General Pharmacology

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الغارُ ليس مجرّد انتكاسةٍ وعَثرة واضطرار،وليسَ شذوذًا عن الطَّريق وليسَ انهزامًا بالضرَّورة ، هو مَرحلةٌ قائمة بذاتها ومن أهم مراحل الطَّريق بل إنها استغرقت قرابة ربع زمن الهجرة إذا اعتبرنا نقطة انتهاء الهِجرة لحظة تحقق السَّلامة وبلوغ المأمن .

لا الشَّمْسُ يَنْبَغِي لَهَا أَنْ تُدْرِكَ الْقَمَرَ وَلاَ اللَّيْلُ سَابِقُ النَّهَارِ ، وكذلكَ لا الغارُ يسبقُ طلوعَ بدرِ الوصول ولا شمس حصول المأمولِ تسبقُ ظلمَة ما تَلقاهُ في طريقِ التَّكليف وبذلِ الأسباب من المشاق والصّعاب ...

كلُّ هذا العَمل بالدُّعاء أن يكون لكم نافعًا ، معينًا غير ضار ولا خاذِل ، لا يتسمُ بالكَمال وسمة من خطَّه النَّقص ، فاعذروا الخطأ والزلل إن وُجِد .

الثلاثاء

3/9/2019

1:20 ص.

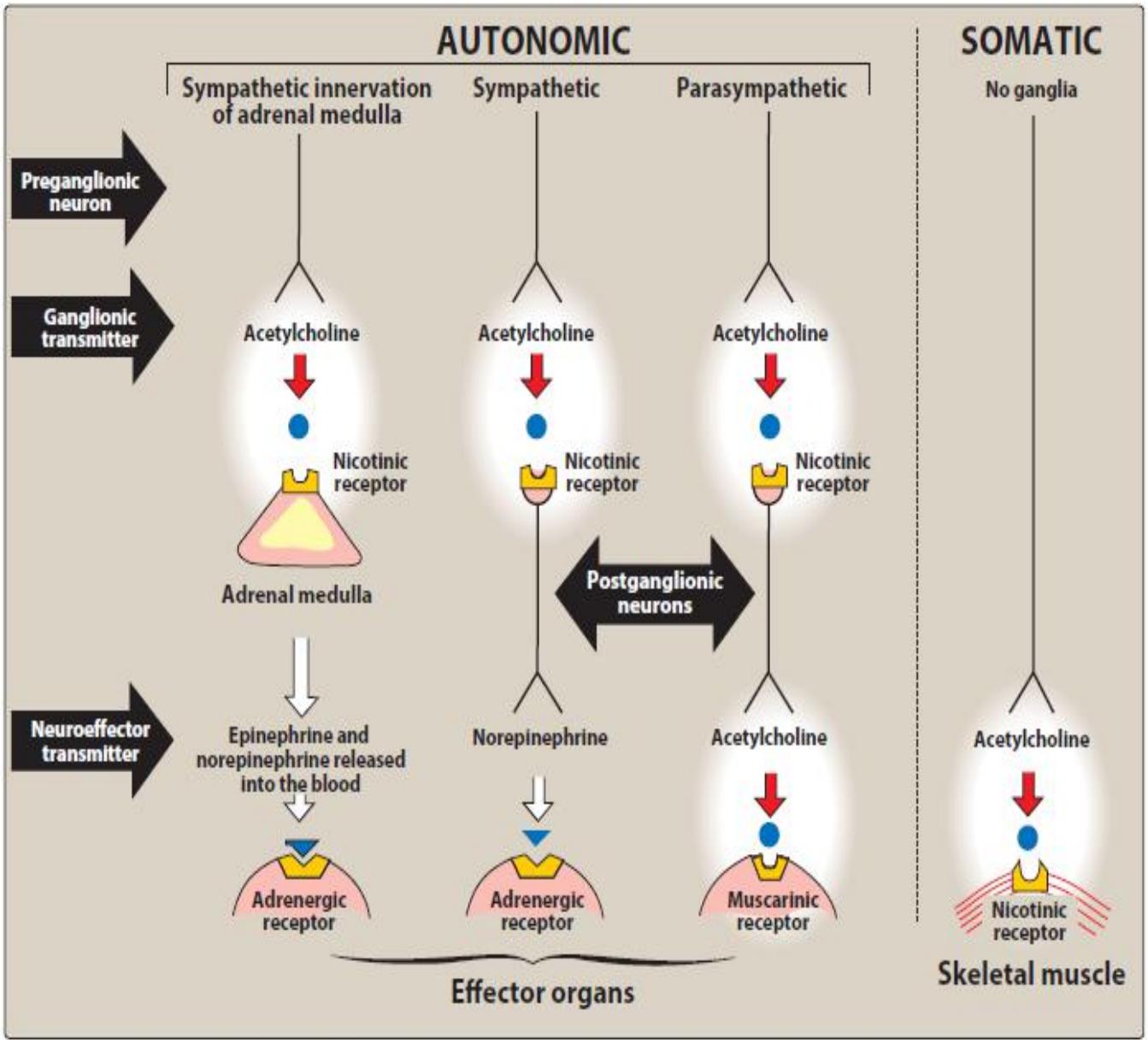
Drugs of the ANS

▪ Drugs affecting the ANS are devided into 2 groups according to the type of neuron involved in their mechanism of action :

(1) The cholinergic drugs ➞ Act on receptors that are activated by Ach .

(2) The adrenergic drugs ➞ Act on receptors that are stimulated by Nepi or Epi .

▪ Study the figure below :



▸ Notes :

(1) ACh is the ganglionic transmitter in both sympathetic and parasympathetic systems .

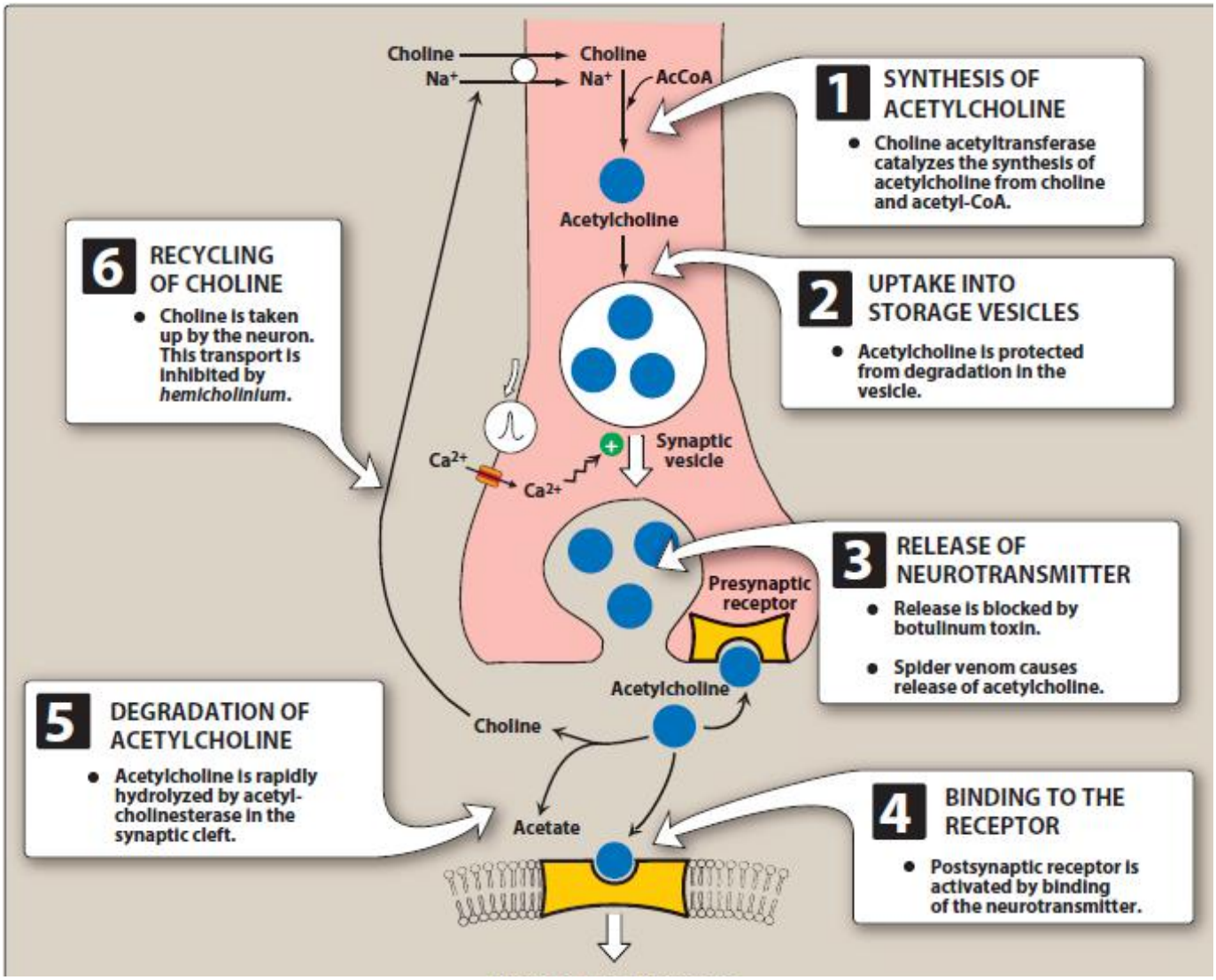
(2) ACh is the neuroeffector transmitter in parasympathetic system .

(3) The neuroeffector transmitter in sympathetic system is : NEpi .

(4) At neuromuscular junction , the neuroeffector transmitter is : ACh .

Neurotransmission at cholinergic neurons

•The figure below shows the steps of cholinergic neurotransmission :



You can watch the video below to memorize the steps :

https://www.youtube.com/watch?v=qZNR3upk9B8&list=PLL3y4VLBMQfhIoxaZXqRlqykC8JCBZFop&index=17&t=0s

•Notes :

1- The **uptake of choline** is the rate-limiting step in ACh synthesis.

2- Transporting the choline from the ECF into the cytoplasm can be **inhibited by hemicholinium**.

3- ***Elevated calcium levels*** promote the fusion of synaptic vesicles with the cell membrane and the release of their contents into the synaptic space, which can be **inhibited by the botulinum toxin**. In contrast, the toxin in black widow spider venom causes all the ACh stored in synaptic vesicles to empty into the synaptic gap.

4- Acetylcholinesterase (AChE) cleaves ACh to **choline and acetate** in the synaptic cleft.

5- Choline may be recaptured by a **sodium coupled, high-affinity uptake system** that transports the molecule back into the neuron.

