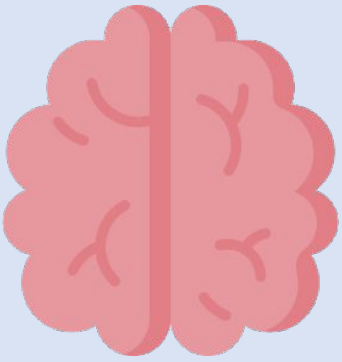

Revised & Approved

Abdullah Alsubaihi
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Pharmacology 439

MED439

Neuropsychiatry Block

Pharmacology Team 439

Helpful video

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Drugs Used in Parkinsonism

Objectives:

1-Recognize the symptoms and pathophysiology of parkinsonism

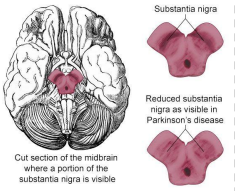
2-Understand the pharmacology of drugs used for treatment of parkinsonism.

3-Define pharmacokinetics, pharmacodynamics and side effects of different drugs used for the treatment of parkinsonism.

Editing file

Parkinson's Disease

A Progressive neurological disorder that occurs mainly in the elderly and can lead to disability unless effective treatment is provided.



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.

Dopamine Pathway

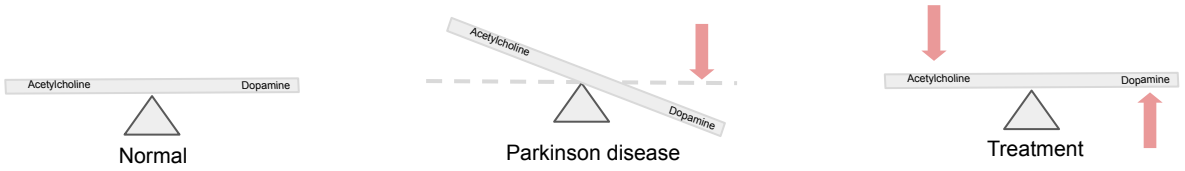
Reward Pathway

DA is manufactured in nerve cell bodies located within the ventral tegmental area (VTA) and is released in the nucleus accumbens and the prefrontal cortex

Motor Pathway

cell bodies in the substantia nigra that manufacture and release dopamine into the striatum

- Note that in parkinson's disease there is Predominance of **Ach** & Deficiency of **Dopamine**



You have to know that the imbalance must be involving dopamine deficiency. Normal dopamine and increased Ach wouldn't cause parkinson's

Causes and Characters of the Disease:

Causes

It is idiopathic disease but some causes may be:

- Genetic.
- Toxins (MPTP*= methyl phenyl tetrahydropyridine).*no need to memorise it
- Head trauma
- Cerebral anoxia.(severe hypoxia)
- Oxidative stress.
- **Drug-induced parkinson's disease e.g.**
  1- antipsychotics as haloperidol.
  2- Dopamine antagonists as metoclopramide (antiemetic) reversible upon stoppage

