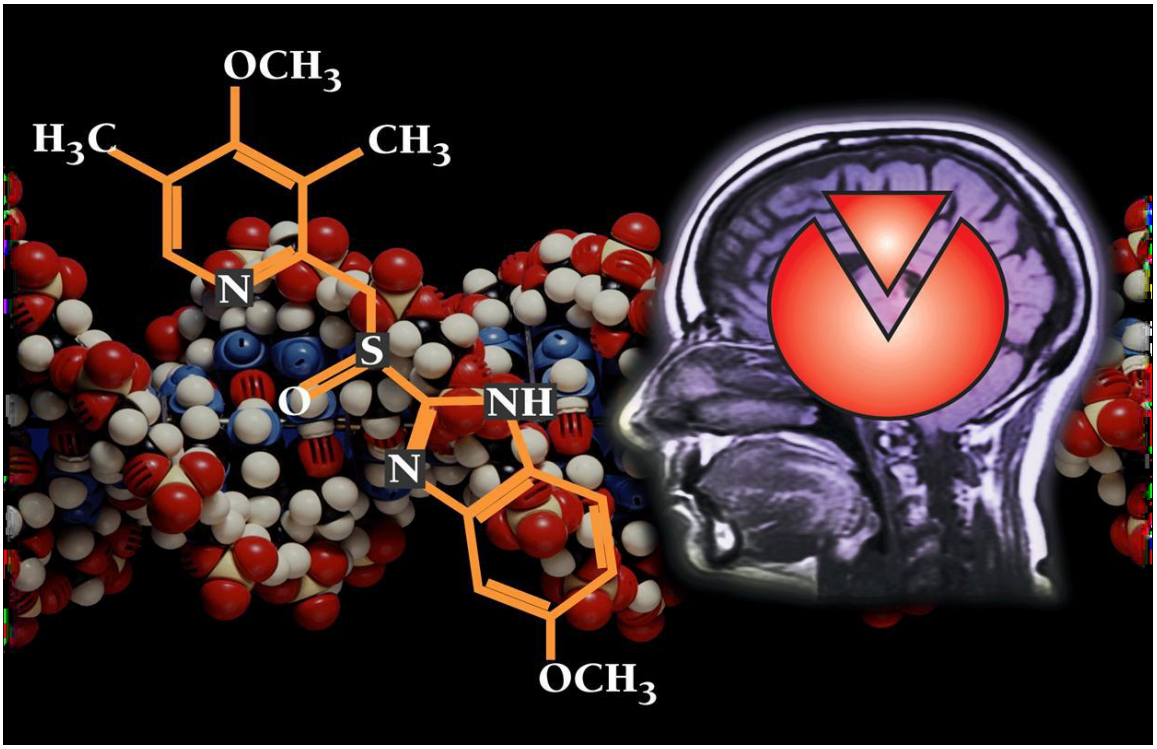
King Saud University
College Of Medicine
Pharmacology Team 430
CNS Block

Drugs used in Parkinson's disease



Note: The first three pages are about the physiology and pathogenesis of Parkinson's disease, and are not required from you in the exam.

Done By:

Mohammed Aldohan

Aisha Almhbob

Dopamine & the basal ganglia

Dopamine Pathways / Areas:

1. **Mesocortical and mesolimbic pathways** : these two areas are responsible for the behavior
2. **Basil ganglia (nigrostriatal system)** : responsible for the neurological activity (movemen)
3. **Tuberoinfundibular pathway:** transmits dopamine from the hypothalamus to the pituitary gland by dopaminergic fibers. This pathway influences the secretion of certain hormones, and inhibits the secretion of prolactin.
4. **Chemoreceptor in the medulla:** has an emetic effect

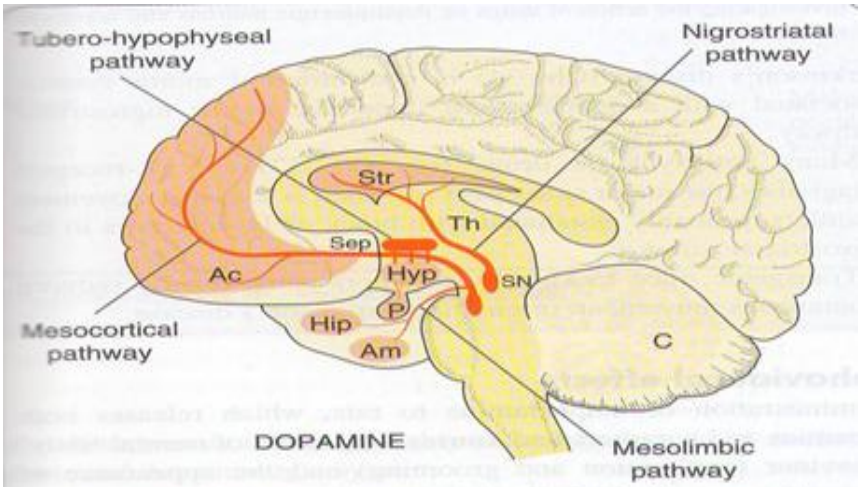


Fig. 33.3 Dopamine pathways in the brain (drawn as in Fig. 33.1). The pituitary gland (P) is shown, innervated with dopaminergic fibres from the hypothalamus. (Ac, nucleus accumbens; other abbreviations as in Fig. 33.1.)