▶let's start by discussing the receptors and the drugs:

✓ We have 2 families of cholinoreceptors: muscarinic and nicotinic.

- **Muscarinic receptors**:

✍ Belong to the class of G protein–coupled receptors (metabotropic receptors).

✍ Locations of muscarinic receptors:

There are five subclasses of muscarinic receptors, however, only M1, M2, and M3 receptors have been functionally characterized.

→M1 receptors are also found on gastric parietal cells.

→M2 receptors on cardiac cells and smooth muscle.

→M3 receptors on the bladder, exocrine glands, and smooth muscle.

✍ Mechanisms of acetylcholine signal transduction:

- example 1:

M1 or M3 receptors are activated▶The receptor interacts with G protein (Gq) which activates phospholipase C ▶leads to the production of the second messengers inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG)▶IP3 increases intracellular ca2+ and DAG activates protein kinase C.

- example 2:

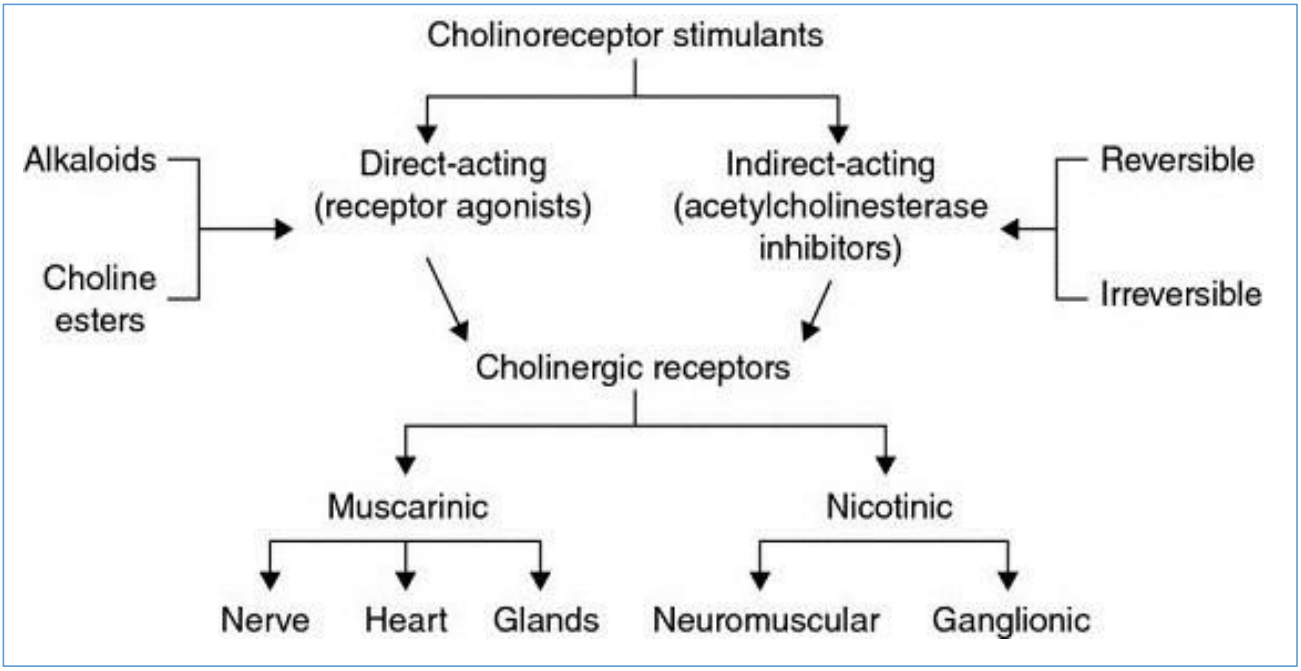
M2 receptor on the cardiac muscle is activated ▶stimulates G protein (Gi) that inhibits adenylyl cyclase and increases K+ conductance▶the heart responds with a decrease in rate and force of contraction.

- **Nicotine receptors**:

✍ Nicotine at low concentration stimulates the receptor, whereas nicotine at high concentration blocks the receptor.

✍ Nicotinic receptors are located in the CNS, the adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ) in skeletal muscles.

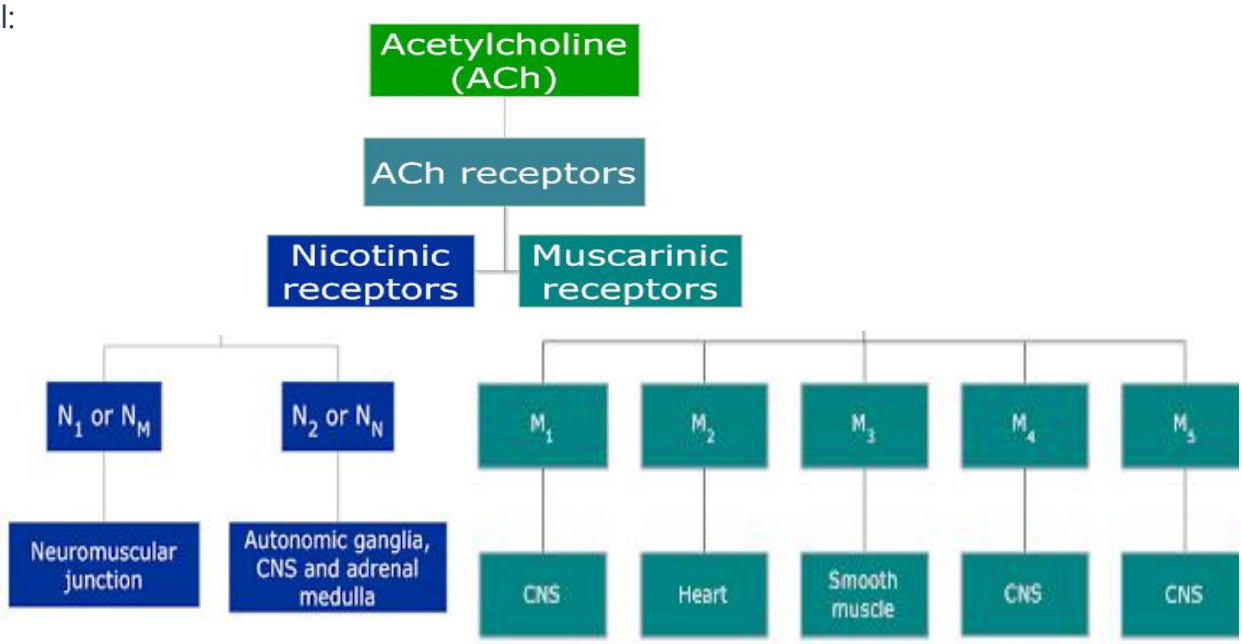
<The following diagram summarizes the basic concepts will be mentioned in the next few pages>

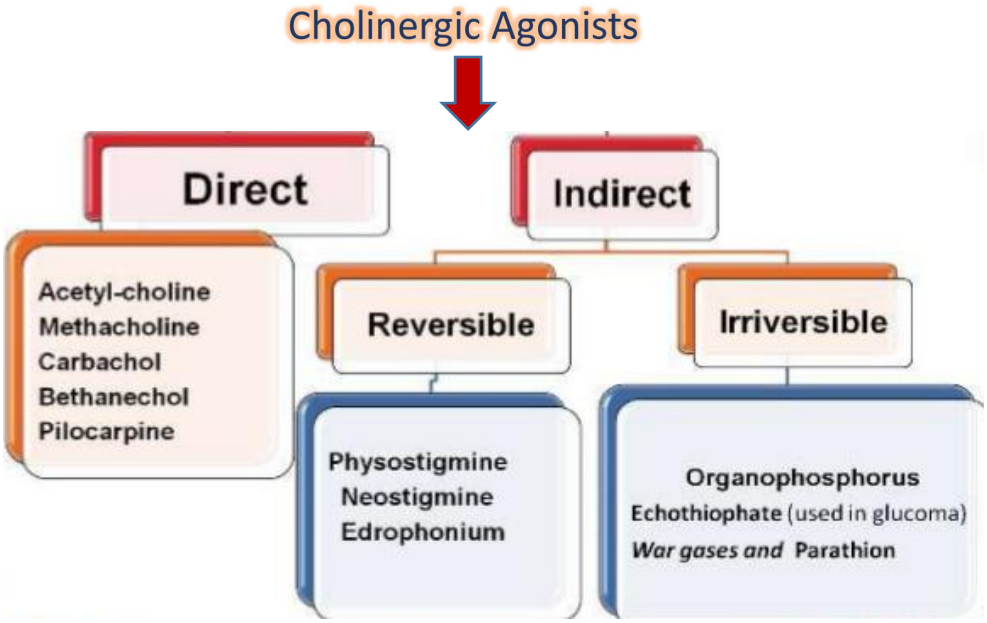


Cholinergic Agonists

▸ This first section talks about the cholinergic drugs , both direct and indirect acting cholinergic agonists :

✍ Recall:





1st: **Direct Acting** Cholinergic Agonists

▸ Cholinergic agonists mimic the effects of ACh by **binding directly** to cholinoceptors (muscarinic or nicotinic).

▫These agents may be broadly classified into two groups:

➞**Endogenous choline esters**.

➞**Naturally occurring alkaloids**, such as **nicotine** and **pilocarpine**

▫All of the direct-acting cholinergic drugs **have a longer duration of action than ACh**.

▫The more therapeutically useful drugs (**pilocarpine and bethanechol**) preferentially bind to muscarinic receptors .

Agent	Structure	Duration of action	Actions	Theraputic uses	Adverse effects
Ach	Quaternary ammonium compound		1. Decrese heart rate and cardiac output 2. Decrease in Bp . 3.Increases salivary secretion and stimulates intestinal secretions and motility. 4.It enhances bronchiolar secretions . 5.Increases the tone of the detrusor muscle, causing urination. 6.Involved in stimulation of ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis	It lacks therapeutic importance because of: 1.Its multiplicity of actions (leading to diffuse effects) . 2.Its rapid inactivation by the cholinesterases .	
Bethanechol	Unsubstituted carbamoyl ester	Has about a 1-hour duration of action	1.Directly stimulates muscarinic receptors, causing increased intestinal motility and tone. 2.It stimulates the detrusor muscle of the bladder, whereas the trigone and sphincter muscles are relaxed >urination	1.In **urologic treatment,** bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention. 2.It is used to treat neurogenic atony as well as megacolon	1.Diarrhea 2.Diaphoresis 3.Miosis 4.Nausea 5.Urinary urgency ✍ Atropine sulfate may be administered to overcome severe cardiovascular or bronchoconstrictor responses to this agent.