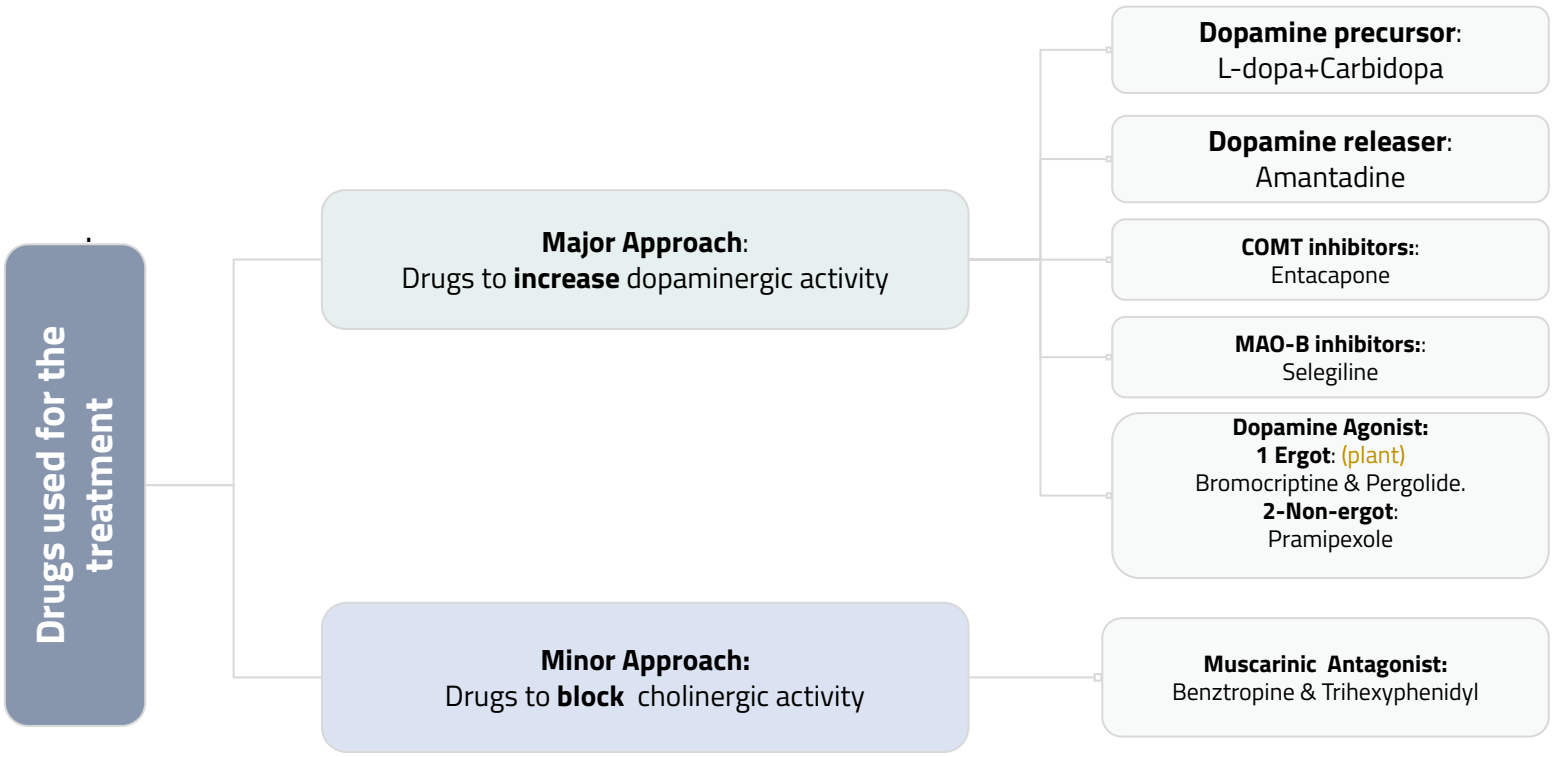
Characters

Simplified be the acronym -TRAAP-

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

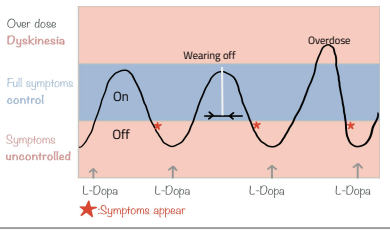
Drugs Used For the Treatment:

Parkinson's disease is untreatable due to the progressive loss of dopaminergic receptors . Therefore Drugs only maintain the quality of life



Dopamine Precursor:

Drug	Levodopa (L-Dopa) First line
Overview	• It is a precursor of dopamine • Is converted into dopamine peripherally and centrally by action of an enzyme called **dopa decarboxylase** (DC). • 99% **L-dopa** is **decarboxylated** to give dopamine in gut and liver. • 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)** (dose reduction to 1/8) **to prevent peripheral conversion of L-dopa to dopamine.**
DC inhibitors **To allow less, more effective doses of L-Dopa**	• E.g Carbidopa , Benserazide • 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 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: - **Prevent peripheral metabolism of L-Dopa** which allows the other effects to happen - Lowers the effective levodopa dose - Increase availability of levodopa to CNS. - Reduce dose of levodopa and side effects

