

# Drugs Used in Parkinsonism

Pharmacology II  
Dr. Heba Khader

• حالة المرض مع الوقت لتسوء ووجه أن الأدوية التي 2 تحكيها ما في حداد بعدت ال progression تأتي ← الدواء فقط يخفف الأعراض

# Parkinsonism

• يزيد مع الوقت (مسألة الأساسية) ↑  
(أهم دالة) ↑

- Parkinsonism (Parkinson's disease): A progressive neurological disease characterized by tremor, rigidity, bradykinesia (sluggish neuromuscular responsiveness) and postural instability.

- It is first described by Dr. James Parkinson in 1817 as "shaking palsey".

- It has a prevalence of 1-2 per 1000 of the general population and 2 per 100 among people > 65 years.

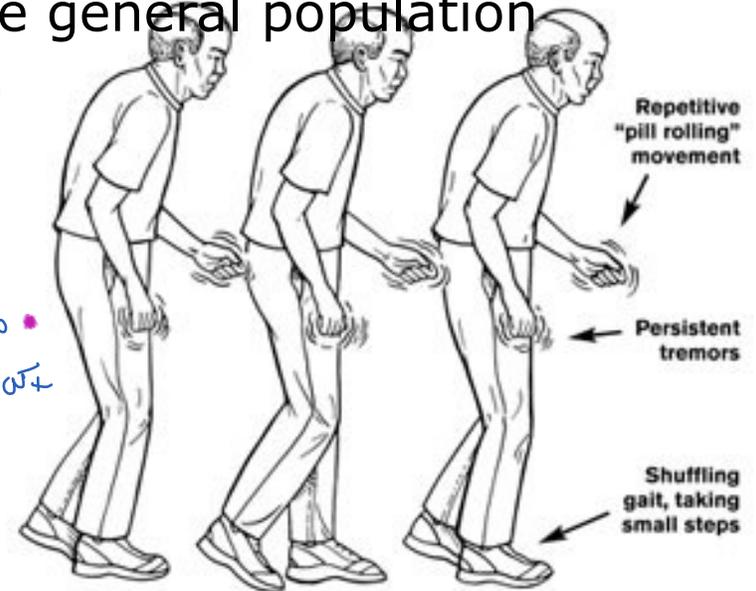
Parkinsonism

- Generally occurs between age 50

and 65.

أكثر عرض يلبش عند 65 وبتيسر أكثر عرضة.

• ممكن يلبش بيسرع عند الأ سنمان بجمراً حتى من 50 ما فوق  
لكن ما تقدم بالمر لى ما زادت الفهمه إنه بيسرعده حالة ال parkinsonism



• ٣ أعراض رئيسية :-  
Symptoms :-

# PARKINSON'S DISEASE

- Onset usually gradual, after age 50.  
(Slowly progressive) *رئي متديوعاة ال slow motion*

*ما بينق تعابير (لامننا ولا منح)*

- Mask-Like, Blank Expression *ومنعية ال دكنا*
- Stooped Posture

• **Bradykinesia**

- Loss of normal arm swing while walking
- ↓ Blinking of the eyelids
- Loss of ability to swallow
- Blank expression
- Difficulty initiating movement



• **Pill Rolling Tremors**

*أطرافه ترتج/تتهتز بشكل واضح... (طريقة استراز مميزة)*  
*اصبح ال دهام يلف (rolling pill)*  
*كانه يلف لشوهد باصبعه*

• **Tremor**

- Commonly in hands and arm
- Pill rolling motion with the fingers
- Occurs most often at rest
- May involve diaphragm, tongue, lips and jaw
- Increases with stress

- Possible Mental Deterioration
- Depression

• **Muscle Rigidity**

- ↑ Resistance to passive movement
- Cog wheel, jerky slow movement

*العضلة تتصلب زي كأنها حجر*

- Shuffling, Propulsive Gait

- Rarely Occurs In Black Population

*Shuffle Shuffle*



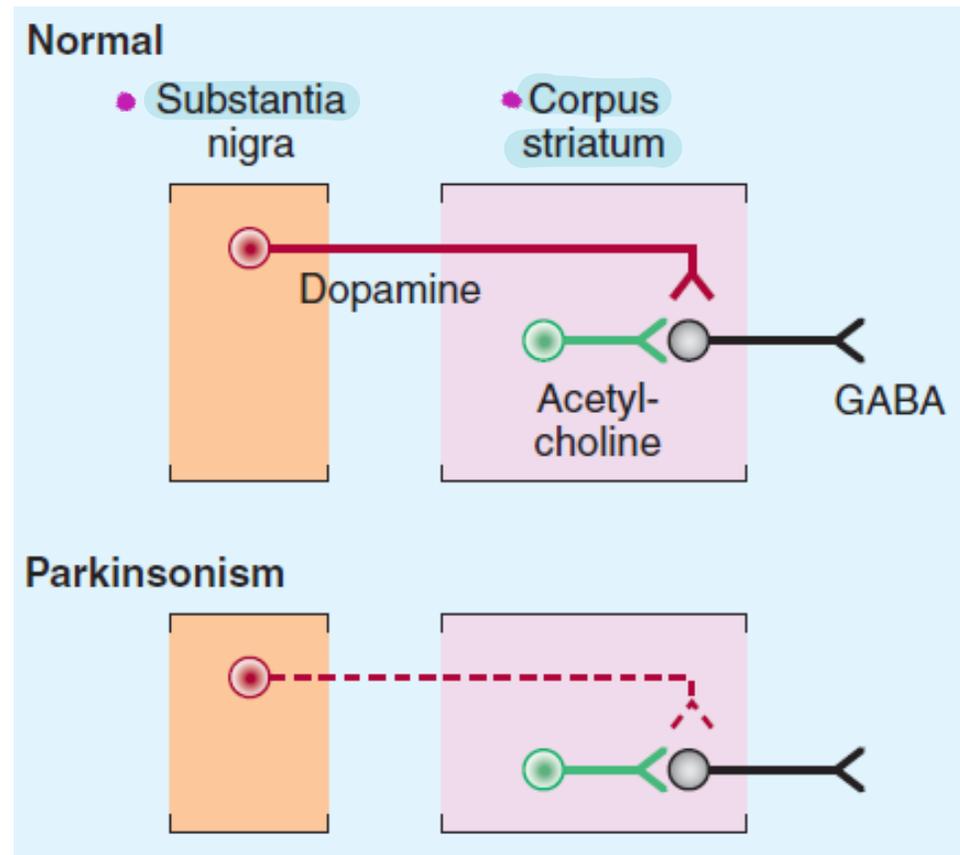
• مشكلة الباركنسون الأساسية هي: كـ (pathophysiology) هو نقص الـ Dopamine ... الذي يصير هو :-

أنا عنده فيا كيم Dopamine و norepinephrine و Acetylcholine ما عرفوا يكون في بينهم Balance وما يصير neurotransmitter يطحن على الثاني ... احنا عننا صنفين في الـ Brain واحدة تنوع الـ Ach وراحة تنوع الـ Dopamine لجال Ach يزيد عن Level معين الـ Dopamine يعمله inhibition والعكس صحيح.. لما الـ Dopamine تزيد كثير الـ Ach في هذال Balance ياخفا على التوازن بين الـ sympathetic والـ parasympathetic والتوازن بين الـ muscle relaxation والـ muscle rigidity يوقفه ...