Carbachol	Ester of carbamic acid (quaternary amine)	Relatively long duration of action	1.Has effects on both the cardiovascular and GI systems because of its ganglion-stimulating activity 2.Locally instilled into the eye, it mimics the effects of ACh, causing miosis	Rarely used therapeutically except in the eye as a miotic agent to treat glaucoma by causing : 1.Pupillary contraction 2.Decrease intraocular pressure	At doses used ophthalmologically , little or no side effects occur due to lack of systemic penetration
Pilocarpine	Tertiary amine		1.Applied topically to the eye, it produces rapid miosis and contraction of the ciliary muscle. 2.One of the most potent stimulators of secretions such as sweat, tears, and saliva, but its use for producing these effects has been limited due to its lack of selectivity. 3.Beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. 4.Sjögren syndrome is treated with oral pilocarpine tablets & Cevimeline .	1.Pilocarpine is used to treat glaucoma and is the drug of choice for emergency lowering of intraocular pressure of both open-angle &angle-closure glaucoma. 2.The miotic action of pilocarpine is also useful in reversing mydriasis due to atropine.	1.Pilocarpine can cause blurred vision, night blindness, and brow ache. 2.Poisoning with this agent is characterized by exaggeration of various parasympathetic effects, including profuse sweating (diaphoresis) and salivation. >Parenteral atropine, at doses that can cross the blood–brain barrier, is administered to counteract the toxicity of pilocarpine.

Misc Notes :

➞Topical carbonic anhydrase inhibitors, such as dorzolamide and β-adrenergic blockers such as timolol, are effective in treating glaucoma but are not used for emergency lowering of intraocular pressure.

➞ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery

➞Bethanechol lacks nicotinic actions (due to the addition of the methyl group) but does have strong muscarinic activity.

➞Carbachol has both muscarinic and nicotinic actions

➞Pilocarpine exhibits muscarinic activity and is used primarily in ophthalmology

2nd : **Indirect Acting** Cholinergic Agonists /anticholinesterase agents

Gp1 **➞Reversible agents**

Drug	Structure	Duration of acrion	Actions	Theraputic uses	Advesre effects
Edrophonium	Quaternary amine	10-20 minutes (short-acting)	1.Diagnosis of myasthenia gravis. 2.Assess cholinesterase inhibitor therapy. 3.Differentiating cholinergic and myasthenic crises. 4.Reverse the effects of nondepolarizing neuromuscular blockers after surgery. *IV injection increases the muscle strength.	_____	Cholinergic crises
Physostigmine	Tertiary amine	30-120 minutes (intermediate-acting).	1..stimulates muscarinic, nicotinic sites of the ANS. 2.stimulate nicotinic receptors of the NMJ.	1.increases intestinal and bladder motility. 2.treatment of anticholinergic drugs.	1.convulsions. 2.bradycardia +hypotension . 3.miosis. 4.paralusis of skeletal muscle
Neostigmine	Quaternary nitrogen	30-120minutes (intermediate-acting).	_____	1.stimulate the bladder and the GIT. 2.antidote for neuromuscular blocking agents. 3.manage symptoms of myasthenia gravis.	Generalized cholinergic stimulation (ex: salivation, flushing, diarrhea)
Pyridostigmine + Ambenonium	_____	**Pyridostimine** (3-6 hours) **Ambenonium** (4-6) hours	_____	Chronic management of myasthenia gravis	Generalized cholinergic stimulation

Tacrine+donepezil +rivastigmine+ galantamine				For Alzheimer	GIT distress

Misc Notes:

1-**Generalized cholinergic stimulation** includes:
a-salivation. b-flushing. c-decreased blood pressure.
d-nausea. e-abdominal pain. f-diarrhea. h-bronchospasm.

2-Neostigmine can't enter the CNS, so it's not used to overcome the toxicity of antimuscarinic agents such as atropine (instead we use phsyostigmine because it can enter the CNS).

3-Neostigmine is contraindicated when intestinal or urinary bladder obstruction is present.

> ✍ A very useful video:
> https://www.youtube.com/watch?v=z_D2PNzAChg

Gp2 →**Irreversible Agents**

- A number of organophosphate compounds that bind covalently to AChE so they are a long acting agents.
- The only drug we will take is **Echothiophate**

1- **Mechanism of action**:
   a- Binds covalently to the active site of AChE.
   b- When step (a) occurs, **AChE is permanently inactivated**, and requires the synthesis new enzyme molecules (new AChE molecules).
   c- AChE will become phosphorylated and releases one of its ethyl groups which is called **aging**
   d- Now it's impossible for the chemical reactivators, such as pralidoxime, to break the bond between the remaining drug and the enzyme.

2- **Actions**:
   a- Generalized cholinergic stimulation.
   b- Paralysis of motor function.
   c- Convulsions.
   d- Intense miosis.
   e- Lowers the intraocular pressure by facilitating the outflow of aqueous humor.

4-**Therapeutic uses**:
Treatment of **open-angle** glaucoma.

Toxicology of Anticholinesterase agents:

- Irreversible AChE inhibitors are used:

   a- As agricultural insecticides in the USA.

b- For suicidal and homicidal purposes.
c- Organophosphate nerve gases such as sarin are used as agents of chemical terrorism.

- Toxicity is manifested as nicotinic and muscarinic signs and symptoms (cholinergic crisis).

Reactivation of AChE:

1- By using pralidoxime(2-PAM):
- Useful in treating the CNS effect of organophosphates.
- If given before aging (loss of alkyl group), it can reverse muscarinic and nicotinic peripheral effects of organophosphates, BUT not the CNS effects.
- At high doses, it can cause side effects similar to other AChE inhibitors.
- It can't overcome toxicity of reversible AChE inhibitors.

2- Atropine:
- Used to prevent the muscarinic side effects of AChE inhibitors.

3- Diazepam:
- Reduce the *persistent convulsion caused by AChE inhibitors .*

Cholinergic Antagonists

- Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.
- They can be:

1.Muscarinic <The most clinically useful of these agents>
2.Ganglionic
3.Neuromuscular-blocking agents

Drug's name	actions	Therapeutic uses	pharmacokinetics	Adverse effects
atropine	•**Eye**: 1-mydriasis. 2-unresponsiveness to light. 3-cycloplegia. •**GIT**: used as an antispasmodic to reduce activity of the GIT (BUT no effect on HCL production, so it's not effective for peptic ulcer treatment). •**CVS** *at **low** doses: decrease heart rate. *at **high** doses: increase heart rate. •Blocks salivary,	a-**ophthalmic**: exerts both mydriatic and cycloplegic effects (very imp: look at note #5 below the table). b-**antispasmodic**: to relax (reduce activity) the GIT. c-**cardiovascular**: to treat bradycardia. d-**antisecretory**: used to block secretions in the upper and lower respiratory tracts prior to surgery. e-**antidote for cholinergic agonists** such as: 1-organophosphates. 2-overdose of clinically used anticholinesterases such as physostigmine. 3-in some types of mushroom poisoning.	1-readily absorbed. 2-partially metabolized by the liver. 3-eliminated primary in urine. 4-has a half-life of about 4 hours.	1-dry mouth. 2-blurred vision (sandy eyes). 3-tachycardia. 4-urinary retention. 5-constipation. 6-CNS effects (restlessness, confusion, hallucinations, delirium, depression, collapse of the circulatory and respiratory systems, and death)

	lacrimal, and sweat glands secretions.			
scopolamine	a-**most effective anti-motions sickness drug**. b-blocks short-term memory. c-produces sedation (but at higher doses, it can produce excitement). d-produces **euphoria**.	a-prevention of motion sickness (it is more effective prophylactically than for treating motion sickness once it occurs). *for motion sickness, it is available as a topical patch that gives an effects for 3 days. b-prevention of **postoperative nausea and vomiting**.	Similar to atropine.	Similar to atropine.
Ipratropium, tiotropium		a-used as a **bronchodilator** for maintenance treatment of bronchospasm associated with COPD. b-ipratropium is used in the **acute management** of bronchospasm in asthma.	1-both are delivered via **inhalation**. 2-can't enter the systematic circulation or the CNS. 2- tiotropium is given **once a day**, while ipratropium is given **4 times daily**.	----------
Tropicamide, cyclopentolate	----------	Used as ophthalmic solutions for **mydriasis** and **cycloplegia**.	Tropicamide produces mydriasis for **6** hours and cyclopentolate for **24** hours.	----------
Benztropine, trihexyphenidyl	----------	Treat Parkinson's disease and other types of parkinsonian syndromes, including antipsychotic-induced extrapyramidal symptoms.	----------	----------
Darifenacin, fesoterodine, Oxybutynin, solifenacin, tolterodine, trospium chloride	----------	To treat **overactive bladder** (how? Look at note #8).	Oxybutynin is available as a transdermal system (topical patch), which is better because it causes less dry mouth than oral formulations.	1-dry mouth. 2-constipation. 3-blurred vision.

•The table below summarizes the basic concepts about each agent :(Muscarinic Blockers)

1-Using **atropine** in patients with **angle-closure glaucoma** may rise intraocular pressure dangerously, so we must pay attention!

2-Atropine and scopolamine are the most potent antispasmodic drugs available.

3-Pirenzepine (M1 muscarinic antagonist) reduces gastric acid secretion, so it's used for peptic ulcer (NOT like atropine).

4-inhibition of sweat glands secretions by atropine can cause elevated body temperature, which can be dangerous in children and the elderly.
5-Cyclopentolate and tropicamide have replaced atropine due to prolonged mydriasis observed with atropine (7-14 days) vs (6-24 hours) with the others.
6-Phenylephrine is preferred for papillary dilation if cycloplegia isn't required (because atropine causes both dilation (mydriasis) and cycloplegia).
7-Atropine and scopolamine are tertiary amine plant alkaloid, while ipratropium and tiotropium are quaternary derivatives of atropine.
8-The last drugs (darifenacin, fesoterodine, etc.) reduce the frequency of bladder contractions by blocking muscarinic receptors in the bladder, so intravesical pressure is lowered and the bladder capacity is increased.