Drug	Cont.. Levodopa (L-Dopa) **First line**
P.k	• Given orally (should be taken on empty stomach) to prevent interactions especially with proteins as L-dopa consists of amino acids • 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).
M.O.A	• Dopamine acts on dopaminergic receptors D1-D5 (G-protein linked receptors) - D1, D5. ⟶ Excitatory - D2, D3, D4 ⟶ inhibitory
Uses	• The **most efficacious therapy** 1st line • The best results of levodopa are obtained in the first few years of treatment. (Within 3-5yrs) • 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 (drug inducing Parkinson's disease as it ↓ dopamine)
ADRs	CNS effects (Psychological disorders): • Mainly depression • Vivid dreams • Delusions • Hallucinations • Confusion • Sleep disturbances (insomnia) Peripheral effect: • Anorexia, nausea,vomiting (due to stimulation of CTZ) • Cardiac arrhythmias (withdraw the drug) • Mydriasis • Orthostatic hypotension.
Limitation	• Dyskinesia (involuntary movements occurs in 40 to 90% of patients) due to fluctuating plasma levels of levodopa (in overdoses) • 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 full symptom control & Off=Akinesia or hypomobility symptoms uncontrolled) • **Wearing off effect** and on-off phenomena occur due to progression of the disease and the loss of striatal dopamine nerve terminals. (Over time there will be a gradual decrease of L-dopa effect as dopaminergic neurons are progressively being destroyed. This is why supportive "different" therapy is required 
Drug interactions **Contraindications**	• High protein meal • Pyridoxine (Vitamin B6) ↑Peripheral metabolism of L-dopa • Non-Selective MAO inhibitors (Phenelzine, Tranylcypromine) **generally MAOI with any drug that ↑catecholamines in the brain ⟶ Hypertensive crisis (Prof. Hanan)**
Contra indications	• Psychotic patient • Cardiac arrhythmias or recent cardial infarction. • Adrenomimetic amines • Glaucoma (due to mydriatic effect) • Patients with history of melanoma, Why? L-dopa is a precursor of melanin

Dopamine Receptor agonist:

1

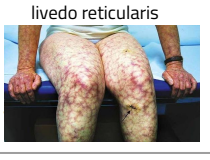
Ergot Derivatives:
Bromocriptine, Pergolide

2

Synthetics (Non-Ergot Derivatives):
Pramipexole, Ropinirole

Drug	Bromocriptine An ergot derivatives	Pramipexole A non-ergot derivatives
Overview	• Have longer duration of action than L-dopa (less likely to cause dyskinesias than levodopa) Less likely to fluctuate.	
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. (Why isn't ↑ L-dopa dose possible? to avoid risk of dyskinesia)	
P.K	• D2 agonist and partial D1 antagonist • Is given orally, absorbed from GIT • T½ = 6-8 h. • Excreted in bile and feces	• D3 agonist • Is given orally • Has the advantage of being free radicals scavenger. (Anti-oxidant) • Rapidly absorbed, excreted unchanged in urine • Renal insufficiency may necessitate dosage adjustment
Uses	• Parkinson's disease (little use) • Hyperprolactinemia (Galactorrhea) increased dopamine⟶ ↓prolactin • Infertility in women caused by ↑ in prolactin levels ⟶ dopamine agonist lowers it	• Used alone as **initial therapy** or in combination with L-dopa • Drug of choice in parkinson's patients whom liver are failing
ADRs	Similar to L-dopa: • Nausea, vomiting, somnolence, postural hypotension • Cardiac arrhythmias • Confusion, hallucinations, delusions • Dyskinesias **(less prominent)**	
Contraindication	• Psychosis • Patients with peripheral vascular disease • **Ergot derivatives Only** (cause severe vasoconstriction ⟶ risk of gangrene) C.I in Peripheral vascular disease and recent **myocardial infarction** (due to to V.C and increased norepinephrine (increased CO which leads potentially to reinfarction) • Active peptic ulcer	