حين انه جسم الانسان يظل بالـ Normal physiology ...

فلكن لسبب غير معروف كدال ان كمية الـ Dopamine في الـ Brain بالذات ويطلق تقريباً موجود ... النتيجة انه الـ Ach رح تقل الـ activity تاعته عالية وزيادة عن حد ما درج يعطينا الـ الأعصاب تاعن الباركنسون الـ الذي حكينا عنها ... دال ان ذنن ما يصير الـ Dopamine يوقف شغل الـ Ach

- Many of the symptoms of parkinsonism reflect an **imbalance between the excitatory cholinergic neurons** and the greatly diminished number of **inhibitory dopaminergic neurons**.
- **Therapy** is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus **reestablishing the correct dopamine/acetylcholine balance**.

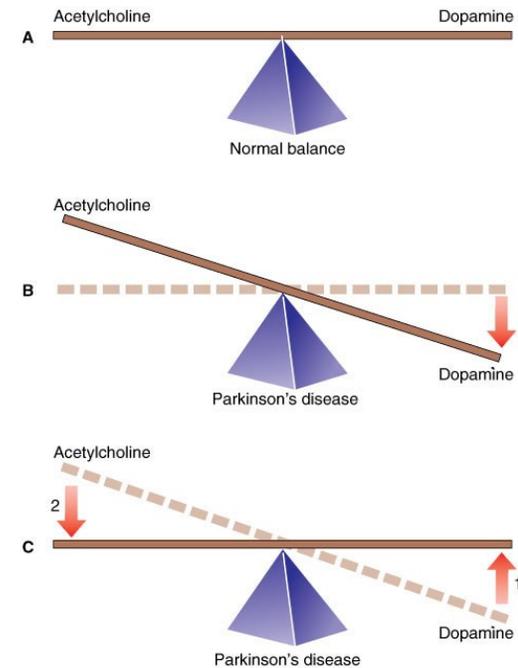


أكل :: بدني أعطي دوبا مني (أي ستيغيزيد الدوبامين أو يعمل مثله) أحوال antimuscarinic drugs ... رح نلاستي مجموعة من الأدوية  
 أعتبها تكون وليغتها انها ترفع الدوبامين في الجسم وأغلبهم

# Drug Therapy of Parkinsonism

- Strategies of drug treatment of parkinsonism involve increasing dopamine activity in the brain, decreasing muscarinic cholinergic activity in the brain, or both.

1. Levodopa/Carbidopa *الأكثر استخداماً*
2. Dopamine receptor agonists *تربط على ال receptor قاع الدوبامين (تستعمل زي الدوبامين)*
3. Monoamine oxidase (MAO) inhibitors
4. Catechol-O-methyltransferase (COMT) inhibitors
5. Amantadine *Antiviral (يعمل بطريقة غير معروفة) (دعوى من امراض الباركنسون)*
6. Antimuscarinic drugs *يقلل ال activity تاغ ال Ach ويقلل امراض الباركنسون (يقلل ال cholinergic transmission)*



A, Normal balance of acetylcholine and dopamine in the CNS.  
 B, In Parkinson's disease, a decrease in dopamine results in an imbalance.  
 C, Drug therapy in Parkinson's disease is aimed at correcting the imbalance between acetylcholine and dopamine. This can be accomplished by either  
 1. increasing the supply of dopamine or  
 2. blocking or lowering acetylcholine levels.  
 Fig. 14-1. The neurotransmitter abnormality of Parkinson's disease.  
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(the Best choose)

# 1. Levodopa

لأنه ما عنده القدرة على دخول الـ BBB خارجياً *peripherally* مما يعطي التأثير المطلوب!

• Dopamine does not cross the blood-brain barrier and if given into the peripheral circulation has no therapeutic effect in parkinsonism.

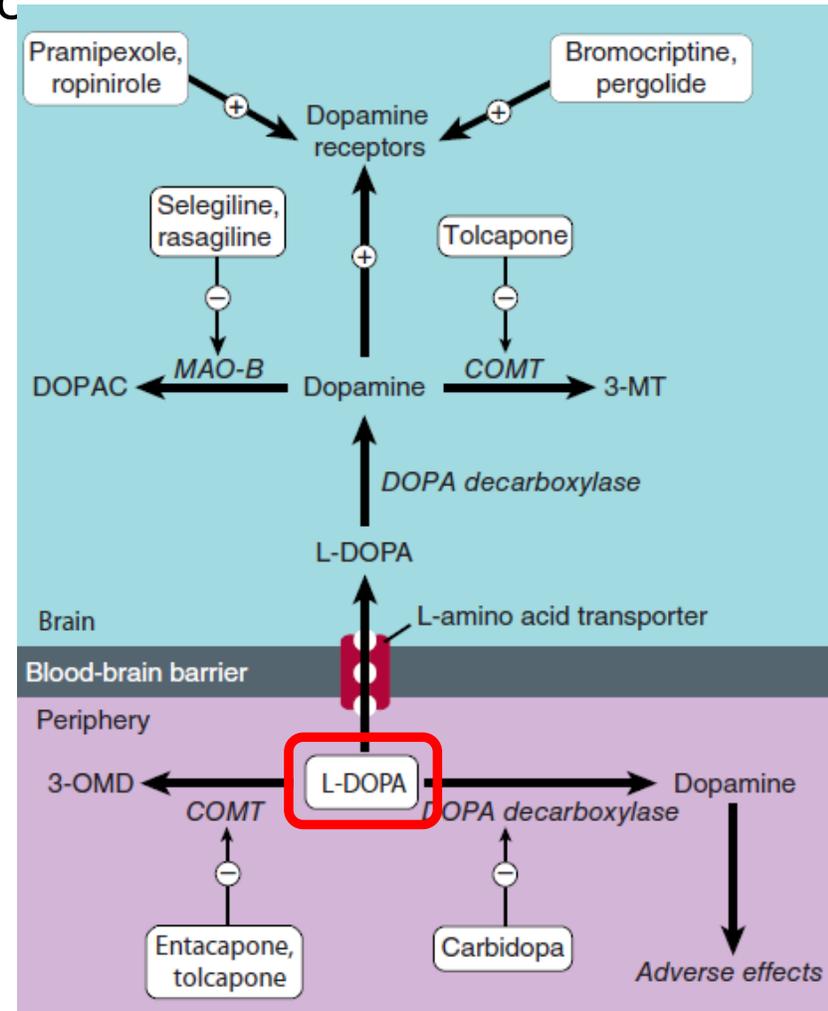
BBB

• However, **levodopa**, the immediate metabolic precursor of dopamine, does enter the brain (via an L -amino acid transporter, LAT), where it is decarboxylated to dopamine by the enzyme aromatic L-amino acid decarboxylase (dopa decarboxylase), which is present in many body tissues, including the brain.