Neurotransmission in basal ganglia

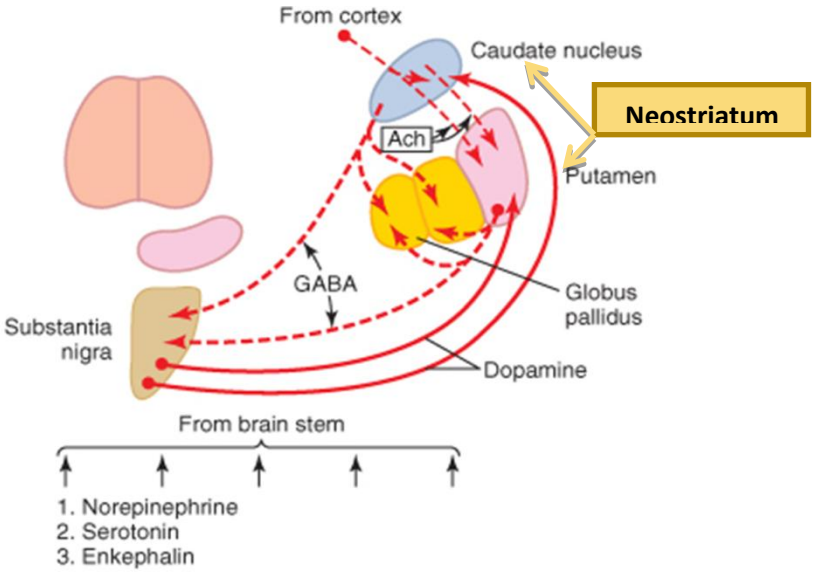
Note: the following figure shows the neurotransmitters in the basal ganglia

(1) Dopamine pathways from the substantia nigra to the caudate nucleus and putamen.

(2) (GABA) pathways from the caudate nucleus and putamen to the globus pallidus and substantia nigra

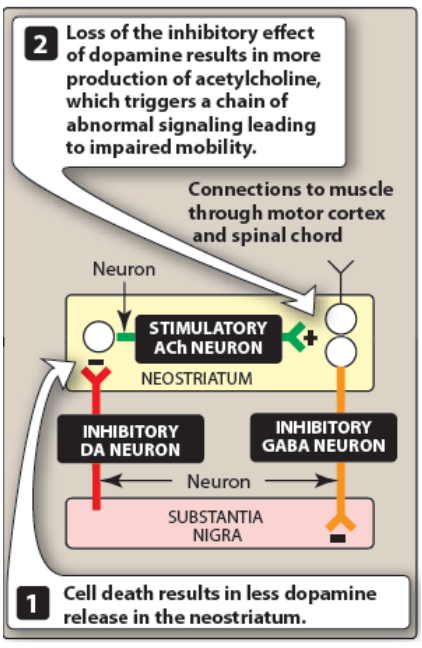
(3) acetylcholine pathways from the cortex to the caudate nucleus and putamen

(4) multiple general pathways from the brain stem



In Parkinson's

The dopamine secreted in the caudate nucleus and putamen is an inhibitory transmitter; therefore, destruction of the dopaminergic neurons in the substantia nigra of the parkinsonian patient theoretically would allow the caudate nucleus and putamen to become overly active and possibly cause continuous output of excitatory signals. This would lead to disturbance of the neurotransmission in the basal ganglia producing the parkinsonian symptoms



Overview of Parkinson's disease

Definition:

It is a progressive neurologic disorder that occurs mainly in the elderly due to loss of dopaminergic neurons in substantia nigra & corpus striatum that are involved in motor control.

Characters of Parkinson's disease:

- Tremors at rest
- Muscle rigidity
- Bradykinesia or Akinesia(slowness in initiating and carrying out voluntary movements)
- Postural and gait abnormalities.