Dopamine releaser

Drug	Amantadine
M.O.A	• less effective than L-dopa, modest effectiveness MOA • Originally introduced as an antiviral. • main action, Inhibits dopamine reuptake, thus increases dopamine release • Acts as an antagonist at muscarinic & NMDA receptors (N-methyl-D-aspartate)
P.k	• Given orally with short half life 2-4h • Most of the drug is excreted unchanged in the urine • Less efficacious than L-dopa • Tolerance develops to its therapeutic effect after 6-8 months.
Uses	• Its 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 uses therapy • Amantadine and the anticholinergics may exert additive effects on mental functioning.
ADRs From the most common to the least common	• Nausea, anxiety, insomnia, confusion, hallucinations (dopamine like side effects) • Dry mouth, urinary retention **(anticholinergic effects)** • Restlessness and hallucinations • Ankle edema, and **livedo reticularis** rare condition, inflamed/swollen and clotted blood livedo reticularis 
Contraindication	• Anticholinergics • History of seizures or heart failure

MAO-B inhibitors

Drug	Selegiline
M.O.A	• It is a selective irreversible inhibitor of **MAO-B**, an important enzyme for dopamine metabolism. **MAO-A** →metabolism of Adrenaline, NA and Serotonin. **MAO-B**→metabolism of Dopamine • The blockade of dopamine metabolism makes more dopamine available for stimulation of its receptors
P.k	Selegiline may have neuroprotective effect due to: • **Antioxidant** activity against toxic free radicals produced during dopamine metabolism, so It slows progression of the disease. • Metabolized to desmethylselegiline, which is **anti-apoptotict.**→inhibit the degradation of dopaminergic neurons
Uses	• As monotherapy, may be effective in the newly diagnosed patient OR 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.
ADRs	**At high doses:** • It may inhibit MAO-A → **(hypertensive crises)** nonselective inhibit both MAO-A,B → ↑NA Conc. • May cause insomnia when taking later during the day. • May Increase L-dopa ADRS
Contraindication	co-administered with: • Tricyclic Antidepressants (hypertensive crisis), meperidine • Selective serotonin reuptake inhibitors (may cause hyperpyrexia, agitation, delirium, coma) • Food restriction **"low tyramine diet"** is required

COMT inhibitors*

*Female slides

Drug	Entacapone	Tolcapone
M.O.A	• 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 • Prolonged the ON-Time	
ADRs	• L-dopa side effects • Orange discoloration of urine	—

Anticholinergic Drugs

Drug	Benztropine	Trihexyphenidyl
M.O.A	• Central muscarinic antagonist, In the striatum • It has modest anti-parkinsonian action	
Uses	• Improve tremor & rigidity but have little effect on bradykinesia • **Provide benefit in drug-induced parkinsonism (due to antipsychotics)** **Drug of choice in drug induced parkinsonism** • Used during early stage of the disease or adjunct to levodopa therapy	
ADRs	• Cycloplegia • Mydriasis • Dry mouth • Urinary retention • Constipation • **At high doses:** Confusion,Delirium & Hallucinations • Trihexyphenidyl may cause withdrawal symptoms in high doses e.g. anxiety and tachycardia	
Contraindication	• Prostatic hypertrophy, Because they cause prostatic hypertrophy • Glaucoma, due to the cycloplegia and mydriasis • Intestinal obstruction, The group itself slows the intestinal motility	

