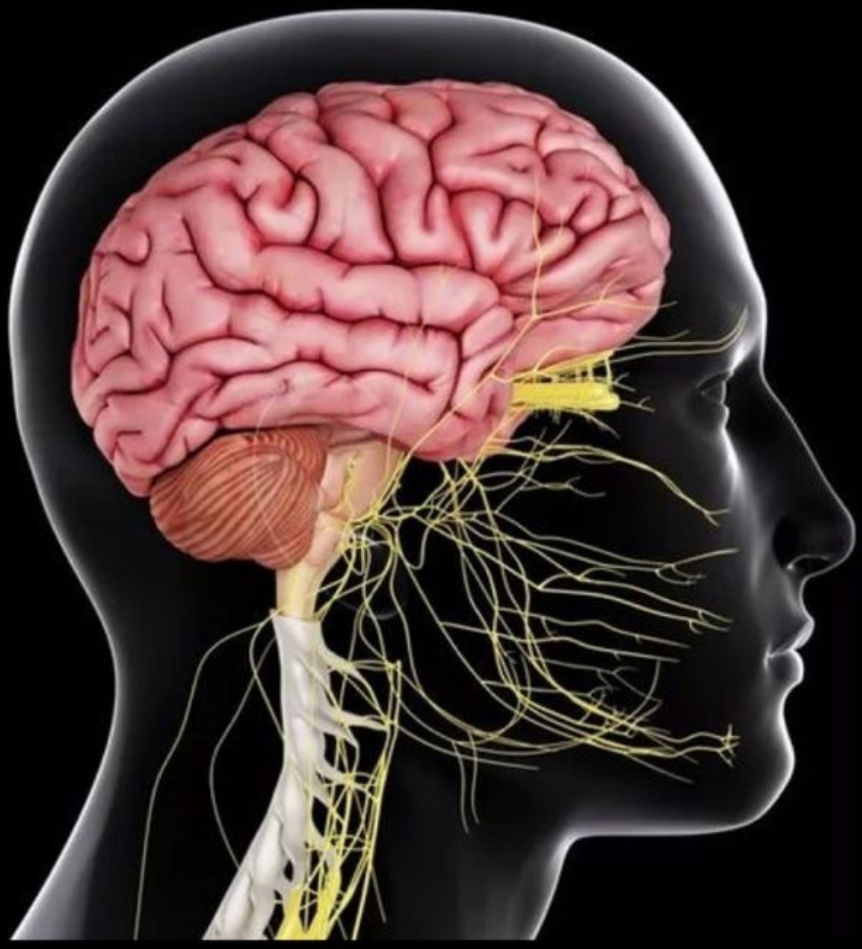
CENTRAL NERVOUS SYSTEM



SUBJECT : Pharmacology

LEC NO. : 4

DONE BY : Batool ALzubaidi

وقل رب زدني علماً

Drugs for Neurodegenerative Diseases

Degenerative disease » they're progressive, characterized by degeneration or destruction of a neurotransmitter, there's physical damage

Pharmacology and Toxicology

Central Nervous System Module

Third Year Medical Students

Tareq Saleh

Faculty of Medicine

The Hashemite University

Textbook: pp. 103-115

idiopathic بنحكي عنه its still unknown ليش بصير etiology ال معروف اما ال pathophysiology ال

Parkinson's Disease: Pathophysiology

Describes the idiopathic form of parkinsonism but parkinsonism is a syndrome that describes the symptoms of parkinson disease it can be due to secondary causes like infection, drugs, electrolyte imbalance

Idiopathic

- Destruction of the dopaminergic neurons in the **substantia nigra** → ↓ dopaminergic stimulation in the corpus striatum.

Low dopamine state in the brain it plays different roles in regulating brain function, it's important for mood regulation, for reward pathway, more importantly the regulation of movement

- The dopaminergic neurons fire **tonically** (not in response to certain stimuli).

