BP404TP

B. Pharm

Drugs used in Parkinsonism

To Understand better

Parkinson's Disease

A progressive **neurodegenerative** diseases disorder that occurs mainly in the elderly and can lead to disability unless effective treatment is provided.

Pathphysiology

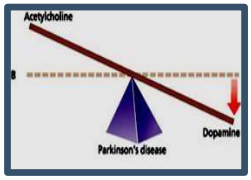
This **movement** disorder occurs mainly due to **dopamine/acetylcholine imbalance** in **basal ganglia** (caudate nucleus, substantia nigra & corpus striatum) that is involved in motor control.

Dopamine pathway

Reward pathway	Motor 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.**	cell bodies in the **substantia nigra** that manufacture and release dopamine into the **striatum**.

In Parkinson's disease

Predominance of Ach



Deficiency of dopamine

Parkinson's Disease

Characters	Causes
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.	It is **idiopathic** disease but 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 antagonists** as **metoclopramide** (antiemetic).

Drug Treatment

Main approach

Drugs to **increase** **dopaminergic** activity.

- **Increase** central DA synthesis
  - **(DA precursors):** **L-dopa**, **L-dopa + Decarboxylase inhibitor**.
- **Inhibition** of DA metabolism
  - ○**COMT inhibitors** (catechol-O-methyltransferase inhibitors)
  - ○**MAO-B inhibitors**
- DA receptor agonists
- DA releaser: **amantadine**

Minor approach

Drugs to **block** **cholinergic** activity → **Muscarinic antagonists**

Take a quick look on the treatment of parkinson's disease

1. In mild cases, **selegiline**, **amantadine** or **antichlinergics** can be used.
2. **Levodopa** and **carbidopa** is the **main** treatment
3. All other medications are adjuncts to levodopa therapy
4. Other useful drugs include :
   - **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.

Mind map

Drugs used in parkinsomnism

- **Mild cases** → **Selegiline**, **Amantadine** or Anticholinergics
- **Main treatment** → **Levodopa** + **Carbidopa**
- **Adjuncts to Levadopa** → All other medications
- **Other useful drugs**
  - Dopamine agonist → **Bromocriptine**
  - MAO-**B** inhibitors → **Selegiline**
  - Enhance dopamine release → **Amantadine**
  - Muscarinic receptor antagonist → **Benztropine** and **trihexyphenidyl**

It is a minor treatment, if he can not take dopamine → give him anti-muscarinic drugs.

Dopamine processing in a synapse:

After release dopamine can either be →
taken up again by the presynaptic terminal, or broken down by enzymes.

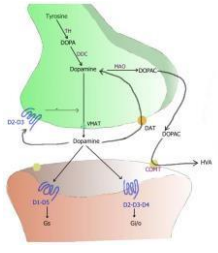
Regarding the picture:

TH: tyrosine hydroxylase **DOPA**: L-DOPA **DAT**: dopamine transporter

DDC: DOPA decarboxylase **VMAT**: vesicular monoamine transporter 2

MAO: Monoamine oxidase **COMT**: Catechol-O-methyl transferase

HVA: Homovanillic acid



Drugs that increase dopaminergic activities (DA precursors)

Drug

Levodopa (L-dopa)

Pharmacokinetic

> a body shamer say's:
> leave dopa = لابا اوكرتا
> *Body shaming: the act of discriminating against other body types.

- It is a precursor of dopamine.
- Is converted into dopamine via **dopa decarboxylase** (DC) peripherally and centrally. → Pathway of L-dopa
- Dopamine formed peripherally is metabolized by **MAO** (monoamine oxidase) & **COMT** (catechol-o-methyl transferase)enzymes).
- 99% L-dopa is **decarboxylated** to give dopamine in gut and liver by **decarboxylase** enzyme.
- **1%** crosses **BBB** to form dopamine centrally.
- Given **orally** (should be taken on **empty** stomach –especially proteins-).
- Absorbed from the small intestine and taken up to CNS by **active** transport system. → so if we take a protein meal → uptake process done by competition process between the amino acids & L-dopa.
- **Short** duration of action (**t½ = 2 hs**) → (fluctuation of plasma concentration).

