PHARMACOLOGY TEAM

Lecture : 11

Parkinsonism

Done by: Mohammed Abalkhail

Revised by: Moudi Al degether , Najoud AlOtaibi

OBJECTIVES

At the end of this lecture you will be able to:-

- ***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***

Characters of Parkinson's disease:

- Tremors at rest
- Bradykinesia(slowness in initiating and carrying out voluntary movements)or Akinesia(no movement)
- Muscle rigidity
- Postural and gait abnormalities
- Anxiety or depression

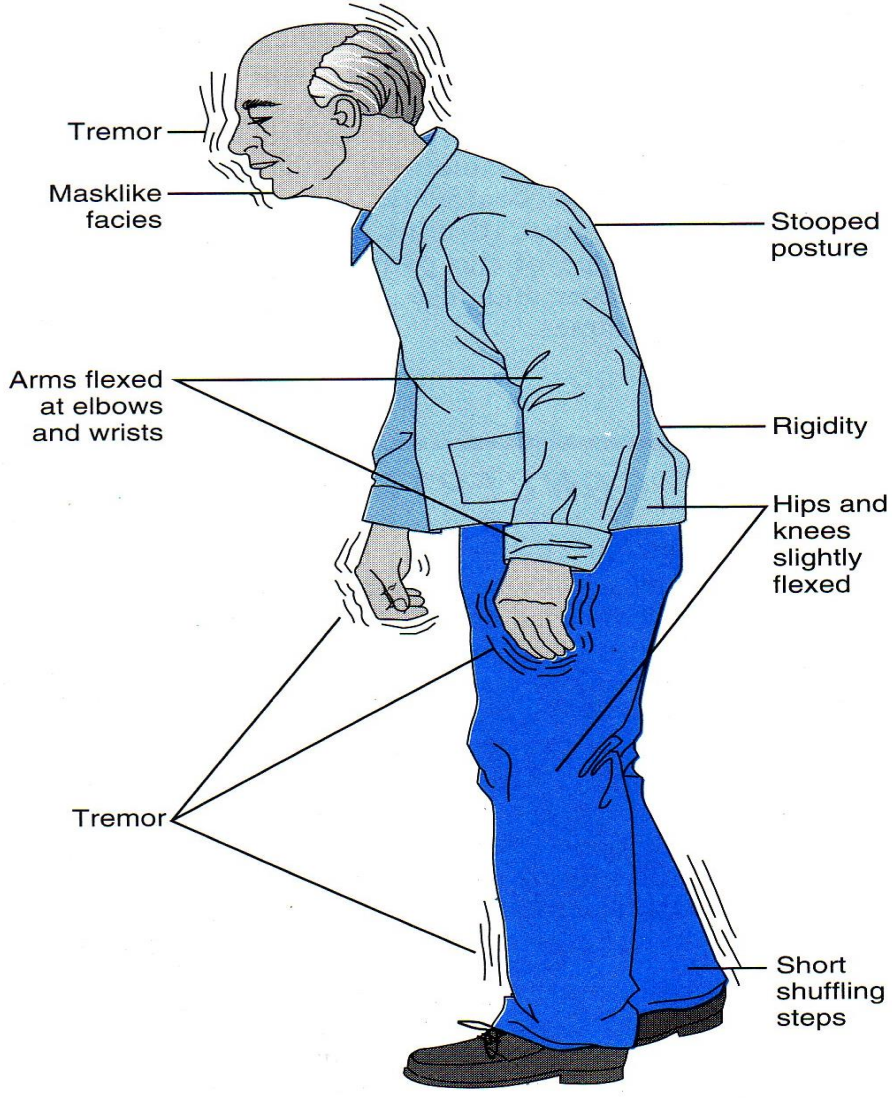
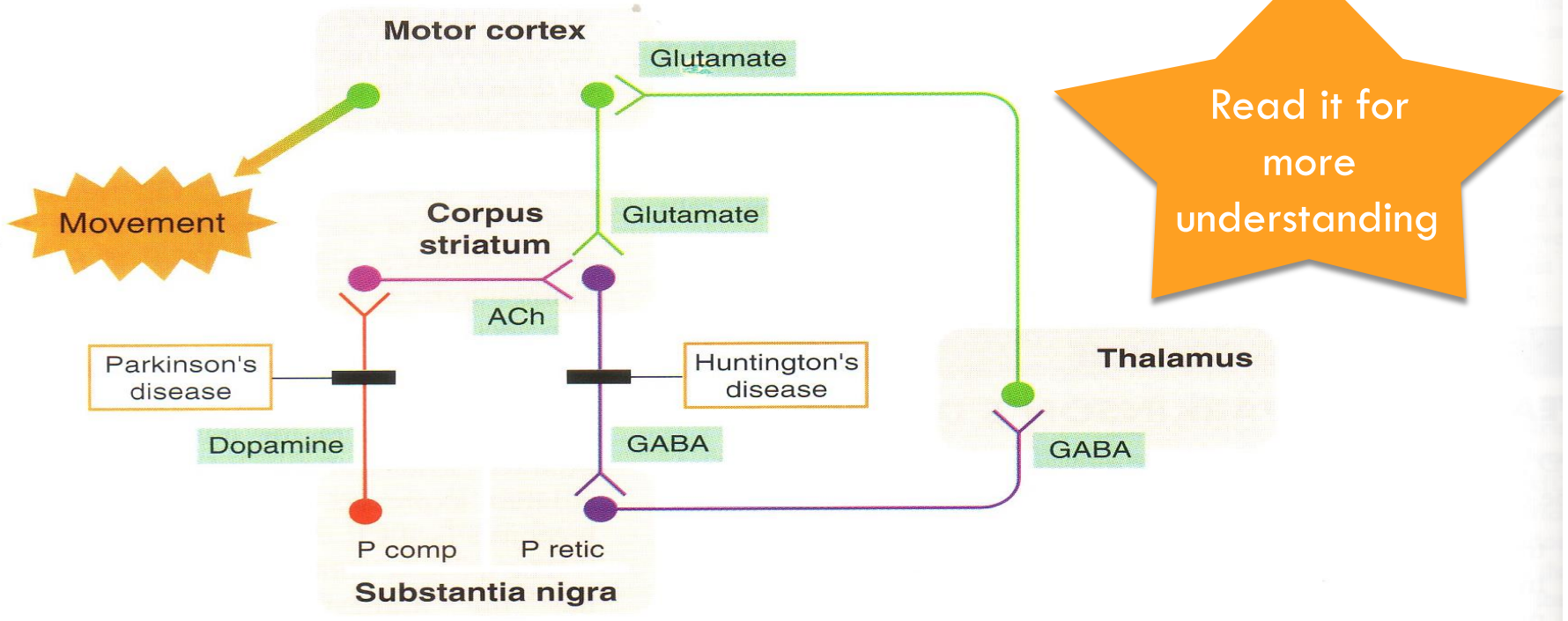