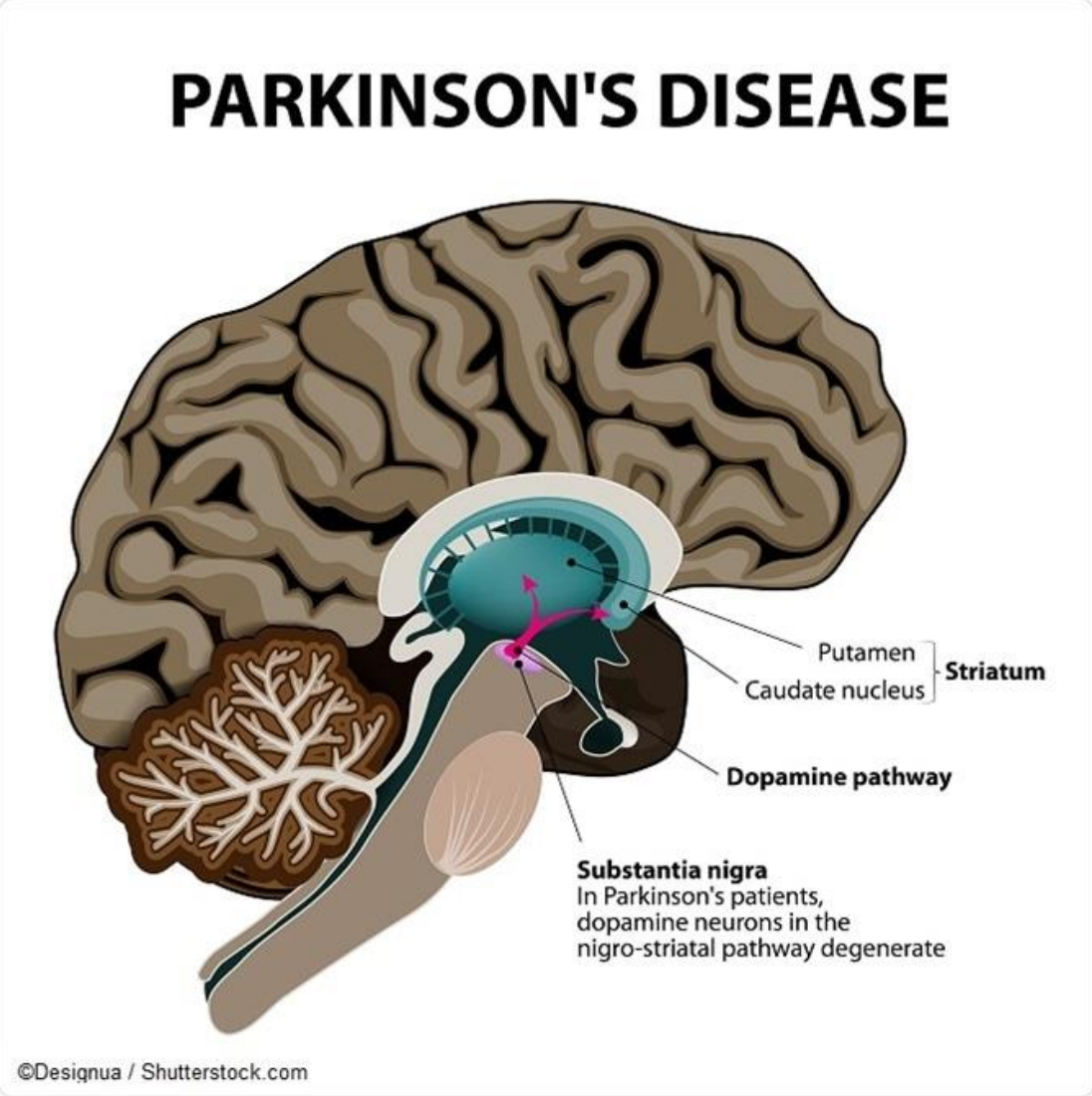
There's always firing you can just increase it or decrease it

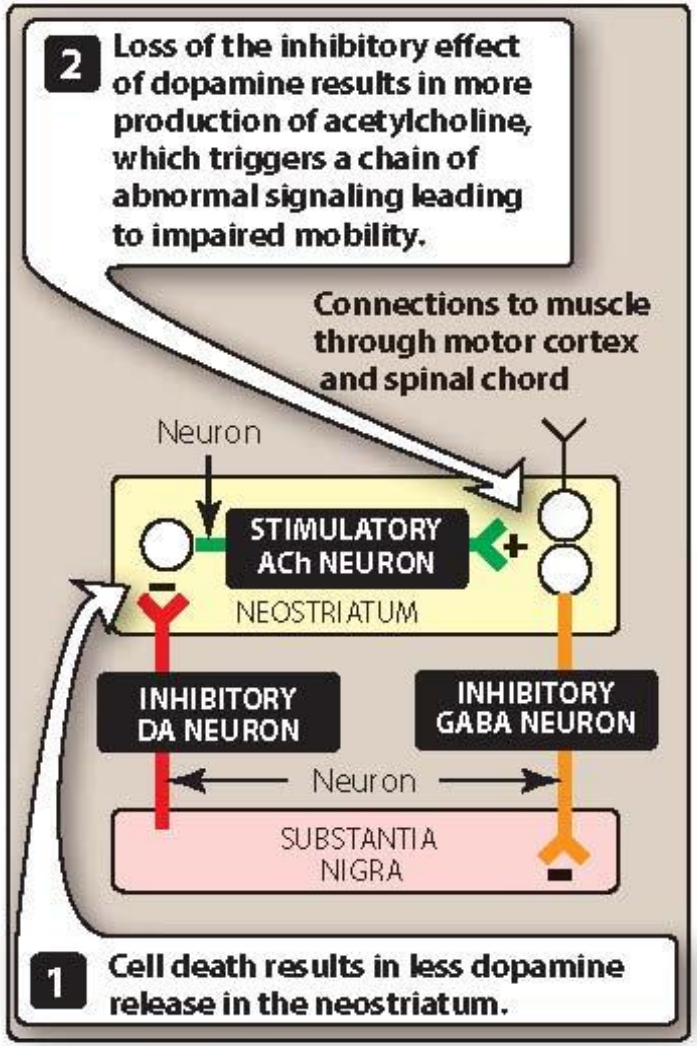
one of the pathways for motor regulation is a projects from a structure called substantia in the midbrain that projects it's neurons to a structure called striatum in the basal ganglia, as a negative feedback mechanism striatum sends inhibitory GABA neurons to substantia to reduce release of dopamine

- Parkinson's results from reduced dopaminergic inhibition of the cholinergic neurons in the neostriatum, resulting in overproduction of acetylcholine→ loss of control on muscle movement.