Causes

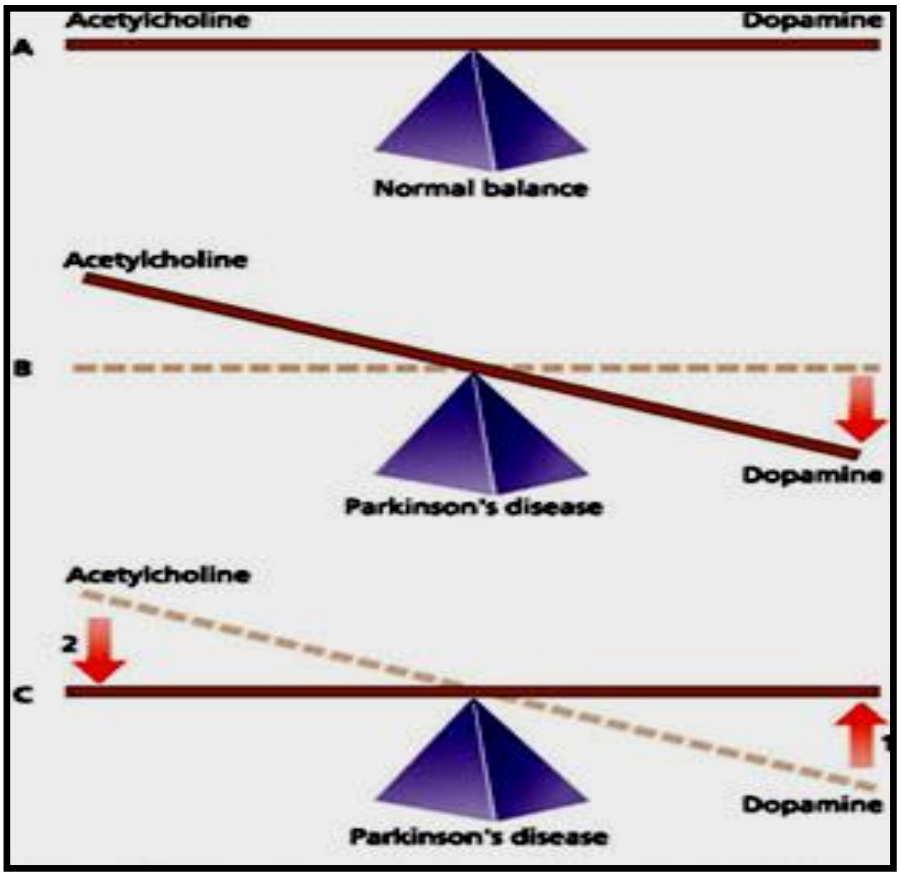
Parkinson's disease is an idiopathic disease but some causes may be:

- Genetic.
- Toxins.
- Head trauma.
- Cerebral anoxia.(a complete lack of oxygen to the brain)
- Drug-induced Parkinson's disease e.g. Antipsychotics like **haloperidol; Reserpine**; **MPTT**(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)

Note: Drugs that induce parkinsonian syndromes either are dopamine receptor antagonists (eg, antipsychotic agents) or lead to the destruction of the dopaminergic nigrostriatal neurons l (eg, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP is a synthetic opioid drug)

Goal of treatment:

Either to **Increase Dopaminergic** Activity (most common approach), or /and **Decrease Cholinergic Activity.**



DRUGS USED IN PARKINSON DISEASE

Currently available drugs offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration caused by the disease.(In time, these drugs would be ineffective)

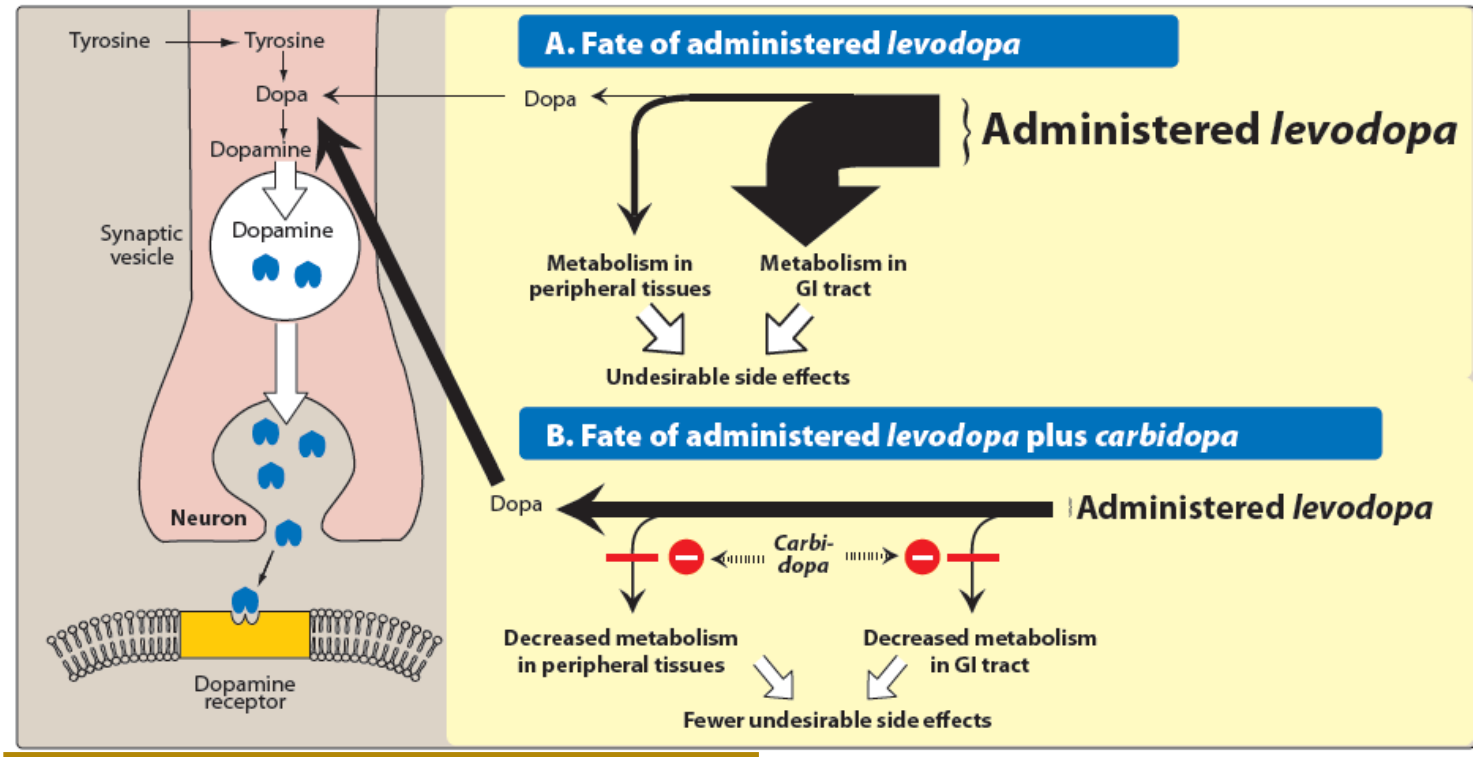
1) Levodopa (dopamine precursor)

