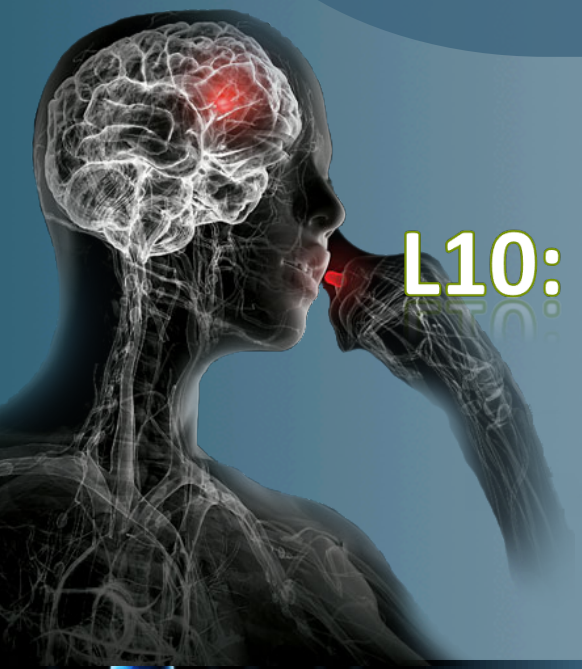
King Saud University

College of Medicine

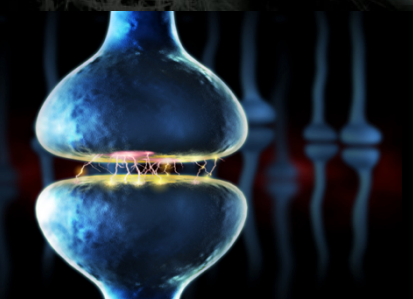
2nd Year, 1st Block

PHARMACOLOGY 433

MED 433 Teams



L10: DRUGS USED IN PARKINSONISM



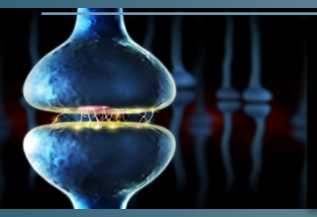
CNS Block

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.

Definitions & Abbreviations

Akinesia	A loss of the ability to move; freezing in place.
Bradykinesia	Extremely slow movement.
Dyskinesia	Involuntary movements
Hypomobility	decrease in the normal movement of a joint or body part
Precursor of dopamine	Converted into dopamine **peripherally** and **centrally**
MAO	Monoamine oxidase
COMT	Catechol-o-methyl transferase
DC	Decarboxylase
MPTP	Methyl phenyl tetrahydropyridine (toxin)



Parkinson's Disease

Definition

- A progressive
- Neurological disorder
- Mainly in the elderly and
- Can lead to disability unless effective treatment is provided.

Characters

T Tremors at rest

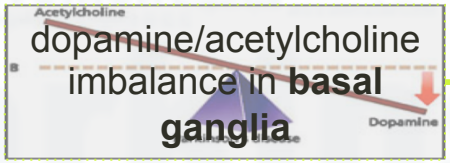
R Rigidity of muscles

A Akinesia or Bradykinesia

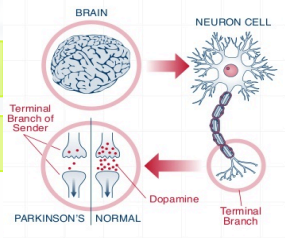
P Postural and gait abnormalities

Anxiety or depression

Pathophysiology



- Deficiency of dopamine
- Predominance of Ach



Causes

Idiopathic but some causes may be:

1. Genetic.
2. Toxins (MPTP)
3. Head trauma.
4. Cerebral anoxia .
5. Oxidative stress
6. Drug-induced Parkinson's disease
   - e.g. antipsychotics like haloperidol.
   - Dopamine antagonists as metoclopramide (antiemetic).