Dopamine is a mixed neurotransmitter » it can be excitatory or inhibitory, in the reward pathway dopamine is mainly excitatory (from frontal segmental area to to the prefrontal cortex), in the case of motor regulation dopamine is inhibitory because most of the receptors are D2

Parkinson's Disease: Pathophysiology

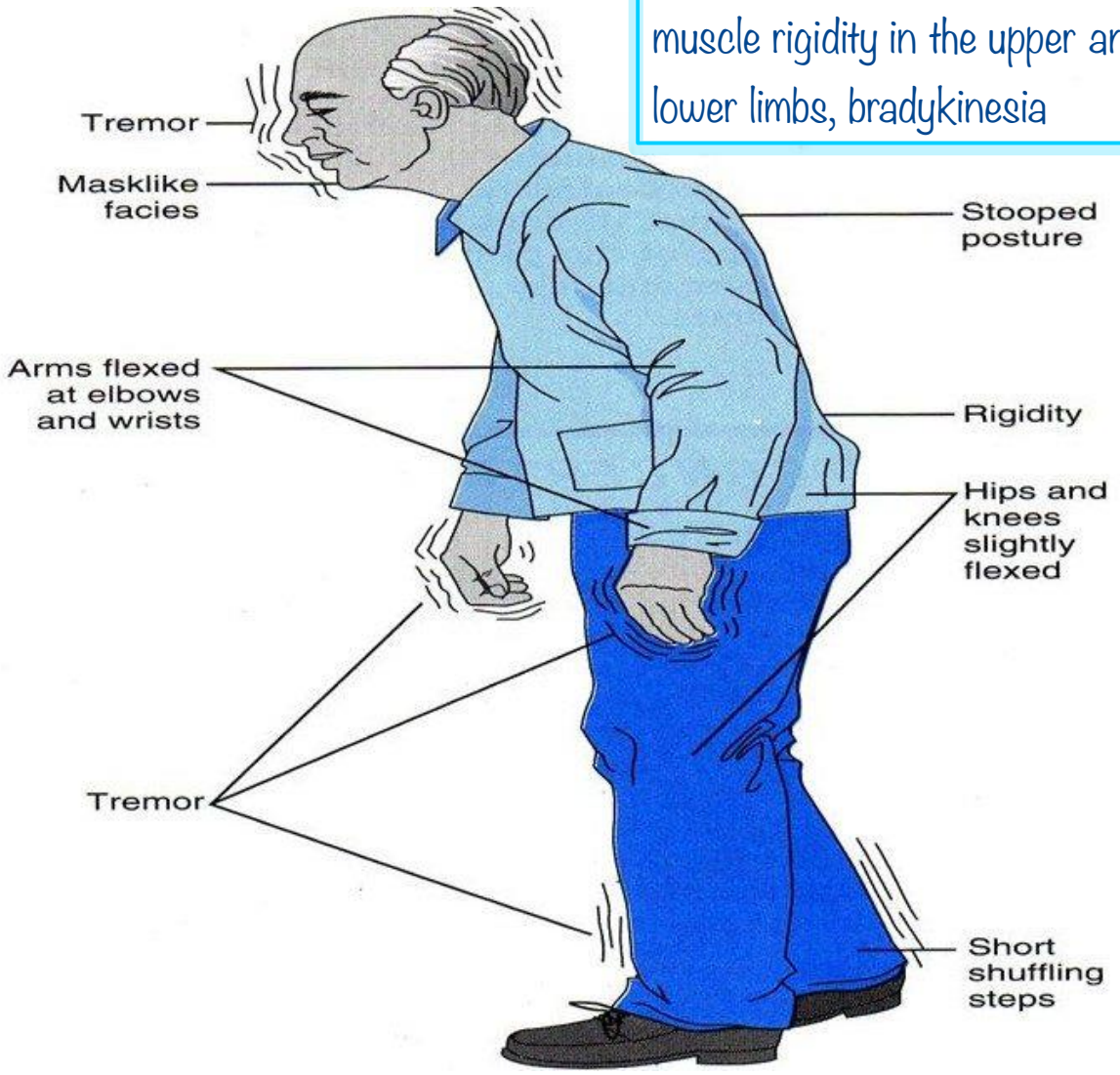


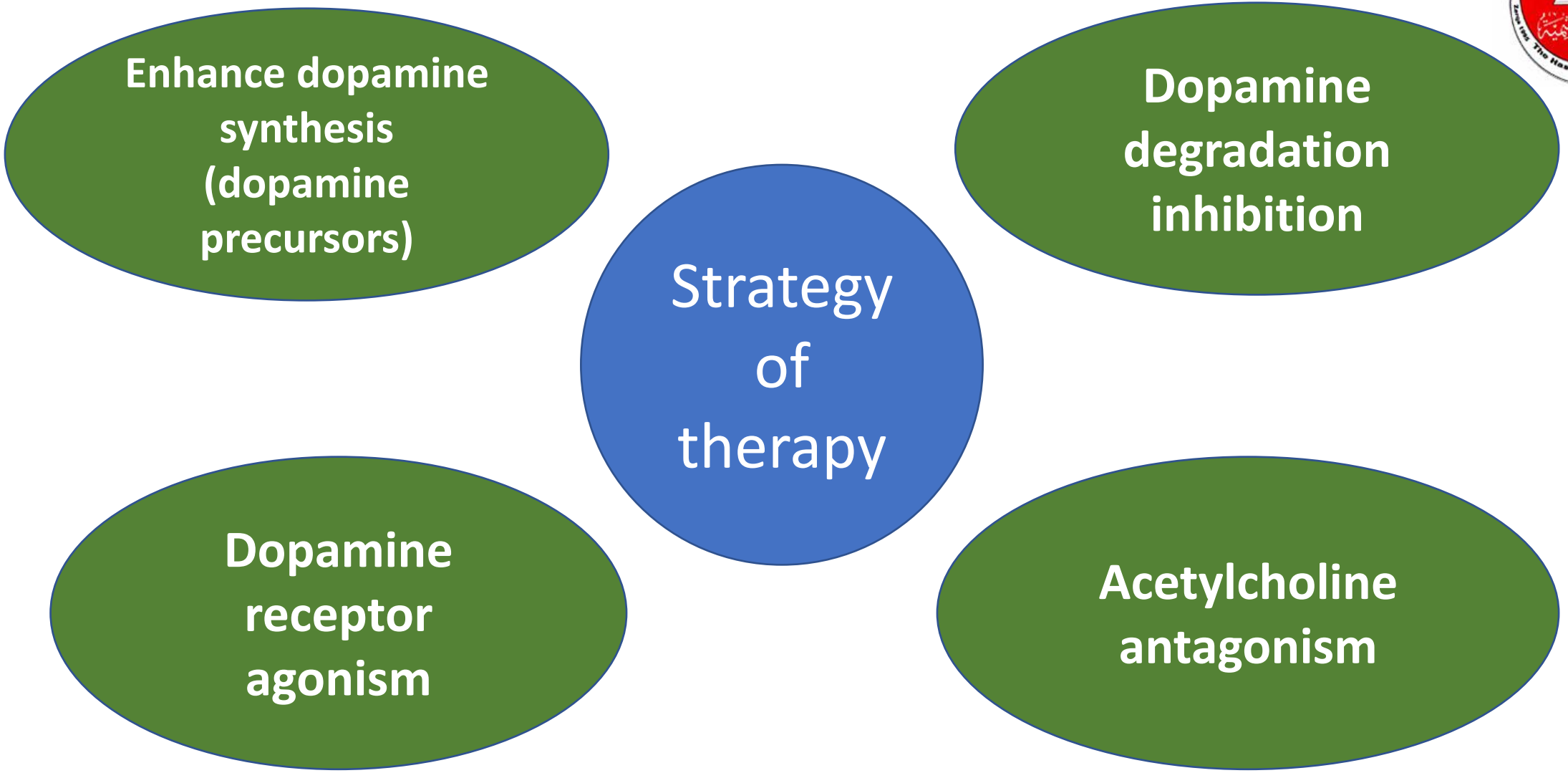


Parkinson's Disease

- **Parkinsonism**: is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia and postural and gait abnormalities.

