism or as an adjunct to levodopa therapy. • Amantadine and the anticholinergics may exert additive effect on mental functioning.
ADRS	• **Dopamine like side effects:**Nausea, hallucinations, anxiety, insomnia, confusion,Restlessness • **Anticholinergic effects:** Dry mouth, urinary retention. • Ankle edema • ★**livedo reticularis** Reduction of blood flow to the skin (harmless/rare) 

4.MAO-B inhibitors

Selegiline

PK	• It is a **selective** irreversible inhibitor of **MAO-B** an important enzyme for dopamine metabolism. • The blockade of dopamine metabolism makes more dopamine available for stimulation of its receptors.
MOA	Selegiline may have neuroprotective effect due to: -**Antioxidant activity** against toxic free radicals produced during dopamine metabolism. -Metabolized to desmethyl-selegiline, which is **Anti-apoptotic.** 
Uses	Adjunctive to levodopa/carbidopa in later-stage Parkinsonism to: -Reduce the required dose of levodopa. -Delay the onset of dyskinesia and motor fluctuations that usually accompany long-term treatment with levodopa.
ADR's	• At high doses, It may inhibit MAO-A "loses selectivity" → **(Hypertensive crises)** • May cause insomnia when taken later during the day.
CI	Co-administered with: • Tricyclic Antidepressants. • Selective serotonin reuptake inhibitors (may cause hyperpyrexia, agitation, delirium, coma) • Food restriction "**low tyramine diet**" is required. "found in wine, cheese,banana..."

5.COMT(Catechol-O-methyl transferase) inhibitors

Drugs	Entacapone	Tolcapone
MOA	• Acts **peripherally** to inhibit COMT enzyme required for L-dopa degradation. • Usually given in combination with L-dopa and carbidopa to diminishes **peripheral** metabolism of L-dopa.	• **Peripheral and central** COMT inhibitor • More lipid soluble than entacapone • More penetration into CNS.
Uses	Used as adjuvant to L-dopa + carbidopa to: -Decrease fluctuations, Improve response and Prolong the ON-Time	
ADR'S	• L-dopa side effects • **Brownish Orange discoloration of urine**	-

6.Anticholinergic Drugs

Drugs	Benztropine	Trihexyphenidyl
MOA	Central muscarinic antagonist, has modest anti-Parkinsonian actions.	
Uses	• Improves tremor & rigidity but have little effect on bradykinesia. • Provide benefit in **drug-induced Parkinsonism** (due to **antipsychotics**). • Used during the early stages of the disease or as adjunct to levodopa therapy.	
ADR's	• Cycloplegia, mydriasis, dry mouth, urinary retention, constipation. • At high doses may occur: confusion, delirium, hallucinations.	
CI	Prostatic hypertrophy, Glaucoma and Intestinal obstruction.	

Summary

Drug	MOA	Uses	ADRs
Levodopa (L-Dopa) First line	Dopamine acts on dopaminergic receptors D1-D5 (G-protein linked receptors):- D1, D5 → Excitatory- D2, D3, D4 → inhibitory	-The **most efficacious therapy**. -the best results in the first few years of treatment. -bradykinesia & rigidity improvement. **-Should not be used in parkinsonism associated with antipsychotic drug therapy.**	• **Peripheral effects:** -Cardiac arrhythmias -Orthostatic hypotension • **CNS effects:**(Psychological disorders) -depression -hallucinations
Bromocriptine	-	-**Parkinson's** disease. -**Hyperprolactinemia** -**Infertility** in women	Similar to L-dopa: - - Nausea, vomiting, cardiac arrhythmias. -Confusions, hallucination, delusions. -Dyskinesias (less prominent).
Pramipexole	-	Used alone as Initial therapy or in combination with L-dopa	
Amantadine mild cases	-Originally introduced as an antiviral. - Inhibits dopamine reuptake, and increase it's release -acts as an antagonist at muscarinic & **NMDA** receptors.	- It's benefits last only for short period and only used for L-dopa resistance. -Useful in the **early** stages of Parkinsonism or as an adjunct to levodopa therapy. -Amantadine and the **anticholinergics** may exert additive effect on mental functioning.	• **Dopamine like side effects:**Nausea, hallucinations, anxiety, insomnia, confusion. • **Anticholinergic effects:** Dry mouth, urinary retention. • Ankle edema • **livedo reticularis** "Reduction of blood flow to the skin (harmless/rare)"
Selegiline mild cases	have neuroprotective effect due to: **-Antioxidant activity** against toxic free radicals produced during dopamine metabolism. -Metabolized to desmethyl-selegiline, which is **Anti-apoptotic.**	Adjunctive to levodopa/carbidopa in later-stage Parkinsonism to: - Reduce the required dose of levodopa - Delay the onset of dyskinesia and motor fluctuations that usually accompany long-term treatment with levodopa.	-At high doses, It may inhibit MAO-A "loses selectivity" → **(Hypertensive crises)** -May cause insomnia when taken later during the day.
Entacapone	• Acts **peripherally** to inhibit COMT enzyme required for L-dopa degradation. • Usually given in combination with L-dopa and carbidopa to diminishes **peripheral** metabolism of L-dopa.	Used as adjuvant to L-dopa + carbidopa to: -Decrease fluctuations - Improve response - Prolong the ON-Time	-L-dopa side effects **-Brownish Orange discoloration of urine**
Tolcapone	• **Peripheral and central** COMT inhibitor • More lipid soluble than entacapone • More penetration into CNS.		-
Benztropine mild cases	-Central muscarinic antagonist -has modest anti-Parkinsonian actions.	-Improves tremor & rigidity but have little effect on bradykinesia. -Provide benefit in **drug-induced Parkinsonism** (due to **antipsychotics**) -Used during the early stages of the disease or as adjunct to levodopa therapy.	-Cycloplegia, mydriasis, dry mouth, urinary retention, constipation. • At high doses: confusion, delirium, hallucinations.
Trihexyphenidyl mild cases			

