

## Lecture: 23

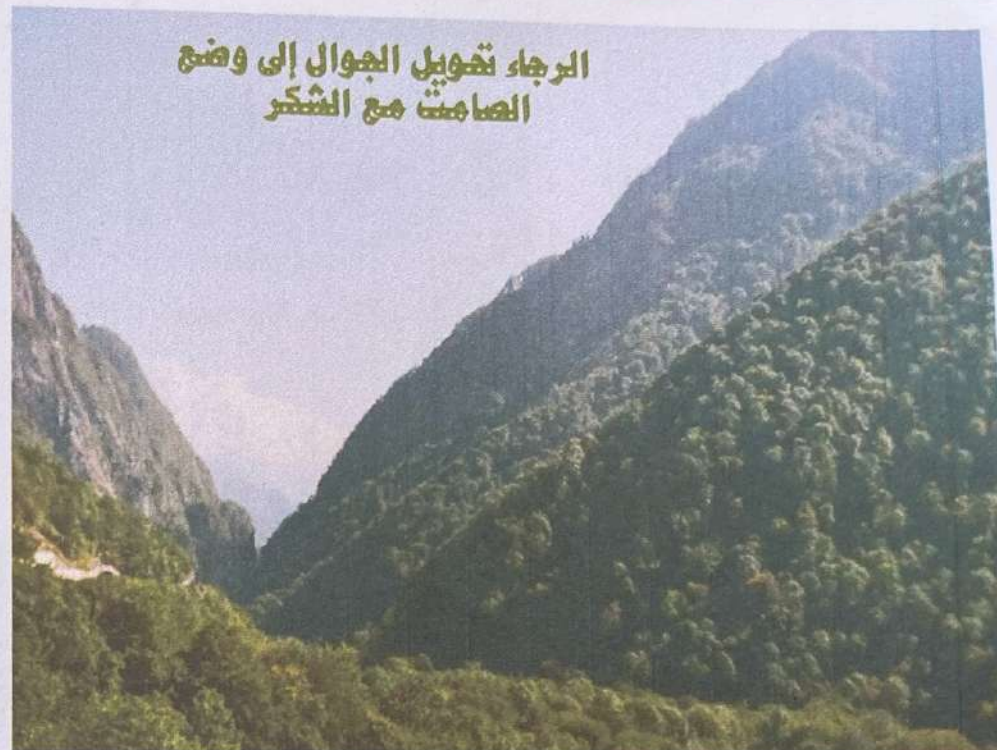


### Movement Disorders-1

#### Akinetic-Rigid Syndrome "Parkinson Disease"

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### Movement Disorders

#### • Akinetic-rigid syndromes:

- Idiopathic Parkinson's disease
- Drug-induced parkinsonism
- Toxin-induced parkinsonism
- Postencephalitic parkinsonism
- Vascular parkinsonism (Post-stroke)
- Parkinsonism-plus
- Childhood akinetic-rigid syndrome (Wilson Dz)

#### • Dyskinesias: (Hyperkinesia)

- Essential tremor
- Chorea
- Hemiballismus
- Dystonia
- Athetosis
- Tic
- Myoclonus

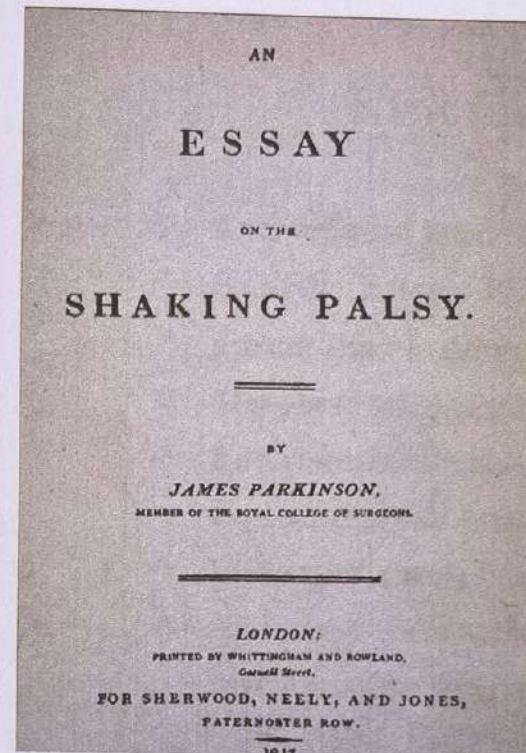
دشاد دام بقل  
عنه اليرافينا  
PD  
لـ لوقل الحرون 70-80%  
Neuron 50-60%  
منه حيتب في نظام  
الغراف PD

### Definition of Parkinson's Disease (PD)

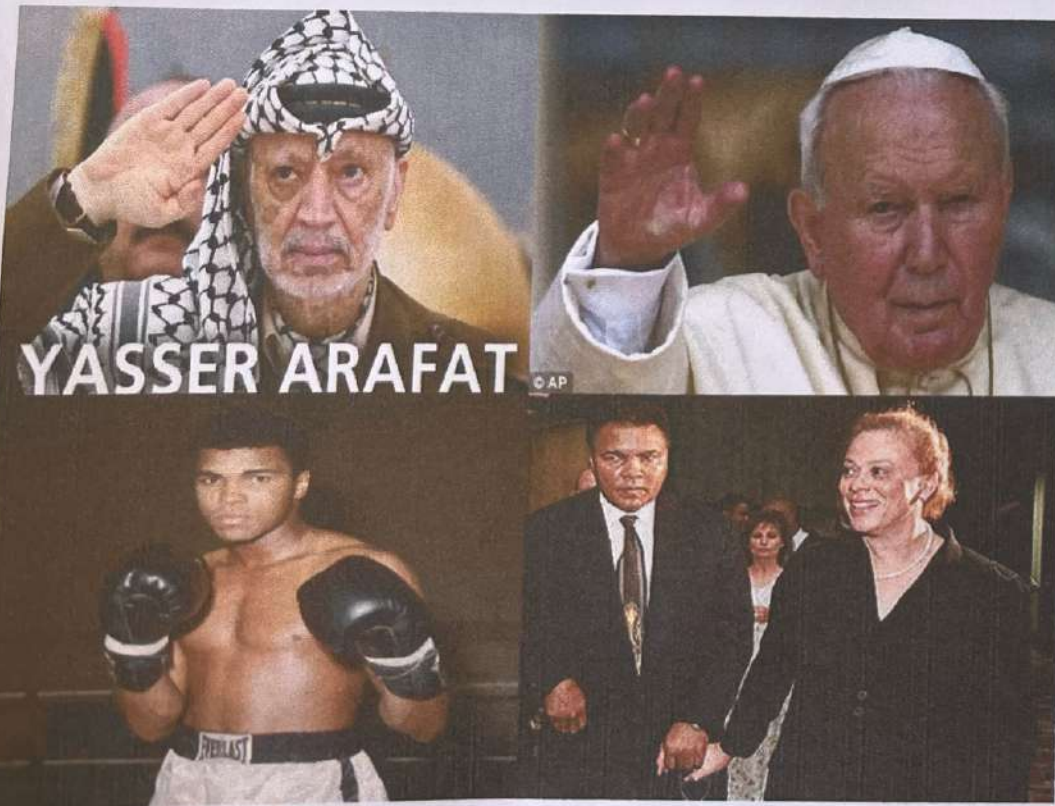
- Chronic slowly progressive, **neurodegenerative** disorder characterized by **loss of pigmented dopaminergic neurons of the substantia nigra** and the **presence of Lewy bodies** causing **tremor at rest, muscle rigidity, hypokinesia** and often with dementia.
- PD symptoms become manifest when about **50-60 %** of the dopamine-containing neurons in the substantia nigra and **70-80 %** of striatal dopamine are lost.