It's charechtarized mail by motor symptoms » shuffling gate, tremor, muscle rigidity in the upper and lower limbs, bradykinesia





Parkinsonism

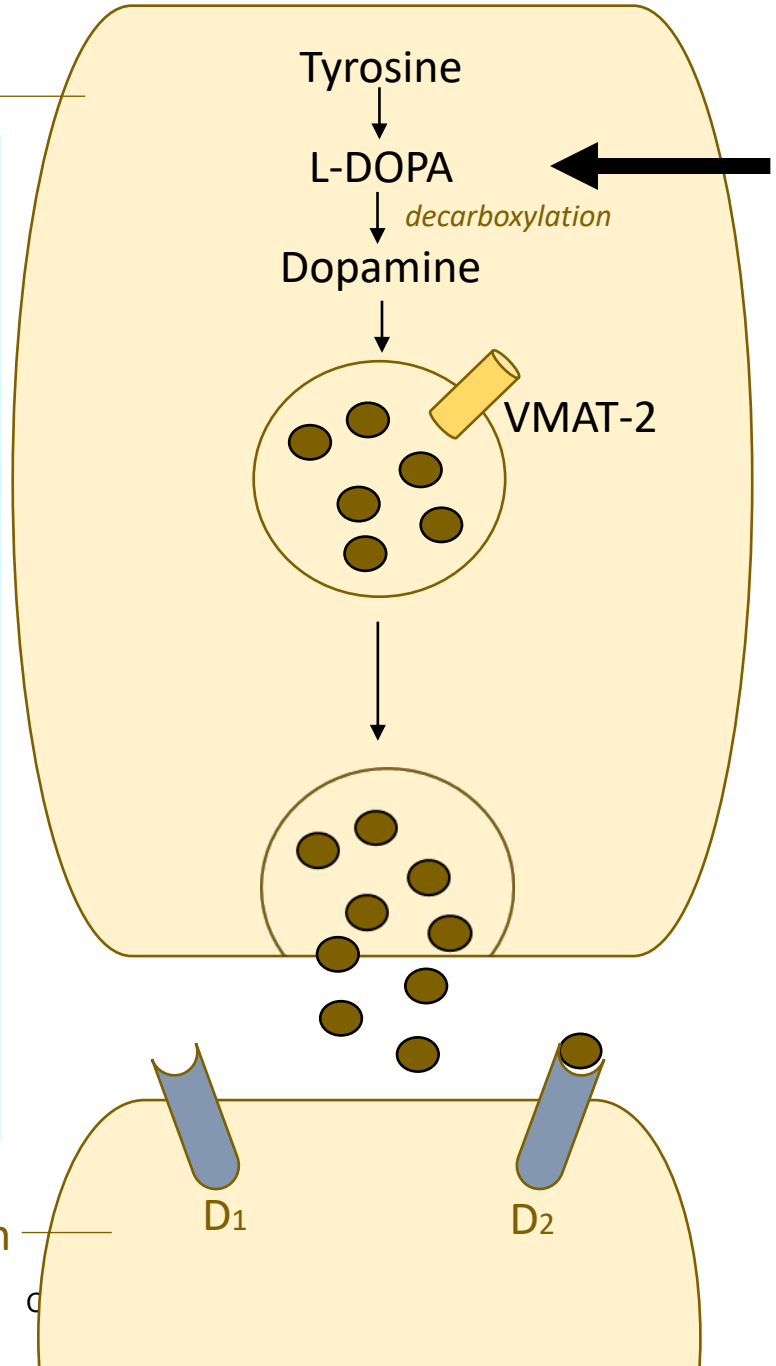
Levodopa and carbidopa

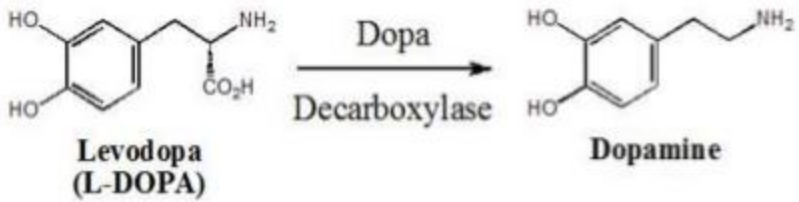
Mechanism of action:

- **Levodopa:** is metabolic precursor of dopamine.
- Levodopa must be administered with carbidopa.
- **Carbidopa** is a decarboxylase inhibitor, that diminishes the metabolism of levodopa in the periphery → increasing the availability of levodopa at BBB.