- Levodopa and carbidopa are the main treatment
- All other medications are adjuncts to levodopa therapy

MCQ

1.Great caution must be exercised in the use of this drug in parkinsonian patients who have prostatic hypertrophy :			
A.Benztropine.	B.Carbidopa.	C.Bromocriptine.	D.Selegiline.
2.A 45-year-old woman complained of blurred vision, dry mouth, palpitations, and constipation. The patient was diagnosed with Parkinson disease 4 months earlier and had been receiving a levodopa/carbidopa combination since then. Recently, her neurologist added a drug to the therapeutic regimen because of an increase in the patient's resting tremor. Which of the following drugs most likely caused the patient's symptoms?			
A.Selegiline	B.Levodopa	C.Amantadine	D.Benztropine
3.Which of the following antiparkinsonian drugs has also been used to treat hyperprolactinemia?			
A.Benztropine	B.Amantadine	C.Levodopa	D.Bromocriptine
4.Antiviral drug found to have anti-Parkinson's properties:			
A.Amantadine	B.Procyclidine	C.Levodopa	D.Reserpine
5.Which of the following is contraindicated in patients with history of melanoma?			
A.Amantadine	B.Entacapone	C.Pramipexole	D.Levodopa

1: A ,2: D ,3:D ,4:A ,5: D

SAQ

01

Mention 3 adverse effects may be caused Levodopa?

Slide 6

02

A 74-year-old man who had been suffering from Parkinson disease for 4 years complained of a purplish red mottling of the skin that began on his thighs and spread to his lower legs. The eruption appeared 2 weeks after a drug was added to his therapeutic regimen. A diagnosis of livedo reticularis was made.
a) Which drug most likely caused this skin eruption??
b) What is it's mechanism of action?

a) amantadine.
b) Inhibits dopamine reuptake, thus increases dopamine release. Acts as an antagonist at
muscarinic & NMDA receptors (N-methyl-D-aspartate)

Team Leaders

Muhannad Al-otabi

Reema Almotairi

Sarah Alajaji

Maryam Alghannam

Team members

Abdulaziz Alamri

Faisal Alateeq

Nazmi M Alqutub

Sultan Almishrafi

Mohammed Maashi

Mohammed Alasmary

Nazmi A Alqutub

Ziad Alhabardi

Mohammed Alrobeia

Mohammed Alhudaithi

Sami Mandoorah

Omar Alamri

Mohammed Alqutub

Reena Alsadoni

Almas Almutairi

Fatimah Alghamdi

Lama Alotaibi

Salma Alsaadoun

Jouri Almaymoni

Faisal alzuhairy

Salma Alkhlassi

Huda bin jadaan

Manar Aljanubi

Wasan Alanazi

Jana Almutlaqah

Farah Abukhalaf

Norah Almalik

Rawan Alqahtani

Aroub Almahmoud

Remaz Almahmoud

Special thanks to norah almania for the amazing logo