<Summary of theraputic uses of each agent explained above>

Drug	Therapeutic uses
Muscarinic blockers	
Trihexyphenidyl *Benztropine*	• Treatment of Parkinson's disease
Darifenacin *Fesoterodine* *Oxybutynin* *Solifenacin* *Tolterodine* *Trospium*	• Treatment of overactive urinary bladder
Cyclopentolate *Tropicamide* *Atropine**	• In ophthalmology, to produce mydriasis and cycloplegia prior to refraction
*Atropine**	• To treat spastic disorders of the GI tract • To treat organophosphate poisoning • To suppress respiratory secretions prior to surgery • To treat bradycardia
Scopolamine	• To prevent motion sickness
Ipratropium *Tiotropium*	• Treatment of COPD

Nicotinic blockers :

•A second group of drugs, the ganglionic blockers, shows a preference for the nicotinic receptors of the sympathetic and parasympathetic ganglia.
•Clinically, they are the **least important of the cholinergic antagonists**

•Except nicotine, the other drugs in this category are **nondepolarizing, competitive antagonists**.

Nicotine effects:

a-**Increased blood pressure and cardiac rate** (due to release of neurotransmitters from adrenergic terminals and the adrenal medulla).
b-**Increased peristalsis and secretions**.
c-BUT, at higher doses, the blood pressure falls because ganglionic blockade and activity in both the GIT and bladder musculature ceases.

Neuromuscular-blocking agents :

Theraputic Uses :

- Useful during surgery to facilitate tracheal incubation
- Provide complete muscle relaxation at lower anesthetic doses, allowing for rapid recovery from anesthesia and reducing postoperative respiratory depression.

<Further details about this group not required, Will be discussed in MSS>

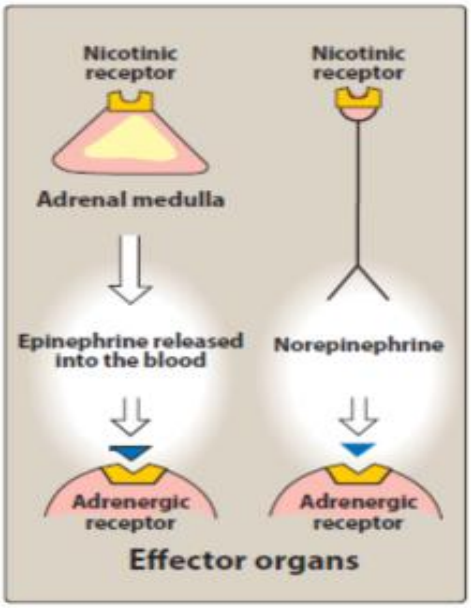
Adrenergic Agonists

- ✓ The adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline) , which are known as adrenergic receptors / adrenoreceptors .
- ✓ Adrenergic drugs that **activate adrenergic receptors** are termed sympathomimetics, and drugs that **block the activation of adrenergic receptors** are termed sympatholytics.
- ✓ Some sympathomimetics directly activate adrenergic receptors (**direct-acting agonists**), while others act indirectly by enhancing release or blocking reuptake of norepinephrine (**indirect-acting agonists**).

- ✓ The Adrenergic Neuron :

Adrenergic neurons ; are found in the central nervous system (CNS) and also in the sympathetic nervous system, where they serve as links between ganglia and the effector organs.

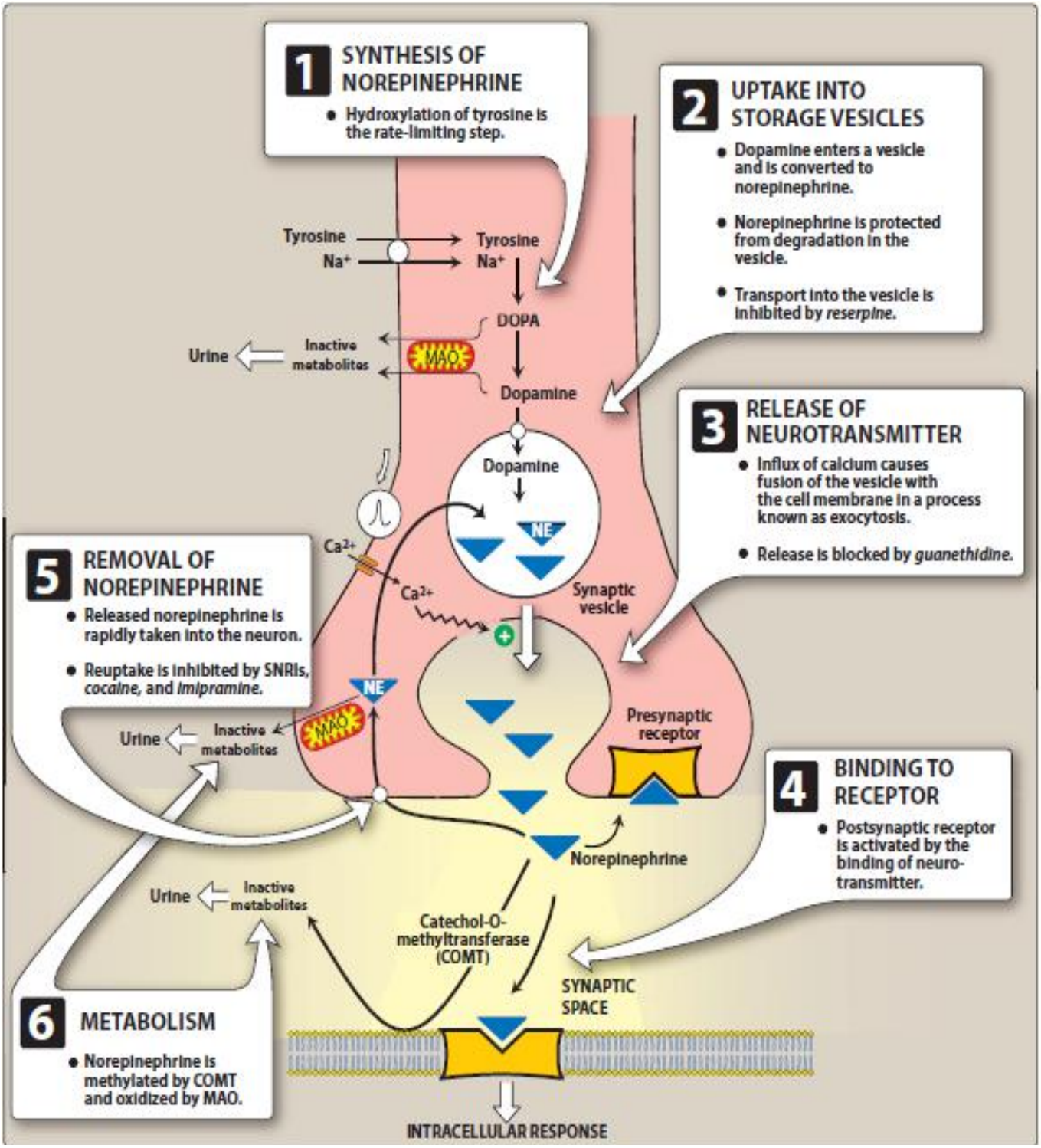
Adrenergic neurons release norepinephrine as the primary neurotransmitter .
Adrenergic drugs act on adrenergic receptors, located either presynaptically on the neuron or postsynaptically on the effector organ.



- ✓ Neurotransmission at adrenergic neurons (basic concepts)

➞Neurotransmission in adrenergic neurons closely resembles that described for the cholinergic neurons, except that norepinephrine is the neurotransmitter instead of acetylcholine.

▶Check the figure in the next page summarizes the steps of adrenergic neurotransmission :



Step1:**Synthesis of Nepi**

•**Hydroxylation** of the aa Tyrosine to DOPA by the enzyme ➞**Tyrosine hydroxylase** (**Rate-limiting step in the formation of Nepi**).

•**Decarboxylation** of DOPA➞Dopamine by the enzyme : **aromatic I-amino acid decarboxylase** .

Step2:**Storage of Nepi in vesicles**

•By **amine transporter system** , Dopamine is transported into synaptic vesicles , then **hydroxylated** by the enzyme **dopamine β-Hydroxylase** to form **Nepi** .

•The **amine transporter system** is blocked by **reserpine** .

Step3:**Release of Nepi**
•The **inc** in **[Ca^{+2}]** in the cytoplasm of the neuron causes synaptic vesicles to fuse with the cell membrane and to undergo **exocytosis** to expel their contents into the synapse.
•This step can be blcoked by **Guanethidine** .

Step4:**Binding to receptors**
•Nepi binidng to its receptors results in formation of **intracellular 2nd messengers** which act as transducers in the communication betweeen the NT and yhe action generated within the effector cell .
•The two systems used in signal transduction are : **cAMP 2nd messenger sys** & **Phosphatidylinositol cycle**

Step5:**Removal of Nepi**
•Termination of Nepi effects can be done by one of the three ways :
(1) Diffuse out of the synaptic space➞systemic circulation
(2) Metabolized by **COMT** in the synaptic space .
(3) **Reuptake back into the neuron** ;this involves **sodium-chloride** (Na+/Cl-)-**dependent norepinephrine transporter** (NET) , inhibited by :
- **Tricyclic antidepressants** (TCAs)such as imipramine
- **Serotonin–norepinephrine reuptake inhibitors** such as duloxetine
- **Cocaine**

Step6:**Potential fates of recaptured Nepi**
•Once norepinephrine re-enters the adrenergic neuron it may undergoes one of the following paths :
(1) Taken up into synaptic vesicles via the **amine transporter system** and sequestered for release by another action potential
(2) Persist in a protected pool in the cytoplasm.
(3) oxidized by **monoamine oxidase** (MAO) present in neuronal mitochondria.

✓ **Adrenoreceptors** :

- Two main families of adrenoreceptors, designated **α** and **β**, are classified on the basis of their responses to the adrenergic agonists **epinephrine**, **norepinephrine**, and **isoproterenol**.
- Each of these main receptor types has a number of specific receptor subtypes that have been identified.

α-Adrenoceptors

- For α receptors, the rank order of potency and affinity is :

epinephrine ≥ norepinephrine >> isoproterenol

- The α-adrenoceptors are subdivided into two subgroups, **α1** and **α2**, based on their affinities for α agonists and blocking drugs ,the **α1 receptors** have a **higher affinity for phenylephrine** than α2 receptors. Conversely, the drug **clonidine** selectively binds to **α2 receptors** and **has less effect on α1 receptors**.

▶α1 Receptors

▪ These receptors are present on the **postsynaptic membrane of the effector organs** and mediate many of the classic effects, originally designated as α-adrenergic, involving constriction of smooth muscle.

▪ Activation of α1 receptors initiates a series of reactions through the **G protein activation** of **phospholipase C**, ultimately resulting in the generation of second messengers :

inositol-1,4,5-trisphosphate (IP3) ➞ initiates the release of Ca2+ from the endoplasmic reticulum into the cytosol

diacylglycerol (DAG) ➞ turns on other proteins within the cell .