Without carbidopa, most of levodopa is metabolized in the periphery.

It's used as a first line treatment with most patients with early disease of Parkinson's when symptoms starts to appear in this stage the majority of patients don't have complete destruction in the substantia nigra there's enough destruction to cause symptoms but 20-30% of neurons in substantia are still present of course they will loose them with time because it's a progressive disease (the destruction continues), but early in the disease we can use a method to stimulate major neurons to produce more dopamine, you can give L-dopa which is the precursor of dopamine (increase in precursor » increase in the product)



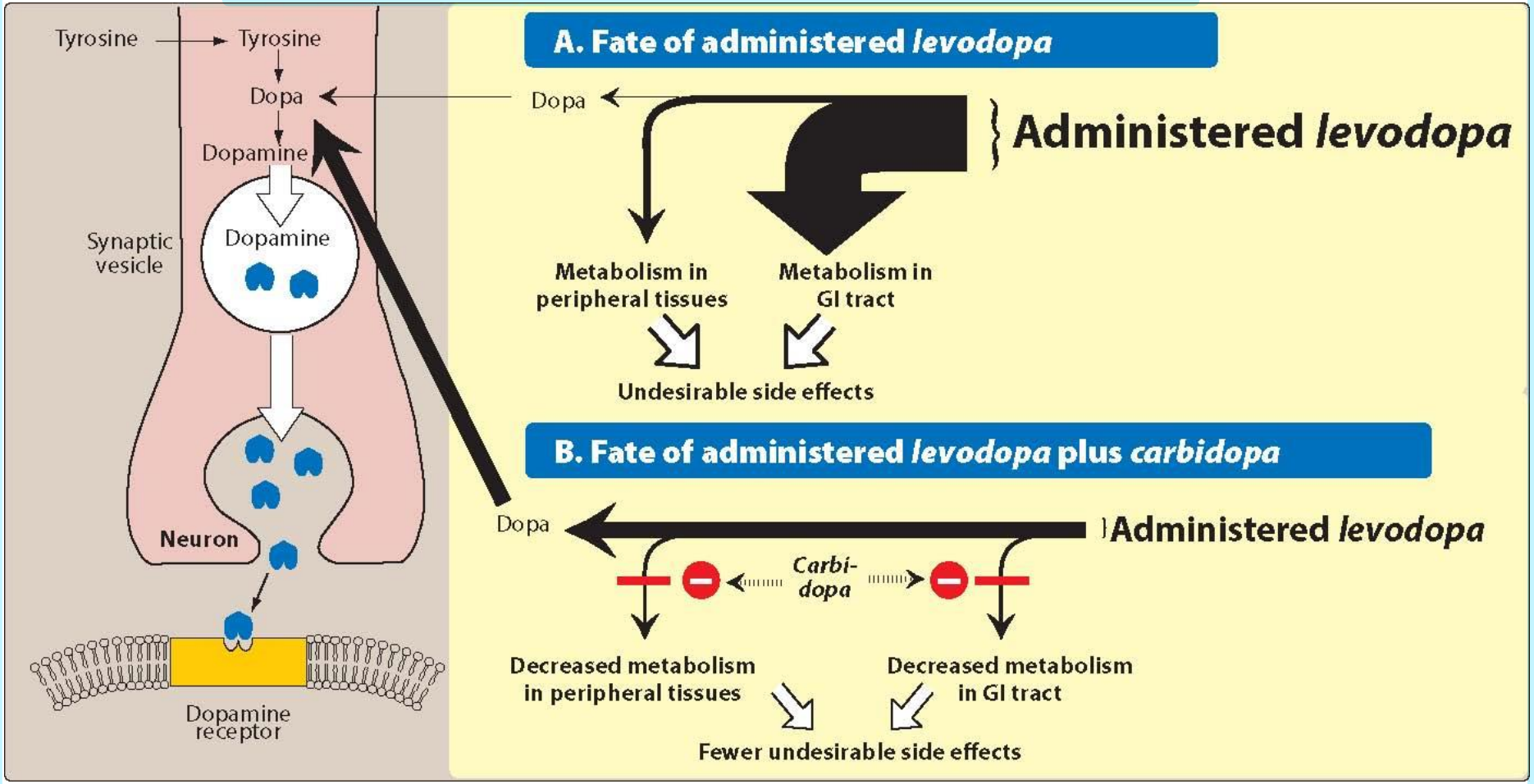


When L-dopa is given there's a chance that it hit be metabolized in the periphery, decarboxylases are present in the gut and liver

Levodopa and carbidopa

Gold standard treatment for Parkinson's disease is this combination

الحل اني استخدم للـ inhibitors peripheral metabolism of زي الـ L-dopa carbidopa الفكرة انه it doesn't cross blood brain barrier ف الـ inhibition بس بصير peripherally



المشكلة هون شغلتين اولا عم بتحول الـ L- dopa لـ dopamine بال peripheral هاد يعني circulation انه بزيد الـ level تاعه و peripherally بسبب adverse effects، و راح يقل نسبة L-dopa الرايحة للدماغ لانه معظمه بتحول برة الدماغ و الـ dopamine doesn't cross blood brain barrier

Levodopa and carbidopa

Therapeutic uses

- Levodopa + carbidopa: the gold standard of symptomatic treatment for Parkinson's disease.