- Precursor of dopamine(it's a prodrug , converted to its active form (dopamine) in the body)
- First line treatment
- used combined with **carbidopa(peripheral dopa decarboxylase inhibitor)**
- L-dopa is absorbed from the small intestine by active transport
- Ingestion of meal especially high protein meal interferes with absorption and transport into CNS ***(taken on an empty stomach).***
- Short duration of action t½= 1-2 h *(fluctuation of plasma concentration).*
- **Note: L-Dopa** Ameliorates the signs of Parkinsonism particularly **Bradykinesia** But does not cure the disease.

Note: Dopamine does not cross the blood-brain barrier and if given into the peripheral circulation has no therapeutic effect **in parkinsonism**. However, **levodopa**, the immediate metabolic precursor of dopamine, does enter the brain.

Levodopa & carbidopa

Much of **Levodopa is decarboxylated to dopamine** in the periphery and GIT, resulting decreased quantities of levodopa that would enter the CNS. Using carbidopa**(peripheral dopa decarboxylase inhibitor)** diminishes the metabolism of *levodopa* in the gastrointestinal tract and peripheral tissues, thereby increasing the availability of *levodopa* to the CNS.(**Note:** carbidoapa does not cross the blood brain barrier).



Why carbidopa is combined with L-dopa

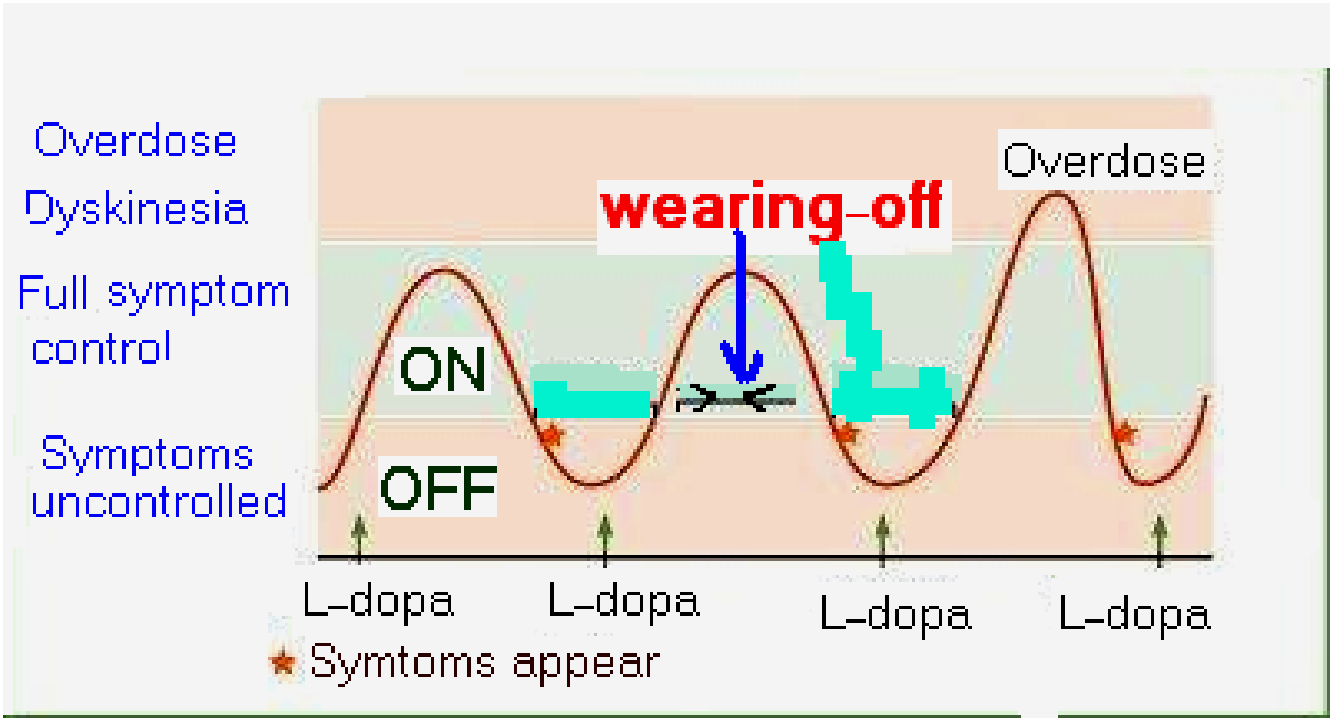
1) inhibit peripheral conversion of L-dopa to dopamine
2) decrease metabolism of L-dopa in peripheral tissues and GIT.Thus, increasing t1/2.
3) increase availability of levodopa
4) reduce dose of levodopa and side effects.