## History of PD

First described in 1817 by an English physician, **James Parkinson**, <sup>شلل الرعاش</sup> "the shaking palsy", but it was later named after him as **Parkinson's disease** by the famous French physician, **Jean-Martin Charcot**



James Parkinson (1755-1824)

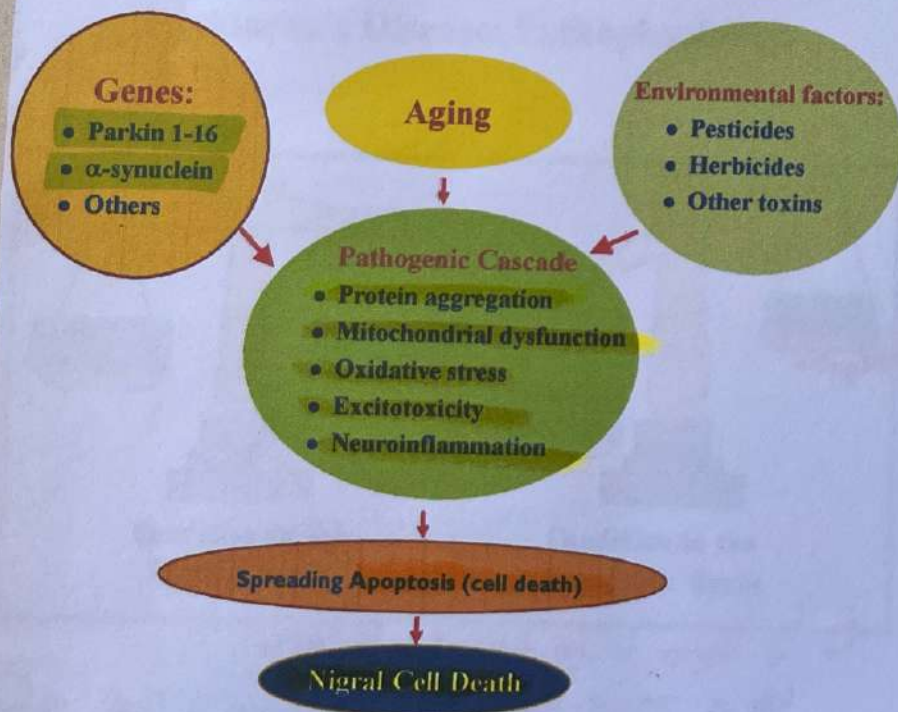


## Epidemiology of PD

- PD is the **second most common neurodegenerative disease**, after AD. → *alzheimer disease*.
- **Annual Incidence:**
  - 5-26/ 100,000 worldwide (USA: 20/100,000).
  - Approximately 60,000 new cases per year in U.S.
- **Age of Onset:**
  - **50 years**. Incidence **peaks** in **65 years** then declines.
  - Rare before age 30.
  - **4-10% cases** before age 40. → *exclusion دماغية, childhood aknetic \$\$\$*
- **Sex Incidence:**
  - Male : Female ratio **3:2**
- **Familial Incidence:**
  - **95%** of the cases are **sporadic**.
  - **5%** Familial "genetic inherited".

## Etiology of PD

- Most cases of Parkinson disease (**idiopathic**) are due to a combination of **genetic and environmental factors**.
- A known genetic cause can be identified in approximately 10% of cases, and these are more common in younger-onset patients.
- **Theories:**
  - Accelerated aging.
  - Gene mutation in young onset: mutation of alpha-synuclein and parkin genes.
  - Environmental factors.



## Risk factors of PD

- ❖ **Age:** the most important risk factor
- ❖ **Genetic factors:** PD in monozygotic twins will be greater than in dizygotic twins.
- ❖ **Male sex:** Male : Female ratio - 3:2
- ❖ **Environmental exposure:** herbicide and pesticide exposure, metals (manganese, iron)
- ❖ **Life experiences:** head trauma, emotional stress.
- ❖ **An inverse correlation between cigarette smoking, caffeine intake and parkinson disease.**

← النيكوتين والكافيين يقللوا الإصابة بـ PD  
• Smoking : Protective

## The Substantia Nigra and the Subthalamic Nuclei

- The **substantia nigra** of the **midbrain** and **subthalamic nuclei of diencephalon** are functionally related to basal ganglia but anatomically they should not be included with them.

- The neurons of the substantia nigra are **dopaminergic**.

لبنوروا دوبايس

## Functional Neuroanatomy of PD

- **Substantia nigra:** the major origin of the dopaminergic innervation of the **striatum**. ← *مخزن فيه الواسية*
- One major function of the striatum is the **regulation of posture and muscle tone**.

## Parkinson's Disease: Pathophysiology



← *قل الواسية فالحالت كذا ال Ach هتزيد*

لذلك بار T. يا هقل Ach فيه balance اذ اعطي Dop.