The disease will be very well managed

two-thirds of patients respond well to levodopa+carbidopa for the first few years then they experience a decline in response.

*(*) "**wearing off" phenomenon** (symptoms of Parkinson's start to return or worsen with progression of the disease)*

Because almost all neurons are destroyed, there are no neurons left to use L-dopa to synthesize dopamine

Levodopa and carbidopa

Pharmacokinetics

- Levodopa is rapidly absorbed from the gut.

  -administered on an empty stomach (high-protein diet interferes with its transport to the brain).

- SHORT half-life (1-2 hours).

  -results in fluctuation in its plasma concentration → fluctuation in motor function.

When levels of dopamine increase in the brain symptoms will be controlled but once it declines symptoms will reappear, that's why dose of treatment in plasma must be consistently maintained

Unpredicted episodes of hypomobility

(*) ***"on-off" phenomenon*** *(sudden swings from mobility to bradykinesia that are not related to plasma levels in a simple way)*

On » normal motor function, off » normal function is lost, Parkinson's symptoms

Levodopa and carbidopa

Adverse effects:

- **Peripheral effects:** Are reduced by adding carbidopa

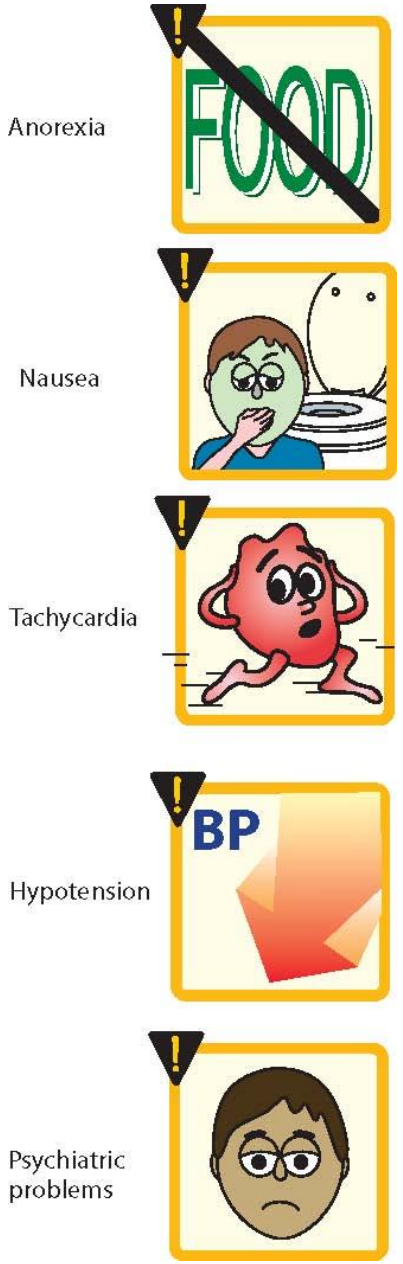
❑ Simulation of chemoreceptor trigger zone: Anorexia, nausea and vomiting

❑ Dopaminergic stimulation of the heart: tachycardia, extrasystole

❑ Adrenergic action on iris: mydriasis

❑ Catecholamines oxidation: melanin pigmentation, brownish saliva and urine.

L-dopa can be converted into some catecholamines that precipitate in the skin or urine



Levodopa and carbidopa

Adverse effects:

- **Central effects:**

❑ Visual and auditory hallucinations

❑ Dyskinesia — Abnormal movements

❑ Mood changes

(These CNS effects are the opposite of parkinsonian symptoms and reflect the overactivity of dopamine at receptors in the basal ganglia)

Catechol-O-methyltransferase inhibitors (COMTIs)
Entacapone and tolcapone

Mechanism of action:

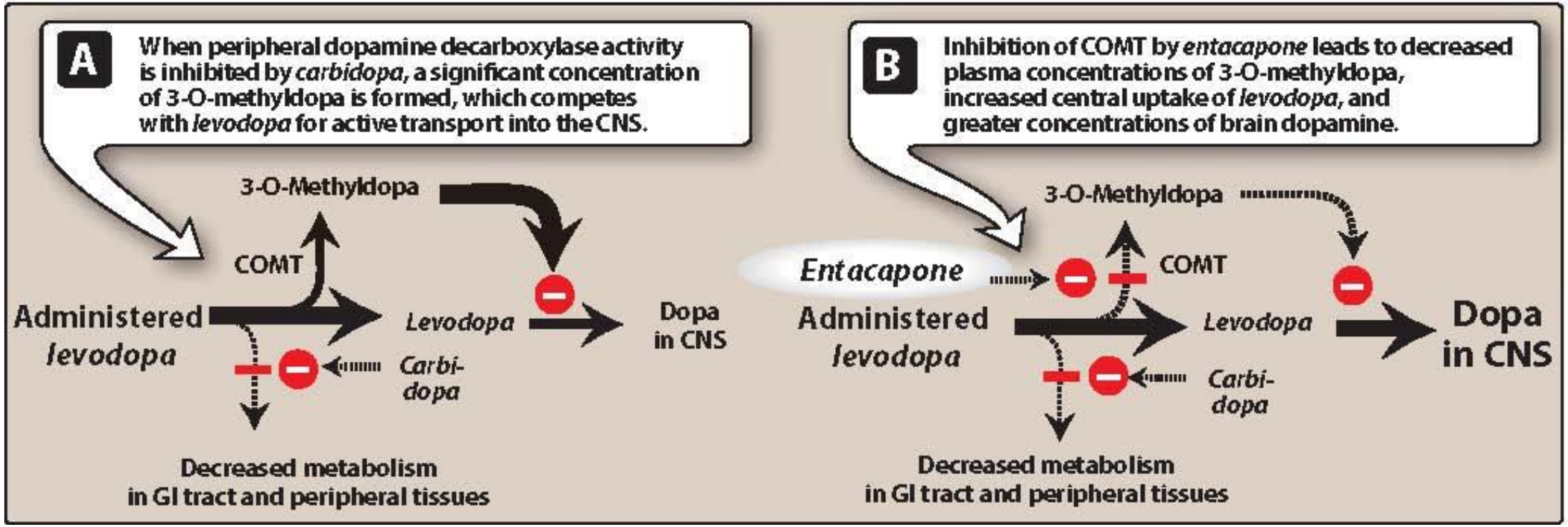
- The methylation of levodopa by COMT to 3-*O*-methyldopa is a minor pathway for levodopa metabolism.
- When carbidopa is used → 1. more 3-*O*-methyldopa is formed by COMT → 3-*O*-methyldopa competes with levodopa transport to the brain.