Summary

Class	Drug	M.O.A	Uses	ADRs D.I
Dopamine Precursor	★ **Levodopa (L-Dopa)** **First line**	Dopamine acts on dopaminergic receptors D1-D5 - 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**	CNS effects (Psychological disorders): • Delusions • Hallucinations • Confusion • Sleep disturbances (insomnia) Peripheral effect: • Cardiac arrhythmias • Orthostatic hypotension.
Dopamine Receptor agonist	**Bromocriptine**	-	• Hyperprolactinemia (Galactorrhea) • **Infertility in women**	Similar to L-dopa: • Nausea,, postural hypotension • Cardiac arrhythmias • Confusion, hallucinations, delusions • Dyskinesias **(less prominent)**
	Pramipexole	-	• Used alone as **initial therapy** or in combination with L-dopa. • DOC in parkinson's with liver failure	
Dopamine releaser	**Amantadine**	• less effective than L-dopa, • Inhibits dopamine reuptake, thus increases dopamine release • Acts as an antagonist at muscarinic & NMDA receptors (N-methyl-D-aspartate)	• Its 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 uses therapy	•(dopamine like side effects) • Dry mouth, urinary retention **(anticholinergic effects)** • Restlessness and hallucinations • Ankle edema, and **livedo reticularis**
MAO-B inhibitors	**Selegiline**	• It is a selective irreversible inhibitor of **MAO-B**	OR Adjunctive to levodopa/carbidopa in later-stage parkinsonism to: • Reduce the required dose of levodopa • Delay the onset of dyskinesia and motor fluctuations	**At high doses:** • It may inhibit MAO-A → **(hypertensive crises)** • May cause insomnia when taking later during the day.
COMT Inhibitors	**Entacapone**	• Acts **peripherally** to inhibit COMT enzyme required for L-dopa degradation	Used as adjuvant to L-dopa + carbidopa to • Decrease fluctuations • Improve response • Prolonged the ON-Time	• L-dopa side effects • **Orange discoloration of urine**
	Tolcapone	• **Peripheral and central** COMT inhibitor		-
Anticholinergic Drugs	**Benztropine** **Trihexyphenidyl**	• Central muscarinic antagonist • It has modest anti-parkinsonian action	• **Drug of choice in drug-induced parkinsonism (due to antipsychotics)** • Used during early stage of the disease or adjunct to levodopa therapy	• Cycloplegia • Mydriasis • Dry mouth • Urinary retention • Constipation • **At high doses:** Confusion,Delirium & Hallucinations

Summary from Dr's slides

1 **Main treatment :**
Levodopa and carbidopa

2 **Mild cases :**
- Selegiline
- Amantadine
- Anticholinergics

3 **All other :**
bromocriptine (dopamine agonist), selegiline (monoamine oxidase-B inhibitor),amantadine (enhances dopamine release) and benztropine (muscarinic receptor antagonist, that is used for parkinsonism caused by antipsychotic drugs.

*Extra, #team438

Dr's case*

M. S. is a 60-year old architect who designs buildings. His drawings are very detailed and they must be drawn to a specific scale. During the past month he has developed a slight tremor in his right hand that causes some embarrassment but does not interfere with function. He has, however, noticed that his writing and drawing have gotten much smaller, causing problems with his work. His primary care physician has referred him to a neurologist for evaluation. On examination, the neurologist notes some motor rigidity in the right arm. He also observes a slight slowing in the patient's walk and a reduction in the swing of his arms as he walks. What is the diagnosis, and how should the patient be treated?

Ans:
The patient is in early-stage parkinsonism, most likely idiopathic (Parkinson's disease). Clinically, the disease is very mild and the neurologist might consider not treating him at this point, but because the micrographia interferes with his work, the neurologist decides to prescribe medication.
Several drugs can be used to treat early-onset parkinsonism, the most commonly used are the dopamine receptor agonists (pramipexole, ropinirole, pergolide) amantadine is also a possibility, and some people get an acceptable response to selegiline (the MAO inhibitor)
Levodopa–carbidopa could also be used; however, most clinicians prefer to delay its use until absolutely needed because of the adverse effects, such as motor fluctuations and dyskinesias, that accompany long-term use of levodopa.

Q1/ 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.