FIGURE 45–5. Clinical manifestations of Parkinson disease. (From Monahan FD, Neighbors M: *Medical-Surgical Nursing: Foundations for Clinical Practice*. Philadelphia, WB Saunders, 1998, p 787.)

occurs mainly due to reduction of dopamine contentin substantianigra& corpus striatum that are involved in motor control.



Read it for more understanding

Fig. 34.3 Simplified diagram of the organisation of the extrapyramidal motor system, and the defects that occur in Parkinson's disease and Huntington's disease. In the former, the inhibitory dopaminergic pathway from the substantia nigra (pars compacta) to the striatum is impaired, increasing the activity of GABAergic cells in the striatum, which in turn inhibit GABAergic cells in the substantia nigra (pars reticulata), thus reducing the restraint on the thalamus and cortex, causing rigidity. The dopaminergic inhibition of the striatal cells is opposed by excitatory cholinergic interneurons, The defect can be counteracted by dopamine (D_2 or D_3) agonists or by acetylcholine (muscarinic) antagonists. In Huntington's disease, the GABAergic striatonigral pathway is impaired, producing effects opposite to the changes in Parkinson's disease. (P comp, pars compacta; P ret, pars reticulata; GABA, gamma-aminobutyric acid; ACh, acetylcholine.)

causes

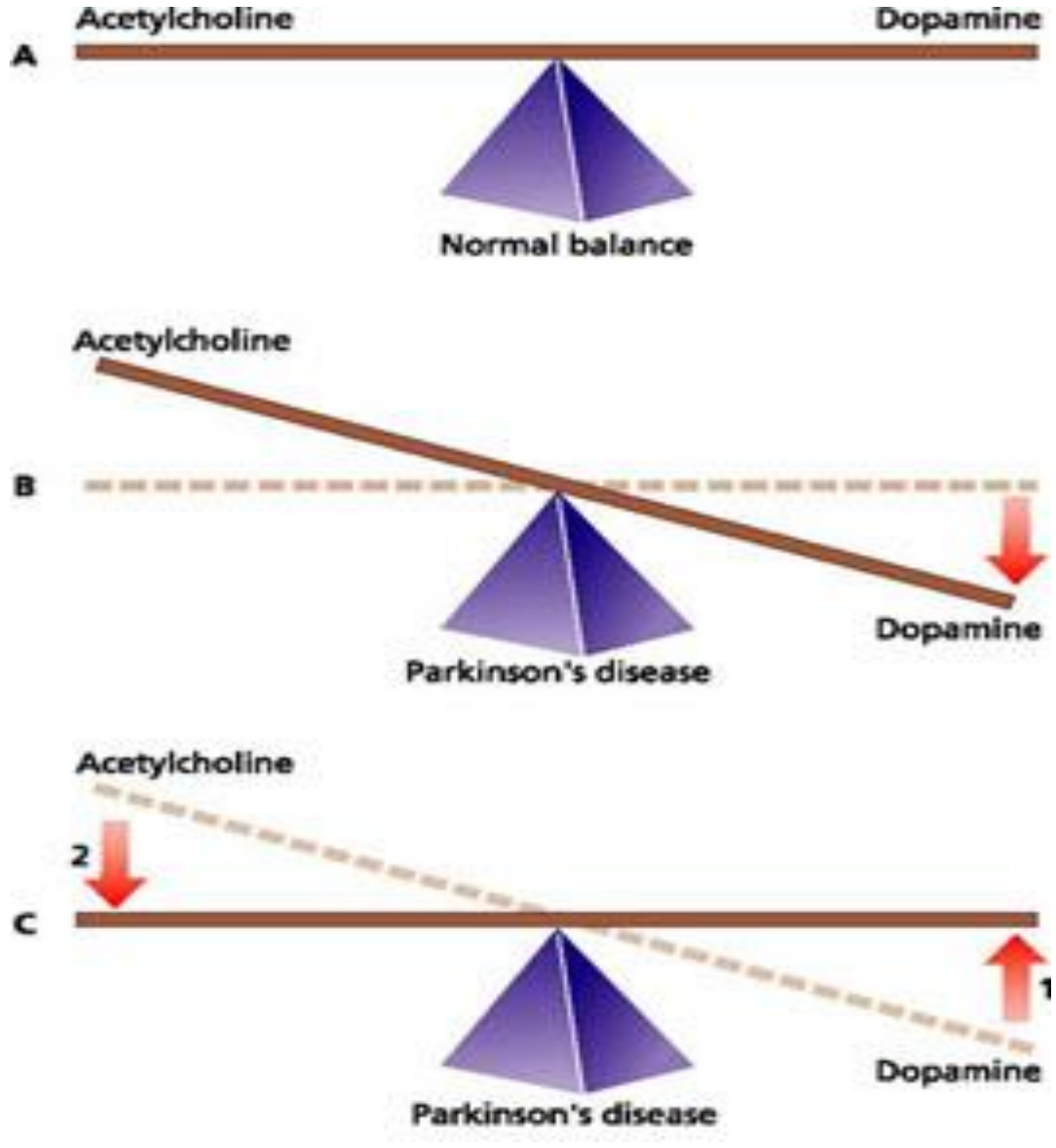
Parkinson’s disease is an idiopathic diseasebut some causes may be:

- Genetic.
- Toxins (MPTP= methyl phenyl tetrahydropyridine)
- Head trauma.
- Cerebral anoxia .
- Oxidative stress
- Drug-induced Parkinson's disease
  - e.g. antipsychotics like haloperidol.
  - Dopamine antagonistsas metoclopramide
  - Reserpine

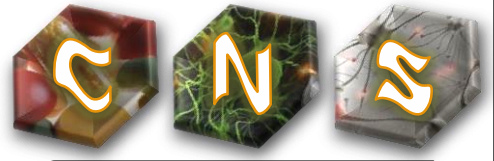
- **Normally**
  - There is balance between ACH & dopamine.

- **Disease**
  - High ACH level
  - Low Dopamine level

- **Management approach**
  - increase dopaminergic activity
  - Block cholinergic activity



Mind Map



Main drug used

Drugs ↑ dopaminergic activity

- **Levodopa**
  - Combined with
    - dopa decarboxylase inhibitors (Carbidopa)
    - COMT inhibtor (entacapone)
- **Dopamine agonist**
  - Pramipexole
  - Bromocriptine
- **MAOI**
  - Selegillin

Other drugs

- Antiviral
  - Amantadine

Drugs ↓ cholinergic activity

- Anticholinergic
  - **muscarinic antagonist**
    - **Benztropine**
    - **Trihexyphenidyl**

Slides | Important | Doctor's Notes | Explanation | Female's Slides

Levodopa

Uses	Pharmacokinetics	Side Effect	Interaction	contraindication
➢ **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.**	✧Given orally (should be taken on empty stomach. ✧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 ($t_{1/2}$ =2 h) **(fluctuation of plasma concentration)(girls slides)** ✧metabolized in the blood and peripheral tissue by Dopa decarboxylase(DC) and catechol-O-methyltransferase(COMT) counter to be 99%, leaving 1% of L-dopa enter brain. (next slide)	✧Peripheral side effects: • anorexia, nausea, and vomiting *(due to stimulation of emetic center).* (due to stimulation of the CTZ). • Orthostatic hypotension ,Cardiac arrhythmias occur in some patients. Mydriasis, orthostatic hypotension ✧CNS adverse effects: • (Psychological disorders) mainly depression • vivid dreams, delusions, hallucinations, confusion and sleep disturbances ✧Dyskinesia and response fluctuations (next slide)	✧Proteins ingested with meals. ✧Nonselective MAO inhibitors (phenelzine). due to peripheral accumulation of norepinephrine ✧Pyridoxine (Vitamin B6).	✗ Psychotic patient. ✗ glaucoma. **(due to mydriatic effect).** ✗ With caution to patients with active ulcer. ✗ Patients with history of melanoma. **Why?** **Note: L-dopa is a precursor of melanin**

