

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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

**By**

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## Norepinephrine (NEP)

### NEP differs from EP in:

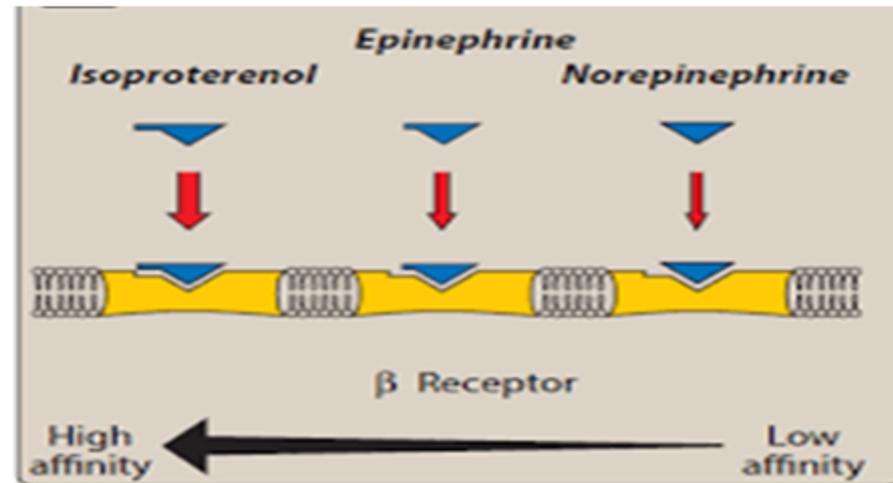
- It acts mainly on  **$\alpha$  and  $\beta_1$ -receptors**
- It has **little effects** on  $\beta_2$  and  $\beta_3$  receptors.
- It causes vasoconstriction and **increases blood pressure** at any dose.
- It may elicit a **reflex  $\downarrow$  in the heart rate** in **high doses**.
- It has weaker metabolic actions than EP.

### Therapeutic uses:

- It is used in **treatment of hypotension** and **shock**.
- It is used by **I.V. infusion**, its action disappears after 1-2 minutes of stopping infusion, so it has a **controllable effect**.

### **Side effects:**

1. **Palpitation**
2. **increase in the BP**
3. headache and anxiety



## Isoproterenol (isoprenaline)

It is **non-selective  $\beta$ -adrenergic agonist** (activates  $\beta_1$  and  $\beta_2$  receptors) without acting on  $\alpha$ -receptors.

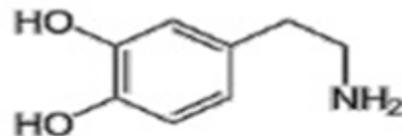
**It causes  $\uparrow$  in heart rate,  $\uparrow$  cardiac conduction and  $\downarrow$  BP.**

**Therapeutic use: bradycardia and heart block.**

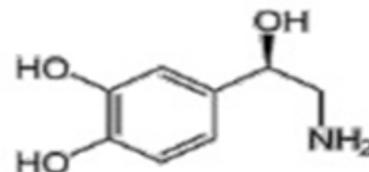
It is not used Now treating bronchial asthma as the selective  $\beta_2$ -agonists are preferable

## CATECHOLAMINES

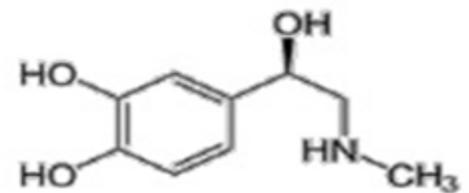
- Norepinephrine – alpha agonist property
- Epinephrine – mixed acting (alpha & beta agonist)
- Isoproterenol – selective beta agonist
- Dopamine – immediate precursor of NE



Dopamine



Norepinephrine



Epinephrine

## **II- Selective $\beta_2$ -adrenergic agonists**

These drugs activates  $\beta_2$ -receptors, with **little effect on the heart** but this **selectivity is lost with large doses**.

### **1-Short acting bronchodilators (duration 3-6 h.).**

**Examples: salbutamol (albuterol) and terbutaline**

□ They are used **orally or by inhalation** in **acute asthma**

### **2-Long-acting bronchodilators (duration 12 h.)**

***e.g. Salmeterol*** is used by inhalation, has slow onset (not suitable in acute asthma) and long duration.

It is used in **treatment of chronic asthma**.