Disadvantages of levodopa.

- **Wearing-off effect.** (duration of "on" states becomes shorter)
- **On-Off** (Off=Akinesai or hypomobility) **phenomenon** (Rx frequent Administration of Levodopa; or s.c injection of **Apomorphine (dopamine agonist), MAOIb**, **Low Protein Diet**)
- **Dyskinesia** (involuntary movements occurs in 40 to 90% of patients) due to fluctuating plasma levels of levodopa and the presence of hypersensitive dopamine receptors.

Note: In prolonged use of levodopa the number of dopaminergic neurons decreases, and fewer cells are capable of taking up exogenously **administered *levodopa*** and converting it to dopamine for subsequent storage and release(Relief provided by *levodopa* is only symptomatic, and it lasts only while the drug is present in the body.).This decrease in dopaminergic neurons may be due to excessive release of dopamine that would release free radicals that damage these neurons.

Note: Certain fluctuations while administering levodopa occur with increasing frequency as treatment continues. In some patients, these fluctuations relate to the timing of levodopa intake, and they are then referred to **as wearing-off reactions or end-of-dose akinesia**. In other instances, fluctuations in clinical state are unrelated to the timing of doses **(on-off phenomenon).** In the 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**(due increased dopamine level).



Adverse drug effects:

Peripheral effects:

1) anorexia, nausea, and vomiting (due to stimulation of emetic center)

Note: The vomiting has been attributed to dopamine stimulating the chemoreceptor trigger zone located in the medulla (area postrema), which is outside the blood-brain barrier.This adverse effect is usually develops when administrating levodopa without carbidopa.In other words, When levodopa is given in combination with carbidopa, adverse gastrointestinal effects are much less frequent

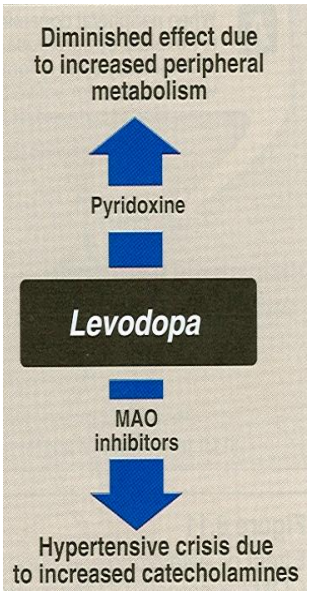
2) Mydriasis, orthostatic hypotension, cardiac arrhythmias.

Note: *Dopamine* is an immediate metabolic precursor of norepinephrine (it enhances Catecholamine production), therefore; *Dopamine* can activate α- and β-adrenergic receptors. **It stimulates β1 cardiac receptors** and **β**2 receptors **(mydriasis)**. In addition, D1and D2 dopaminergic receptors, distinct from the α- and β-adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of *dopamine* produces **vasodilation.**

CNS effects:

(Psychological disorders) mainly psychosis, delusions, hallucinations, confusion, sleep disturbances and depression.(due to increased levels of dopamine).

Note: low doses of certain atypical antipsychotic agents are sometimes used to treat levodopa-induced psychiatric symptoms.



Drug Interactions:

- **Proteins ingested with meals (**interferes with absorption of levodopa and its transport into CNS
- **Pyridoxine (Vitamin B6)**------ (The vitamin pyridoxine (B6) increases the peripheral breakdown of levodopa and diminishes its effectiveness)
- **Nonselective MAO inhibitors (phenelzine**). (can produce a hypertensive crisis caused by enhanced catecholamine production).

