

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

**Drugs modifying noradrenergic
transmission (Part 2)
Adrenergic agonists**

By

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$\alpha_1 \rightarrow v.c \rightarrow \uparrow B.P$

Selective α_1 -adrenergic agonists

normal doses β ←
higher doses β ←
يعمل عليها في
بصير بتتغل على

* in local anesthetic
epinephrine
sympathomimetic
ويعمل
V.C

Pharmacological actions

➤ Vasoconstriction

❑ Decongestant effect

❑ Increase blood pressure → (baro-reflex) → bradycardia. / ↓HR

❑ Decrease intraocular pressure (IOP)

هذا النبي يعالج ديارل الضغط
buffer

➤ Mydriasis of dilator pupil muscle

➤ Contract prostate and urinary bladder sphincter can cause urinary retention

Adverse effects of alpha 1 agonists

1. Vasoconstriction ^{in fingers → زغنيينا} and elevation of blood pressure.

2. Urinary retention .

3. Mydriasis (photophobia and blurred vision) ^{عدم وضوح الرؤية}

حدة العين لما تكون وللمسة ليدخل هونو أكثر

4. Piloerection (goose pumbs) ^{انتصاب الشعر}

شعر ورة

VC
 mydriasis
 contract ← sphincter
 pressure
 ← يعمل على الإرخاض في الملامية
 ← in high doses can activate β Receptors
 ← non catecholamin so I can use it orally

I- Phenylephrine

برد
 بوسير
 (تقريباً) صحتنا
 عين [منزوية/ Horner / ماضية / كوخ]

summary
 بوسير

It is a selective α_1 -agonist but ↑ doses may activate β -receptors.

It is used orally or IV or topically. It has long duration.

Phenylephrine is susceptible to metabolism by MAO.

act Localized decongestion effect. (علاج البرد)

MAO inhibitor
 لو الشخص اخذ
 توديس ١.٥؟
 Do metabolism of phenylephrine
 hypertension
 فيزيولوجي
 cerebral homeostasis

Uses:

Exam [مركز الدكتور]

1. Treatment of **hypotension** (example: during spinal anesthesia).

Used oral or IV.

ملامية
 o ccasional
 ضعيف
 orally
 ملامية
 emergency
 anesthesia
 I.V

2. To relief **nasal decongestant**. (oral) or topical preparation are available for treating common cold

with paracetamol

3. Rectal **suppositories** to decrease congestion of **hemorrhoids**.

4. Ocular uses:

➤ It is used as eye **decongestant**.

➤ To induce **Mydriasis in the eye** (for retinal examination or to diagnose Horner syndrome)

علاج البواسير عن طريق اف
 يصرف الالفا ع. لا .. بوسير
 phent...

فتلازمة يتم فيها ضغط
 sympathetic supply
 from eye.
 فينضج على Rec
 من اجل فحص
 mydriasis

لعصا بنية

➤ Injected into the eye to stop bleeding during operations in the eye globe.



Recently, the FDA issued a proposed order (مقترح) in November 2024 to remove oral phenylephrine from the list of drugs that drug-makers can include in over-the-counter products (OTC) monograph for the temporary relief of nasal congestion.



➤ In the absence of reflex bradycardia (due to a neuronal disease or a drug), a 10-fold **lower dose of phenylephrine** is required to produce a similar increase in blood pressure than normal individuals.

➤ Patients who have an impairment of autonomic function (such as **diabetic autonomic neuropathy**) may have **exaggerated increases in heart rate or blood pressure** when taking sympathomimetics.

سهول فاعلية
Parasympathetic
Reflex
فارتقاء ضغط
عندم يكون خطر
phenylephrine

Phenylephrine should be used cautiously in:

- 1- **Hypertension**
- 2- **Hyperthyroidism**
- 3- **Raynaud's syndrome** (vasoconstrictor disease)
- 4- **Diabetic** patients with autonomic **neuropathy**.
- 5- Patients receiving **MAO inhibitors**
- 6- People with **prostate** problems .