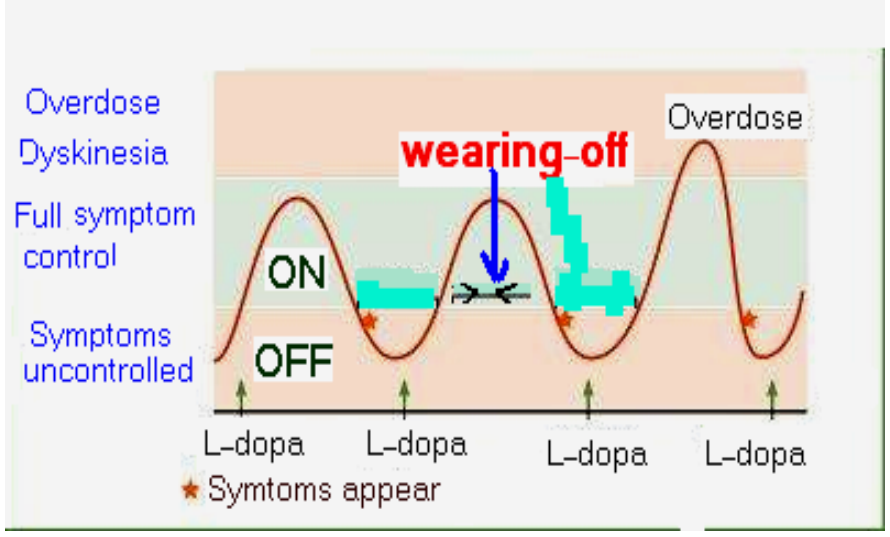
Levodopa

- Dyskinesia and response fluctuations (which going to be after few years of treatment)

- **Dyskinesia** (involuntary movements occurs in 40 to 90% of patients) **due to fluctuating plasma levels of levodopa.**reduced by lowering the dosage; however, the symptoms of parkinsonism may then reappear.

- **Wearing-off effect** (duration of "on" states becomes shorter). It's meant to be type of tolerance.

- **On-off phenomenon** (On= improved mobility & Off=Akinesia or **hypomobility**).



Combination of Levodopa

L-Dopa + Dopa Decarboxylase Inhibitors (carbidoapa)

L-Dopa + COMT Inhibitors (entacapone)

Female's Slides

Why carbidopa is combined with L-dopa?

diminsh peripheral metabolism of L-dopa in GIT and other peripheral tissues (thus increasing t1/2).

increase availability of levodopa to CNS.

reduce dose of levodopa and side effects.

L-Dopa will always combined with Carbidopa or Entacapone or even both, they are working in periphery to decrease metabolization of L-Dopa, so an adequate amount will reach CNS.

Dopamine receptor Agonist

- long duration of action , less likely to cause dyskinesias than levodopa.
- As monotherapy, the dopamine agonists are less effective than levodopa.
- We use it **as initial theraby.**

Drug	Pharmacokinetics	Indication	Side Effects	Contraindication
Bromocriptine (ergot)	‣ Is an ergot derivative ‣ D2 agonist ‣ Is given orally ‣ Half life=6-8h	‣ Parkinson's disease ‣ Hyperprolactinemia (galactorrhea). ‣ Infertility in women.	‣ Nausea, vomiting, postural hypotension ‣ Cardiac arrythmias ‣ Confusion, hallucinations, delusions ‣ Dyskinesias (less prominent).	‣ Psychosis ‣ Peripheral vascular disease ‣ Recent myocardial infarction ‣ Active peptic ulceration.
Pramipexole (Non Ergot)	‣ D3 agonist ‣ Is given orally ‣ Has the advantage of being free radicals scavenger. ‣ Non Ergot dopamine agonist	‣ Used alone as initial therapy or in combination with L-dopa.	‣ similar to L-dopa, but less dyskinesias.	

Amantadine

- originally introduced as an antiviral.
- Less efficacious than L-dopa
- Its benefits last only for short period (few weeks) and only used for L-dopa resistance

Pharmacokinetics	Side effects
▸ Amantadine increases dopamine release. ▸ acts as an antagonist at muscarinic and NMDA (N-methyl-D-aspartate) receptors. ▸ given orally with short half life ▸ most of the drug being excreted unchanged in the urine	▸ Nausea, anxiety, insomnia, confusion, hallucinations (dopamine like side effects). ▸ Dry mouth, urinary retentionblurred vision, constipation (anticholinergic effects). ▸ Restlessness and hallucinations (NMDA antagonist).

MAO-B Inhibitors

- **Selegiline may have neuroprotective effect.**
- **Has *antioxidant activity* against *toxic free radicals* produced during dopamine metabolism.**
- **Selegiline is metabolized to desmethylselegiline, *Which is antiapoptotic***

