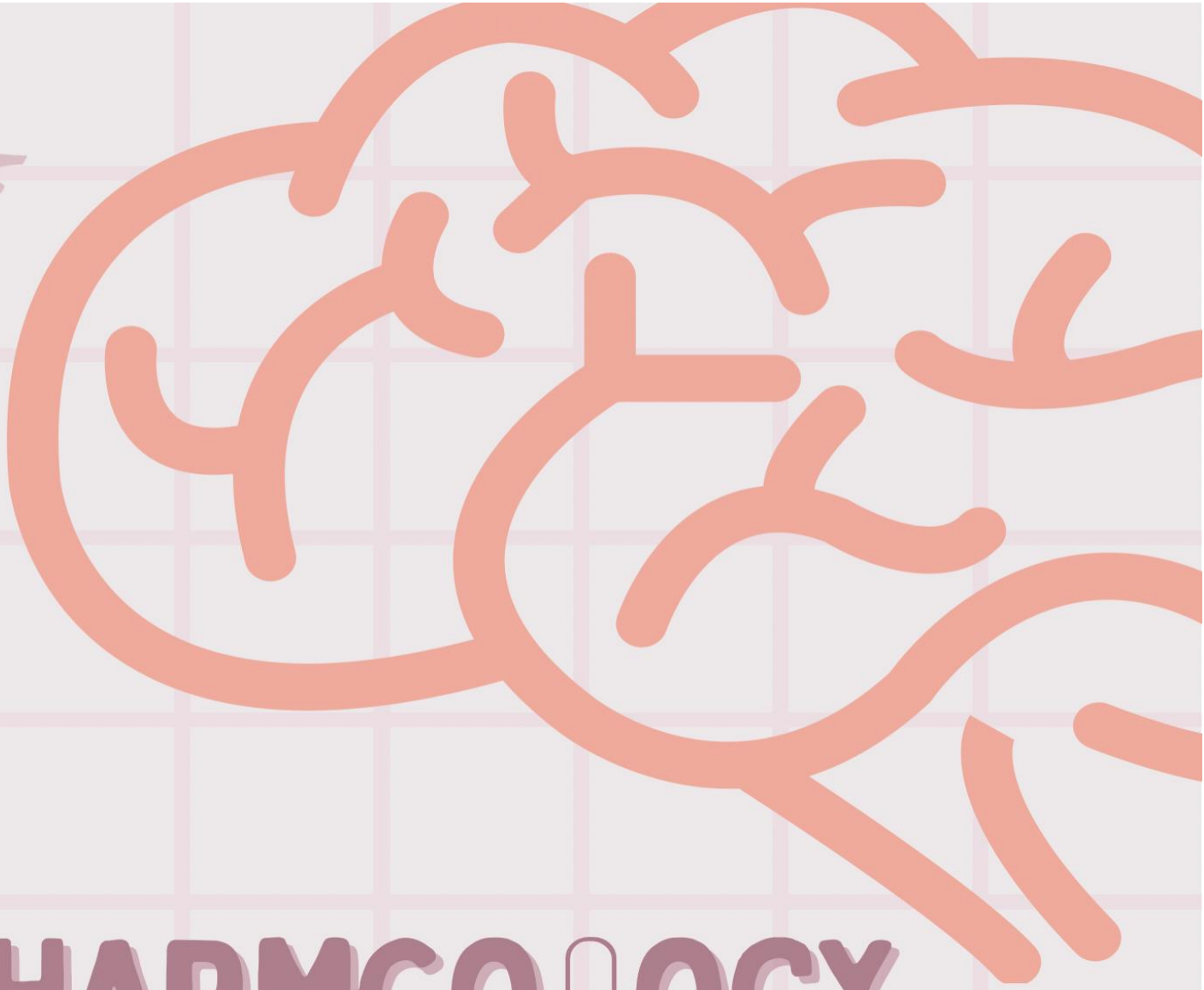

# PHARMCOLOGY

SHEET NO. 10

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## Parkinsonism drugs:

Parkinsonism:

• Is characterized by a combination of ***rigidity***, ***bradykinesia***, ***tremor at rest***, & ***postural instability***.

• **Cognitive decline** may occur as the disease advances.

• Is generally a **progressive incurable** disorder.

• Associated with **decreased dopamine concentration in the substantia nigra** ➡️ …

1. **cholinergic predominance**.
2. **release of the inhibition** of output of GABAergic cells in the corpus striatum.