### **3- Drugs used in gynecology**

□ **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 beta agonists:

1-Tremors (stimulation of  $\beta_2$  receptors in skeletal muscle).

2-Tolerance (receptor down regulation, with chronic use).

3-Tachycardia (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**).

### III- Selective $\alpha_1$ -adrenergic agonists

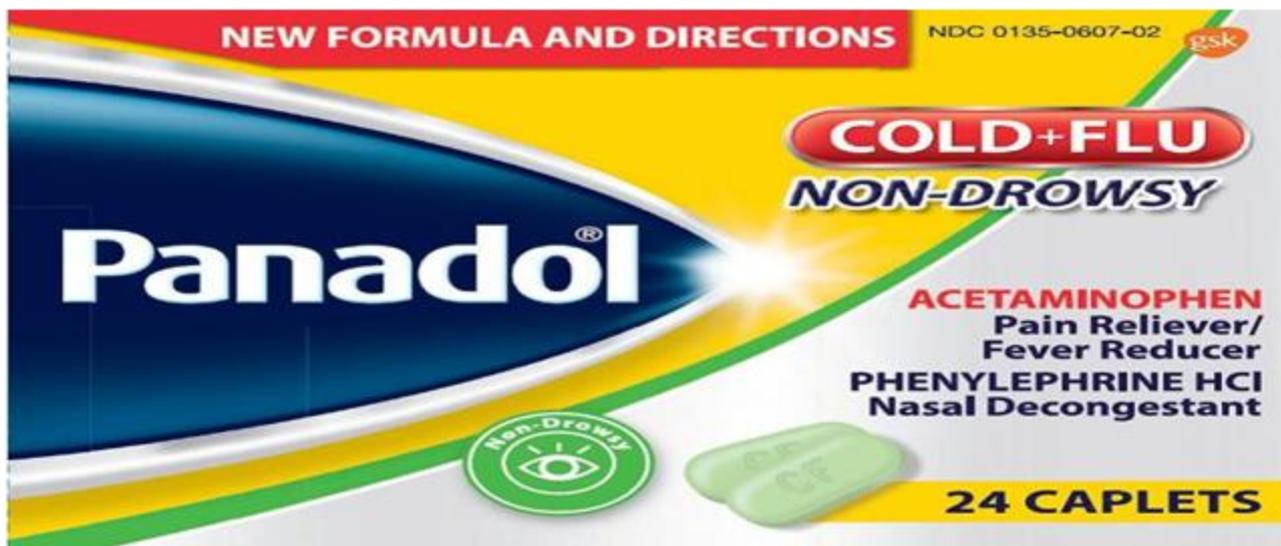
#### 1) Methoxamine:

- ❑ Activates  $\alpha_1$ -receptors causing vasoconstriction & marked  $\uparrow$  B.P that may cause reflex bradycardia (vagal stimulation).
- ❑ It is used I.V. in treatment of hypotension.

#### 2) Phenylephrine:

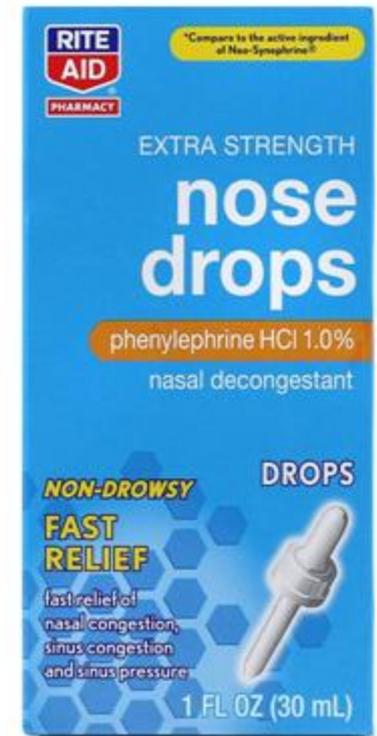
- ❑ It is a selective  $\alpha_1$ -agonist that  $\uparrow$  the BP with reflex bradycardia.
- ❑ Higher doses can activate  $\beta$ -receptors.
- It is used orally or topically in:
  1. Treatment of hypotension as during spinal anesthesia.
  2. Treatment of congestion in the eyes and nose.
  3. as mydriatic in the eye.
  4. Topical treatment of hemorrhoids

3-Midodrine ( $\alpha_1$  agonists) used orally for treatment of hypotension.