Selgiline	
Pharmacokinetics	‣ is a selective irreversible inhibitor of MAO-B at normal doses. ‣ It inhibits dopamine degradation by MAO-B in CNS. ‣ It increases endogenous dopamine available for its receptors
Indication	‣ Adjunctive to levodopa / carbidopa in later-stage parkinsonism to: ‣ reduce the required dose of levodopa ‣ delay the onset of dyskinesia and motor fluctuations that usuallyaccompany long-term treatment with levodopa.
Side Effects	‣ At high doses, selegiline may inhibit MAO-A *(hypertensive crises).* ‣ May cause insomnia when taken at night.
Contraindication	✗ Selegiline should not be co-administered with tricyclic antidepressants, or selective serotonin reuptake inhibitors *(may cause hyperpyrexia, agitation,delirium, coma)*

Female's Slides

COMT Inhibitors
(Catechol-O- methyl transferase) Inhibitors

Entacapone		
Function	Uses	Side Effects:
Acts Peripherally To Inhibit COMT Enzyme Required For L-dopa Degradation Diminishes Peripheral Metabolism Of L-dopa	As Adjuvant To L-dopa To: ✓ Decrease Fluctuations ✓ Improve Response ✓ Prolonged The On-time	L-dopa Side Effects. Orange Discoloration Of Urine.

Anticholinergic

Benztropine & trihexphenidyl			
Pharmacokinetics	Indication	Side Effects	Contraindication
‣ Central Muscarinic Antagonist. ‣ Has Modest Anti-Parkinsonian Actions.	‣ Improve 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 An Adjunct To Levodopa Therapy	‣ Cycloplegia, Mydriasis, Dry Mouth, Urinary Retention, **Constipation.** ‣ Confusion, Delirium, And Hallucinations May Occur At Higher Doses.	✗ Prostatichypertrophy ✗ Glaucoma ✗ Intestinal Obstruction

SUMMARY

- Parkinson is not cure able but we can control its manifestation.
- L-Dopa not given to drug induced Parkinsonism patient.
- Long term using of L-Dopa causes fluctuation and dyskinesia.
- To Reduce the dose of L-Dopa and prevent the fluctuation and dyskinesia
  - Give Dopamine Agonist + L-Dopa\carbidopa.
  - Give MAO-B inhibitors + L-Dopa\carbidopa.
  - Give COMT inhibitors + L-Dopa\carbidoap.
- high dose Selegiline cause hypertension crisis.
- Nonselective MAOI (Phenezline) have drug interaction with L-Dopa.
- Amantadine increases dopamine release.
- Anticholinergic drugs for drug-induced parkinsonism patient due to antipsychotics.
- All drugs have psychotic and physical side effect.

QUESTIONS

1. Neurological presentations of Parkinsonism EXCEPT:
   (A)- rigidity
   (B)- hyperkinesia
   (C)- tremor
   (D)- postural disturbances.
   (E)- poor balance

2. Carbidopa is useful in treatment of Parkinson's disease because:-
   (A) Is a precursor of levodopa
   (B) Is a dopamine receptor agonist
   (C) Prevents peripheral biotransformation of L-dopa
   (D) Prevents a breakdown of dopamine
   (E) Promotes a decreased concentration of L-dopa in the nigrostriatum

3. Great caution must be exercised in the use of this drug in parkinsonian patients who have prostatic hypertrophy :-
   (A) Benztropine
   (B) Carbidopa
   (C) Levodopa
   (D) Bromocriptine
   (E) Selegiline

4. A drug that is used in the treatment of parkinsonism and will also attenuate reversible extrapyramidal side effects of neuroleptics is
   (A) Amantadine
   (B) Levodopa
   (C) Pergolide
   (D) Selegiline
   (E) Trihexyphenidyl

QUESTIONS

5. Which one of the following statements about bromocriptine is accurate?

(A) It should not be administered to patients taking antimuscarinic drugs

(B) Effectiveness in Parkinson's disease requires its metabolic conversion to an active metabolite

(C) The drug is contraindicated in patients with a history of psychosis

(D) The drug should not be administered to patients already taking levodopa

(E) Mental disturbances occur more commonly with levodopa than with bromocriptine.

1/B - 2/C - 3/A - 4/E - 5/C

THE END

Leaders

Abullah AL-Anazi &TuqaAlkaff

E-Mail

pharmacologyteam1@gmail.com