سواء يدخل عن طريقه؟

لأنه يدخل الـ Brain، يتحول لـ dopamine عن طريقه، انزيم

اسمه (dopa decarboxylase)



مثلاً لو اعطينا المريض 10 mg من ال Levodopa كم الكمية التي تدخل ال Brain ؟ نسبة 1-3 mg

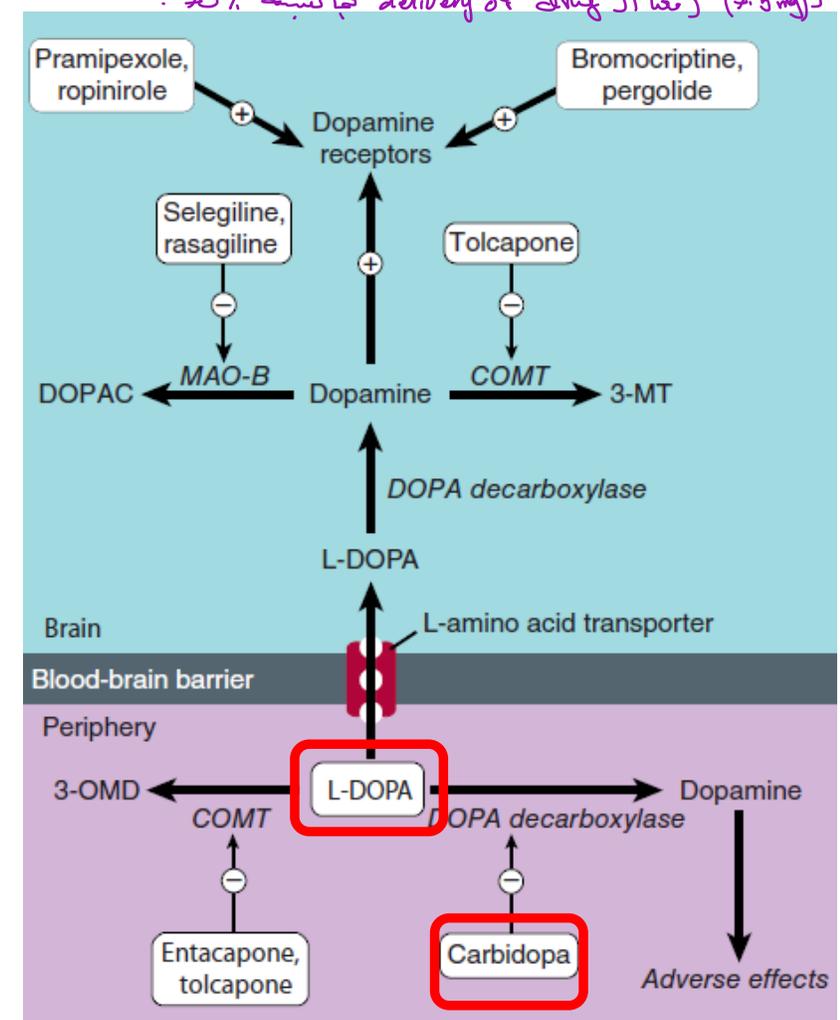
هاي تعتبر نسبة قليلة لذلك أنا أحتاج dose عالية اعطيا المريض عشان أوصول الكمية التي تحليني ال effect في ال target tissue .  
 [ اعطي نسبة عالية عشان أوصول الكمية المطلوبة ] جيني شو السبب ؟

# 1. Levodopa

ال (7-9) دين راحو ؟؟ ال dopa decarboxylase هذا الإنزيم موجود في جميع أنحاء الجسم في الدماغ وباقي ال tissues ناخزي كثير من ال Levodopa بتحول ل dopamine خارج الدماغ وبالتالي ما راح يدخل ال Brain ... فدها الخزي الكبير ما نستفيد منه ... اكل ؟؟  
 اكل هو رانه اعطي مع ال Levodopa ال Carbidopa الذي يعمل (inhibitor of dopa decarboxylase)  
 فها يعني كمية أكبر من ال Levodopa وبالتالي لزيادة الكمية ال (7.5 mg) ونفعا ال هدف ال delivery ما نسبتة 10% .

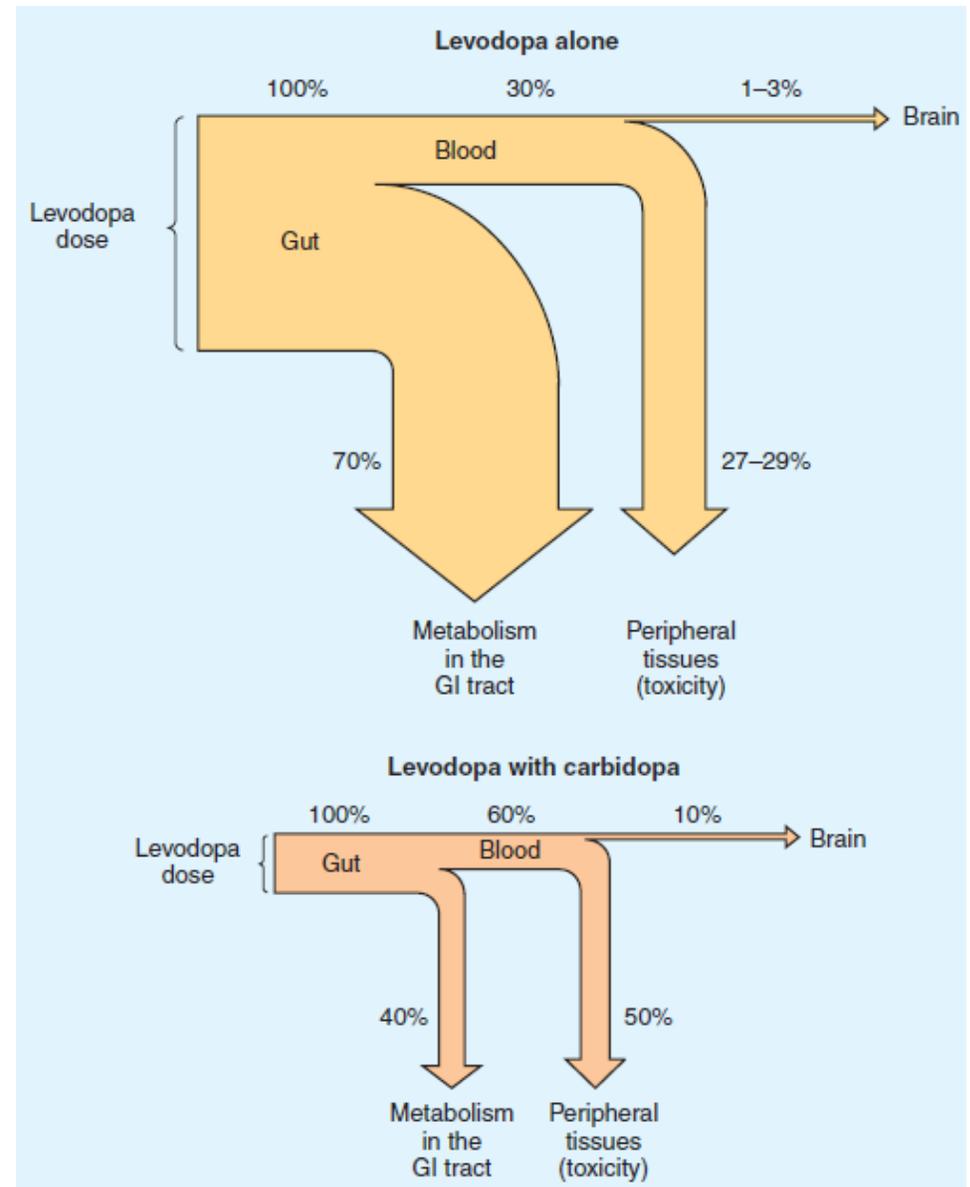
- Levodopa is usually given with **carbidopa** (a peripheral dopa decarboxylase inhibitor that does not cross the blood brain barrier), which diminishes the metabolism of levodopa in the gastrointestinal tract and peripheral tissues but not in the CNS, thereby increasing the availability of levodopa to the CNS.