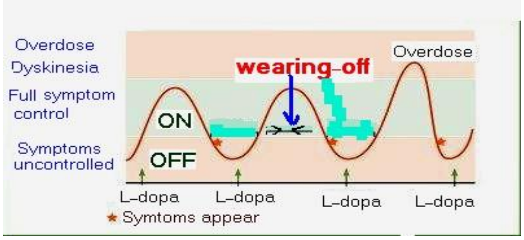
Limitation

Limitation of L-DOPA treatment:

- **Dyskinesia** (involuntary movements occurs in 40 to 90% of patients)
  → due to fluctuating plasma levels of **levodopa**.(صقتيو ديزي تباث ريغ هزيكرت ينعي)
- 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) → قي تكلإ نولأا نا اهانعم ل
  أب ابود للاإ قح
- **On-off phenomenon** (On= improved mobility & Off=Akinesia or hypomobility)→ bc of short $T_{1\backslash 2}$

  On في ءاودلا therapeutic range
  Off تكرحلاب ضيرملا رقف هلاعف قف مدلاا في هزيكرت قل ءاودلا . حار امق هل لوقو سلاج نوكي لاف
  تكرحلاب مكحتلا في هلاعف قل يلاتلاو قل ءاودلا زيكرت ناشع اذه لك ؛ملاكلا في هقتي وأ ؛موقي ردقي

  - Wearing off effect and on-off phenomena occur due to → **progression** of the disease and the **loss** of striatal dopamine nerve terminals.



therapeutic لااف ءاودلا نايعي ،رضخلاا يلطتسلااف
on phenomenon ريصيو اندع لاrange

فوق لاطتسلا يبصر هزيكرت يلاع في مدلاا ،تحتو لاطتسلا يفل
off phenomenon لاتركيز ،وصير اندع لا

drug

Levodopa (L-dopa) Cont.

P.D

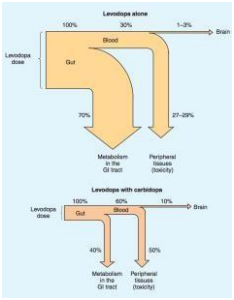
- Dopamine acts on dopaminergic receptors D1-D5 (**G-protein linked receptors**)
  - **D1, D5** → Excitatory.
  - **D2, D3, D4** → Inhibitory.

prescription

- **L-dopa** is usually combined with **carbidopa** or **beserazide** (**DC inhibitor**).

→ Why? → because **Carbidopa** is a peripheral **dopa decarboxylase inhibitor** → prevent GIT & peripheral conversion of L-dopa to dopamine. → It acts only peripherally because it does **not** cross BBB → ↑ $T_{1\backslash 2}$ → Why only peripherally? Because when it acts also centrally, we won't take the benefit because L-dopa will not degraded to produce dopamine.

- **Benefit of L-dopa + carbidopa combination**:
  - **Lowers** the effective levodopa dose.
  - **Increase availability** of L-dopa to CNS.
  - **Reduce side effects** of L-dopa.



Click on the pic

Indications

- The most efficacious therapy. → 1st line treatment.
- 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.

Drug interaction

- High proteins meals.
- **Pyridoxine** (Vitamin **B6**). → ↓ effect of L-dopa due to ↑ peripheral metabolism by Vit.B6.
- **Nonselective MAO inhibitors** (**phenelzine**). → **Hypersensitivity crisis** due to ↑ catecholamines → sever elevation of BP → Do not take MAOIs w\ any drug has catecholamine effects, because it will increase their level → hypersensitivity crisis. * **tyramine** has similar effect of MAO inhibitors.

ADRs

Peripheral

- Anorexia, nausea, **vomiting** (due to stimulation of chemoreceptor trigger zone). → They are more common w\ combination of DC inhibitors.
- Cardiac arrhythmias. → because of increased catecholamines peripherally.
- **Mydriasis** → May occur and participate in acute glaucoma.
- **orthostatic (postural) hypotension** → w\ higher doses.

CNS

Mainly **depression**, delusions, confusion, insomnia, **hallucinations**.

C.I

- Psychotic patient. → bc it may exacerbate the mental disturbance.
- **Glaucoma** (due to mydriatic effect).
- Patients with history of **melanoma.**

Why? → L-dopa is a precursor of **melanin** → so it may activate malignant melanoma.