## Neurotransmitter Substances

### Acetylcholine (Ach)

- Synthesized by **small cells of the striatum**.
- Greatest concentration in striatum

### γ-Aminobutyric acid (GABA)

- Synthesized from glutamate in the **striatum and globus pallidus**.
- Deficiency of GABA associated with **HUNTINGTON'S CHOREA**

### Dopamine (Dop)

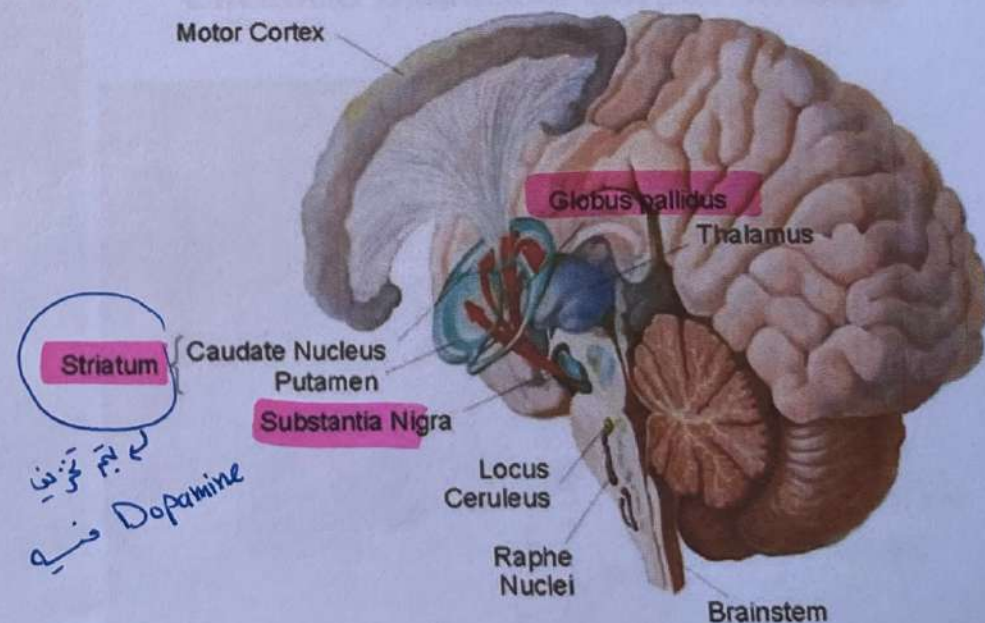
- Synthesized by **cells of substantia nigra** and nigral projections in striatum.
- Greatest concentration in substantia nigra
- **Ach and Dop transmitters normally in balance.**
- **Dop depletion (with Ach excess)- results in the movement disorder of PD.**
- **Dop excess (with Ach depletion)- results in the movement disorder of CHOREA.**

PD ← *Dopamine ↓ و Ach ↑ \**

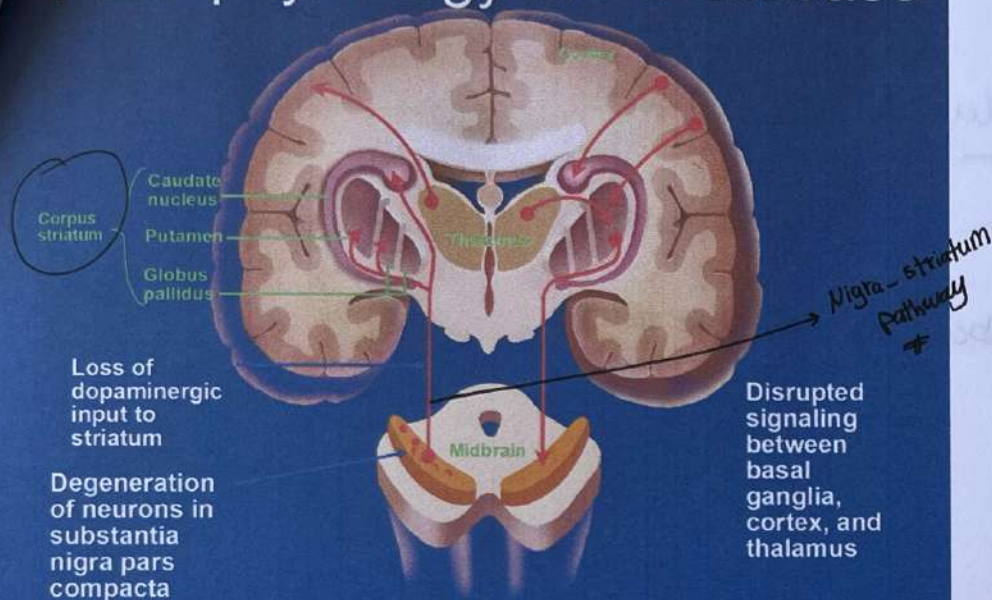
Chorea ← *" ↑, " ↓*

Huntington ← *↓ GABA \**

## Brain Regions Affected by Parkinson's Disease



# Pathophysiology of PD Disease



- ❑ Reduction of Dop transmitter presynaptically

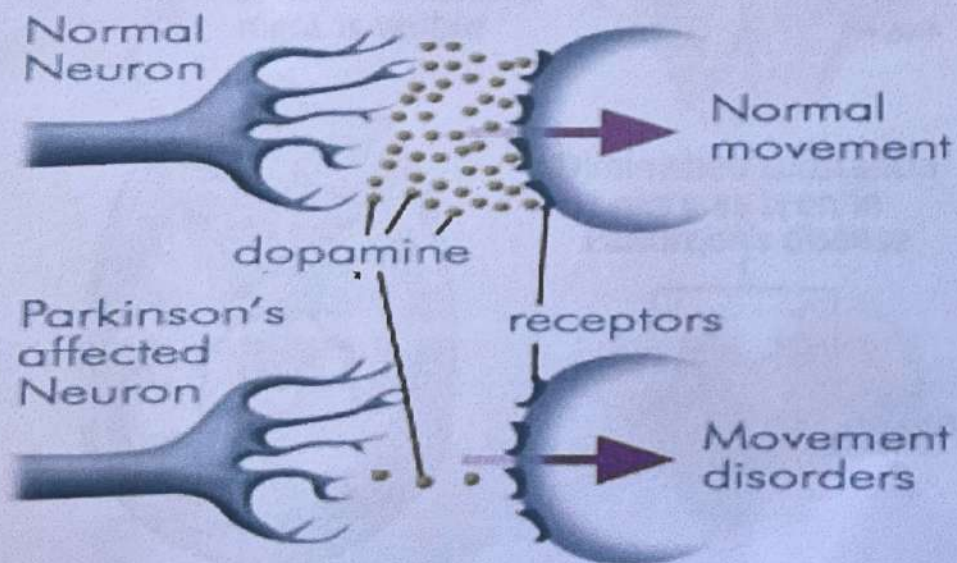
Both reduce effective Dop and create a relative excess of Ach