- With this combination:
  - the plasma half-life is prolonged
  - lower doses of levodopa are effective
  - and there are fewer peripheral side effects.



# 1. Levodopa

- When levodopa is given alone, only about 1–3% of administered dose actually enters the brain unaltered.
- Concomitant administration of a peripheral dopa decarboxylase inhibitor such as carbidopa may reduce the daily requirements of levodopa by approximately 75%.



(يؤخذ على معدة فارغة)

إذا كان في أكل في المعدة أو الأمعاء رج يؤخذ على امتحانه

فأفضل وقت لأخذه هو قبل الأكل من ٣٠ دقيقة إلى ساعة أو العكس بعد الأكل

ب ٤ ساعات

# 1. Levodopa

## Absorption and metabolism:

- The drug is absorbed rapidly from the small intestine (when empty of food).
- Ingestion of food delays the appearance of levodopa in the plasma.
- Moreover, certain amino acids from ingested food can compete with the drug for absorption from the gut and for transport from the blood to the brain.
- Thus, levodopa should be taken on an empty stomach, typically 30-60 minutes before a meal.

# 1. Levodopa

- **Clinical Use**
- The best results of levodopa treatment are obtained in the first few years of treatment. The benefits of levodopa treatment often begin to diminish after about 3 or 4 years of therapy:
  1. This is sometimes because the daily dose of levodopa must be reduced over time to avoid adverse effects at doses that were well tolerated initially.
  2. In other cases, some patients become less responsive to levodopa, perhaps because of loss of dopaminergic nigrostriatal nerve terminals.

هذا الدواء زي السحر من أول حبة تلبس معظم الأعراف تنتهي ... هو لا يستعمل مع أمراض الأستيا  
ولا الكتابة حتى .. هذه الأمراض تقل تدريجياً ..

# 1. Levodopa

## Pharmacologic effects:

- Effective in eliminating most of the symptoms of parkinson disease
  - Bradykinesia and rigidity respond quickly
  - Reduction in tremor effect with continued therapy
  - Handwriting , speech, facial expression and interest in life improves gradually

وفي مشكلة أساسية بعض النظر عن انه الأمر انه كفف ... هو انه كرفنا **progressive** يعني انه يزيد مع الوقت ...  
يعني الألياف التي تنتج الدوبامين في الدماغ تموت مع الوقت وبعون معها ال dopamine receptors .. يعني مع الاستعمال  
ال Levodopa مع (٣-٤) سنوات يظل يعطي مفعول ( ما يكون في receptors تستقبل الدواء ) ... خلايا ال Brain و العصب  
ناتج خلية تموت ال receptors تاخونها ...  
نعتبرها انه يتلف قلبه يستعمل ال Levodopa من أول يوم اكتشاف للمرض ... وبعد (٥-٦) سنة يظل يعطي المفعول ...  
هل لو أكلنا ال Levodopa نجد سنتين مثلاً و اعنيه الأوية الثانية ... تدرج ريس؟ عليك أفضل رزته إلا مبادئه آخر  
خيار لأنه جدا استخداه وانها مفعولها في ستي ومثلان يأخذه بوجه !  
لذلك فلي ال Levodopa آخر خيار ... الظاهر ( لكن لسامش مؤكدا ) انه ال Levodopa يسرع موت الدوبامين أكثر .

# 1. Levodopa

## Adverse effects:

### 1. Peripheral effects:

1. Anorexia, nausea, and vomiting due to stimulation of the chemoreceptor trigger zone of the medulla.
2. Tachycardia result from dopaminergic action on the heart.
3. Hypotension may also develop.

### 2. CNS effects: Visual and auditory hallucinations, mood changes, depression, and anxiety.

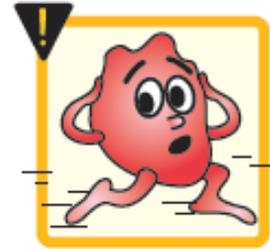
### 3. Dyskinesia and response fluctuation: "On-Off phenomenon" off-periods of marked akinesia (loss or impairment of voluntary movement) alternate over the course of a few hours with on-periods of improved mobility but often marked dyskinesia (abnormal involuntary movements).



Anorexia



Nausea



Tachycardia



Hypotension



Psychiatric problems

المبتكاه اذنه :- عند بعض الأستخدام تحدث حالة [on-off phenomenon] نقطة رجوع (مثل عند الأكل).

• امر يفينا يأخذه ٣ مران باليوم كن 8 ساعات

المعزذ فوائده ال Sale ما يظهر أي من الأثر اذ الإفني آخر ساعته من ال ٨ ساعات ... و لكن مران تقصير الأثر اذنا تظهر

بعد أخذ الدواء ساعة أو ساعتين و ممكن الأثر اذنا صرنا من ال (١-٢) ساعات ... زني أأ نقما أخذنه (هو أخذنه و لكن ما يبذل !)

← ما اذنا نقلاه بشي و مني هذه الكالة ! ما نقدر نقضيه حبة ثانية من ال levodopa (ما هو السبي اذنا ما وعار مني للآن)

# [drug - drug interaction]

## 1. Levodopa

ليساعد على تكبير ال Levodopa خارج ال Brain  
(كولا ل dopamine ببرا الدماغ) ← فاقلا من تأثيره.

### Drug interactions:

1. Pharmacologic doses of **pyridoxine (vitamin B6)** enhance the extracerebral metabolism of levodopa and may therefore prevent its therapeutic effect unless a peripheral decarboxylase inhibitor is also taken.
2. Levodopa should not be given to patients taking **monoamine oxidase A inhibitors**, such as phenelzine, or within 2 weeks of their discontinuance because such a combination can lead to **hypertensive crises**.

ما يبسر ينطوي مع ال (MAO inhibitors)

لانه (مع برفع نسبة ال dopamine peripherally وال Levodopa برفه و لرفع نسبة ال dopamine في الجسم ... اذا ارتفع ال dopamine كثير في الجسم ← رفع يوصل hypotensive Crises في ال ضغط الدم يرتفع بشكل كثير و يمكن ان يوصل لجلطة عند المريض).

• يرتبط مع ال receptor تابع ال dopamine (مثل كيتريدينوا من ال Levodopa).  
 بعض الكبر.

النوع الثاني من الأدوية

## 2. Dopamine Receptor agonists

- This group of anti-Parkinson compounds includes:

- Bromocriptine** and **pergolide**, are **ergot derivative** (rarely used).