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

N.B. all oral anti-cold medications containing any sympathomimetics like alpha agonists should be avoided or given with cautions for patients suffering from hypertension



- 4) Topical decongestants (Zolines)
- ❑ Xylometazoline & Oxymetazoline (for the nose).
  - ❑ Tetrahydrozoline & Naphazoline (for the eyes )

### Adverse effects of alpha 1 agonists

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



## IV- Selective $\alpha_2$ -adrenergic agonists

### (1) Clonidine

#### Mechanism of action:

It acts by direct stimulation of *Presynaptic  $\alpha_2$ -receptors* to suppress sympathetic outflow from the brain causing vasodilation and decrease in the BF. Clonidine is used to:

1. Suppress withdrawal manifestations of narcotics and alcohol.
2. Help in cessation of smoking.
3. Decrease the doses of general anesthesia and analgesia
4. Decrease menopausal hot flashes (**transdermal route**)
5. Treat severe hypertension (but rarely used now)
6. Prevent migraine

#### Side effects:

1-Dry mouth and sedation.

2-Sexual dysfunction and bradycardia.

3-Withdrawal reactions in the form of hypertensive crisis on sudden withdrawal.

## 2) $\alpha$ -methyl dopa

It is metabolized in the neurons to  $\alpha$ -methyl-dopamine then  $\alpha$ -methyl NE which is a potent stimulator to the presynaptic  $\alpha_2$ -receptors in the CNS, so it **decreases the sympathetic outflow.**

➤  $\alpha$ -methyl dopa causes dopamine depletion in the CNS.

➤  $\alpha$ -methyl dopa is used in treatment of ***hypertension during pregnancy*** (pre-eclampsia) due to its effectiveness and previously known safety to the mother and the fetus.

### Side Effects of alpha methyldopa:

- 1-**Sedation**, ↓in mental acuity, and psychic **depression** (↓ dopamine)
- 2- **Parkinsonism** like **tremors** (due to ↓ dopamine)
- 3-**Hyperprolactinemia** (due to ↓ dopamine).
- 4-**Dry mouth** and **bradycardia**.
- 5-Postural **hypotension**.
- 6-**Edema** due to salt and water retention.
- 7-**Hypersensitivity** reactions: fever, hemolytic anemia, leucopenia, thrombocytopenia and **hepatitis**.

## V- Indirect acting agonists

### (1) Amphetamine

It ↑ release of catecholamines in the CNS and autonomic fibers.

1- It is used in treatment of **Narcolepsy** (attacks of sleep)

2- Treatment of **Obesity** (suppress appetite)

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

ADHD occurs in children and is characterized excessive motor activity and difficulty in attention. Now, methamphetamine and dextroamphetamine (derivatives of amphetamine) can be used.

- Amphetamine produces CNS & CVS stimulation, Euphoria, and **addiction** could occur.
- Acute toxicity of amphetamine may cause **Death** due to CNS stimulation and **convulsions** or **hypertension**.

## -Treatment of acute amphetamine toxicity:

- a) **Acidification of urine** by  $\text{NH}_4\text{Cl}$  (as amphetamine is a weak base) to increase excretion.
- b ) Symptomatic treatment: as the use of sedative, **anticonvulsive** and **antihypertensive drugs**.

## (2) 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 increases 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)

#### (4) 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.

#### (4) Ephedrine:

It acts indirect by releasing NE and directly on  $\alpha$  and  $\beta$ -receptors (dual mechanism) but the primary action is the indirect one.

It causes CNS stimulation, euphoria, and addiction.

it is used in management of hypotension due to spinal anesthesia

Ephedrine is a potent nasal decongestant in common cold. Now, pseudoephedrine is used in treatment of common cold instead of ephedrine (to avoid addiction).

## **Side effects and toxicity of indirect sympathomimetics:**

1- CNS stimulation:, anxiety, **insomnia, tremors, convulsions & vomiting**. In high toxic doses; hallucinations and suicidal or homicidal tendencies.

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)**.

A white, hand-drawn style thought bubble sticker is centered on a brown corkboard. The bubble has a small tail pointing towards the bottom center. Inside the bubble, the words "Thank" and "you!!" are written in a black, casual, handwritten font. "Thank" is on the top line and "you!!" is on the bottom line, slightly indented to the right.

Thank  
you!!