- ❑ Block of Dop receptors postsynaptically

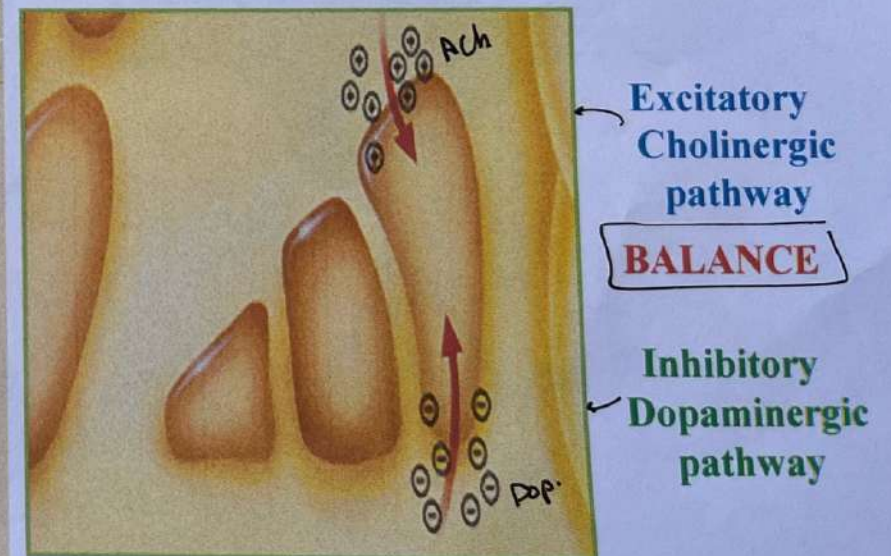
inbalance Bw Ach/Dop.

**PARKINSON'S DISEASE**

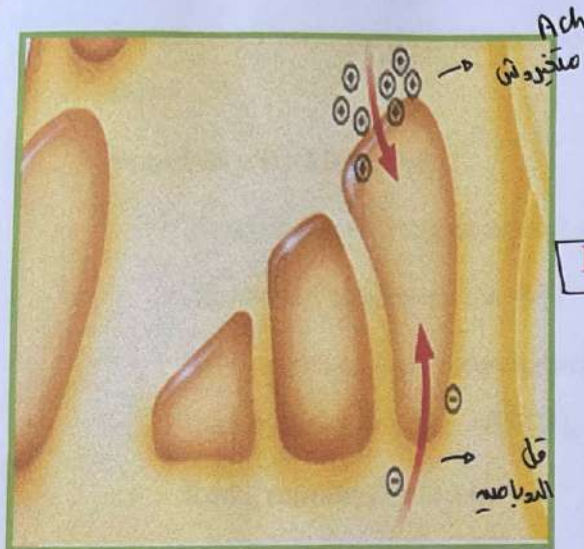
Dopamine levels in a normal and a Parkinson's affected neuron.



## Chemical Balance in Corpus Striatum



## Chemical Imbalance in Corpus Striatum



Excitatory  
Cholinergic  
pathway

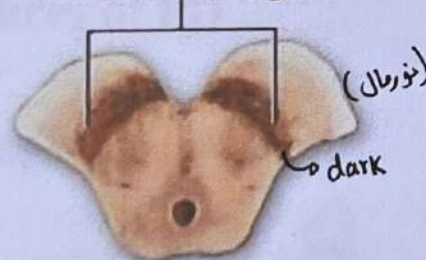
IMBALANCE

Inhibitory  
Dopaminergic  
pathway

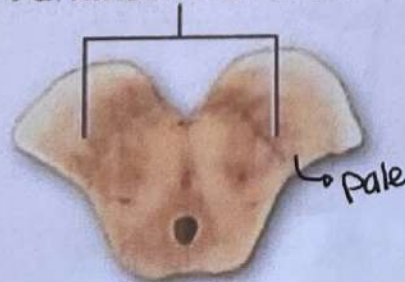


Cut section  
of the midbrain  
where a portion  
of the substantia  
nigra is visible

Substantia nigra



Diminished substantia  
nigra as seen in  
Parkinson's disease



## Pathology of PD

- The substantia nigra contains pigmented cells (**neuromelanin**) which give **black appearance** (macroscopic). These cells are lost in **PD** and substantia nigra becomes **pale**.
- The presence of **Lewy bodies** "cells contain atypical **eosinophilic inclusion bodies**".
- Lewy bodies may be found in other neurodegenerative diseases.
- **Biochemically**: loss of dopamine and melanin in the striatum

## Human Midbrain



Parkinson's  
disease



Normal

## Classification of Parkinsonism

- Idiopathic Parkinson's disease – 85% of all parkinsonism cases
- Secondary Parkinsonism:
  - Drug induced Parkinsonism – 7-9%
  - Vascular Parkinsonism -3%
  - Toxin-induced parkinsonism: e.g. methyl-phenyl-tetrahydro-pyridine (MPTP),
  - Recurrent head trauma
  - Post encephalitis
  - Post - stroke

## Clinical Features of PD

### Classic Tetrad Cardinal Symptoms:

1. Tremor at rest.
2. Bradykinesia (generalized slowness of movements).
3. Muscle rigidity.
4. Postural instability.



## Clinical Subtypes of PD

The major subtypes are as follows:

1. Tremor dominant
2. Akinetic-rigid
3. Postural instability and gait difficulty

### Classic Tetrad Cardinal Symptom



Bradykinesia



Postural Instability



Muscle Rigidity

Resting Tremor

Rhythmic tremor often occurs at first in one hand, where it resembles the motion of rolling a pill between the thumb and forefinger

Leaning forward or backward



Muscle rigidity shows itself in the cogwheel phenomenon



(Difficulty rising from a sitting position)



Parkinson's disease

## Clinical Features of PD: Bradykinesia

occur in 80%

بطء الحركة

- **Bradykinesia (hypokinesia)**- slowness of movement.
- Difficulty with daily activities such as **writing**, **shaving**, using a knife and fork, and **opening buttons**, **tying shoes**
- Difficulty initiating movement
- Decreased blinking and slowness of expression muscles (**Mask like appearance**)
- **Dysarthria**, **dysphagia** and **dribbling** due to **slowness of mastication**, **speech** and **swallowing muscles**.