No dopaminergic neurons = no inhibition.

• There is a loss of dopaminergic neurons in the substantia nigra which inhibit the output of GABAergic cells in the corpus striatum.

• Can be **precipitated by dopamine receptor antagonists (antipsychotics)**.

• **MPTP** (methylphenyl tetrahydropyridine) ▯ **destruction of nigrostriatal neurons**.

• Neurotoxins & oxidation reactions generating **free radicals** may participate in pathogenesis of idiopathic parkinsonism.

• **Genetic factors** are involved in ~10-15% of cases. so it tends to be in families.

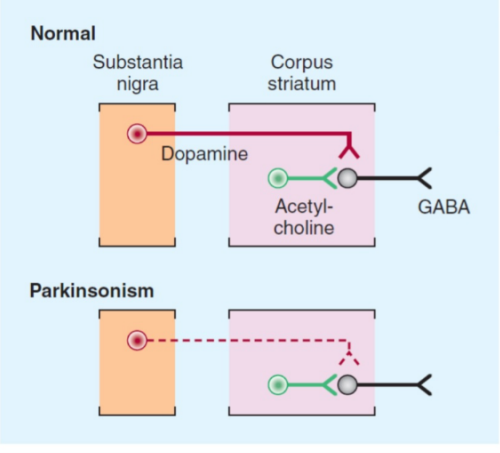



**FIGURE 28–2:** Schematic representation of the sequence of neurons involved in parkinsonism. **Top: Dopaminergic neurons (red) originating in the substantia nigra normally inhibit the GABAergic output from the striatum, whereas cholinergic neurons (green) exert an excitatory effect. Bottom: In parkinsonism, there is a selective loss of dopaminergic neurons (dashed, red).**

Drugs for Parkinsonism

1. Levodopa.
2. Dopamine receptor agonists: Bromocriptine, Pergolide, Pramipexole, Ropinirole.
3. Monoamine oxidase (MAO) inhibitors: Selegiline, Rasagiline.
4. Catechol-O-methyltransferase (COMT) inhibitors: Tolcapone, Entacapone.
5. Amantadine. (antiviral agent, accidental discovery).
6. Anticholinergic drugs: Benztropine, Biperiden, Orphenadrine, Procyclidine, Trihexyphenidyl.

## Levodopa:

• Dopamine has no therapeutic effect in parkinsonism if given systemically, because it does NOT cross the blood-brain-barrier.

• L-dopa, the immediate precursor of dopamine does enter the brain (lipid soluble) by the L-amino acid transporter, and is decarboxylated to dopamine.

• The benefits of dopaminergic antiparkinsonism drugs depend mostly on stimulation of D2 receptors, but D1 receptor stimulation may also be required for maximal benefit.

• One of the newer drugs is D3 selective.

*Dopamine has 5 receptors, D2 is the main one, D2 is an assistant.

## Pharmacokinetics:

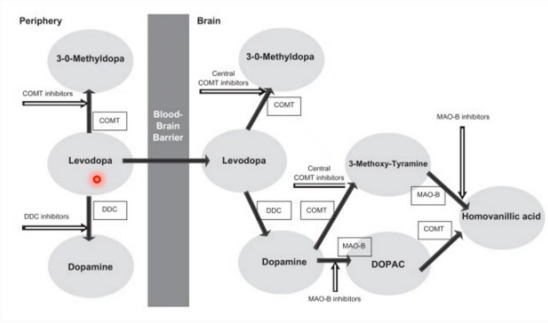
• Levodopa is **rapidly absorbed** from the intestine, but **food delays its absorption**.

• Certain amino acids from ingested food can compete with it for absorption and transport into the brain.

• Peaks in plasma **1-2 hours** after the dose.

• Plasma t½ is ~ 1-3 hours.

• It is metabolized in the *periphery* to **homovanilic acid** & **dihydroxyphenyl acetic acid**, and only 1-3% of the dose enters the brain.




• The rest is decarboxylated to **dopamine** in the *periphery* and does not enter the brain.

• Therefore, it should be given in large doses if used alone.

Note: what happens in the periphery also happens centrally (exactly).

• 65% of the dose appear in urine within 8 hours of an oral dose.

• **The peripheral metabolism is reduced by giving a peripheral dopa decarboxylase inhibitor, carbidopa,** which does **not** enter the brain ➡️ higher plasma levodopa levels (10% of dose enter the brain), and longer half-life.