Drug Treatment for Parkinson's Disease

A/ Drugs to increase dopaminergic activity

- **Dopamine precursor**
  - L-dopa + Carbidopa
- **Dopamine agonists**
  - **Ergot derivatives**
    - Bromocriptine
    - Pergolide
  - **Non ergot derivatives**
    - Pramipexole
- **Dopamine releaser**
  - Amantadine
- **COMT inhibitors**
  - Entacapone & Tolcapone
- **MAO-B inhibitors**
  - Selegiline

B/ Drugs to block cholinergic activity(anticholinergic)

- **Muscarinic antagonists**
  - Benzatropine
  - Trihexphenidyl

A- 1st ; Dopamine precursor

Levodopa (L-dopa)

Doctor notes

Mechanism of action	① precursor of dopamine ② L-dopa $\xrightarrow{DC}$ dopamine ③ 99% L-dopa is decarboxylated to give dopamine in gut and liver.
Without carbidopa	① Dopamine formed peripherally is metabolized by MAO & COMT enzymes ② 1% crosses BBB to form dopamine centrally.
L-dopa with carbidopa	① prevent peripheral conversion of L-dopa to dopamine in GIT and other peripheral tissues →thus increasing t1/2 ② increase availability of levodopa to CNS. ③ reduce dose of levodopa and side effects.
What's Carbidopa?	Is a peripheral dopa decarboxylase inhibitor→ Inhibits peripheral conversion of L-dopa to dopamine Acts only peripherally because it is polar and can not enter brain
pharmacokinetics	① Given orally (should be taken on empty stomach). To prevent the competition for absorption ② Absorbed from the small intestine and taken up to CNS by active transport system ③ High protein meal interferes with its absorption and transport into CNS ④ Short duration of action (t½ =2 h)
Uses	✓ **The most efficacious therapy** and 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.(because these drugs reduce dopamine while levodopa increase it, so it will erase antipsychotic drug effect that's why in theses cases we give **anticholinergic drugs**)

Con. Levodopa (L-dopa)

Doctor notes

Adverse drug effects

1	Peripheral effects:	① Anorexia, nausea, vomiting (due to stimulation of chemoreceptor trigger zone, CTZ). ② Cardiac arrhythmias. ③ Mydriasis, orthostatic hypotension	
2	CNS effects: Psychological disorders	Mainly depression, delusions, hallucinations, confusion, sleep disturbances (insomnia).	
3	Dyskinesia and response fluctuations	Dyskinesia (involuntary movements occurs in 40 to 90% of patients) due to fluctuating plasma levels of levodopa. The dyskinesia can be reduced by lowering the dosage; however, the symptoms of parkinsonism may then reappear.	
4	Wearing-off effect	Duration of "on" states becomes shorter. "On" means the duration in which the drug is effective and working ,So after few years this drug effectiveness may reduce	occur due to **progression of the disease and the loss of striatal dopamine nerve terminals**. If happened other drugs should be given with (L-dopa +carbidopa)
5	On-off phenomenon	On= improved mobility & Off=Akinesia or Hypomobility. Sudden changes in the patients activity while using the drug	