Dopamine receptor agonists

Overview

- Have **longer** duration of action than **L-dopa** (less likely to cause **dyskinesias** than **levodopa**) **Dyskinesia** 3:01 min

Clinical use

- **As monotherapy,** the dopamine agonists are **less effective** than **levodopa**. Thus can only be used as initial therapy for **early** stages of the disease.
- **In advanced stages, dopamine agonists are used as an adjunct to levodopa,** they may contribute to clinical improvement and reduce **levodopa** dosage needs.
- Lippincott: Dopamine agonists may delay the need to use *levodopa* therapy in early Parkinson disease and may decrease the dose of *levodopa* in advanced Parkinson disease.

Ergot derivatives: Bromocriptine, pergolide	**Non ergot derivatives:** Pramipexole

Bromocriptine

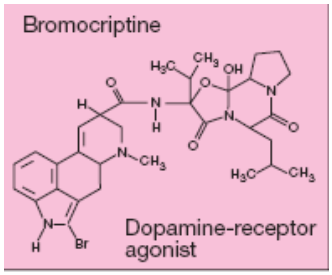
- D2 agonist
- Is given orally
- T½ = 6-8 h. Longer than Levodopa (t½ =2 h)
- Used for the **treatment** of:

1. Parkinson's disease
2. Hyperprolactinemia (**galactorrhea**): a condition of elevated serum prolactin «نومرهلا», which induces infertility in women. Secretion of prolactin is under **inhibitory** control by dopamine. → املك نيعلولا يوتسم قوف تيكلاورلا داز.
3. **Infertility in women**.

Pramipexole

- D3 agonist
- Used alone as **initial therapy** or in combination with L-dopa.
- Is given **orally**, excreted unchanged in urine.
- Has the advantage of being **free radicals scavenger**.

→ For example, *cimetidine*, which inhibits renal tubular secretion of organic bases, increases the half-life of *pramipexole* by 40%.



Ergot refers to a group of fungi of the genus Claviceps. This fungus grows on rye and

Dopamine receptor agonists (cont.)

Adverse effects

Similar to **L-dopa**:

- Nausea, vomiting, postural hypotension
- Cardiac arrythmias
- **Confusion, hallucinations, delusions**
- Dyskinesias (less prominent).

Contraindications

- **Psychosis**
- Peripheral vascular disease (**only ergot derivatives**, which cause severe vaso**constriction** and may cause gangrene with high dosage)
- Recent **myocardial infarction** .

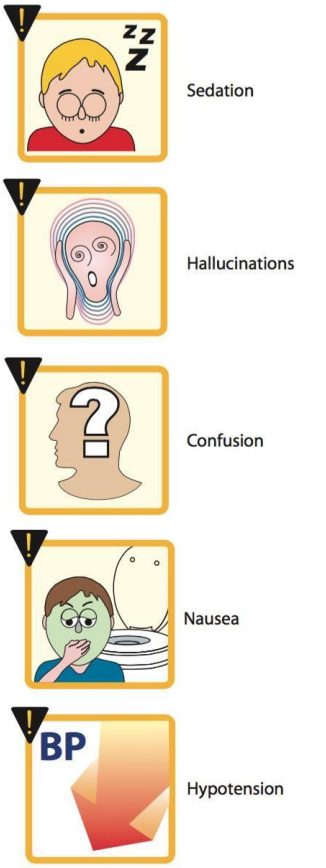


Figure 8.11
Some adverse effects of dopamine agonists.

The actions of *bromocriptine* are similar to those of *levodopa*, except that hallucinations, confusion, delirium, nausea, and orthostatic hypotension **are more common**, whereas **dyskinesia is less prominent**. In **psychiatric illness**, *bromocriptine* and *levodopa* may cause the mental condition to worsen. **Serious cardiac problems** may develop, particularly in patients with a history of **myocardial infarction**. In patients **with peripheral vascular disease**, a worsening of the vasospasm occurs, and in patients with **peptic ulcer**, there is a worsening of the ulcer. Unlike the ergotamine derivatives, *pramipexole* and *ropinirole* **do not exacerbate peripheral vasospasm**, and they do not cause fibrosis. Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are among the more distressing side effects of these drugs, **but dyskinesias are less frequent than with *levodopa*.**
- Lippincott, page 106