فاكحة اليقظة
استحضار هون في
عثر اوجة الناس
الى ما عذب واحده
هنا في اسرار
vitamin
use Atropin

10mg	1mg
عسر	عسر

of hands / finger
صحتك بيسر فوعزنا في
↑ B.P
نوفا ما

urine retention

II- Topical decongestants (zolines)

A- Xylometazoline & Oxymetazoline

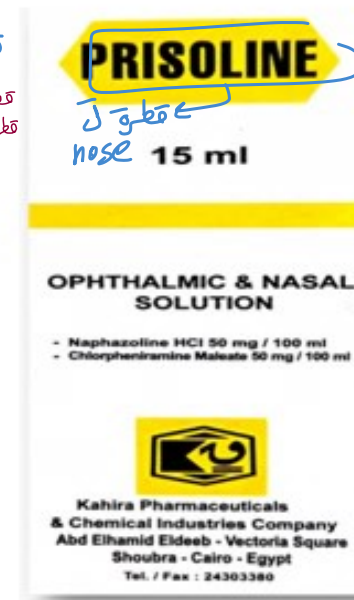
- They can be **topically** as **decongestants in the nose**.
- Both decrease nasal resistance during inspiration and expiration and \uparrow the volume of nasal airflow.
- xylometazoline** had a slightly **faster** onset than **oxymetazoline**.



قطرات العين معقمة أكثر من غيرها.
قطرات عين حبيباتها في الأنف : ماني مشكلة
قطرات أنف حبيباتها في العين : مابصر

B- Tetrahydrozoline & Naphazoline

- Used topically in the **eye** to relieve congestion and redness.
- Naphazoline may be used for **nasal congestion**.



أدوية بحالجه hypotension ←

III- Vasopressor alpha agonists

α1-agonist

Methoxamine

It was used I.V. in treatment of hypotension

Exam

Midodrine

الحلج الاول و الثاني و الثالث
Soral
pro drug
بجاءه شغل

- It is used orally for treatment of hypotension.
- It is a pro-drug: the maximal effects need 1 hour after use.

بحالجه تنشيطه

Mephentermine

- Acts directly and indirectly (through releasing NE).
- It was used (IV, IM or orally) for treatment of hypotension and as decongestant.

السحب من داخل الدم و منه السورين
بصارت ان هه

➤ Psycho-stimulation and misuse limited its use and availability in most countries (including USA), but still available in India

Metaraminol

It was used IV for treatment of hypotension and priapism.
Acts indirectly & in higher doses acts directly also (mixed).

Selective α_2 -adrenergic agonists

1- Clonidine

It acts by direct stimulation of **Presynaptic α_2 -receptors** and **suppressing sympathetic outflow** from the brain leading to decrease in the Blood Pressure.

Clonidine may bind to central **imidazoline** receptors

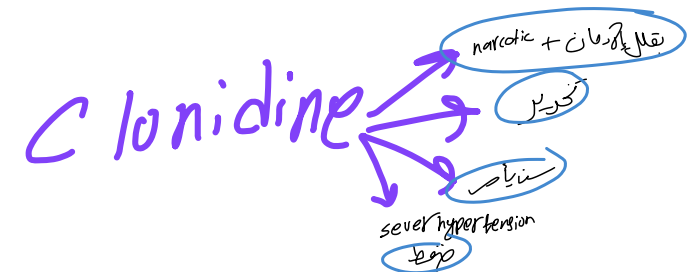
It produces marked **sedation**.

- It is Used to suppress narcotic and alcohol withdrawal manifestations and help in cessation of smoking.
- It is used to decrease the doses of general anesthesia and analgesia
- It decreases the incidence of menopausal hot flashes.
- ❑ It is rarely used now for treatment of severe hypertension.