2. تاني مشكلة ما بقدر اصنع منه dopamine

- **Entacapone and tolcapone** are selective and reversible inhibitors of COMT → decrease plasma concentration of 3-*O*-methyldopa → enhance levodopa transfer to the brain.

Both drugs decrease "wearing off" phenomenon.

هيك بتضمن انه النسبة الاكبر من ال l-dopa تروح للـ brain و استخدمها بتصنيع ال dopamine



Catechol-O-methyltransferase inhibitors (COMTis)
Entacapone and tolcapone

Pharmacokinetics

- Both drugs are orally administered.
- Highly bound to plasma albumin.
- Tolcapone has a longer half-life.

Catechol-O-methyltransferase inhibitors (COMTis)
Entacapone and tolcapone

Adverse effects:

- Both drugs have similar side effects profile as levodopa+carbidopa
- Tolcapone: fulminating hepatic necrosis (does not occur with entacapone)

MAO Inhibitors: Selegiline and Rasagiline

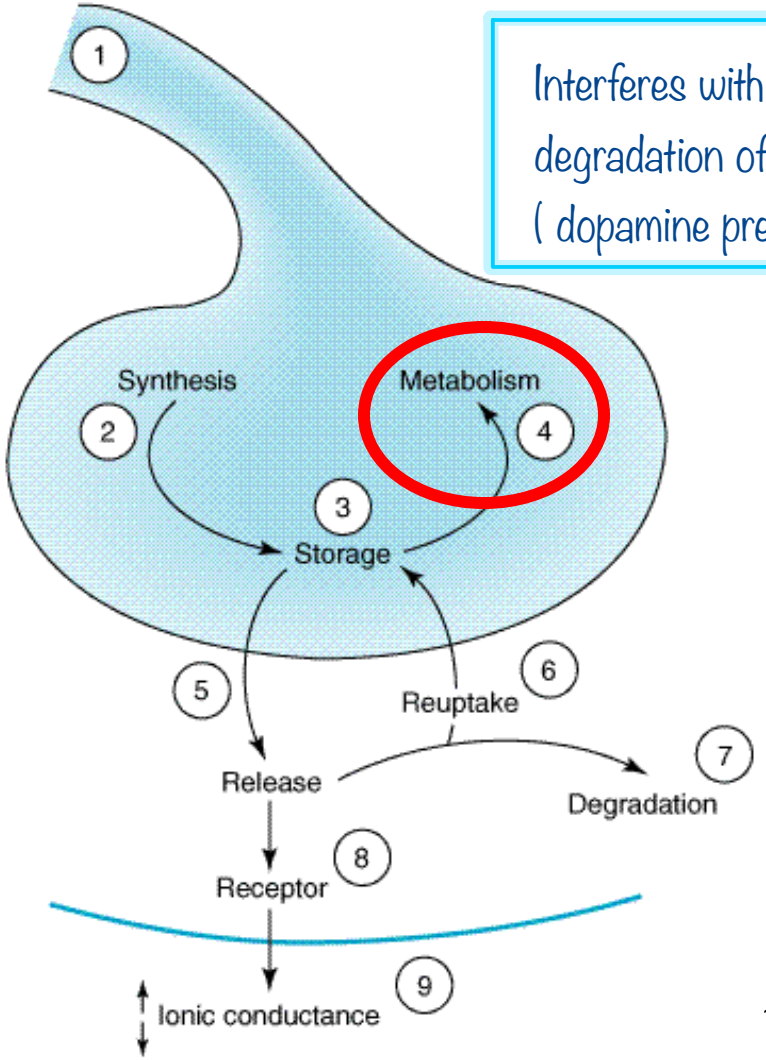
Mechanism of action:

- **Selegiline:** selective MAO B inhibitor → decreases dopamine degradation → increases dopamine levels in the brain.

both MAO A and MAO B efficiently metabolize dopamine however type B degrades dopamine more. (MAO A predominantly metabolizes norepinephrine). And for serotonin

- **Rasagiline** is an irreversible and selective inhibitor of brain MAO B and is **5 times** more potent than selegiline.