يستخرج من الفطريات

استخدامهم صار قليل لأنه هارمون أدوية مهتصة وال side effect تاها قليل

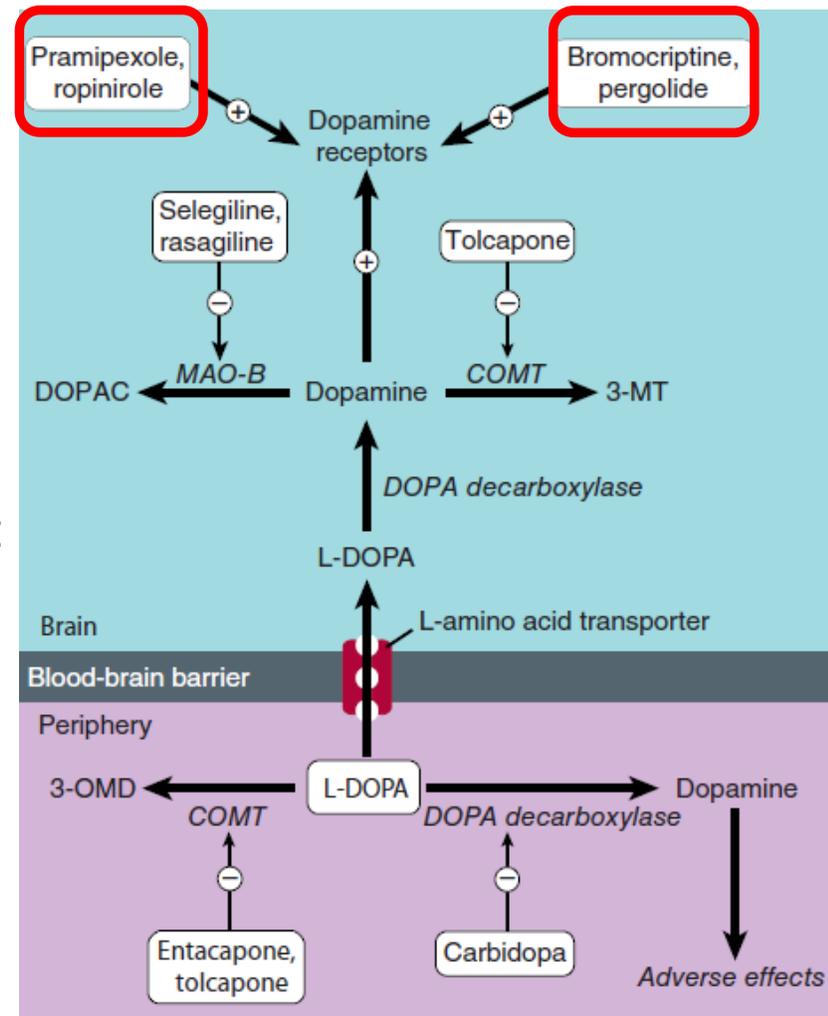
- Ropinirole**, **pramipexole**, a newer, non-ergot drugs.

مثل

- Rotigotine** delivered daily through a **skin patch**, is approved for treatment of early Parkinson's disease.

نبتع في الجلد لفترة طويلة ويعمل Sustained release

نبتع في الجلد لفترة طويلة (زي كأنه لاصق)



تعطى معقول بالي حرم مازي ال Levodopa دومات ممكن يكون ا حسن عن الاستخا op اللي يصير عنده هم  
 Fluctuation → (on-off) طبيعيا  
 فوفه

## 2. Dopamine Receptor agonists DRA

- These agents have durations of action longer than that of levodopa and, thus, have been effective in patients exhibiting fluctuations in their response to levodopa.
- However, these drugs are ineffective in patients who have shown no therapeutic response to levodopa.

Dopamine receptors  
 على عتق  
 Apomorphine ال

المorphine ما يرتبط على ال

• **Apomorphine** is a potent dopamine receptor agonist, apomorphine injected **subcutaneously** may provide rapid (within 10 min) but temporary relief (1-2 h) of "off-periods" of akinesia in patients on optimized dopaminergic therapy.

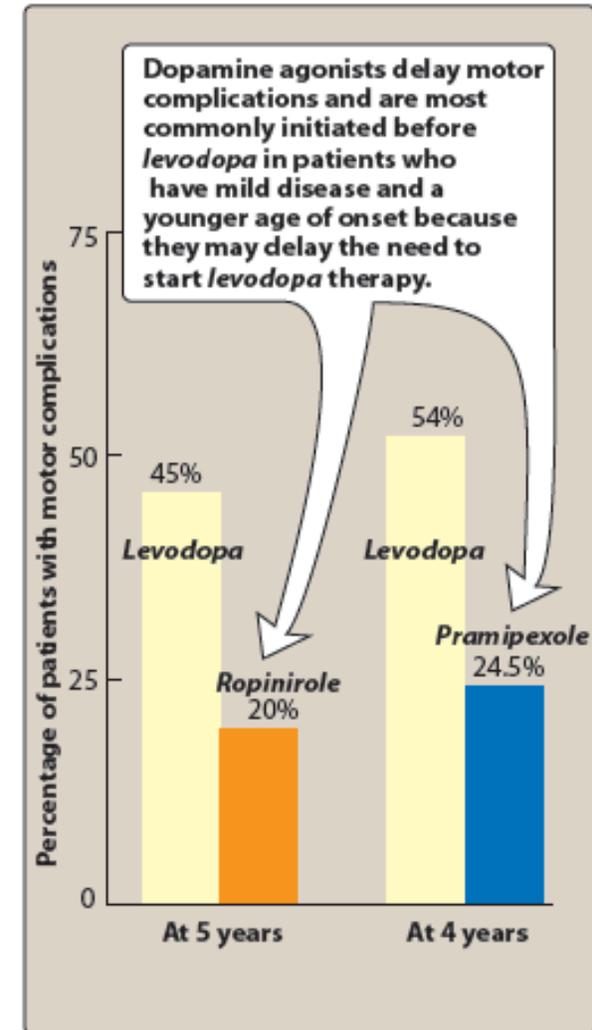
اختيار  
 DRA  
 قطعاً إذا مرين ما نشي على دوار ال Levodopa وما يجي عنده نتيجة نهائياً ← ما ع يشيبي نهائياً ال  
 لأنهم يشتغلوا بنفس ال mechanism تقريباً ..

ال apomorphine ممكن نستعمله فوحالة ال (on-off period) .. يعني إذا استمرنا عند التشنج ٣ ساعات ممكن انتركلها  
 هذه ال اعراضا قلش أو اعطيه injection من ال apomorphine يستمر تأثيره من (١-٢ ساعة)  
 عند استعمالنا لعمتي انه استعمل ال apomorphine هم :- ① انه ال duration تاخذه فاعلية (١-٢) ساعة فلاذا استعمله كاله  
 دوع الباركنسون ع يأخذه مريب من (٢٤-١٢) injection بالعوج .

## 2. Dopamine Receptor agonists

### Pharmacologic Effects:

- 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.
- Apomorphine is meant to be used for the acute management of the hypomobility "off" phenomenon.



# 2. Dopamine Receptor agonists

## Adverse Effects:

- **Gastrointestinal Effects**

- Anorexia and nausea and vomiting may occur when a dopamine agonist is introduced and can be minimized by taking the medication with meals.