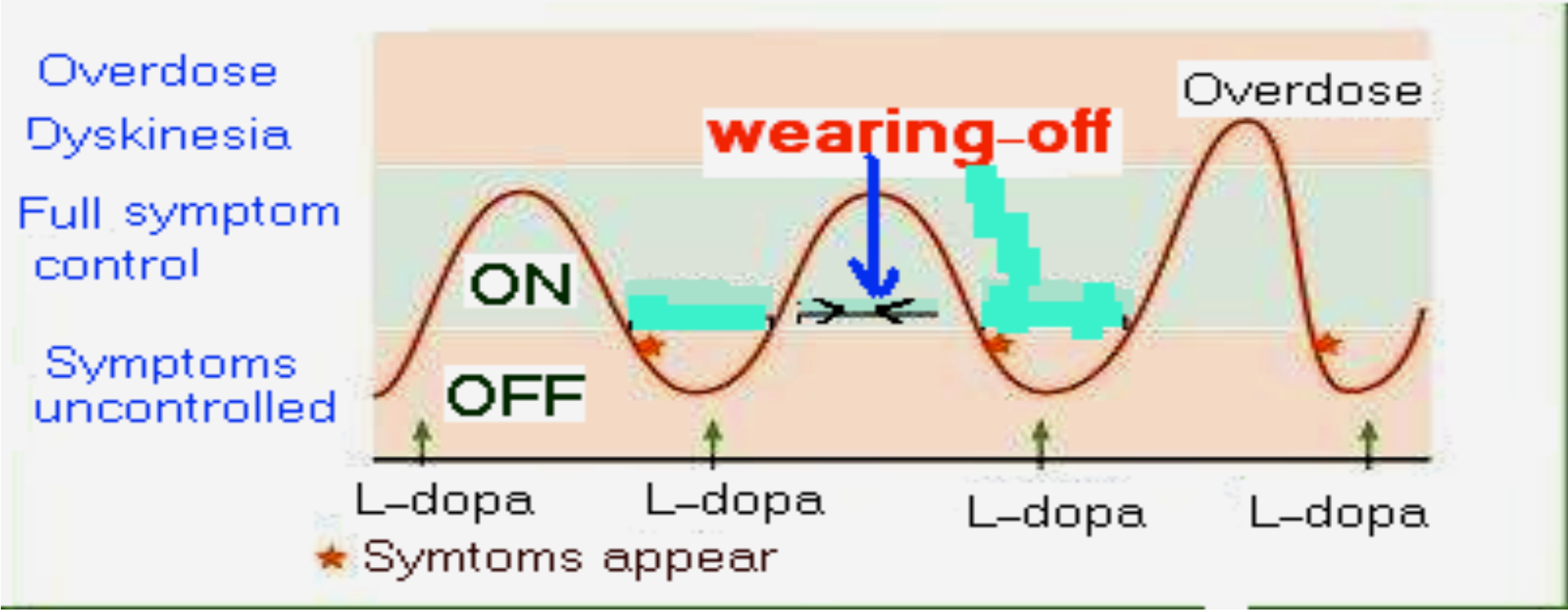
Drug Interactions:-

① High proteins meals.
② Pyridoxine (Vitamin B6).
③ **Non selective MAO** inhibitors (phenelzine)

Contraindications

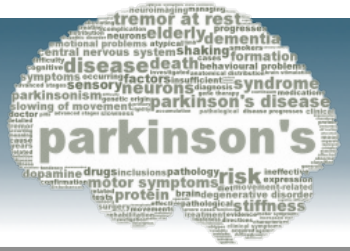
① Psychotic patient.
② Glaucoma (due to mydriatic effect).
③ Patients with history of melanoma (L-dopa is a precursor of melanin)

Fluctuating
الارتجاع او التذبذب



Fluctuating Means the level of therapeutic does of the drug in the blood **is not constant** it might goes up sudden or down SO If I increase the does of L-Dopa = overdoes then the patient will develop Dyskinesia AND if I decrease the does he will develop the rest symptoms !! So I have to reduce the does of L-dopa and combine another drug to it

A- 2nd ; Dopamine receptor agonists*



* Please recheck the classification of this group in slide 4

Bromocriptine, pergolide, Pramipexole

Doctor notes

Characteristics	① Have longer duration of action than L-dopa ② As monotherapy, they are less effective than levodopa.* ③ In advanced stages, dopamine agonists are used as an adjunct to levodopa (they may contribute to clinical improvement and reduce levodopa dosage needs) ④ less likely to cause dyskinesias than levodopa	
Classification	**Ergot derivatives**	**Non ergot derivatives**
E.g	**Bromocriptine**	**Pramipexole**
pharmacokinetics	✓ D2 agonist ✓ Is given orally ✓ Half life= 6-8 h	✓ D3 agonist ✓ Is given orally ✓ Has the advantage of being free radicals scavenger
Uses	**1. Parkinson's disease** **2. Hyperprolactinemia (galactorrhea).** **3. Infertility in women**	**Alone as initial therapy or in combination with L-dopa.**
Adverse drug effects	**1. Nausea, vomiting, postural hypotension** **2. Cardiac arrythmias** **3. Confusion, hallucinations, delusions** **4. Dyskinesias (less prominent).**	**Similar to L-dopa, but less dyskinesias.**
Contraindications	**1. Psychosis** **2. Peripheral vascular disease (only ergot-derived)** **Because they cause vasoconstriction** **3. nists) Recent myocardial infarction**	

A-3rd ; Dopamine releaser

Amantadine

pharmacokinetics	▪Originally an antiviral. ▪increases dopamine release, but **Less efficacious than L-dopa** ▪acts as an antagonist at muscarinic and NMDA receptors (N-methyl-D-aspartate). ① given orally with short half life ② most of the drug being excreted unchanged in the urine
Uses	**only used for L-dopa resistance.**
Disadvantages	① Less efficacious than L-dopa ② Tolerance develops to its therapeutic effect after 6-8 months ③ Its benefits last only for short period ④ Amantadine and the anticholinergics may exert additive effects on mental functioning
Adverse effects	① Nausea, anxiety, insomnia, confusion, hallucinations (dopamine like side effects). ② Dry mouth, urinary retention (anticholinergic effects). ③ Restlessness and hallucinations (NMDA antagonist).