Sites and Mechanisms of CNS Drug Action



Interferes with degradation of L-dopa (dopamine precursor)

Metabolism:

•COMT and MAO

They inhibit degradation / metabolism of dopamine in the brain

- Antiparkinsonian
- Antidepressants

MAO Inhibitors: Selegiline and Rasagiline

Therapeutic uses:

- **Seligiline** is often administered with levodopa:

delays breakdown of nigrostriatal dopamine→ prolongs levodopa action → decreases fluctuation in motor function. “on-off phenomenon”

MAO Inhibitors: Selegiline and Rasagiline

Adverse effects:

- Insomnia: due to its metabolism to methamphetamine and amphetamine.

Unlike selegiline, rasagiline is not metabolized to amphetamine-like substances → less insomnia.

Dopamine Receptor Agonists

Drugs:

Associated with adverse effects like pulmonary fibrosis

- Bromocriptine (ergot derivative)
- Rotigotine, apomorphine, pramipexole and ropinirole (nonergot derivatives).

Preferred for parkinson

Dopamine Receptor Agonists

Mechanism of action

- Direct dopamine receptor 2 (D_2) agonism.

Dopamine Receptor Agonists

Therapeutic uses:

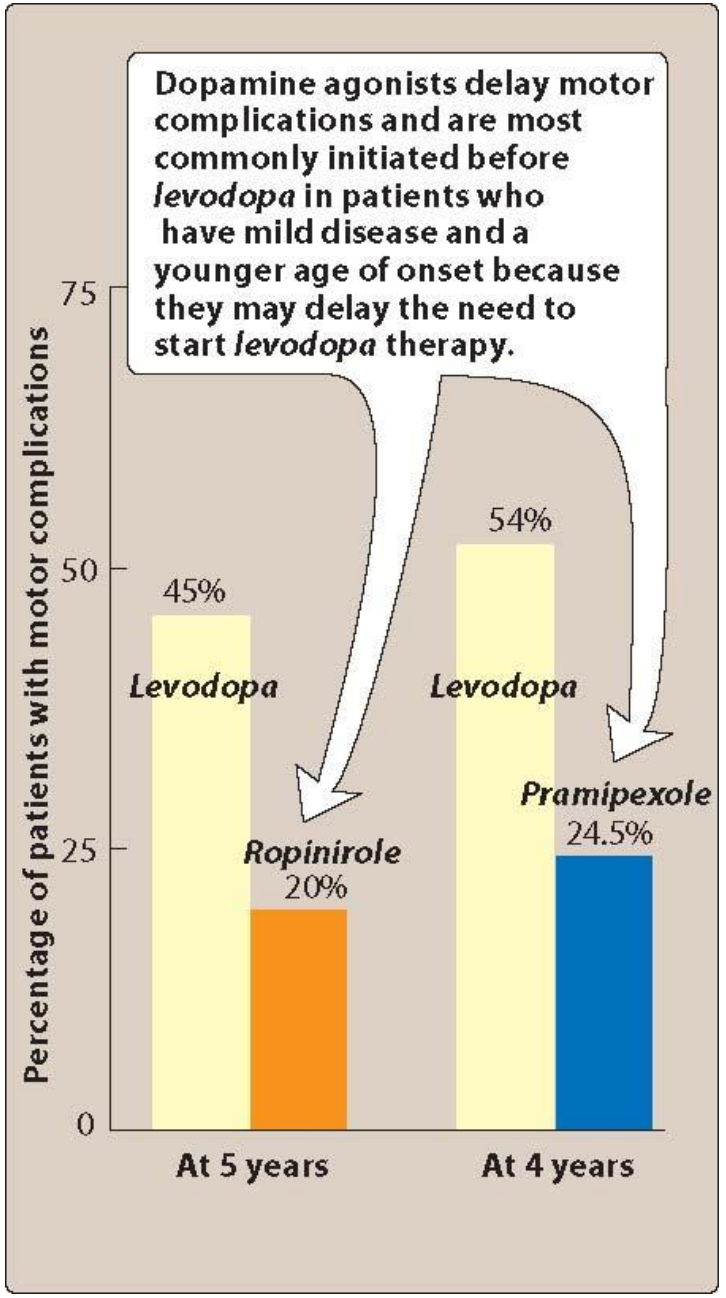
- Patients exhibiting fluctuation in response to levodopa.
- Parkinson's disease complicated by motor fluctuations and dyskinesia.
- Ineffective in patients who have not responded to levodopa.
- Apomorphine is given by injection to treat severe and advanced stages of Parkinson's disease (also given in emergencies to treat sudden freezing i.e. immobility "off" phenomenon)

Complete loss of mobility

Therapeutic advantage of dopamine agonists

With long term treatment they have advantage in reducing the need to start levodopa treatment and delay the wearing of the phenomena when given to patients younger in age who started there treatment early

من الرسمة المرضى الي اخدوا dopamine agonists نسبة الي صار معهم motor complication بالاخير ال offاقل ب 50% من الي ما اخدوا dopamine agonists

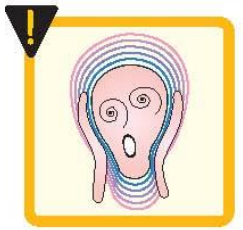


Dopamine Receptor Agonists

Adverse effects

- Similar to levodopa.
- Bromocriptine: pulmonary and retroperitoneal fibrosis
- nonergot derivatives do NOT cause fibrosis.

Sedation


Hallucinations


Confusion


Nausea

Hypotension

Antimuscarinic agents

Drugs

- Benztropine
- Trihexyphenidyl
- Procyclidine
- Bioperiden

Antimuscarinic agents

Mechanisms of action

- Blockade of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission → correct the imbalance of dopamine/acetylcholine ratio.

Antimuscarinic agents

Therapeutic uses

- Much less efficacious than levodopa and always used in adjuvant to other antiparkinsonian therapy.
- Anticholinergics are mainly used in antipsychotic-induced parkinsonism.