## Clinical Features of PD: Tremor

- **Most common first symptom (70-75%)**: Involuntary rhythmical alternating movement.
- Usually begins **asymmetric, unilaterally** – upper limb and spread to the other limb.   
 يمين يمين < 14 < 14  
 اليسار اليسار
- **'Pill Rolling'** between the thumb and forefinger.   
 واحد بسبح
- 20 % never develop it. → 20% لا PD (able → tremor) لا
- Tremor occurs at rest, improves with movement and disappears during sleep.

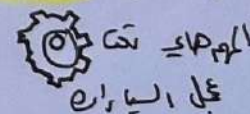
## Clinical Features of PD: Rigidity

Tremor → interrupted ← lead pipe  
Continuous " " ← Cogwheel  
له طاء نوعين

- **Rigidity**- muscle hypertonia.
- Resistance to passive movement
- Affecting flexor and extensor muscle groups equally and is described as **plastic or rigidity**
- When tremor is superimposed upon rigidity it produces **cogwheeling or cogging** quality.

Resistance

عند رجل الحيات هلامه فريس



## Additional Clinical Features of PD

- **Gait Disturbance: Shuffling gait.** → Freezing, short step
- Difficulty getting out of a chair or rolling over in bed.
- Frequent falls or tripping.
- Speech changes- soft speech (e.g., whispering, rapid speech).
- "monotonous speech"
- Smaller handwriting. (micrographia)

## Drug-Induced Parkinsonism

- **Antipsychotics/neuroleptics:** phenothiazine  
(Block dopamine receptors). least movement S/E : Quetiapine
- **Antiemetics drugs:** metoclopramide (Block dopamine receptors).
- **Dopamine depletors:** methyl dopa, reserpine  
(Depletion of intraneuronal dopamine stores).

**Postural instability:** shifting forward of posture into a stoop due to loss of postural reflexes.

**Dysfunction of the autonomic nervous system:** impaired gastrointestinal motility (**constipation**), bladder dysfunction, excessive sweating and **seborrhoea** (greasy skin), decreased sense of smell, sexual difficulties, insomnia and orthostatic hypotension.

**Depression, Anxiety & Psychosis:** mild to moderate depression in 50 % of patients.

**Cognitive impairment:** cognitive decline and dementia

**Parkinsonism-plus** ← مهم ازاف PD + اُراف

- Progressive supranuclear palsy (Steele-Richardson syndrome) is the most parkinsonism-plus disorder.
- Consists of parkinsonism, rigidity, dementia and inability to move the eyes vertically or laterally.
- Other examples are multiple system atrophies such as olivo-ponto-cerebellar degeneration.
- No response to levodopa.

هذه المجموعة لا يستعملوا لـ  $\text{Leubdys}$  ..

## Differential diagnosis between the PD & Parkinson-Plus syndrome

### Parkinson's Disease

- Slow progressive onset of asymmetric bradykinesia
- Excellent response to Levodopa
- Onset with either classic pill-rolling tremor or rigidity

### Parkinsonism-Plus Disorders

- Early instability
- Rapid disease progression
- Poor response to Levodopa
- Pyramidal and cerebellar signs
- Early dysarthria, dysphasia

## Investigations of PD

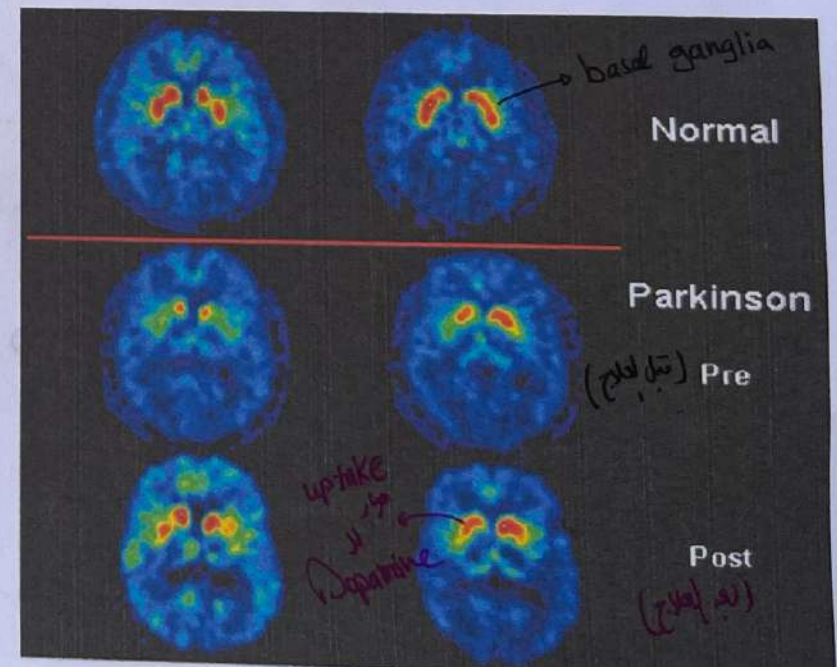
- Brain CT and MRI to exclude structural lesion
- Functional imaging: Positron emission tomography (PET) and single photon emission CT (SPECT) may be helpful for the early diagnosis of PD

## Investigations of PD

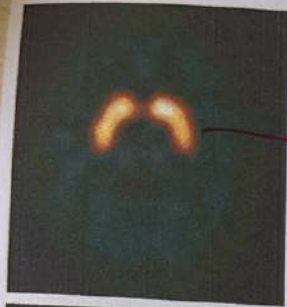
**Laboratory Studies:** No laboratory biomarkers exist for Parkinson disease:

Serum ceruloplasmin concentration, 24-hour urinary copper and slit lamp examination of the eyes (for Kayser-Fleischer ring detection) also should be obtained in patients who present with parkinsonian symptoms when younger than 40 years to exclude Wilson disease.

## Positron Emission Tomography (PET)



## Single Photon Emission CT (SPECT)



- In **normal** cases a transverse slice through the striatum shows a "**comma**" shaped putamen on each side and a circular "**full stop**" shaped caudate.



- Loss of uptake in the putamen regarded as **abnormal**. Uptake in the caudate is initially preserved.