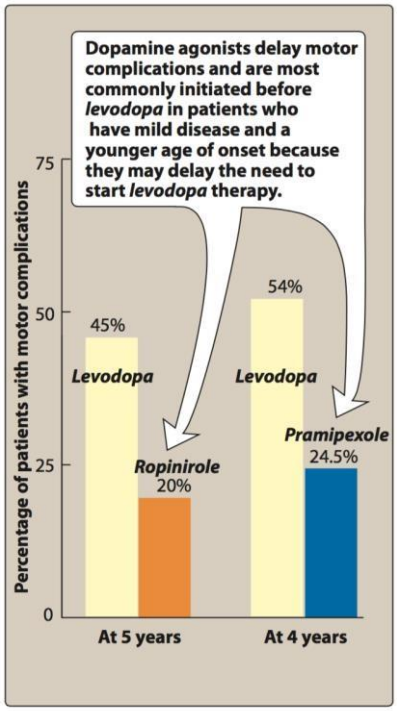
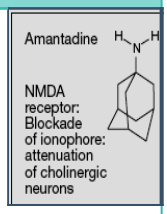


Figure 8.12
Motor complications in patients treated with *levodopa* or dopamine agonists.

Amantadine

Characteristics



- originally introduced as an **antiviral**.

Action:

1. **Increases dopamine release**. → Also decrease the reuptake of DA.
2. Acts as an **antagonist at muscarinic receptors**
3. **Antagonist at NMDA** receptors (N-methyl-D-aspartate) (glutamate receptors)

Administration:

- given **orally** with short half life.

Excretion:

- most of the drug is excreted unchanged in the **urine**

Efficacy:

- Less efficacious than L-dopa
- **Tolerance** develops to its therapeutic effect after **6-8** months. (tolerance is after 3-5 years for levodopa)
- Its benefits last only for **short period** and only used for **L-dopa resistance** (which is caused by variation in response among patients)
- **Amantadine** and the anticholinergics may exert **additive effects on mental functioning**. (A muscarinic receptor antagonist effect)
- Useful in the **early stages** of parkinsonism or as an **adjunct to levodopa therapy**.

Adverse effects

- Nausea, anxiety, insomnia, confusion, hallucinations (**dopamine** like side effects).
- Dry mouth, urinary retention (**anticholinergic** effects).
- Restlessness and **hallucinations** (**NMDA antagonist**). → NMDA is a type of glutamate receptors & glutamate is an excitatory neurotransmitter, antagonizing it will thus cause restlessness and hallucinations.
- **Ankle edema**, and livedo reticularis. 

It was accidentally discovered that the antiviral drug *amantadine* [a-MAN-ta-deen], which is effective in the treatment of influenza has an antiparkinsonism action. *Amantadine* has several effects on a number of neurotransmitters implicated in causing parkinsonism, including **increasing the release of dopamine, blockading cholinergic receptors, and inhibiting the N-methyl-D-aspartate (NMDA)** type of glutamate receptors. The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur. *Amantadine* is less efficacious than *levodopa*, and tolerance develops more readily. However, *amantadine* has fewer side effects. The drug has little effect on tremor, but it is more effective than the anticholinergics against rigidity and bradykinesia.

- Lippincott, page 107

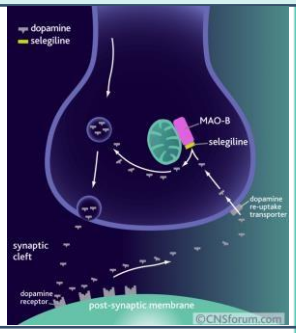
Monoamine oxidase-B (MAO-B) inhibitors

Selegiline

Drug

Mech. of action

- It is a **selective irreversible inhibitor of MAO-B**, an important enzyme for **dopamine metabolism**.
  *MAO-A → metabolize **NE, 5-HT, DA**
- The blockade of dopamine metabolism makes **more** dopamine available for stimulation of its receptors.



P.K

Metabolized to **desmethylselegiline**, which is **anti-apoptotic**.
- **Selegiline** may have **neuroprotective effect**.
- Has **anti-oxidant activity** against toxic free radicals produced during dopamine metabolism.

Indications

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**) → as a result, do not prescribe seligiline w\ drugs that increase the level of catecholamines.
- May cause **insomnia** when taking later during the day.