However, **guanfacine**, **guanabenz** are alpha 2 agonists that are useful in the treatment of hypertension

Side effects:

- 1-Dry mouth (xerostomia) and sedation.
- 2-Sexual dysfunction and bradycardia.
- 3-Sudden Withdrawal causes hypertensive crisis.



b. vesic heart
severe hypertension
sympathetic

قليل ضغط
HR

بعض الأحيان

فمنها زلزال
منه كذا

2- α -methyl dopa

→ acts as α_2 agonist
→ treatment of hypertension during pregnancy.
→ prolong active action

Mechanism of action:

→ يتخلل في α_2 في الدماغ

It is metabolized in the neurons to α -methyl-dopamine then α -methyl NE which is a potent stimulator to the presynaptic α_2 -receptors in the CNS, so it decreases the sympathetic outflow.

It is preferable in treatment of **Exdm) hypertension during pregnancy** (pre-eclampsia) due to its effectiveness and previously known safety to the mother and the fetus. → so, no adverse effect no teratogenicity

3- **Dexmedetomidine**: Prominent **sedative** effects and used in **anesthesia** and intensive care units. ^{sedation}
_{دواء مخدر في مركزه}

4- **Tizanidine**: Used as a **muscle relaxant** **Exlam**

5- **Apraclonidine and brimonidine**: Used topically in **glaucoma** to reduce intraocular pressure (Alpha2 agonists increase the outflow of aqueous humor from the eye).

Brimonidine is used to decrease facial redness in **Rosacea**.

ب يتخلل في أوعية الوجه و يوسعها و يزيل الحكة
b. vessels in face & Vc
Rec

مرض الوردية

III- Selective β_2 -adrenergic agonists

برونشيتالمت
Short t_{1/2}
ديتيسر والسوية

isoproterenol
adrenalin
Chefectolamin هو ليعت ليعت

Branchi توسيع
relaxant pregnant uterus
Inhalation i.v oral

Mechanism of action:

These drugs have relative specificity for β_2 -receptors, with **little effect on the heart** but this selectivity is lost with large doses.

Advantages:

So, can activate β_1
So \rightarrow tachycardia

- Less stimulant effect on the heart.
- They have good oral bioavailability.
- They have longer duration (They are not substrate for COMT)
- They are given in small doses by inhalation in aerosol form, so act mainly on lungs with little systemic adverse effects.
- They are effective in bronchial asthma, and used orally, inhalation or IV in emergencies.
- **Salbutamol (albuterol)** is used for treatment of bronchial asthma.

Ritodrine has selective action on uterus, It is used as a tocolytic agent (relax the uterus in pregnant females). It can be used to delay or prevent premature delivery.

مانع تضيق الرحم
يعمل استرخاء الرحم يمنع الولادة المبكرة
في حديثي الولادة يكون (RS) في حديثي الولادة
Immature

Side effects of beta2 agonists:

^{Handwritten: 1- Tremors}
^{Handwritten: ↳ in children commonly}
1- **Tremors** (skeletal muscle contains ^{Handwritten: Facilitate Ach Action} **beta 2** receptors), it is the most common side effect. It is not common with inhalation route.

2- **Tolerance** (desensitization due to receptor down regulation, it occurs with chronic use).

3- **Tachycardia** may occur due to stimulation of beta 1 receptors in high doses.

4- **Hyperglycemia**: due to increased glucose production from the liver.

5- **Hypokalemia.**

Exam

The regular use of these drugs for long time may cause **bronchial hyper-reactivity** with failure to control bronchial asthma (it can be avoided through using **inhaled corticosteroids** with them).

علاج

Indirect-acting sympathomimetics

MAO inhibitor
* محتوي تقيي
ح
↳ non catecholamin
✓ BBB
- Long duration

1. **Amphetamine-like** or “displacers.” if the **drug enters** the **sympathetic nerve ending** and **displace stored catecholamine transmitter**.
يعني منك قلب noradrenalin منك
2. **Reuptake inhibitors** (Cocaine –like), they **inhibit the reuptake of released transmitter** by **interfering with the action of the norepinephrine transporter**.
neuron فرغ جوا
3. **MAO inhibitors** and **COMT inhibitors**

ADHD ←
cns stimulant ←
anorectic effect ←
(1) Amphetamine → enter the brain and drop of NE

- ❑ It causes **psycho-stimulation of CNS**.
- ❑ amphetamine enters the CNS and displaces NE and dopamine.
- ❑ it has marked stimulant effects on mood (Euphoria) and alertness and a depressant effect on appetite.
- ❑ It causes Cardiovascular and respiratory stimulation.
- ❑ Amphetamine causes marked CNS stimulation, and **addiction**.