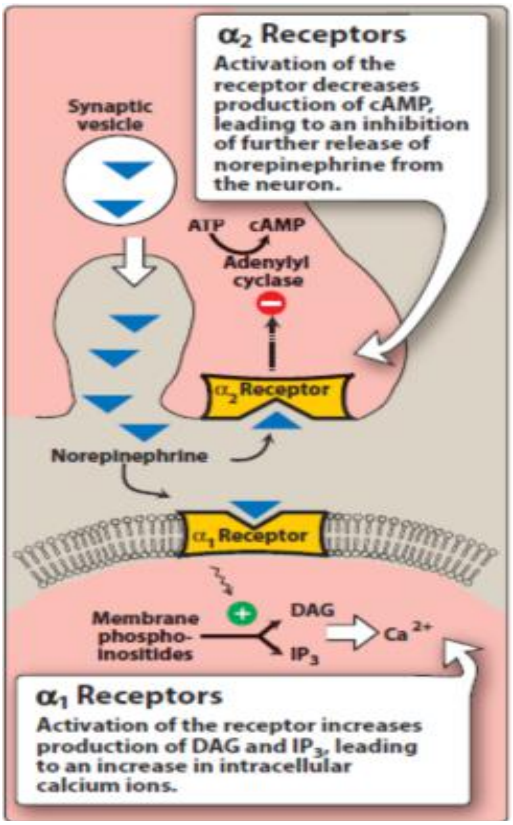
▶α2 Receptors

▪ These receptors are located primarily on **sympathetic presynaptic nerve endings** and control the release of norepinephrine ,α2 receptors are also found on **presynaptic parasympathetic neurons**.

▪ Stimulation of α2 receptors causes feedback inhibition and **inhibits further release of norepinephrine from the stimulated adrenergic neuron**.This inhibitory action serves as a local mechanism for **modulating norepinephrine output** when there is high sympathetic activity , by inhibiting further output of norepinephrine from the adrenergic neuron, these receptors are acting as **inhibitory autoreceptors**.

▪ Norepinephrine released from a presynaptic sympathetic neuron can diffuse to and interact with these receptors, **inhibiting acetylcholine release**. In these instances, these receptors are behaving as **inhibitory heteroreceptors**.

➞In contrast to α1 receptors, the effects of binding at α2 receptors are mediated by **inhibition of adenylyl cyclase** and by a **fall in the levels of intracellular cAMP**.



▶The α1 and α2 receptors are **further divided into**

✓ **α1A, α1B, α1C, and α1D** .

✓ **α2A, α2B, and α2C**.

•This extended classification is necessary for understanding the selectivity of some drugs.

•For example, **tamsulosin** is a selective α1A antagonist that is used to treat benign prostatic hyperplasia.

•The drug has fewer cardiovascular side effects because it targets α1A subtype receptors found primarily in the urinary tract and prostate gland and does not affect the α1B subtype found in the blood vessels.

β-Adrenoceptors

- For β receptors, the rank order of potency is :

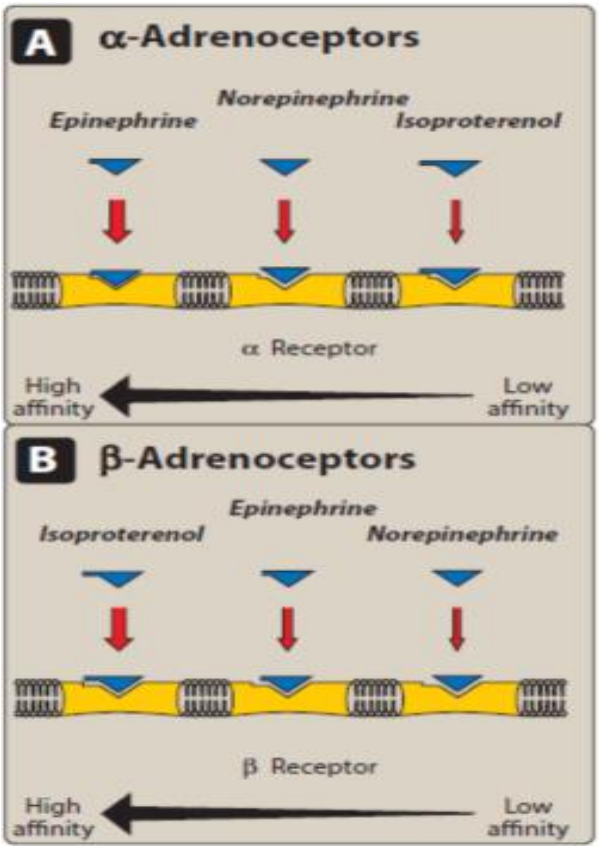
Isoproterenol > epinephrine > norepinephrine

- The β-adrenoceptors can be subdivided into three major subgroups, **β1, β2, and β3**, based on their affinities for adrenergic agonists and antagonists :

✓ β1 receptors have approximately **equal affinities for epinephrine and norepinephrine** .

✓ β2 receptors have a **higher affinity for epinephrine than for norepinephrine**. Thus, tissues with a predominance of β2 receptors (such as the vasculature of skeletal muscle) are particularly responsive to the effects of circulating epinephrine released by the adrenal medulla.

✓ β3 receptors are involved in **lipolysis** and also have effects on the **detrusor muscle of the bladder**.



✓ Distribution of adrenoreceptors :

- Adrenergically innervated organs and tissues usually have a **predominant type of receptor**→ tissues such as the vasculature of skeletal muscle have both α1 and β2 receptors, but the β2 receptors predominate.

- Other tissues may have **one type of receptor almost exclusively**→the heart contains predominantly **β1** receptors.

Characteristic responses mediated by adrenoceptors

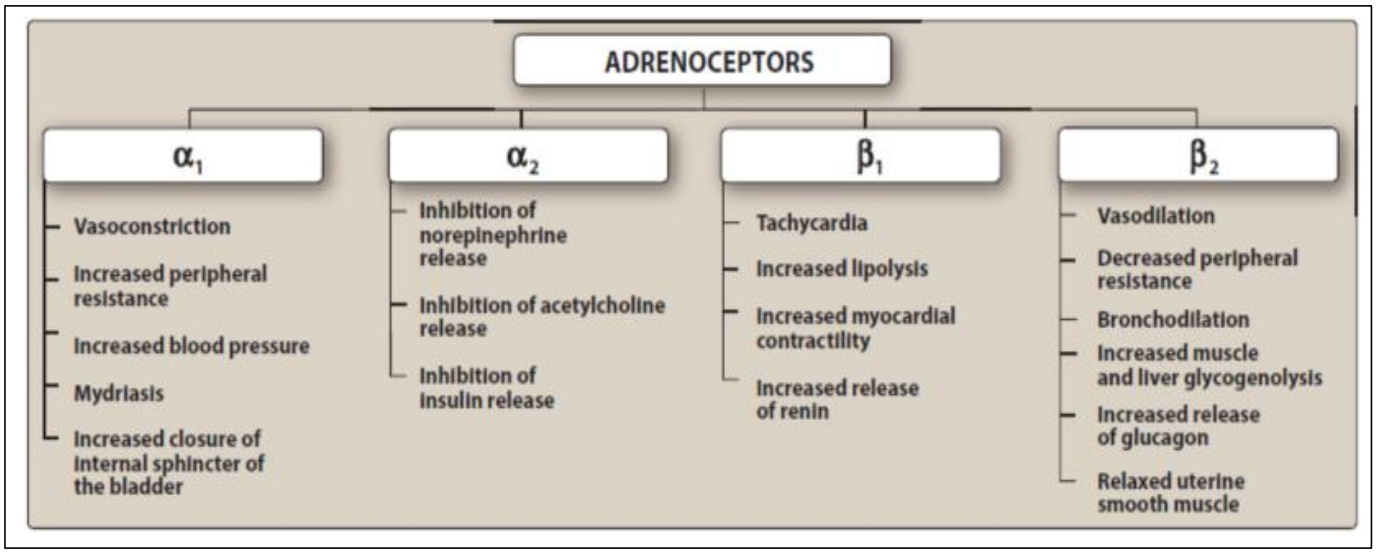
- As a generalization,

✓ **stimulation of α1 receptors** characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and **blood pressure.**

✓ **Stimulation of β1 receptors** characteristically causes cardiac stimulation (increase in heart rate and contractility) .

✓ **Stimulation of β2 receptors** produces vasodilation (in skeletal muscle vascular beds) and smooth muscle relaxation.

<See the figure below , imp one >



Desensitization of receptors

- Three mechanisms have been suggested to explain this phenomenon:

Sequestration of the receptors so that they are unavailable for interaction with the ligand .

Down-regulation, that is, a disappearance of the receptors either by destruction or by decreased synthesis .

Inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side.

▶Characteristics of adrenergic agonists :

•Most of the adrenergic drugs are derivatives of **β-phenylethylamine**.

•Two important structural features of these drugs are :

✓ The number and location of OH substitutions on the benzene ring and

✓ The nature of the substituent on the amino nitrogen.

Catecholamines	Noncatecholamines
▪ Sympathomimetic amines that contain the 3,4-dihydroxybenzene group ▪ These include **epinephrine, norepinephrine, isoproterenol, and dopamine** . ▪ These compounds share the following properties: (1) **High potency** . (2) **Rapid inactivation** . (3) **Poor penetration into the CNS** ,they are polar and, therefore, do not readily penetrate into the CNS. ▪ Catecholamines have only a brief period of action when given parenterally, and **they are inactivated (ineffective) when administered orally**.	▪ Compounds lacking the catechol hydroxyl groups have longer halflives, because they are not inactivated by COMT. ▪ These include **phenylephrine, ephedrine, and amphetamine**. ▪ These agents are poor substrates for MAO (an important route of metabolism) and, thus, show a prolonged duration of action. ▪ Increased lipid solubility of many of the noncatecholamines (due to lack of polar hydroxyl groups) permits **greater access to the CNS**.

▶Mechanism of action of adrenergic agonists :

▪ Based on MOA , adrenergic agonists can be classified into 3 classes ➞

(1) **Direct-Acting agonists**

✓ These drugs act **directly on α or β receptors**, producing effects similar to those that occur following stimulation of sympathetic nerves or release of epinephrine from the adrenalmedulla

✓ These include ,epinephrine, norepinephrine, isoproterenol, and phenylephrine.