## Antiparkinsonian Drugs

100 film-coated tablets/  
comprimidos con cubierta pelicular

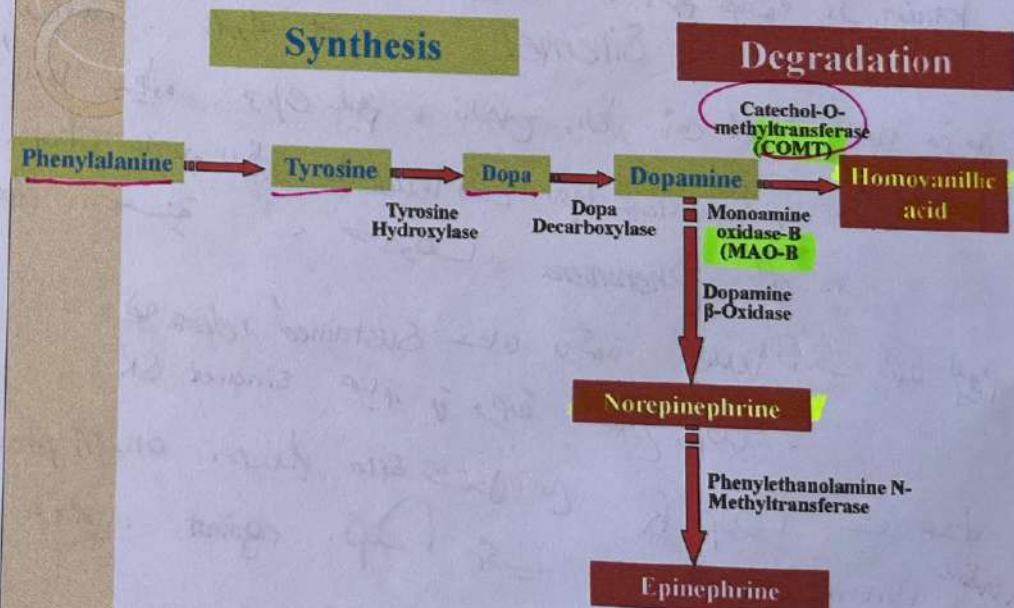
**Stalevo**<sup>®</sup>  
150/37.5/200 mg  
levodopa carbidopa entacapone



## Prognosis of PD

- Before the introduction of levodopa, PD caused severe disability or death in 25% of patients within 5 years of onset, 65% within 10 years, and 89% within 15 years.
- The rate of progression is very variable
- Usually the course is over 10-15 years
- Cause of death is bronchopneumonia (aspiration)

## Pathway of Dopamine Metabolism



## Antiparkinsonian Drugs

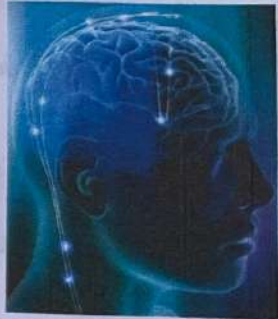
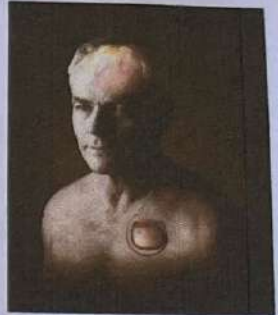
1. **Levodopa/Dopamine agonists:** Levodopa/Carbidopa (**Sinemet** or **Dopicar**), the **gold standard** of treatment.
2. **Dopamine receptor agonists:** Bromocriptine, pramipexole, and cabergoline). → **oral** ↑ **Transdermal Patch** ↑ **rotigotine**
3. **Catechol-O-methyltransferase (COMT) inhibitors:** Tolcapone, entacapone. → **peripheral and central COMT inhibition** (orange ↓ **كلوا البيلي** ↓ **Co hepatotoxic**)
4. **Monoamine oxidase-B (MAO-B) inhibitor:** **Selegiline** or **Jumex**. **anti viral** (كأن مضاد فيروسي)
5. **Anticholinergic:** Trihexyphenidyl (**Artane**).
6. **N-methyl-D-aspartic acid inhibitors:** **Amantadine**. → ↓ Tremor, rigidity
7. **Stalevo:** Combination drug of levodopa, carbidopa, and entacapone  
(50/12.5/200, 100/25/200, 150/37.5/200 mg and 200/50/200mg) : **3 tabs.**  
Nausea, hypotension, serotonin # : **S.E**

## New Researches

- Nicotine
  - Intake of nicotine has shown to slow the degeneration of neurons.
  - Acts similar to levodopa.
- Melatonin

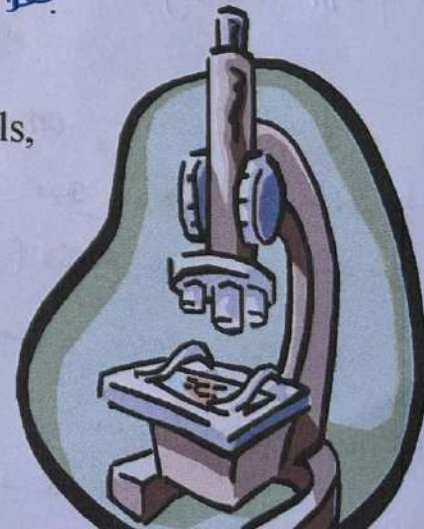
## Surgical Management of PD

- **Deep brain stimulation:**
  - **Thalamic stimulation:**
    - Improves tremor in 90% of patients.
    - No effect on muscle rigidity and bradykinesia
  - **Pallidal and subthalamic stimulation:**
    - Improves muscle rigidity and dyskinesia
- = stereotactic surgery "
- جراحه دقيقه بيفتح جنب basal ganglia  
dopamine عن طريق stimulation



## Future Management of PD

- Neural transplantation
  - Dopamine-producing cells, ex. fetal nigral cells.
- Gene therapy



## Akinetic-Rigid syndromes in Children

### Wilson's Disease

#### Hepatolenticular Degeneration

basal ganglia  
لثة Cu  
liver

An autosomal recessive disorder characterized by defect of cellular copper export with accumulation of copper, in the liver and in other tissues, particularly the basal ganglia.

#### Pathogenesis:

Cell - يتلف مع Ceruloplasmin و يوجد في bile و يتخلص منه في البول

- Deficiency of Ceruloplasmin ( $\alpha_2$  globulin) - which normally binds 98% of copper in the plasma.
- In Wilson's disease, there is decreased transport of copper from the liver into bile  $\rightarrow$  leading to copper excess  $\rightarrow$  accumulation it initially in the liver, basal ganglia, eyes, kidney, bone, and in other tissues.