- **Cardiovascular Effects**

- Postural hypotension may occur, particularly at the initiation of therapy.

- **Dyskinesias**

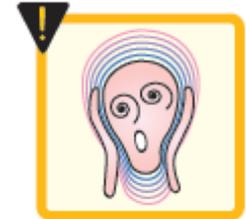
- Abnormal movements similar to those introduced by levodopa may occur and are reversed by reducing the total dose of dopaminergic drugs being taken.

- **Mental Disturbances**

- Confusion, hallucinations, delusions, and other psychiatric reactions are potential complications of dopaminergic treatment and are more common and severe with dopamine receptor agonists than with levodopa.
- various impulse control disorders (such as gambling disorders or compulsive shopping)



Sedation



Hallucinations



Confusion



Nausea



Hypotension

(هذه الأعراض قد تظهر بعد الاستخدام الأول)

النوع الثالث من الأدوية

# 3. MAO-B Inhibitors

صنوع اعطيت مع ال levodopa... كانه ممكن

- Two types of monoamine oxidase have been distinguished in the nervous system:

[فوجين]

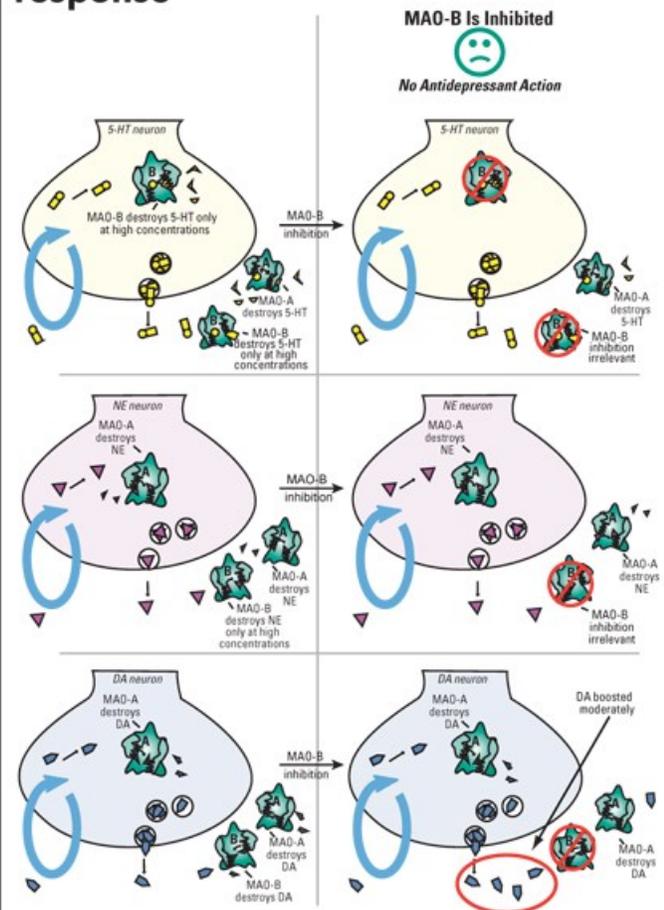
- Monoamine oxidase A** metabolizes norepinephrine, serotonin, and dopamine. *degradation of*
- Monoamine oxidase B** metabolizes dopamine selectively. *degradation of*

more selective =>

ال target كاعني هو ال dopamine لانك رعا على ال inhibition of MAO-B. (more targeted)

- لح ال levodopa ال... من ال... اذا ال inhibition ال... [يعطي مفعولاً من]

**FIGURE 2.** Selective MAO-B inhibition cannot produce an effective antidepressant response\*



\* This is due to the selectivity of MAO-B for DA metabolism (bottom panel) compared with 5-HT metabolism (top panel) and NE metabolism (middle panel), plus the fact that MAO-A continues to metabolize DA when MAO-B is inhibited selectively. Thus, selective inhibition of MAO-B has somewhat limited effects on DA concentrations (red circle, bottom panel), apparently insufficient to exert antidepressant actions but sufficient to boost the actions of DA from levodopa administration in Parkinson's disease.

MAO=monoamine oxidase; 5-HT=serotonin; NE=norepinephrine; DA=dopamine.

# 3. MAO-B Inhibitors

دوائیں • **Selegiline** and **rasagiline** are selective inhibitors of monoamine oxidase type B, the form of the enzyme that metabolizes dopamine.

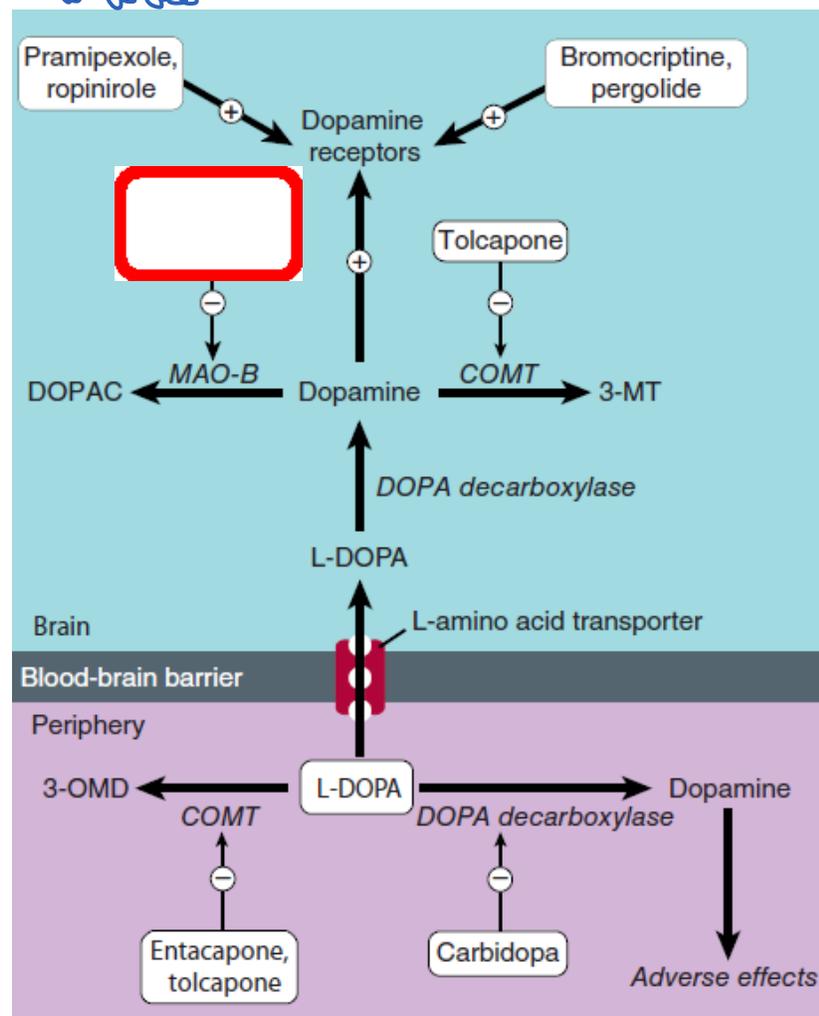
(2) (3) dopamine degradation ... وکری لی (یعنی) الفعالیۃ  
 تاقت ال Levodopa ... ما افسر انا یرتبط ال  
 دوائیں

## Clinical uses:

- **Selegiline** has minimal efficacy in parkinsonism if given alone but can be **used adjunctively** with levodopa.
- **Rasagiline** is more potent and has been **used as monotherapy in early symptomatic parkinsonism** as well as in combinations with levodopa.