A1/ A

Q2/ 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

A2/ A,E

MCQs

Q1: A selective monoamine oxygenase B (MAO B) inhibitor			
A- Levodopa	B-Amantadine	C-Selegiline	D-Entacapone
Q2: A 63-year-old man recently diagnosed with Parkinson disease started treatment with levodopa/carbidopa. Which of the following actions most likely mediated the therapeutic effect of levodopa in the patient's disease?			
A- Downregulation of dopaminergic receptors in the striatum	B-Increased synthesis of dopamine in the subthalamic nucleus	C-Increased synthesis of dopamine in the striatum	D-Inhibition of dopa decarboxylase in the striatum
Q3: The main reason for giving levodopa, the precursor of dopamine, instead of dopamine is ?			
A- Dopamine does not cross the blood-brain barrier	B-Dopamine may induce acute psychotic reactions	C-Dopamine is intensively metabolized in humans	D-All of the above
Q4: A peripheral inhibitor of catechol-O-methyltransferase (COMT)			
A- Levodopa	B-Amantadine	C-Entacapone	D-Benztropine
Q5: 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
Q6: A 67-year-old man presented to the clinic complaining of vague chest pains and difficulty in breathing. Medical history revealed that the patient had been diagnosed with Parkinson disease 10 years earlier and had been using several antiparkinson drugs since then. Physical examination revealed prominent breath sounds and end-inspiratory crackles, primarily at the lung bases. An x-ray showed extensive honeycombing. A diagnosis of pulmonary fibrosis was made. Which of the following drugs would have been most likely to cause the patient's disorder[1]			
A- Bromocriptine	B-Benztropine	C-Selegiline	D-Amantadine
Q7: The mechanism of carbidopa's action is?			
A- Stimulating the synthesis, release, or reuptake of dopamine	B-Inhibition of dopa decarboxylase	C-Stimulating dopamine receptors	D-Selective inhibition of catechol-O-methyltransferase
Q8: Which of the following antiparkinsonian drugs has also been used to treat hyperprolactinemia?			
A- Benztropine	B-Amantadine	C-Levodopa	D-Bromocriptine

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

(1) Bromocriptine is an ergot-derived dopamine agonist. Ergot-derived drugs may cause connective tissue proliferation leading to fibrosis in different organs, including pulmonary, pleural, and retroperitoneal fibrosis. The exact mechanism of this adverse effect is still unknown, but bromocriptine is no longer used in Parkinson disease due to this effect.

SAQ

Q1)A 29-year-old woman is undergoing treatment for secondary infertility after resection of a pituitary adenoma. She is reviewed in the endocrinology clinic and tells you that she has been suffering from headache, dizziness on standing, and symptoms suggestive of Raynaud's phenomenon since starting a new medication prescribed at her previous clinic appointment. Which drug is most likely to be the cause of these adverse effects?

Q2) Mention 3 adverse effects may be caused Levodopa?

Q3) 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?

Q4) A 72-year-old man with a 4 -year history of Parkinson's disease comes to the physician for evaluation of his medication. since his last visit one year ago, he has had increased tremor and bradykinesia up to an hour before his next scheduled dose and sometimes feels like he does not respond to some doses at all. one week ago he was entirely unable to move for about a minute when he wanted to exit an elevator. the physician prescribes a drug that increases the bioavailability of levodopa by preferentially preventing its peripheral methylation by COMT.

a) The drug was most likely prescribed by the physician was?
b) Name another drug that has the same M.O.A?

Answers

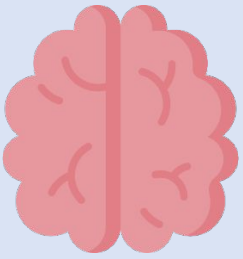
A1) Bromocriptine

A2) depression, hallucination, delusions...

A3) a) amantadine. b) Inhibits dopamine reuptake, thus increases dopamine release. Acts as an antagonist at muscarinic & NMDA receptors (N-methyl-D-aspartate)

A4) a) Entacapone b) Tolcapone

Feedback Form



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