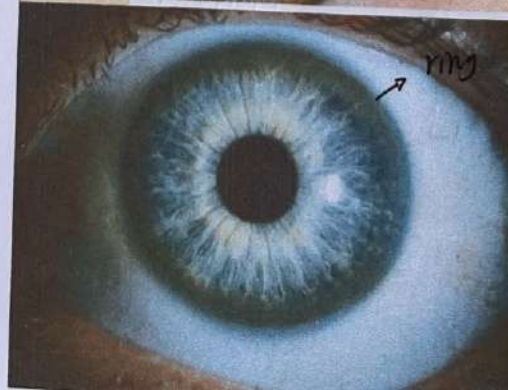
في 98% من Cu لا يرتبط مع Ceruloplasmin بل مع other protein و يخرج في urine

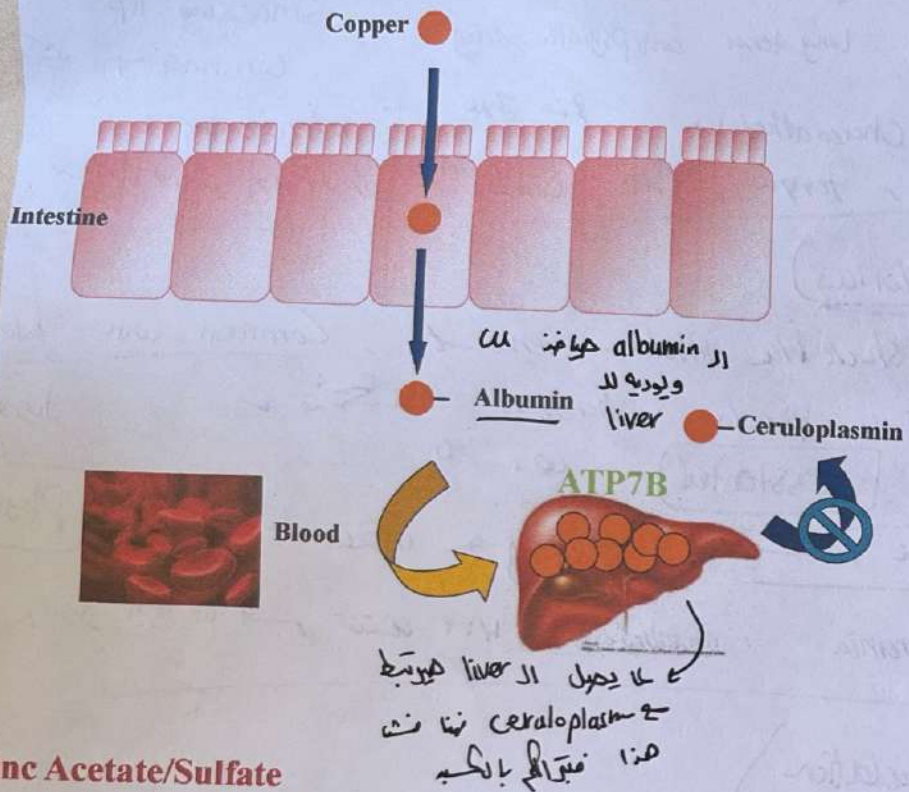
#### Diagnosis and treatment of Wilson's Disease

- Low caeruloplasmin (less than 20 mg/dl)
  - Serum copper is usually reduced but can be normal
  - High urinary copper excretion (24-hour urinary copper excretion)
  - Liver biopsy in terminal stages
  - **Brain MRI:** thalamic and putaminal hyperintensity
  - **Ophthalmological examination:** deposition copper in the cornea (Kayser-Fleischer ring) detectable on slit lamp examination
- Treatment:** D-penicillamine and trientine, oral zinc, liver transplantation in terminal stage.

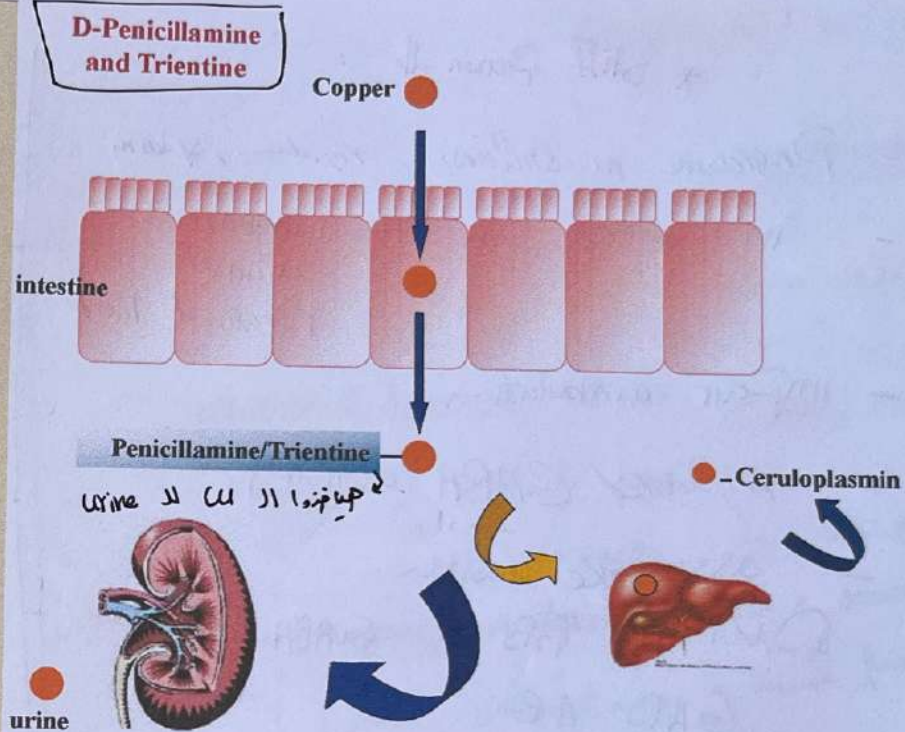
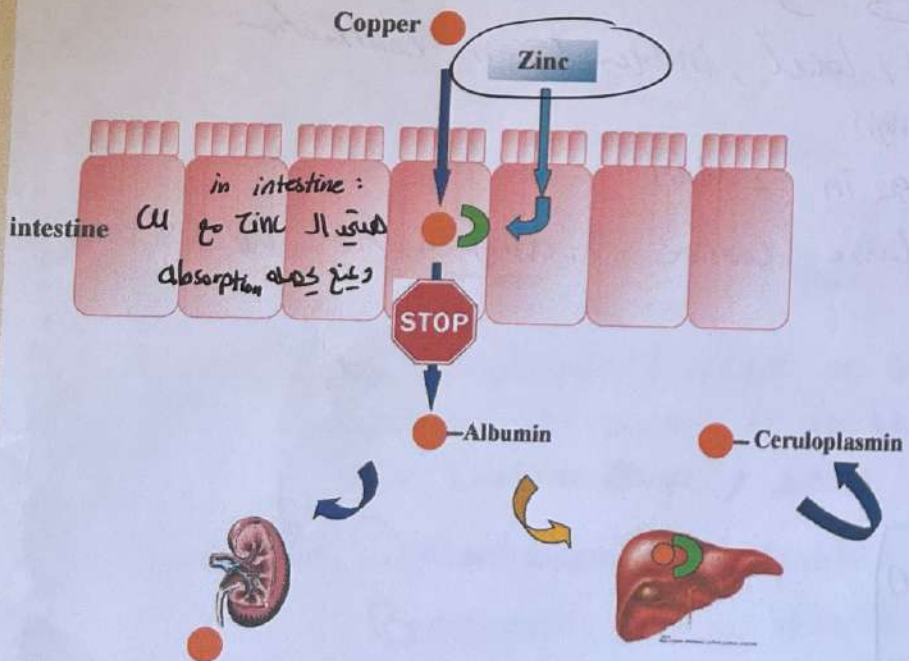
#### Clinical Feature of Wilson's Disease