## Adverse effects:

- Adverse effects of monoamine oxidase inhibitors include insomnia, mood changes, dyskinesias, gastrointestinal distress, and hypotension.



في عننا دوائى يعالج inhibition لا MCA-B وبالآى يقل ال degradation ل dopamine قطعاً قدرته ومعالجته طارح تكون زي ال Levodopa في طارح نبي لاي بانتاج الدوبامين ولا عنده القدرة على الارتباط على ال dopamine receptors وبالآى هيا المحبوبة من الادوية استغيد منها ب سخلين اللى هم :-

1- إنها تكون adjunctive therapy مع ال Levodopa لشيء مساعد ممكن اعطى ال Levodopa مع أحد هذه الادوية .

2- أو rasagiline بالذات ممكن اعطيه كإله في حالة monotherapy في بداية الباركنسون (early parkinsonism) (ح) يحطينا علاج جبر كإله في بداية فقط لكن لقدام ممكن يبطل ينفع ..

• في ال وضع الطبيعي أنا لما اعطى ال Levodopa حكتنا انه في جبر يتكسر عن طريق ال dopa decarboxylase وجزء ثاني منه كان يتكسر عن طريق ال COMT ويتحول ل 3-O-Methyldopa ...

لما كنا اعطى ال Levodopa كإله (في البداية) بدون Carbidopa ... كانت الحمية الاكبر من ال Levodopa اللى تكسر عن طريق ال dopa decarboxylase تتحول ل dopamine و اللى عن الطريقة الثانية (عن طريق ال COMT) اللى تتحول ل 3-O-Methyldopa .. كانت حمية قليلة جداً (ما لها اي تأثير) ولكن لما هربنا تستخدم ال Carbidopa

هيا رت ال pathway الثانية (اللى هيا ال COMT) هيا اللى تستغل أكثر (هيا رت مؤثرة) بالأول ما كان لها تأثير و هيا هيا شغلها أكبر ده مؤثر جبر ماعلمنا inhibition of dopa decarboxylase هيا رت ال COMT تستغل أكثر على ال Levodopa هيا رت يكسر حمية أكبر أو يحول حمية أكبر للدماغ (metabolite)

ليس يتنافس مع ال Levodopa على ال carriers اللى تدخل ال Brain (Competition) ف هيا رت تأثيره :- ال COMT يكسر جزء من ال Levodopa ويحول ل 3-O-Methyldopa

ف لقل حمية ال dopamine اللى رت قوتها للدماغ ① و اللى رت قوتها من عملية ال Metabolism ل Levodopa

اللى هو 3-O-Methyldopa هيا رت حيا يتنافس على ال transporters ل Levodopa اللى تدخله على ال BBB

ف هيا رت قوتها من كمية ال Levodopa اللى تدخل ال Brain معناها هيا رت في عننا حاجة ل دوار ثالث عشان مع

Levodopa & Carbidopa + دوار ثلث ⇒ COMT inhibitor (entacapone)

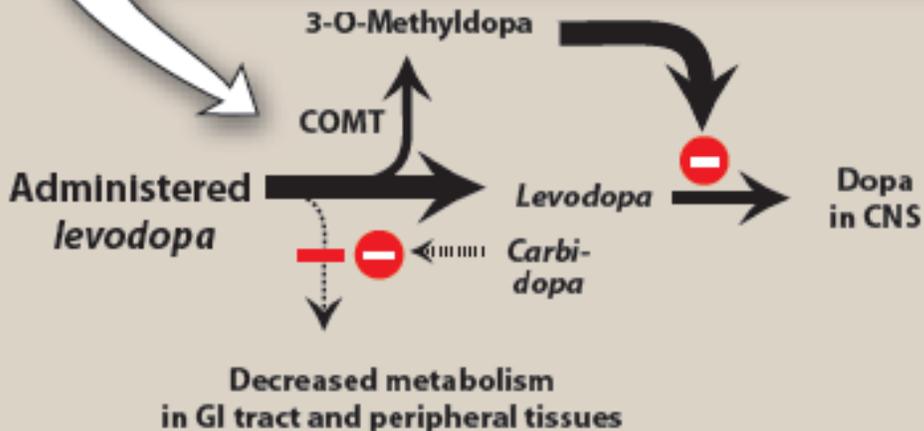
⇐ يعطى effect أكثر ..

شرح عوامر ↑

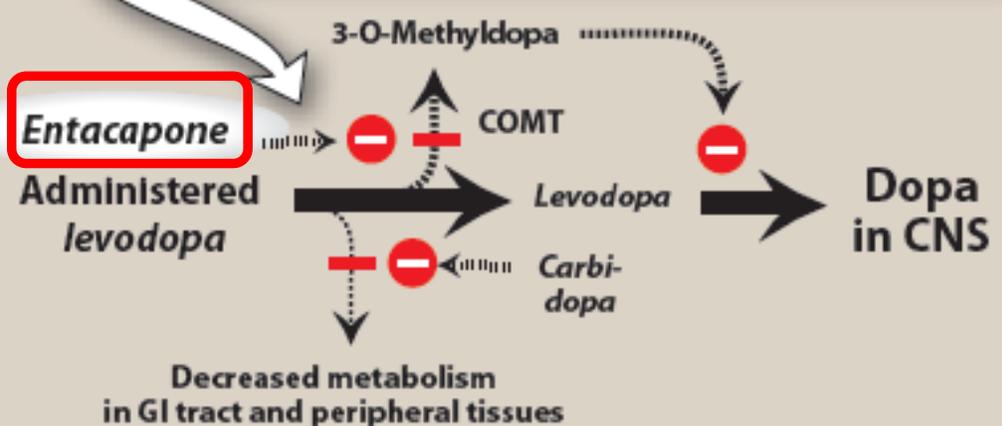
# 4. COMT Inhibitors *enzymes* → *degradation of dopamine.* *تقل*

- Normally, the methylation of levodopa by catechol-O-methyltransferase (COMT) to 3-O-methyldopa is a minor pathway for levodopa metabolism.
- However, when peripheral dopamine decarboxylase activity is inhibited by carbidopa, a significant concentration of 3-O-methyldopa is formed that competes with levodopa for active transport into the CNS.

**A** When peripheral dopamine decarboxylase activity is inhibited by *carbidopa*, a significant concentration of 3-O-methyldopa is formed, which competes with *levodopa* for active transport into the CNS.



**B** Inhibition of COMT by *entacapone* leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine.



# 4. COMT Inhibitors

- Inhibition of COMT by **entacapone** or **tolcapone** leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine. Both of these agents have been demonstrated to reduce the symptoms of “wearing-off ” phenomena seen in patients on levodopa–carbidopa.
- **Tolcapone** has both **central and peripheral effects**, whereas the effect of **entacapone is peripheral**.
- Tolcapone is slightly more potent and has a longer duration of action.
  - **Tolcapone** is taken in a standard dosage of 100 mg **three times** daily; some patients require a daily dose of twice that amount. By contrast, **entacapone** (200 mg) needs to be taken with each dose of levodopa, **up to five times daily**.