A-4th &5th ; MAO-B & COMT Inhibitors

	Monoamine oxidase-B inhibitors	Catechol-O- methyl transferase) Inhibitors
	Selegiline	**Entacapone & Tolcapone**
	✓ is a selective irreversible inhibitor of MAO-B, an important enzyme for dopamine metabolism ✓ Blockade of dopamine metabolism makes more dopamine available for stimulation of its receptors	✓ Acts peripherally to inhibit COMT enzyme required for L-dopa degradation ✓ Diminishes peripheral metabolism of L-dopa = reduce side effect of L-Dopa
Advantages	① Selegiline may have neuroprotective effect. ② It has antioxidant activity against toxic free radicals produced during dopamine metabolism. ③ Is metabolized to desmethylselegiline, Which is antiapoptotic.	
Uses	Adjunctive to levodopa / carbidopa in later-stage parkinsonism to: 1. Reduce the required dose of levodopa 2. Delay the onset of dyskinesia and motor fluctuations that usually accompany long-term treatment with levodopa.	As adjuvant to L-dopa to: 1. Decrease fluctuations 2. Improve response 3. Prolonged the ON-Time
ADE	① At high doses, selegiline may inhibit MAO-A (hypertensive crises). ② May cause insomnia when taken later during the day.	① L-Dopa side effects. ② Orange discoloration of urine.
Contraindications	Should not be co-administered with tricyclic antidepressants, or selective serotonin reuptake inhibitors (may cause hyperpyrexia, agitation, delirium, coma).	

Doctor notes

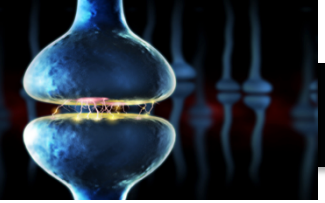
B-Anticholinergic Drugs

Benztropine, Trihexphenidyl

Characteristics	① Central muscarinic antagonist. ② Has modest anti- parkinsonian actions. ③ They improve tremor & rigidity but have little effect on bradykinesia. ④ Provide benefit in drug-induced parkinsonism (due to antipsychotics).
Uses	• **During the early stages of the disease or as an adjunct to levodopa therapy.** • Used in parkinsonism associated with antipsychotic drug therapy
Adverse effects	① Cycloplegia, mydriasis, dry mouth, urinary retention, constipation. ② Confusion, delirium, and hallucinations may occur at higher doses.
Contraindications	① Prostatic hypertrophy ② Glaucoma ③ Intestinal obstruction

Most of the drugs that can be used in parkinson contraindicated with **Psychotic patients** so the only drug we can use to treat patient who have **both** parkinson's disease and Psychotic problem is ((Anticholinergic Drugs))

Doctor notes

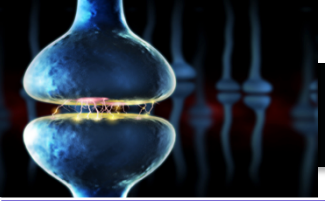


Summary of Drugs used in Parkinsonism

Drugs	Uses	Side Effects	Contraindications
Levodopa (dopamine precursor)	The most efficacious therapy to treat parkinsonism **(you Must accompany it with Carbidopa)** .	Anorexia, nausea, vomiting , Cardiac arrhythmias, Mydriasis, orthostatic hypotension,depression, delusions, hallucinations, confusion, (insomnia), Dyskinesia.	Psychotic patient, Glaucoma, Patients with history of melanoma . **You don't combine the L-Dopa with NON selective MAO inhibitor.**
Bromocriptine (Dopamine agonist ; Ergot derivative)	Parkinson's disease, Hyperprolactinemia, Infertility in women. (the less prolactin you have the more Dopamine and Estrogen you have).	Nausea, vomiting, postural hypotension, Cardiac arrythmias, Confusion, hallucinations, delusions, Dyskinesias (less prominent then L-dopa).	Psychosis, Peripheral vascular disease (only ergot-derived agonists), Recent myocardial infarction .
Pramipexole (dopamine agonist ; NON Ergot derivative)	Used alone as initial therapy or in combination with L-dopa. Has the advantage of being free radicals scavenger.	similar to L-dopa, but less dyskinesias.	Psychosis

Q1: why we don't give dopamine directly instead of it's precursor ?
Q2: why dyskinesia happen during the use of L-dopa ?
Q3: why carbidopa acts only peripherally?
Q4: why it is contraindication to give L-dopa to a patient with history of melanoma?