• Carbidopa reduces levodopa dose by 75%.

## Therapeutic Use:

• Levodopa can ameliorate all of the clinical features of parkinsonism, particularly the **bradykinesia** & the **disabilities** resulting from it.

• One problem: on administration, 1/3 of patients respond well, and 1/3 less well. The remainder are either not able to tolerate the medication or do not respond at all.

• **Tolerance develops** to levodopa, & responsiveness may be lost completely because of the **disappearance of dopaminergic nigrostriatal nerve terminals** due to progressive neuronal damage, or some **pathologic process involving dopamine receptors**.

• Usually the benefits begin to diminish after about **3-4 years** of therapy.

• It does **not** stop the progression of parkinsonism, but it may reduce mortality rate.

• Levodopa is usually given in **combination with carbidopa**, which is available as 25/100 and 25/250 (**carbidopa/levodopa**) (in the same pill we have both carbidopa & levodopa).

• It should be taken 30–60 minutes **before** meals.

## Adverse Effects:

### A. Gastrointestinal effects:

• *When given without carbidopa*, ~ 80% of patients develop **anorexia**, **nausea & vomiting**. The vomiting is due to stimulation of the chemoreceptor trigger zone located in the brain stem but **outside** the BBB. Tolerance develops to vomiting.

• **Domperidone** (antiemetic, a D2 receptor antagonist, and it is a prokinetic drug, we can give it cause it doesn't cross the BBB, and vomiting centers are also outside the BBB, so doesn't interefere with L-dopa) it may relieve persistent nausea.

• *When given with carbidopa*, less than 20% of patients experience this adverse effect.

### B. Cardiovascular effects:

1. Cardiac **arrhythmias** including **tachycardia**, **ventricular extrasystoles** & **atrial fibrillation** due to increase catecholamine formation peripherally.

• *Reduced when levodopa is given in combination with carbidopa.*

2. **Postural hypotension** is common but often asymptomatic and tend to diminish with

continuing treatment.
3. **Hypertension** occurs especially in the presence of nonselective **MAOIs**, **sympathomimetics**, & with **massive levodopa doses**.

**C. Dyskinesias:** (abnormal movement)

• Occur in 80% of patients of patients receiving levodopa therapy for more than 10 years.
• Vary between patients but tend to be constant in individual patients.
• It is dose-related.
• **Choreoathetosis** (chorea in latin means dancing, and athetosis means twisting, it it an abnormal movements) of the **face** and **distal extremities** is the most common.

**D. Behavioral effects:**

• **Depression, anxiety, agitation, insomnia, somnolence, delusions, hallucinations, nightmares, euphoria**, and other changes in mood or personality.
• These adverse effects are **more common** when **levodopa** is given in combination with **carbidopa**. These effects are dose-dependent, & carbidopa increases the

**E. Fluctuations in response:**

1. **Related to timing** of levodopa intake: (When drug levels decrease in the body)
**Wearing-off reactions** or **end-of-dose akinesia**.
2. **Unrelated to timing** of levodopa intake: (happens any time)
• "**On-off phenomenon**". Off-periods of marked akinesia alternate over the course of a few hours with on-periods of improved mobility but often marked dyskinesia. The exact mechanism is unknown.

**F. Other adverse effects:**

• **Mydriasis**, which may precipitate an attack of **acute glaucoma**.
• **Blood dyscrasias** (abnormalities in the blood).
• **Positive Coombs test** with evidence of **hemolysis**.
• **Hot flushes**.
• Aggravation or precipitation of **gout**.
• Abnormalities of **smell & taste**.
• **Brownish discoloration** of saliva, urine, or vaginal secretions.
• **Priapism** (nonsexual erection, pathologic).
• Mild and transient **elevations of urea, liver enzymes & bilirubin**.

Drug Interactions:

1. **Pyridoxine (vitamin B6) enhances the extracerebral metabolism** of levodopa & may **interfere with its therapeutic effect unless carbidopa is also given** (so vitamin B6 shouldn't be given with L-dopa).
2. Levodopa should **not** be taken with **MAO-A inhibitors** or within 2 weeks of their discontinuation, because **hypertensive crisis** may develop.
(MAO-A normally breaks down levodopa peripherally, so if we inhibit it, levodopa will stay for a long time peripherally & cause catecholamines (sympathomimetic) effects).
(MAO-B breaks down levodopa centrally, so we need to inhibit it, to prolong drug's action).