# 4. COMT Inhibitors

## Clinical uses:

- COMT inhibitors are used as adjuncts to levodopa-carbidopa, decreasing fluctuations and improving response.
- A formulation combining levodopa, carbidopa, and entacapone is available, simplifying the drug regimen.

## Adverse effects:

- Adverse effects related partly to increased levels of levodopa include dyskinesias, gastrointestinal distress, and postural hypotension.
- Levodopa dose reductions may be needed for the first few days of COMT inhibitor use.
- Other side effects include sleep disturbances and orange discoloration of the urine.
- Tolcapone increases liver enzymes and has reports of fatal liver toxicity, necessitating routine monitoring of liver function tests.



واحد من الأدوية (Antiviral drug) لكن في الواقع لا يصرف على مرضى الباركنسون كما انهم معروفون  
و لكنه يقلل من أعراضه بطريقة جديدة ويكث تأثيره

## 5. Amantadine

مارع يطول (يمكن أخذ أسبوع فقط)

من سترى سيخبره امرهنا لسواح . (يمكن استخدامه بدرجة ظهور المرض نتستخدم كما يبطل لدينا مفعول

- **Amantadine**, an antiviral agent, was by chance found to have antiparkinsonism properties.
- Its mode of action in parkinsonism is unclear, but it may potentiate dopaminergic function by influencing the synthesis, release, or reuptake of dopamine.
- The drug also has muscarinic blocking actions, requiring a decrease in the dosage of the anticholinergic drugs when amantadine is added.

### Pharmacologic effects:

- **Amantadine** may improve bradykinesia, rigidity, and tremor but is usually effective for only a few weeks.
- The standard dosage is 100 mg orally two or three times daily.

# 5. Amantadine

## Adverse effects: بسيطة

- Amantadine has a number of undesirable central nervous system effects, all of which can be reversed by stopping the drug. These include restlessness, agitation, insomnia, confusion, hallucinations. With doses several times higher than recommended, convulsions have occurred.
- **Dermatologic reactions** include livedo reticularis, a diffuse rose-color mottling of the skin, and usually clears within 1 month after the drug is withdrawn. شعيرات دوسج حث اكد ( عاظة شبلة )
- **Miscellaneous effects** may include gastrointestinal disturbances, urinary retention, and postural hypotension.
- Amantadine also causes peripheral edema, which responds to diuretics.
- Amantadine should be used with caution in patients with a history of seizures or heart failure.



المسح النوع الأخير  
 اعراض الباركنسون هي تنبيه زيافة ال Activity كاتما ال Ach ... هذا المجموعة  
 ادمية تقلل ال Activity كاتما ال Ach

# 6. Anti-muscarinic Drugs

→ atropine زيال

- A number of centrally-acting antimuscarinics (eg, benztropine, biperiden, orphenadrine) decrease the excitatory actions of cholinergic neurons on cells in the striatum by blocking muscarinic receptors.
- **Pharmacologic effects:**
- These drugs are more effective for tremor and rigidity of parkinsonism but have little effect on bradykinesia. They are used adjunctively in parkinsonism.
- Treatment is started with a low dose of one of the drugs in this category, the dosage gradually being increased until benefit occurs or until adverse effects limit further increments.
- If patients do not respond to one drug, a trial with another member of the drug class is warranted and may be successful.

**TABLE 28-1** Some drugs with antimuscarinic properties used in parkinsonism.

| Drug                 | Usual Daily Dose (mg) |
|----------------------|-----------------------|
| Benztropine mesylate | 1-6                   |
| Biperiden            | 2-12                  |
| Orphenadrine         | 150-400               |
| Procyclidine         | 7.5-30                |
| Trihexyphenidyl      | 6-20                  |

# 6. Anti-muscarinic Drugs

## Adverse effects:

- CNS toxicity includes drowsiness, inattention, confusion, delusions, and hallucinations.
- Peripheral adverse effects are typical of atropine-like drugs which include dry mouth (hard candies may be helpful); decreased sweating, resulting in decreased tolerance to heat; urinary retention; constipation and increased intraocular pressure.
- If medication is to be withdrawn, this should be accomplished gradually rather than abruptly to prevent acute exacerbation of parkinsonism.

# General Comments on drug management of patient with parkinsonism

مو من بداية اعرف يحتاج للعلاج ... لما وصل لهاي المرحلة ... رجّة بسيطة ما يحتاج للعلاج ... ابدأ اذا كانت

• تتبرعنا ان  
Quality of  
Life so  
we need  
to give  
drugs

• When symptomatic treatment becomes necessary, a trial of rasagiline, amantadine, or an antimuscarinic drug (in young patients) may be worthwhile. (نبدأت منهم نبي البانج)

- With disease progression, dopaminergic therapy becomes necessary. This can conveniently be initiated with a dopamine agonist, either alone or in combination with low-dose carbidopa-levodopa therapy (25/100 three times daily).
- Alternatively, especially in older patients, a dopamine agonist can be omitted and the patient started immediately on carbidopa-levodopa.
- Most patients ultimately require carbidopa 25 mg, levodopa 250 mg three or four times daily.

عندي مرغبين باركنسون ... تشا اولاشي د البانج معو ؟

نبدأ بأدوية خفيفة مع progression بلجالد dopamine agonist كاله اروع دماي آخر (Carbidopa) وملكنا

## CASE STUDY

A 64-year-old architect complains of left-hand tremor at rest, which interferes with his writing and drawing. He also notes a stooped posture, a tendency to drag his left leg when walking, and slight unsteadiness on turning. He remains independent in all activities of daily living. Examination reveals hypomimia (flat facies), hypophonia, a rest tremor of the left arm and leg, mild rigidity in all limbs, and impaired rapid alternating movements in the left limbs. Neurologic and

general examinations are otherwise normal. What is the likely diagnosis and prognosis? He is started on a dopamine agonist, which he seems to tolerate well, and the dose is gradually built up to the therapeutic range. About a year later, he and his wife return for follow-up. It now becomes apparent that he is spending large sums of money, which he cannot afford, on gambling and refuses to stop, despite his wife's entreaties. To what is his condition due and how should it be managed?

## CASE STUDY ANSWER

The relation of the tremor to activity (rest tremor) in this case is characteristic of parkinsonism. Examination reveals the classic findings of Parkinson's disease—rest tremor, rigidity, bradykinesia, and a gait disturbance; an asymmetry of the abnormalities is common in Parkinson's disease. The prognosis is that symptoms will become more generalized

with time. Pharmacologic treatment would involve a dopamine agonist (pramipexole or ropinirole) but may not need to be started now unless the patient is disturbed by his symptoms. The patient developed an impulse control disorder (gambling) after starting on an agonist, and this may require dose reduction or discontinuation of the agonist.

# Questions??

إنا نشاء الله نكونوا استفدتم من التقرير .. ما ننسوا

المسكن المستحصين في خزة وعلسطين وسوريا وكن بلاد  
اعين من دعائكم ...

أي استفسار أو تعليقه على التقرير ياربي تتواجلوا مع الأكاديمي

لتحسين التقرير بجون الله تعالى .. دعوائكم .