نشوة مزاجية
source sensation of emotional well being
#15 الوراثة على التخصصية وواي كدبع عصب
أنياب، هناك بيوت إدمان

إدمان

Uses of amphetamines

- 1- treatment of **Narcolepsy**: (attacks of sleep occur suddenly).
- 2- Treatment of **Obesity** as it has anorectic effect (↓ appetite). Exam
- 3- Treatment of **Attention deficit hyperactivity disorder (ADHD)**.
It occurs in children with excessive motor activity and difficulty in attention.

انعدام الرغبة - بالأكل
سهة قتلانية فيها الحيرة وتشوش الانتباه عن الأطفال

Now, methamphetamine and dextroamphetamine (derivatives of amphetamine) can be used.

Acute toxicity of amphetamine may cause **Death** due to CNS stimulation and **convulsions** or **hypertension**.

Amphetamin
هناك استعماله
بشكل واسع
فوق الحد
موت
سبب تفرغ
CNS
Amphetamin
هناك استعماله
بشكل واسع
فوق الحد
موت
سبب تفرغ
CNS

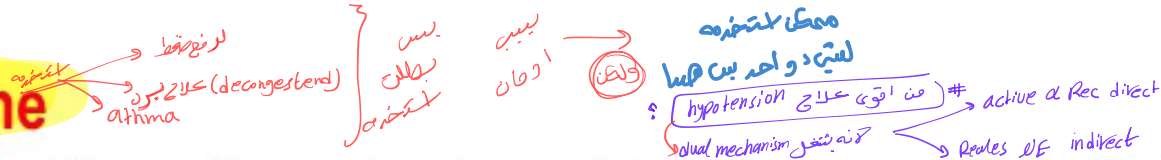
- **Treatment of acute toxicity:** its basic drug so not reversed in urine. drug anti

- a) **Acidification of urine** by NH_4Cl (as amphetamine is a weak base) to increase excretion. ammonium chloride
- b) Symptomatic treatment: as the use of sedative, **anticonvulsive** or **antihypertensive drugs**.

(2) Methamphetamine called meth is used for **treatment of ADHD**; it is widely abused drug (high risk of addiction). no available antagonist for Methamphetamine

- It causes euphoria and \uparrow the ability for **mental and physical work**.
- It causes **teeth loss** (Meth mouth) سبب تساقط الأسنان
- It causes **weight loss** (due to anorexia).
- It causes **mydriasis** (due to increased NE).
- IT causes **vasoconstriction** and may cause **arrythmias**.
- It causes marked CNS stimulation, agitation and even **psychosis**. هناك استعماله بشكل واسع
- Acute **toxicity** may cause **convulsions**, **cerebral hemorrhage**, and even **death**.

(3) Ephedrine



- ❑ It is present in various plants and has been used in China for more than 2000 years; it was introduced into Western medicine in 1924 as the first orally active sympathomimetic drug (it has high bioavailability and a relatively long duration of action).
- ❑ It acts indirect by releasing NE and directly on α and β -receptors (dual mechanism) but the primary action is the indirect one. *direct and indirect sympathomimetics* **Exam**
- ❑ It causes CNS stimulation, euphoria, and addiction
- ❑ it is used in treatment of hypotension due to spinal anesthesia *تخدير نصفي* (as treatment or prophylactic).
- ❑ Ephedrine is a potent nasal decongestant in common cold.
- ❑ The ability of ephedrine to activate β receptors probably accounted for its earlier use in asthma.