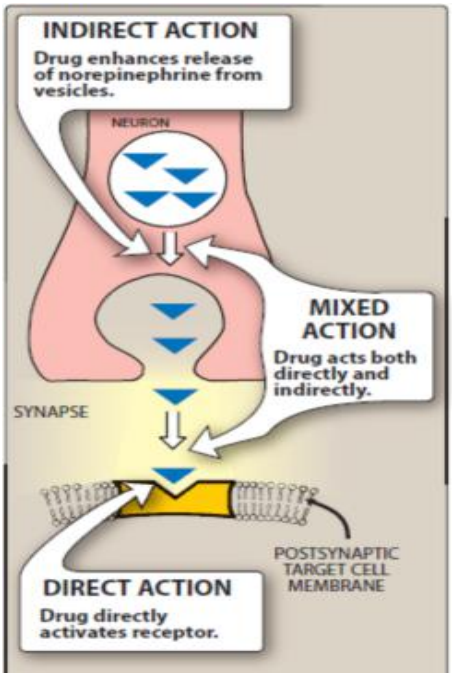
(2) **Indirect-Acting agonists**

✓ These agents may block the reuptake of norepinephrine (cocaine) or cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron (amphetamines). The norepinephrine then traverses the synapse and binds to α or β receptors.

(3) **Mixed-Action agonists**

✓ Stimulate adrenoceptors directly and release norepinephrine from the adrenergic neuron.

✓ Ex : Ephedrine and its stereoisomer, pseudoephedrine



▶Direct-Acting adrenergic agonists

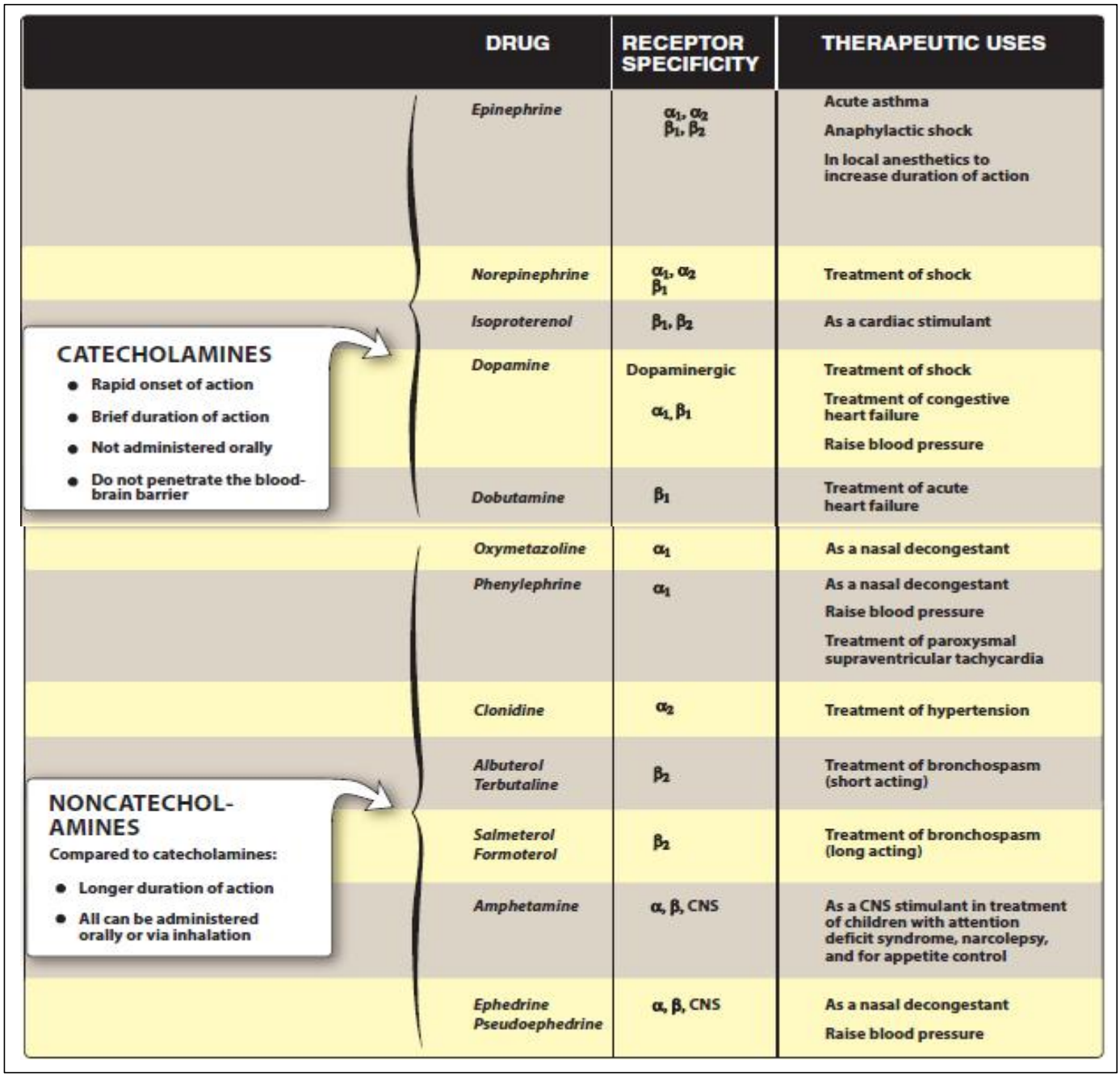
<The table below summarizes basic concepts mentioned in the slides >

Name of the drug	Actions	Theraputic uses	Pharmacokinetics	Adverse Effects
Epinephrine	▪ CVS a-Strengthens the contractility of the myocardium (+ve inotrope) … "β1 effect". b-increases the rate of contraction (+ve chronotrope) … "β1 effect". So, cardiac output increases (which increase O2 demands on the myocardium). ▪ Kidney activates β1 receptors to cause renin release which is involved in the production of angiotensin II (for vasoconstriction). ▪ At high doses, constricts arterioles in the skin, mucous membranes, and viscera (α effect). ▪ At low doses, dilates vessels going to the liver and skeletal muscle (β2 effects). ▪ Respiratory: a-causes bronchodilation by acting on bronchial smooth muscle (β2 action). b-Inhibits the release of allergy mediators such as histamines from mast cells. ▪ Hyperglycemia: Has a hyperglycemic effect because of: a-Increased glycogenolysis in the liver (β2 effect). b-Increased release of glucagon (β2 effect). c-Decreased release of insulin (α2 effect). ▪ Lipolysis: through actions on β receptors of adipose tissues.	1-Bronchospasm: a-The primary drug used in the **emergency treatment** of respiratory conditions when bronchoconstriction has occurred. b-The drug of choice for acute asthma and anaphylactic shock. 2-Anaphylactic shock: the drug of choice for type 1 hypersensitivity reactions (including anaphylaxis) in response to allergens. 3-Cardiac arrest: used to restore cardiac rhythm in patients with cardiac arrest. 4-Anesthetics: increases the duration of anesthesia. 5-May be applied topically to vasoconstrict mucous membranes and control oozing of capillary blood.	1-Rapid onset and short duration of action. 2-The preferred route is IM. 3-In emergency, it is given IV. 4-May be given subcutaneously or by inhalation. 5-Rapidly metabolized by MAO and COMT and the metabolites are excreted in urine.	1-CNS effects. 2-Cardiac arrhythmias. 3-Pulmonary edema. 4-Enhances CVS actions in patients with hyperthyroidism 5-Tachycardia (by inhalation anesthetics). 6-Increase the release of glucose.

Norepinephrine	▪ CVS a-vasoconstriction. b-Baroreceptor reflex	It is used to treat shock, because it increases vascular resistance and, therefore, increases blood pressure.	1-It is given IV. 2-Duration of action: 1-2 min. 3-Metabolized by MAO and COMT, and inactive metabolites are excreted in urine	1-Similar to epinephrine. 2-Causes blanching and sloughing of skin. 3-Can cause necrosis 4-Should not be administered in peripheral veins (if possible).
Isoproterenol	1-Has β1 and β2 activity. 2-Its action on α receptors is insignificant. 3-Produces intense stimulation of the heart by increasing: a-HR. b-Contractility. c-Cardiac output. 4-Dilates the arterioles of skeletal muscles, resulting in decreased peripheral resistance .	1-A potent bronchodilator, but it has been replaced by other drugs because of its nonselectivity. 2-May be useful in atrioventricular block.		Similar to epinephrine
Dopamine	▪ CVS: a-Stimulates β1 receptors of the heart, having both positive inotropic and chronotropic effects. b-At high doses, it activates α1 receptors on the vasculature, leading to vasoconstriction. ▪ Renal and Visceral: a-Dilates renal and splanchnic arterioles by activating dopaminergic receptors, so it increases blood flow to the kidneys and other viscera.	1-It is the drug of choice for cardiogenic and septic shock. 2-Increases cardiac output by stimulating β1 receptors on the heart. 3-Increases total peripheral resistance by acting on α1 receptors on blood vessels. 4-Enhcances perfusion to the kidney (causes diuresis) and splanchnic areas. 5-Treating hypotension.	Rapidly metabolized by MAO and COMT.	1-Overdose of dopamine causes same effects as sympathetic stimulation. 2-Nausea. 3-hypertension. 4-arrhythmias.
Fenoldopam	Act as a vasodilator on: 1-Coronary arteries. 2-Kidney arterioles. 3-Mesenteric arteries.	To treat severs hypertension in hospitalized patients.	1-Undergoes extensive first-pass metabolism. 2-Has a 10 min elimination half-life after IV infusion	1-Headache. 2-Flushing. 3-Dizziness. 4-Nausea. 5-Vomiting. 6-Tachycardia.
Dobutamine	Increases cardiac output with few vascular effects (BUT, it doesn't increase O2 demand on the myocardium .	1-Increases cardiac output in acute heart failure. 2-For inotropic support after cardiac surgery.		1-Similar to epinephrine. 2-Increases AV conduction (so it must be used with caution in patients with atrial fibrillation). 3-Tolerance may develop with prolonged use.