Contraindication:

- Psychotic patient.
- Closed angle glaucoma (due to mydriatic effect)
- Patients with history of melanoma.(levodopa is also a Precursor of melanin)

2-Dopamine receptor agonists

- **Ergot derivatives** Bromocriptine, pergolide
- **Non ergot derivatives** Pramipexole, ropinirole.
- **Have longer duration of action than L-dopa** (less likely to cause dyskinesias than levodopa)
- **Dopamine agonists are used in advanced Parkinson's disease with fluctuation and dyskinesia. However, less effective if the patins could not respond to L-Dopa.**

1-Bromocriptine (a derivative of the vasoconstrictive alkaloid: ergotamine)

- is an agonist at D2-receptors.
- Is given orally, short t1/2

Adverse drug effects: they are Levodopa like

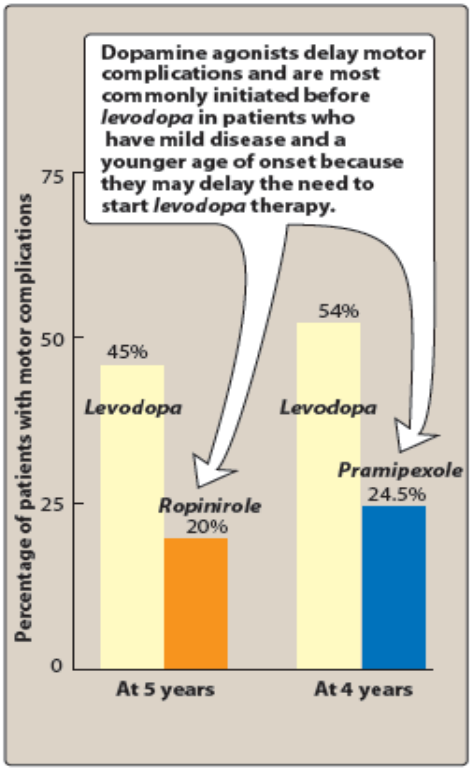
- Nausea, vomiting & postural hypotension ,
- Confusion, hallucinations, delusions.
- Dyskinesia (less prominent)
- To minimize adverse effects, the dose is built up slowly over 2 or 3 months.

Uses:

- Used in advanced Parkinson's disease with fluctuation and dyskinesia.
- Rx of hyperprolactinemia (galactorrhea)
- Rx of infertility in women.

Contraindications:

- **Patients with a history of psychotic illness.**
- **Avoided in patients with peripheral vascular disease (It is a derivative of a vasoconstrictive alkaloid)**
- Recent myocardial infarction
- Active peptic ulceration. (*bromocriptine* is an ergot derivative, it has the potential to cause retroperitoneal fibrosis.)



2- Pramipexole:

- Non Ergot dopamine agonist
- Used alone (in Mild cases) or in combination with L-Dopa.
- Side effects: similar to L-Dopa, but less dyskinesias.
- Has the advantage of being free radicals scavenger.

Note: Dopamine agonists like **pramipexole** may delay the need to use *levodopa* therapy in early Parkinson disease and may decrease the dose of *levodopa* in advanced Parkinson disease**.**

Note: A possible neuroprotective effect has been suggested by **Pramipexole's** ability to scavenge hydrogen peroxide and enhance neurotrophic activity in mesencephalic dopaminergic cell cultures. (it removes the harmful free-radicals that would damage dopaminergic neurons

3- Drugs that release dopamine: (Amantadine)

- Originally introduced as an antiviral.
- **Amantadine increases dopamine release and inhibit uptake**.
- Also acts **as an antagonist at muscarinic and NMDA *(N-methyl-D-aspartate)* receptors**,which is type of glutamate receptors. .
- Given orally with short half-life.
- **Most of the drug being excreted unchanged in the urine**. (which means a small portions of it was used)

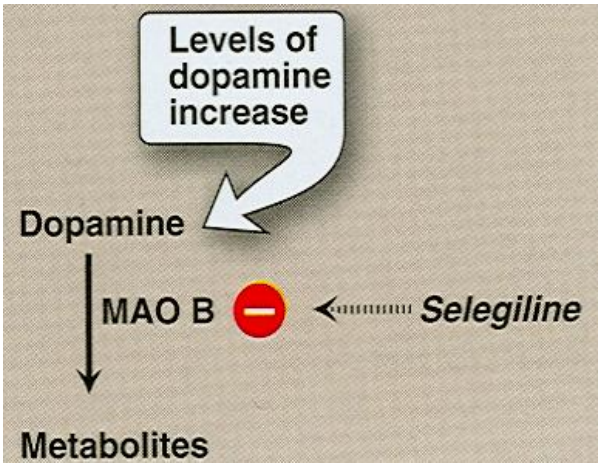
Uses: modestly effective in treating symptoms of Parkinsonism but last only for short period (few weeks) **and only used for L-Dopa resistance**

Adverse effects:

- Nausea, anxiety, insomnia, confusion, hallucinations **(dopamine like side effects).**
- Dry mouth, urinary retention **(anticholinergic effects).**
- Restlessness and hallucinations **(NMDA antagonist).**

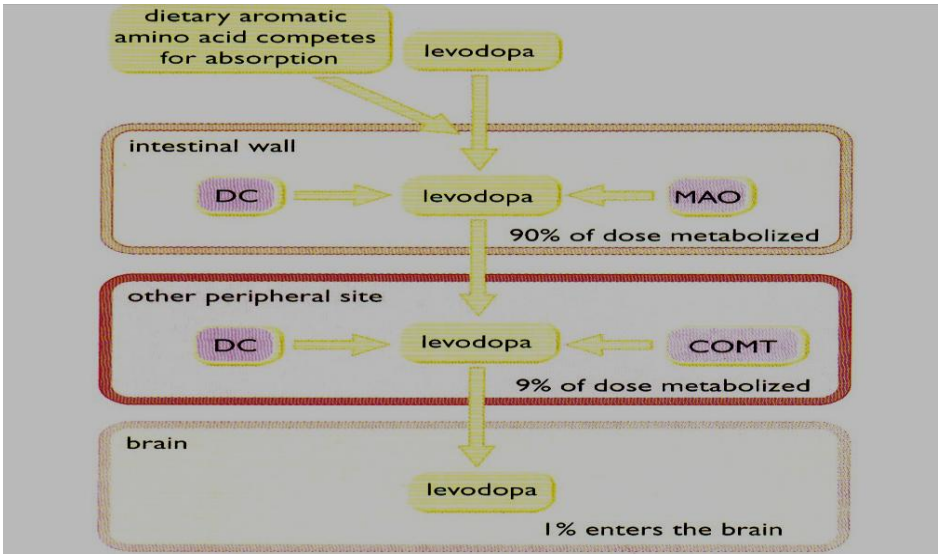
4- MAO-B inhibitors (Selegiline also called deprenyl)

- Selegiline is an irreversible inhibitor **of MAO-B (selective inhibitor).**
- It inhibits dopamine degradation **by MAO-B** in CNS.
- It increases dopamine available for its receptors.
- **It slows the disease progression by reducing the formation of *toxic free radicals* produced during dopamine metabolism (*antioxidant*).**
- Selegiline is metabolized **to desmethylselegiline**, Which is an anti-apoptotic. **(the programed cell death of dopaminergic neurons would be reduced)**



Uses

- As monotherapy, may be effective in the newly diagnosed patient with parkinsonism.
- Combined with levodopa / carbidopa in later-stage parkinsonism to:
- **Reduce the required dose of levodopa, and delay the onset of dyskinesias and motor fluctuations that usually accompany long-term treatment with levodopa.**



Adverse effects

- At high doses, selegiline may inhibit MAO-A *(hypertensive crises).*
- May cause insomnia when taken later during the day

.

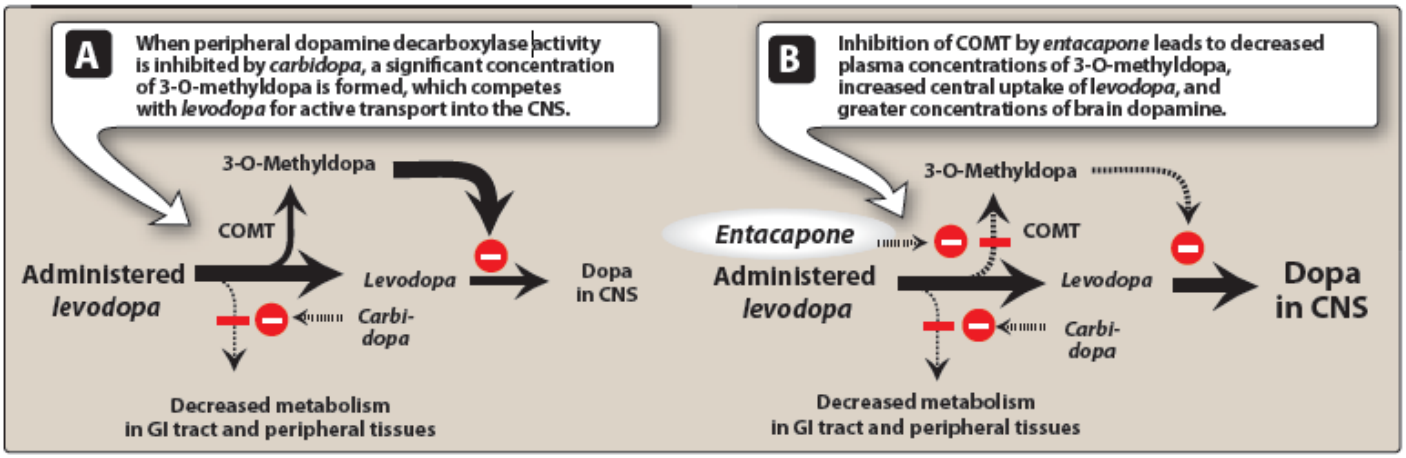
Note: Selegiline is metabolized to **methamphetamine and amphetamine**, whose stimulating properties may produce insomnia if the drug is administered later than midafternoon

