

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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

By

Dr. Mohammad Salem Hareedy

2024

Selective α_1 -adrenergic agonists

Pharmacological actions

➤ Vasoconstriction

- Decongestant effect
- Increase blood pressure → (baro-reflex) → bradycardia.
- Decrease intraocular pressure (IOP)

➤ Mydriasis

➤ Contract prostate and urinary bladder sphincter

Adverse effects of alpha 1 agonists

1. Vasoconstriction and elevation of blood pressure.
2. Urinary retention .
3. Mydriasis (photophobia and blurred vision)
4. Piloerection (goose pumbs)

I- Phenylephrine

- ❑ It is a selective α_1 -agonist but \uparrow doses may activate β -receptors.
- ❑ It is used orally or IV or topically. It has long duration.
- ❑ Phenylephrine is susceptible to metabolism by MAO.

Uses:

1. Treatment of hypotension (example: during spinal anesthesia).
Used oral or IV.
2. To relieve nasal decongestant. (oral or topical preparation are available for treating common cold)
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).
 - 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.

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 .

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 ↑ the volume of nasal airflow.
- **xylometazoline** had a slightly **faster** onset than **oxymetazoline**.



B- Tetrahydrozoline & Naphazoline

Used topically in the **eye** to relieve congestion and redness.

- Naphazoline may be used for nasal congestion.

III- Vasopressor alpha agonists

Methoxamine

It was used **I.V.** in **treatment of hypotension**

Midodrine

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

Mephentermine

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

2- α -methyl dopa

Mechanism of action:

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 *hypertension during pregnancy* (pre-eclampsia) due to its effectiveness and previously known safety to the mother and the fetus.

3-Dexmedetomidine: Prominent sedative effects and used in anesthesia and intensive care units.

4- Tizanidine: Used as a muscle relaxant

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.

III- Selective β_2 -adrenergic agonists

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:

- 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.

Side effects of beta2 agonists:

1-Tremors (skeletal muscle contains 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**.

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).

Indirect-acting sympathomimetics

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

(1) Amphetamine

- ❑ 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**.

Uses of amphetamines

1- *treatment of **Narcolepsy***: (attacks of sleep occur suddenly).

2- *Treatment of **Obesity*** as it has anorectic effect (\downarrow appetite).

3- *Treatment of **Attention deficit hyperactivity disorder (ADHD)**.*

It occurs in children with excessive motor activity and difficulty in attention.

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.

-Treatment of acute toxicity:

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

(2) Methamphetamine is used for treatment of ADHD; it is widely abused drug (high risk of addiction).

- It causes euphoria and \uparrow the ability for mental and physical work.
- It causes teeth loss (Meth mouth)
- It causes weight loss (due to anorexia).
- It causes mydriasis (due to increased NE).
- IT causes vasoconstriction and may cause arrhythmias.
- It causes marked CNS stimulation, agitation and even psychosis.
- 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.
- ❑ It causes **CNS stimulation, euphoria, and addiction**
- ❑ it is used in **treatment of hypotension due to spinal anesthesia** (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**.

(4) Pseudoephedrine

- Pseudoephedrine acts by releasing NE from nerve terminals and by direct activation of alpha receptors.
- 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.

Congestal

For Common Cold and Flu

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

20 Tablets



(5) Tyramine

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.

(6) Cocaine

- 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:

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

Foods Containing Tyramine

High	Moderate	Low
<p data-bbox="320 624 689 679">Aged cheese</p> <p data-bbox="266 715 743 831">Aged and fermented meats</p> <p data-bbox="273 871 757 927">Broad bean pods</p> <p data-bbox="315 962 714 1078">Spoiled meats and fish</p> <p data-bbox="367 1118 663 1174">Soy sauce</p> <p data-bbox="389 1209 640 1265">Tap beer</p> <p data-bbox="320 1300 689 1356">Yeast extract</p>	<p data-bbox="999 624 1263 679">Red wine</p> <p data-bbox="983 715 1279 770">White wine</p> <p data-bbox="960 805 1301 861">Canned beer</p>	<p data-bbox="1615 624 1901 679">Avocados</p> <p data-bbox="1637 715 1879 770">Bananas</p> <p data-bbox="1637 805 1879 861">Bouillon</p> <p data-bbox="1615 896 1901 952">Chocolate</p> <p data-bbox="1554 987 1962 1043">Fresh cheeses</p> <p data-bbox="1585 1078 1930 1134">Fresh meats</p> <p data-bbox="1644 1169 1872 1225">Peanuts</p> <p data-bbox="1637 1260 1879 1316">Soy milk</p>

Side effects and toxicity of indirect sympathomimetics:

- 1- CNS stimulation:, anxiety, **insomnia**, **tremors**, **convulsions** & **vomiting** (due to stimulation of chemoreceptor trigger zone). hallucinations and suicidal or homicidal tendencies (in high toxic doses).
- 2- CVS: **tachycardia**, **palpitation**, **hypertension**, **arrhythmia** and **angina pectoris**.
- 3- **Tachyphylaxis** or Rapid tolerance (pharmacodynamic due to depletion of the NE).
- 4- Physical **dependence** and **addiction** on prolonged use. Sudden withdrawal occurs if the drug stopped suddenly.
- 5- The use of **MAO inhibitors** with these drugs causes high elevation of NE and **hypertensive crisis (like cheese reaction)**.



Thank
you!!