Oxymetazoline	Stimulates α receptors on blood vessels supplying the nasal mucosa and conjunctiva, thereby producing vasoconstriction and decreasing congestion.	1-For congestion. 2-Relief of redness of the eyes associated with colds and swimming	1-Found over-the-counter as nasal sprays decongestants as well as ophthalmic drops 2-Abosorbed in the systemic circulation regardless of the route of administration.	1-Nervousness. 2-Headaches. 3-Trouble sleeping. 4-Local irritation and sneezing with intranasal route. 5-Rebound congestion and dependence may occur with long-term use.
Phenylephrine	1-A vasoconstrictor, but has no effect on the heart. 2-It induces reflex bradycardia when given parenterally.	1-Treat hypotension in hospitalized or surgical patients. 2-Act as nasal decongestant when given topically or taken orally. 3-For mydriasis in ophthalmic solutions.		Large doses may cause hypertensive headache and cardiac irregularities
Clonidine	Acts on presynaptic α2 receptors to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery.	1-Treatment of hypertension. 2-Minimize the symptoms associated with withdrawal from opiates and smoking		1-Lethargy. 2-Sedation. 3-Constipation. 4-Xerostomia. 5-Abrupt discontinuance must be avoided to prevent rebound hypertension.
Albuterol and terbutaline	short-acting β2 agonists used primarily as bronchodilators	1-Albuterol is used for the management of acute asthma symptoms. 2-Terbutaline is used off-label as uterine relaxant to suppress premature labor.		1-Tremor. 2-Restlessness. 3-Apprehension. 4-Anxiety. 5-Tachycardia or arrhythmia when administered orally. ✍ don't use it with MAO inhibitors.
Salmeterol and formoterol	long-acting β2 agonists (LABAs)used primarily as bronchodilators .	When combined with a corticosteroid , they are agents of choice for treating nocturnal asthma in symptomatic patients taking other asthma medications.	1-Gives sustained bronchodilation over 12 hours, compared to 3 hours for albuterol. 2-Salmeterol has a delayed onset of action .	
Mirabegron	β3 agonist that relaxes the detrusor smooth muscle and increases bladder capacity.	used for patients with overactive bladder		It increases levels of digoxin and also inhibits the CYP2D6 isozyme

▶Summary of the therapeutic uses of adrenergic agonists



	DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
CATECHOLAMINES • Rapid onset of action • Brief duration of action • Not administered orally • Do not penetrate the blood-brain barrier	*Epinephrine*	α_1, α_2 β_1, β_2	Acute asthma Anaphylactic shock In local anesthetics to increase duration of action
	Norepinephrine	α_1, α_2 β_1	Treatment of shock
	Isoproterenol	β_1, β_2	As a cardiac stimulant
	Dopamine	Dopaminergic α_1, β_1	Treatment of shock Treatment of congestive heart failure Raise blood pressure
	Dobutamine	β_1	Treatment of acute heart failure
NONCATECHOL-AMINES Compared to catecholamines: • Longer duration of action • All can be administered orally or via inhalation	*Oxymetazoline*	α_1	As a nasal decongestant
	Phenylephrine	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
	Clonidine	α_2	Treatment of hypertension
	Albuterol *Terbutaline*	β_2	Treatment of bronchospasm (short acting)
	Salmeterol *Formoterol*	β_2	Treatment of bronchospasm (long acting)
	Amphetamine	α, β, CNS	As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control
	Ephedrine *Pseudoephedrine*	α, β, CNS	As a nasal decongestant Raise blood pressure

<The table below summarizes effect of some adrenergic drugs on **BP** >

Name of the drug	Systolic blood pressure	Diastolic blood pressure
Epinephrine	Increases	Decreases
Norepinephrine	Increases	Increases
Isoproterenol	Increases	Decreases
Phenylephrine	Increases	Increases

<Imp notes you have to be familiar with >

✓ **In the adrenal medulla**, norepinephrine is methylated to yield epinephrine, which is stored in chromaffin cells. On stimulation, the adrenal medulla releases about 80% epinephrine and 20% norepinephrine.

✓ How does epinephrine induce **Lipolysis** ?
Increased levels of cAMP stimulate a hormone-sensitive lipase, which hydrolyzes TGs to free fatty acids and glycerol.

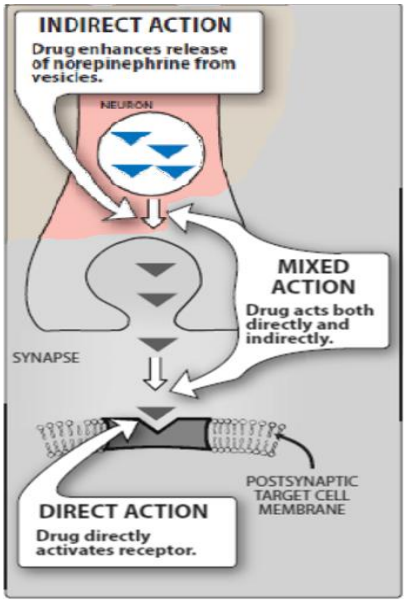
✓ **Impaied circulation** from norepinephrine may be treated with **α receptor antagonist phentolamine**.

✓ Dopamine, the immediate metabolic precursor of norepinephrine, occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla.

- Let's move to the 2nd class of adrenergic agonists , **Indirect-acting adrenergic agonists :**

✍Recall:

✓ Indirect-acting adrenergic agonists cause the release, inhibit the reuptake, or inhibit the degradation of epinephrine or norepinephrine,they potentiate the effects of epinephrine or norepinephrine produced endogenously, but do not directly affect postsynaptic receptors.



Amphetamine

- Can **increase blood pressure** significantly by **α1 agonist action** on the vasculature, as well as β1-stimulatory effects on the heart.
- Its actions are mediated primarily through an increase in nonvesicular release of catecholamines such as dopamine and norepinephrine from nerve terminals.

Tyrosine

- Tyrosine is not a clinically useful drug, but it is important because it is found in fermented foods, such as aged cheese and Chianti wine.
- Normally, it is oxidized by MAO in the gastrointestinal tract, but, if the patient is taking MAOIs, it can precipitate serious vasopressor episodes.
- Like amphetamines, tyramine can enter the nerve terminal and displace stored norepinephrine.

Cocaine

- **Have the ability to block the sodium-chloride (Na+/Cl-)-dependent norepinephrine transporter** required for cellular uptake of norepinephrine into the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine.
- Like amphetamines, it can increase blood pressure by α1 agonist actions and β stimulatory effects.

▶The 3rd class of adrenergic agonists , and the last to be discussed , is : **Mixed action adrenergic agonists**

✍**Recall :** **These agents are not only release stored norepinephrine from nerve endings but also directly stimulate both α and β receptors .Thus, a wide variety of adrenergic actions ensue that are similar to those of epinephrine, although less potent.**

- We will take only 2 drugs in this group: Ephedrine and pseudoephedrine.

→Pharmacokinetics:

1-Poor substrates for COMT and MAO so these drugs have a long duration of action.
2-Have excellent absorption **orally**.

3-Penetrate into the CNS (BUT **pseudoephedrine** has fewer CNS effects).
4-Ephedrine is eliminated largely unchanged in urine, and pseudoephedrine undergoes incomplete hepatic metabolism before elimination in urine.

→Actions:

1-For **Ephedrine**:

a-Raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation and can be used to treat hypotension.

b-Produces bronchodilation, but it is less potent and slower acting than epinephrine or isoproterenol.

c-Was previously used to prevent asthma attacks but has been replaced by more effective medications.

d-Produces a mild stimulation of the CNS which increases alertness, decreases fatigue, and prevents sleep.

e-It also improves athletic performance.

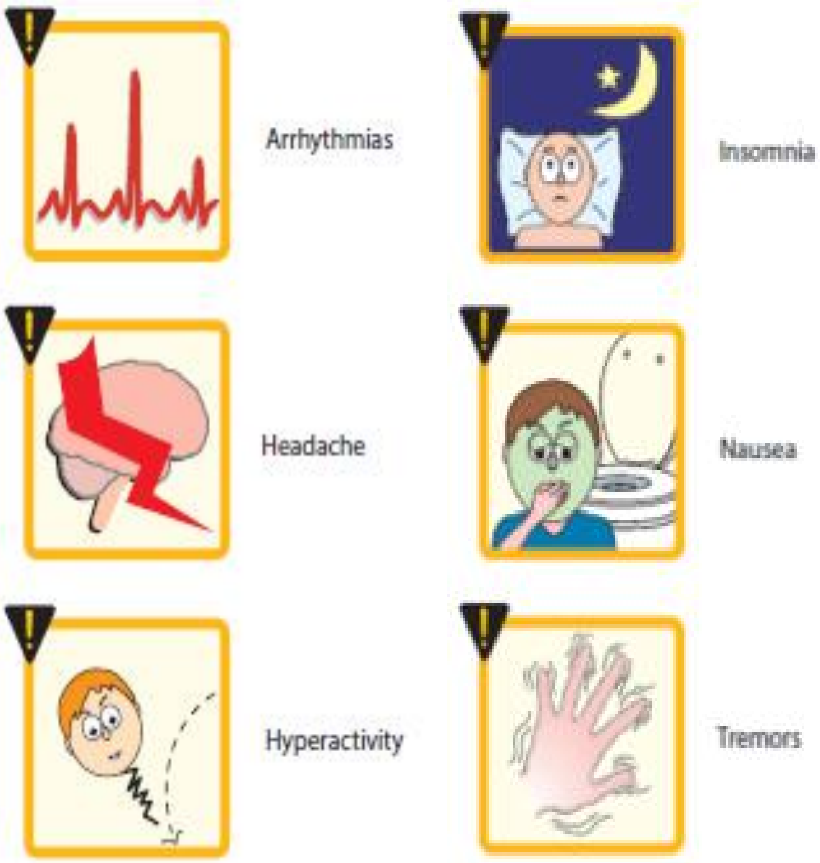
*The clinical use of ephedrine is declining because of the availability of better, more potent agents that cause fewer adverse effects.

2-For **Pseudoephedrine**:

a- Primarily used orally to treat nasal and sinus congestion.