Contraindications:

Selegiline should not be co-administered with tricyclic antidepressants, or selective serotonin reuptake inhibitors (may cause hyperpyrexia, agitation, delirium, and coma).--------(Anything that would be excitatory)

5- COMT Inhibitors (Catechol-O- methyl transferase) Inhibitors (Entacapone and Tolcapone)

- Acts **peripherally and centrally to inhibit COMT enzyme required for dopamine degradation**
- It is used: **as adjuvant to L-Dopa to:**
  1) **Decrease fluctuations**
  2) **Improve response**
  3) **Prolong the ON-Time**



Adverse Effects:

- L-Dopa side effects.
- Orange discoloration of urine.

6- Anticholinergic Drugs: e.g. Benztropine, Trihexyphenidyl

- Act by blocking muscarinic receptors in the striatum.
- Have modest antiparkinsonian actions. (effective in treating tremors)
- Used during the early stages of the disease or as an adjunct to levodopa therapy.
- Provide benefit in drug-induced parkinsonism.(caused by **antipsychotics**)

Adverse effects:

- **Cycloplegia (**paralysis of the ciliary muscle; paralysis of accommodation)**, dry mouth, urinary retention, and constipation.**
- **Confusion, delirium, and hallucinations may occur at higher doses.**

Contraindications:

- **Prostatic hypertrophy** (this drug cause urinary retention)
- **Glaucoma**
- **Intestinal obstruction**

Clinical practice: The Life Extension Foundation's protocol for Parkinson's disease is based on studies showing that low doses of several drugs work better than high doses of a single drug. The many components that compose this protocol are suggested because of evidence of their safety and benefits in treating the multiple underlying neurological disorders linked to the disease.

Summary:

- Drugs That Increase Dopaminergic Activities: **Levodopa+ carbidopa**, **MAO-B inhibitors: selegiline**, **COMT inhibitors: entacapone**,**Dopamine agonists** :**Ergot derivatives: bromocriptine** , **Non ergot derivatives: pramipexole**, and **dopamine releaser: Amantadine**
- Drugs that Decrease Cholinergic Activity are Anticholinergic Drugs: e.g. Benztropine, Trihexyphenidyl
- Levodopa and carbidopa are the main treatment of Parkinson's
- All other medications are adjuncts to levodopa therapy
- Other useful drugs **include bromocriptine (dopamine agonist), selegiline (monoamine oxidase-B inhibitor), amantadine (enhances dopamine release)** and benztropine **(muscarinic receptor antagonist, used for parkinsonism caused by antipsychotic drugs.**
- **Levodopa, dopamine agonists, selegiline drugs are contraindicated to be combined with antipsychotic drugs.However, some atypical antipsychotic drugs maybe used.**
- The **use of Antioxidants (vit E and Coenzyme Q10**) may help decreasing the incidence of the Disease, which would reduce the number of free radicals produced by dopamine metabolism.

Review questions

1-Which one of the following combinations of antiparkinson drugs is an appropriate therapy?

A. Amantadine, carbidopa, and entacapone.
B. Levodopa, carbidopa, and entacapone.
C. Pramipexole, carbidopa, and entacapone.
D. Ropinirole, selegiline, and entacapone.
E. Ropinirole, carbidopa, and selegiline.

Correct answer = **B**. To reduce the dose of levodopaand its peripheral side effects, the peripheral decarboxylase inhibitor, carbidopa, is coadministered. As a result of this combination, more levodopa is available for metabolism by catechol-O-methyltransferase (COMT) to 3-methyldopa, which competes with dopa for the active transport processes into the central nervous system. By administering entacapone (an inhibitor of COMT), the competing product is not formed, and more dopa enters the brain. The other choices are not appropriate, because neither peripheral decarboxylase nor COMT nor monoamine oxidase metabolizes amantadine or the direct-acting dopamine agonists, ropinirole and pramipexole.

2- Peripheral adverse effects of levodopa, including nausea, hypotension, and cardiac arrhythmias, can be diminished by including which of the following drugs in the therapy?

A. Amantadine.
B. Bromocriptine.
C. Carbidopa.
D. Entacapone.
E. Ropinirole.

Correct answer = **C.** Carbidopa inhibits the peripheral decarboxylation of levodopa to dopamine, thereby diminishing the gastrointestinal and cardiovascular side effects of levodopa. The other agents listed do not ameliorate levodopa's adverse effects.

3- Which of the following antiparkinson drugs may cause peripheral vasospasm?

A. Amantadine.
B. Bromocriptine.
C. Carbidopa.
D. pramipexole.
E. Ropinirole.

Correct answer = **B.** Bromocriptine is an ergot-derived dopamine receptor agonist that may cause vasospasm.