علاج

indirect + direct
 علاج مزاجي (oral) decongestion
 can cross BBB #
 ولها يتغلغل
 فيجفروا ويتغلغل

(4) Pseudoephedrine

- Pseudoephedrine acts by releasing NE from nerve terminals and by direct activation of alpha receptors. *Dual mechanism*
- It can cross to the brain less than amphetamine and CNS stimulation is limited.
- Now, pseudoephedrine is used in treatment of common cold (OTC) instead of ephedrine to avoid addiction.
- Pseudoephedrine has been restricted in some countries due to a potential for use in the illicit synthesis of methamphetamine.
- Phenylephrine is used as an alternative to pseudoephedrine as a decongestant.

selective α_1 agonist

pseudoephedrin بهرين بفتح د

phenylephrine د

يحيي الناس تعلى توليل لصاد الدواء ويصنعوا منط methamphetamine

كشان هيلك لوبيدي اعالي البرد آفكي اول شي د

Congestal

For Common Cold and Flu

Paracetamol 650 mg, Chlorpheniramine maleate 4 mg
Pseudoephedrine hydrochloride 60 mg

20 Tablets



availability: صفر
تو نه يتكس او
ما يستخدمه كعلاج ابريا
مضاد X
صالح
فوق ما يجري DBB بل يتطلع كعلاج عند
طريق التمران للأشخاص (يتصل على الطريق)

(5) Tyramine

MAO-inhibitor

It acts by releasing of NE.

It is not a drug but presented in fermented foods (as cheese, beer and wine), chicken liver, creams and chocolate.

It is ineffective orally as it is metabolized by MAO A in GIT but if the patient used MAO-inhibitors, then tyramine will be absorbed orally and cause severe increase in the BP (cheese reaction).

Tyramine has no powerful effects on CNS.

MAO inhibitor allows Absorption of Tyramine
Tyramine route → NE → hypertension [cheese reaction]

(6) Cocaine

prevent reuptake of NE
act on CVS

- Cocaine is a local anesthetic (block Na channels) and an indirect sympathomimetic (increase the release of NE and inhibits its neuronal reuptake)
- it causes potent CNS stimulation, euphoria, and addiction.
- It causes increased sympathetic activity (tachycardia, vasoconstriction, hypertension and mydriasis).
- Not used therapeutically due to high risk of addiction.

(3) Tricyclic antidepressants:

تفيس مبريا
Cocaine

They inhibit its neuronal reuptake of NE (cocaine-like effects).



Foods Containing Tyramine

High	Moderate	Low
<p>Aged cheese</p> <p>Aged and fermented meats</p> <p>Broad bean pods</p> <p>Spoiled meats and fish</p> <p>Soy sauce</p> <p>Tap beer</p> <p>Yeast extract</p>	<p>Red wine</p> <p>White wine</p> <p>Canned beer</p>	<p>Avocados</p> <p>Bananas</p> <p>Bouillon</p> <p>Chocolate</p> <p>Fresh cheeses</p> <p>Fresh meats</p> <p>Peanuts</p> <p>Soy milk</p>

Side effects and toxicity of indirect sympathomimetics:

1- CNS stimulation: ^{مخاض} anxiety, insomnia, tremors, convulsions & vomiting (due to stimulation of chemoreceptor trigger zone).

hallucinations and suicidal or homicidal tendencies (in high toxic doses).
يقتل نفسه *يقتل غيره*

2- CVS: tachycardia, palpitation, hypertension, arrhythmia and angina pectoris. *cerebral hemorrhage*

3- **Tachyphylaxis** or Rapid tolerance (pharmacodynamic due to depletion of the NE). *= bid tolerance*
الحذت الدواء بشكل سريع
فأصبح بطل يتأثر منه

4- Physical dependence and addiction on prolonged use. Sudden withdrawal occurs if the drug stopped suddenly.
(إذا توقفت الدواء فجأة - يمكنك يموت منها)

5- The use of MAO inhibitors with these drugs causes high elevation of NE and hypertensive crisis (like cheese reaction).

→ Tyramine

B-Receptor
تأثير

Exam