- Proximal tremor  $\rightarrow$  Chorea + athetosis.
- Choreoathetoid movements
- Bradykinesia
- Psychosis, behavioral disorders and dementia
- Dysarthria, dystonia and rigidity
- Liver involvement common





### Zinc Acetate/Sulfate



# Parkinson

\* عنا جة بار basal ganglia اسمها : (Substantia nigra)

melanin تيجي أسود ، لأن الخلايا الـ فيها بتطلع

فهمنا الخلايا جدير الها degeneration ، فتجبر Pale من سودا  
 (Dopamine) ← منتج البرايمية في الحسنة  
 ← يعني لان من تطلع

inclusion سموم : bodies  
 (Lewy bodies) ، اتضح انه الـ bodies ده  
 أحسن عبارة عـ : (Prion) ← [smallest infectious organism]

\* LL (Primary parkinsonism)

= (2<sup>nd</sup> p.)

① (Atherosclerosis) أشهر سبب ، زي "تيرغزات" له عجه "

② (encephalitis) زي اوبالا

③ (repeated head trauma)

④ (drugs) ← reserpin (دواء ضغط لـه يفتح قديماً)

Chemical LSD (lysergic acid diethylamide) أولاً تتراب تفتح

## \* Clinical pic //

1) **loss emotion expression** → **masked face**  
monotonous speech  
infrequent blinking (كلا فني، فني لا عومي)

2) **rigidity** (↑ Tone : **flexor** خاضعة بار)

flexion in Trunk, UL, LL : قتلاني

(ape like or Gorilla like attitude) : حق بسعوها ✓

لا غني لازم ذبح، حلتنا نزل extension ، نزل لانه عنده

Tone عالي اوده بار flexor بنت صفة، يلى Extension

(Shuffling gait)

3) **Tremor**

(pill rolling) : حبة بار hand ، بسعوها

لانه يسرج بليه (جود)

تزيد Tremor مع emotion stress

تقتفي مع Voluntary movement يعني لو صد اليه تقتفي اربعة  
لانه نبيس (static tremor) لانه مع ص. م. وانشاء لازم تقتفي

في عكس Tremor اكي بتجي مع عيان ataxia في عنده

مسكة بار cerebellum بيتكون (kinetic tremor)

لحق لا بعد ايم هزعت

\* ال primary P. ← progressive يعني الآخر

Dementia

Tremor < rigidity

\* 2nd P. : =

Progressive ← **atheroscl**

Tremor < rigidity

regressive (لن inf. يعني) ← **encephalitis**

Tremor = rigidity

مت ب حبة ال basal ganglia ، هت هتوز

ال hypothalamus ، متلاقي عنه other lesion :

Dyphagia , hypersomnia , Diabetes insipidus  
تأثر ليه

excessive sebaceous gland secretion : حلاصو زنت وياح

sialorrhea : مري

Oculogyric crisis → sudden vertical deviation of eye upward

فجأة حول لنود طاكطلي عليه تبدل



هو مستحقة  $\rightarrow$  نقص درباريه  
 $\rightarrow$  زياده Ach

لو اوفينا Dopamin oral حيتك بار 1.6

منينكي مع حبل L-Dopa حيتك وبيدك ايم فضا بقول ليدوپامين  
 فريب ايم حيرج للبي بكم نالاولم لكح قليل من اكل ؟ ازود ال dose ؟

لو زودتها حيدك : Chorea , Vomiting , Palpitation , Tachycardia

فائل  $\Leftarrow$  حيدك مع L-dopa - Carbidopa  
 ليدوپامين ايم ، لما يوصلوا ال brain ، L-dopa بيدك  
 Carbidopa صيدك بيدك ال BBB ، ايم حيدك بار brain  
 ليدوپامين . الراء ايم : **Sinemet**

بالاول لانوا بيطوه حيرج ايم ، فالصبح ، الفكر ايم level للدماء منيد  
 Chorea على يد الفكر قبل level بيقو نيدل Parkinsonism عبال متافه  
 ال dose المتاسية : حوها : on-off Phenomena

الكل ؟ نفقه Sustained release عبال يكون level ثابت طول اليوم  
 Sinemet SR صيدك في وحدة الصبح ، حيدك .

on-off phen حيدك ، حيدك حابو تشغل مع Dop R حيدك  
 L-Dopa ، حيدك : Dop. against : حيدك

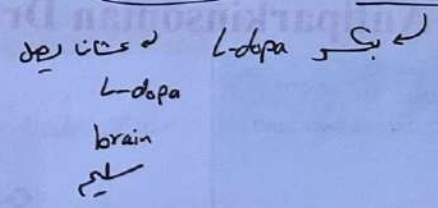
amanatidine , Bromocriptine : حيدك  
 SE: Severe nausea, vomiting

Dopamine  
 Drug S-E

- nausea, vomiting
- orthostatic hypotension
- excessive sleepiness
- Dyskinesia
- convulsion , حولة
- dizziness
- headache

\* Carbidopa inhibit

Peripheral decarboxylase



\* short half life of levodopa  
 90 min

on-off phenom

- | on symptom                           | off s.          |
|--------------------------------------|-----------------|
| - wearing off                        | - dyskinesia    |
| - freezing of gait                   | - <del>ab</del> |
| - sympt return 3-4 h after each dose |                 |

# de LST >