Contraindications:

1. **Psychotic patients** (may exacerbate the mental disturbance).
2. Patients with angle-closure **glaucoma**.
3. Cardiac **arrhythmias**. 4. **Peptic ulcer** disease.
5. May activate **malignant melanoma** (levodopa is a precursor of skin melanin).

## Dopamine Receptor Agonists:

• Drugs acting **directly** on postsynaptic dopamine receptors:
1. Older drugs (**ergot derivatives**): **Bromocriptine & pergolide**.
2. Newer agents: **Pramipexole & ropinirole**.
• Unlike levodopa, they do **not** require enzymatic conversion to an active metabolite, act directly on the postsynaptic dopamine receptors, have **no** potentially toxic metabolites, and do **not** compete with other substances for active transport into the blood and across the blood-brain barrier.
•Drug selectively affecting certain dopamine receptors may have more limited side effects.
• Have an important role as **first-line therapy** for Parkinson's disease as the disease progresses.
• Have lower incidence of response fluctuations & dyskinesias.
• Provide **less symptomatic benefit** & are **more likely to cause mental side effects, somnolence, and edema**.
• May be **given to** patients with parkinsonism who are **taking levodopa** and who have **end-of-dose akinesia** or **on-off phenomenon** or are becoming **resistant to treatment with levodopa**.
• The response to dopamine agonists is disappointing in patients who never responded to levodopa.

## Bromocriptine:

• Is a **D2 agonist**.
• This drug has been widely **used** to treat Parkinson's disease in the past but is now rarely used fin favour of the newer dopamine agonists.

## Pergolide:

• It stimulates **both D1 & D2 receptors**.
• It **increases "on-time"** among response fluctuators (advantage).
• It permits **levodopa** dose to be **reduced**.
• Its use has been associated with clinical or subclinical **valvular heart disease** in 1/3 of pts.

## Pramipexole:

• Is **not an ergot derivative**.
• It has preferential affinity for **D3 receptors**.
• It is **effective as monotherapy** for **mild** parkinsonism.
• It is helpful in patients with advanced disease, allowing the dose of levodopa to be reduced, and smoothing out response fluctuations.
• It may ameliorate affective symptoms.
• It can **scavenge hydrogen peroxide & enhance neurotrophic activity in mesencephalic dopaminergic cell culture** (in-vivo experiments show its effectiveness) & is thought to be **neuroprotective**.
• **Rapidly absorbed** after **oral** administration, & excreted largely unchanged in urine. Renal insufficiency require dosage adjustment.

## Ropinirole

• It is not an ergot derivative.
• Is relatively pure D2 agonist.
• Effective in monotherapy for patients with mild disease.
• Is effective in smoothing the response to levodopa in patients with more advanced disease & response fluctuations.
• It is metabolized by CYP1A2.

### Dopamine Receptor Agonists Adverse Effects:

#### A. GIT effects:

• **Anorexia**, **nausea**, & **vomiting** (can be minimized by taking the drug with meals).
• **Constipation**.
• **Dyspepsia**, and **reflux esophagitis**.
• **Bleeding from PUD** (**Peptic ulcer disease).**

#### B. Cardiovascular effects:

• **Postural hypotension**.
• **Painless digital vasospasm** with long-term use of the ergot derivatives.
• Cardiac **arrhythmias**.
• Peripheral **edema**.
• Cardiac **valvulopathy** with pergolide.

C. Dyskinesias: like those of levodopa.

D. Mental disturbances: **Confusion**, **hallucinations**, **delusions**, & other psychiatric reactionswhich are more common & severe than with levodopa.

• **Disorders of impulse control** may occur either as an exaggeration of a previous tendency or as a new phenomenon and may lead to **compulsive gambling, shopping, betting, sexual activity, & other behaviors**. They relate to activation of **D2 or D3** dopamine receptors in the mesocorticolimbic system.

#### E. Others:

• **Headache**, **nasal congestion**, **increased arousal**.
• Pulmonary infiltrates, pleural & retroperitoneal fibrosis (ergots).
• **Erythromelalgia**: consists of red, tender, painful, swollen feet, and occasionally hands, may be associated with **arthralgia**.
• **Uncontrollable tendency to fall asleep** at inappropriate times, particularly in patients receiving pramipexole or ropinirole.
• This requires discontinuation of the medication.

### Contraindications:

• **Psychotic** illness, recent **MI**, **PUD**, & **peripheral vascular disease** (ergots).