C.I

Should NOT be co-administered with:
- **Trycyclic** Antidepressants
- Selective serotonin reuptake inhibitors (this causes **hyperpyrexia**, agitation, delirium, coma.) → Serotonin toxicity.
- Food restriction "**low tyramine diet**" is required. → increase release of E & NE → sever elevation in BP (**cheese effect**)

COMT Inhibitors

(Catechol-O-methyl transferase) Inhibitors

Drug	Entacapone	Tolecapone
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. - **Tole** = Total = Central & peripheral
Indications	Used as adjuvant to **L-dopa** + **carbidopa** to: - Decrease fluctuations - Improve response - Prolonged the **ON-Time** → ركّا نقو سلاج نيلولا نلا ضيرملا تلاح نسحي	
ADRs	- **L-dopa** side effects. - **Orange** discoloration of urine.	

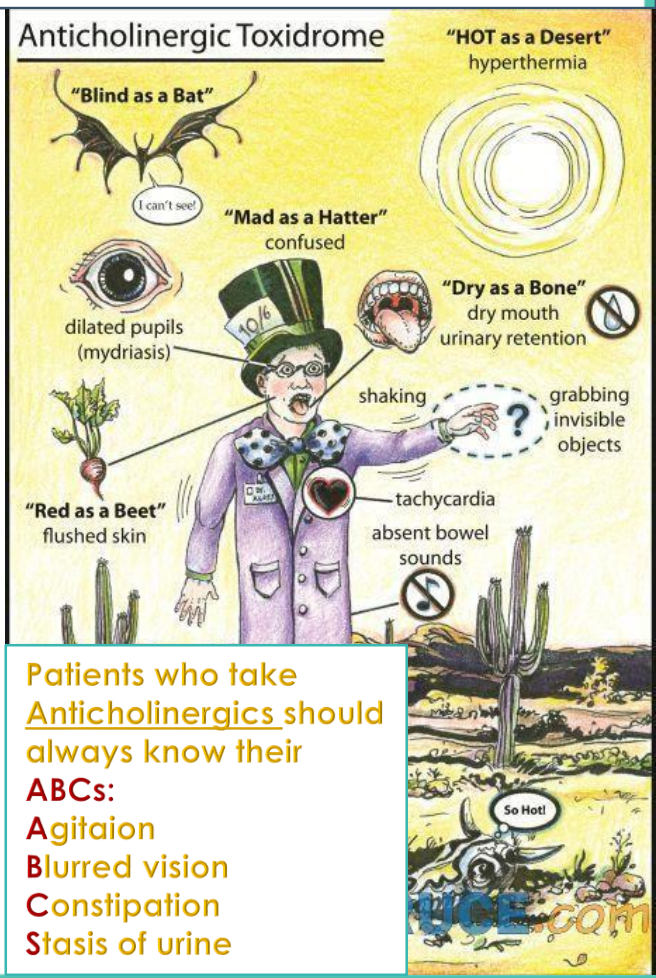
Anticholinergic Drugs

Drug	Benztropine	Trihexphenidyl
MOA	- **Central muscarinic antagonist**. - It has **modest** anti-parkinsonian action.	
Indications	- **Improve tremor & rigidity**. (but have little effect on **bradykinesia**. - Provide benefit in **drug-induced parkinsonism** (due to **antipsychotics**). - Used during **early** stage of the disease - Used as an **adjunct** to **levodopa** therapy.	

ADRs	- Cycloplegia
	- Mydriasis
	- Dry mouth
	- Urinary retention
	- **Constipation**
		- **At high doses**:
		  - Confusion
		  - Delirium
		  - Hallucinations

C.I	- Prostatic hypertrophy - Glaucoma - **Intestinal obstruction**.	

Figure 8.14
Adverse effects of acetyl-cholinesterase inhibitors.



Patients who take Anticholinergics should always know their ABCs:
Agitaion
Blurred vision
Constipation
Stasis of urine

Summary-1

Levodopa (L-dopa)

P.D Drug

– ↑ Central DA synthesis. - G-protein linked receptor

P.K

- Converted to dopamine via **DC** (dopa decarboxylase) peripherally & centrally.
- Dopamine formed peripherally is metabolized by MAO & COMT.
- Orally (**empty** stomach)
- Taken by CNS by **active** transport system.
- T½ = 2h.

prescription

- L-dopa is combined with carbidopa or beserazide (**DC inhibitor**).
- Carbidopa is a peripheral DC inhibitor → prevent peripheral conversion of L-dopa to dopamine.
- Benefit of L-dopa + carbidopa combination:
  - Lowers the effective levodopa dose.
  - Increase availability of L-dopa to CNS.
  - Reduce side effects of L-dopa.