A1/Because dopamine is polar and cannot cross BBB.
A2/Due to fluctuating plasma levels of levodopa.
A3/Because it is polar and can not enter brain.
A4/ Because L-dopa is a precursor of melanin.



Summary of Drugs used in Parkinsonism

Drugs	Uses	Side Effects	Contraindications
Amantadine (Dopamine releaer)	Less efficacious than L-dopa. Tolerance develops to its therapeutic effect after 6-8 months	Nausea, anxiety, insomnia, confusion, hallucinations (dopamine like side effects). Dry mouth, urinary retention (anticholinergic effects). Restlessness and hallucinations (NMDA antagonist).	Shouldn't be co-administered with anti cholinergic drugs.
Entacapone (COMT inhibitor)	used with L-dopa	L-Dopa side effects , Orange discoloration of urine.	
Selegiline (MAO-B inhibitor)	Adjunctive to levodopa +carbidopa in later-stage of parkinsonism Has antioxidant and antiapoptotic actions	At high doses, selegiline may inhibit MAO-A (hypertensive crises). May cause insomnia when taken later during the day.	should not be co-administered with TCA's or SSRI's
Benzatropine (anticholinergic) ; reduce Ach.	Used with parkinsonism accompany by psychosis \ the use of antipsychotics	Cycloplegia, mydriasis, dry mouth, urinary retention, constipation. Confusion, delirium, and hallucinations may occur at higher doses.	Prostatic hypertrophy, Glaucoma, Intestinal obstruction

Q : why we give Carbidopa in combination with L-dopa ?

Without Carbidopa 99% of L-dopa will convert to dopamine in the peripheral tissues , and dopamine formed peripherally is metabolized by MAO & COMT enzymes so only 1% will reach the brain and this amount is not effective.

So we give Carbidopa to prevent peripheral conversion of L-dopa to dopamine.

Quiz yourself

Q1: Which of the following is used in case of Parkinson's Patient accompany by psychosis ?
A) L-dopa + Amantadine.
B) L-dopa + Carbidopa.
C) Amantadine.
D) Benzotropine.

Q2: which of the following is used to treat infertility in women?
A) Selegiline.
B) Entacapone.
C) Bromocriptine.
D) Pramipexole.

Q3: which of the following is an antiviral?
A) Selegiline.
B) Amantadine.
C) Pramipexole.
D) Entacapone.

Q4: which of the following is Contraindication in patient with peripheral Vascular disease accompany with Parkinson's ?
A) Pramipexole.
B) L-Dopa.
C) Benzotropine.
D) Bromocriptine.

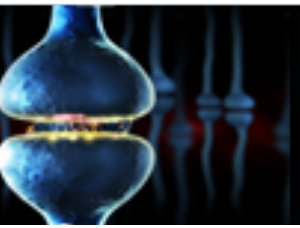
Q5: which of the following is Non Ergot Dopamine agonist ?
A) Bromocriptine.
B) Selegiline.
C) Pramipexole.
D) Benzotropine.

Q6: which of the following Can NOT induce Parkinson's ?
A) Head Trauma.
B) Dopamine antagonist.
C) Oxidative Stress.
D) Brain Tumor.

Q7: which of the following causes Orange discoloration of the urine?
A) Benzotropine.
B) Selegiline.
C) Entacapone.
D) Bromocriptine.

Q8: which of the following has antiapoptotic action?
A) Selegiline.
B) Amantadine.
C) Entacapone.
D) Pramipexole.

Answers: 1: D , 2: C , 3: B , 4: D , 5: C , 6: D , 7: C , 8: A



CNS Block

PHARMACOLOGY 433

THIS WORK WAS DONE BY :

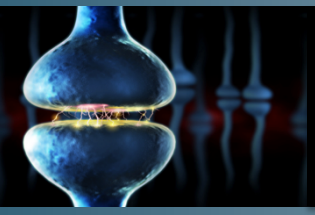
Contact us for any questions or comments :

Pharma_433@yahoo.com

@pharma_433

Raneem Alotaibi	Ahmed Aldakhil
Sara alkharashi	
Areej alwahaib	
Latifa AlAnazi	

We hope that we made this lecture easier for you
Good Luck !



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