Indications

- The most efficacious therapy.
- 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.

Interaction

- High proteins meals, Pyridoxine (Vitamin **B6**), Nonselective MAO inhibitors (phenelzine).

Limitation

Limitation of L-DOPA treatment:

- **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.
- **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.

ADRs

Peripheral effects:

- Anorexia, nausea, vomiting
- Cardiac arrhythmias.
- Mydriasis, orthostatic hypotension.

CNS effects:

Mainly **depression**, delusions, confusion, insomnia, hallucinations.

C.I

- Psychotic patient.
- Glaucoma - Patients with history of melanoma

Summary-2

Dopamine receptor agonists

Drug	Ergot derivatives: pergolide, **Bromocriptine**	Non ergot derivatives: **Pramipexole**
P. D	- D2 agonist.	- D3 agonist.
P. K	- Longer T½ than levodopa. - Given orally.	
Indications	- Parkinson's disease. - Hyperprolactinemia (galactorrhea) - Infertility in women.	- Used alone as **initial therapy** or in combination with L-dopa. - Has the advantage of being free radicals scavenger.
	- **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.	
ADRs	- Similar to L-dopa: - Nausea, vomiting, postural hypotension. - Cardiac arrythmias - Confusion, hallucinations, delusions. - Dyskinesias (less prominent).	
C.I	Psychosis, Peripheral vascular disease (for ergot **derivatives** only), Recent myocardial infraction.	

Drug	**Amantidine** (Antiviral)
P. D	- ↑ Dopamine release. - Antagonist at **muscarinic** receptors. - Antagonist at **NMDA** Rs. - Efficacy: Less efficacious than L-dopa, Tolerance after 6-8 months & **Amantadine** and the anticholinergics may exert **additive effects on mental functioning**.
P.K	Orally, short T½ , excreted unchanged in the urine.
Indications	- Its benefits last only for **short period** and only used for **L-dopa resistance.**
ADRs	- Nausea, anxiety, insomnia, confusion, hallucinations (dopamine like side effects). - Dry mouth, urinary retention (anticholinergic effects). - Restlessness and hallucinations (NMDA antagonist).

Drug	**Selegiline**		
P. D	- **selective irreversible inhibitor of MAO-B.** → imp for dopamine metabolism. → more dopamine available. - Has anti-oxidant activity against toxic free radicals produced during dopamine metabolism.		
P.K	- Metabolized to desmethylselegiline, which is anti-apoptotic.		
Indications	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: - May inhibit MAO-A → (hypertensive crises) - May cause **insomnia** when taking later during the day.	C.I	- Should **NOT** be co-administered with **Trycyclic** Antidepressants or selective serotonin reuptake inhibitors or Food restriction "low **tyramine** diet" is required.

Summary-3

	COMT inhibitors	Anti-cholinergic
Drug	**Entacapone & Tolecapone**	**Benztropine & Trihexphenidyl**
P.D	- Act <u>peripherally</u> → Both - Acts Centrally → Tolcapone - Inhibit **COMT** enzyme which is required for **L-dopa** degradation. - Diminishes peripheral metabolism of **L-dopa**.	- Central muscarinic antagonist. - It has modest anti-parkinsonian action.
Indications	Used as adjuvant to **L-dopa** to: - Decrease fluctuations - Improve response - Prolonged the **ON-Time**	- Improve tremor & rigidity. (but have little effect on **bradykinesia**). - Provide benefit in drug-induced parkinsonism (due to antipsychotics). - Used during **early** stage of the disease - Used as an adjunct to levodopa therapy.
ADRs	- **L-dopa** side effects. - **Orange** discoloration of urine.	Cycloplegia, Mydriasis, Dry mouth, Urinary retention, Constipation. - <u>At high doses</u>: Confusion, Delirium, Hallucinations.
C.I		Prostatic hypertrophy, Glaucoma, **Intestinal obstruction**.