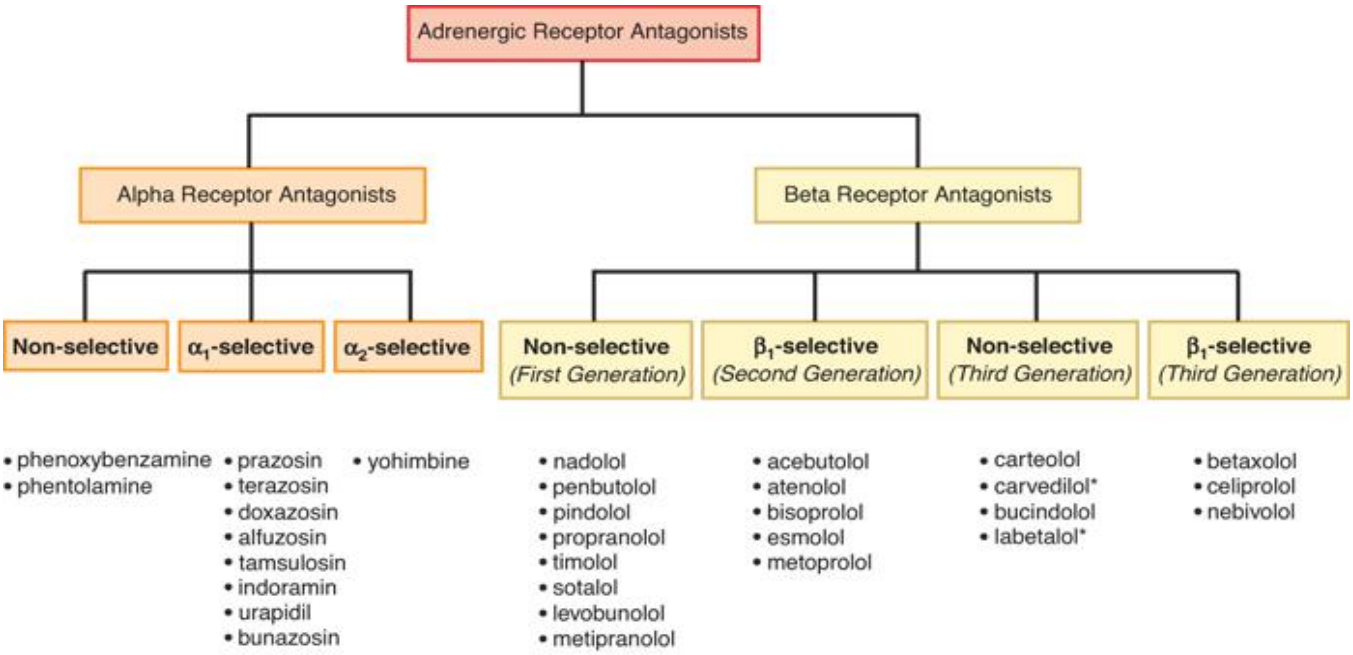
b- used illegally to produce methamphetamine.

→Adverse effects:



Adrenergic Antagonists

- ✓ The adrenergic antagonists (aka **adrenergic blockers** or **sympatholytics**) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects.
- ✓ These drugs act by either reversibly or irreversibly attaching to the adrenoceptors, thus **preventing activation by endogenous catecholamines**.
- ✓ Like the agonists, the adrenergic antagonists are classified **according to** their relative affinities for **α** or **β** receptors in the sympathetic nervous system.
- ✓ Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat **diseases associated with the cardiovascular system**.



✍ The first class to be discussed is :**α-Adrenergic Blocking Agents**

▪ Drugs that block α adrenoceptors profoundly affect blood pressure.

▪ Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α-adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in **decreased peripheral vascular resistance ,this induces a reflex tachycardia resulting from the lowered blood pressure.**

▪ The magnitude of the response depends on the sympathetic tone of the individual when the agent is given.

▪ β receptors, including β1 adrenoceptors on the heart, **are not affected by α blockade .**

✍ The first agent to be discussed is ➞ **Phenoxybenzamine**

✓ Limited clinical application.

✓ **Non-selective**,linking **covalently** to both **α1** and **α2** receptors.

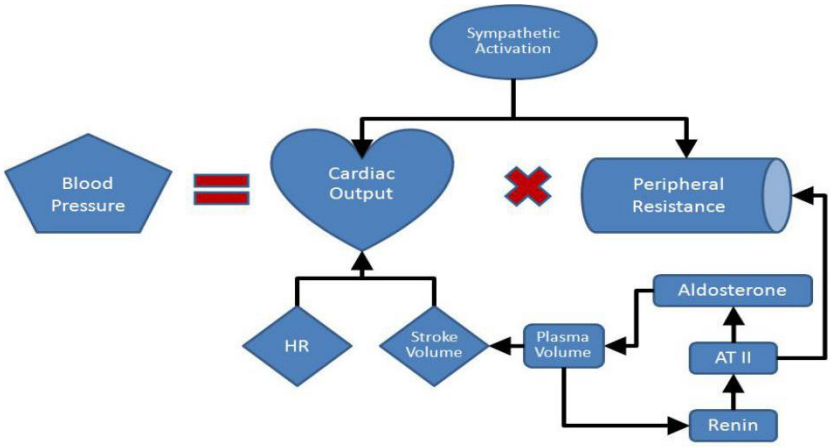
✓ The block is **irreversible** and **noncompetitive**, and the only way the body can overcome the block is to **synthesize new adrenoceptors**, which requires a day or longer ➞the actions of phenoxybenzamine **last about 24 hours**.

✓ After the drug is injected, a **delay of a few hours** occurs before a blockade develops.

Cardiovascular effects

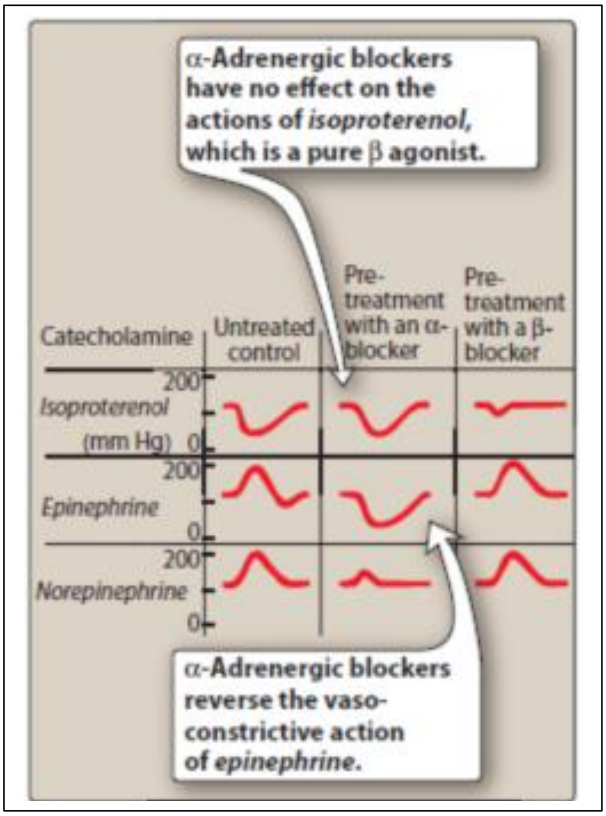
Prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines ▶The decreased peripheral resistance provokes a **reflex tachycardia.**
Furthermore, the ability to **block** presynaptic inhibitory α2 receptors in the heart can contribute to an **increased cardiac output**▶Results in more norepinephrine release, which stimulates **β1** receptors on the heart, increasing cardiac output.

- It is no longer used for this purpose because the drug has been **unsuccessful** in maintaining lowered blood pressure in hypertension.



Epinephrine reversal

- All α-adrenergic blockers **reverse the α agonist actions of *epinephrine*.** For example, the vasoconstrictive action of *epinephrine* is **interrupted**, but vasodilation of other vascular beds caused by stimulation of β2 receptors is not blocked.
- In the presence of *phenoxybenzamine*, the systemic blood pressure decreases in response to *epinephrine*.
- The actions of norepinephrine are not reversed but are diminished because norepinephrine lacks significant β agonist action on the vasculature.
- Phenoxybenzamine has no effect on the actions of **isoproterenol**,a synthetic derivative of adrenaline,which is a pure β agonist.

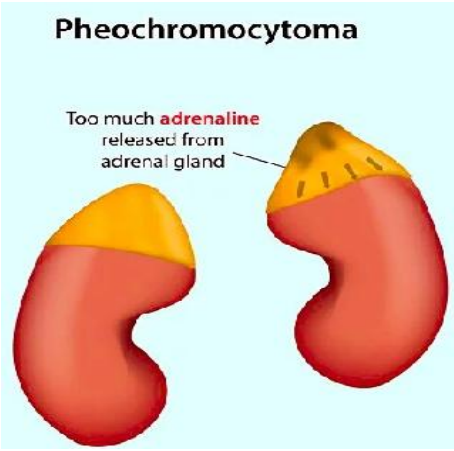


Theraputic uses :

➞Phenoxybenzamine is used in the treatment of pheochromocytoma

> **Pheochromocytoma** is a catecholamine-secreting tumor of cells derived from the **adrenal medulla**.

It may be used prior to surgical removal of the tumor to prevent a **hypertensive crisis**, and it is also useful in the chronic management of inoperable tumors.



➞Phenoxybenzamine is sometimes effective in treating **Raynaud disease** and **frostbite**.

Adverse Effects:

(1)Postural hypotension, nasal stuffiness.
(2)May inhibit ejaculation.
(3)May also induce reflex tachycardia, which is mediated by the baroreceptor reflex.

✍ The Second agent to be discussed is ➞ **Phentolamine**

▪ Produces a **competitive** block of **α1** and **α2** receptors that lasts for approximately **4 hours** after a single injection.
▪ Like phenoxybenzamine, it produces postural hypotension and causes *epinephrine* reversal.
▪ *Phentolamine*-induced reflex cardiac stimulation and **tachycardia** are **mediated by**:
1-The baroreceptor reflex
2- Blocking the α2 receptors of the cardiac sympathetic nerves.

▪ *Phentolamine* can also trigger :
➞Arrhythmias
➞Anginal pain

▪ Cont. Ind :
Phentolamine is **contraindicated** in patients with coronary artery disease.
▪ Theraputic Uses :
(1)Short-term management of pheochromocytoma
(2)Prevent dermal necrosis following extravasation of *norepinephrine*.
(3)Treat hypertensive crisis **due to** abrupt withdrawal of *clonidine* and from ingesting tyramine-containing foods in patients taking monoamine oxidase inhibitors.

✍ Now let's move to study : **Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin**

▪ In contrast to phenoxybenzamine and phentolamine, they are useful in the treatment of hypertension.
▪ ***Tamsulosin*** and ***alfuzosin*** are examples of other selective α1 antagonists indicated for the treatment of **benign prostatic hyperplasia** (BPH).

Tamsulosin has the least effect on blood pressure because it is less selective for α1B receptors found in the blood vessels and **more selective for α1A receptors** in the prostate and bladder.

➞Blockade of the α1A receptors decreases tone in the smooth muscle of the bladder neck and prostate and **improves urine flow**.

▪ Metabolism leads to inactive products that are excreted in urine **except for those of doxazosin**, which appear in feces. Doxazosin is the **longest acting of these drugs**.

▪ MOA :

✓ All of these agents decrease peripheral vascular resistance and lower blood pressure by causing **relaxation of both arterial and venous smooth muscle**.

✓ These drugs, unlike phenoxybenzamine and phentolamine, cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.

▪ Theraputic Uses :

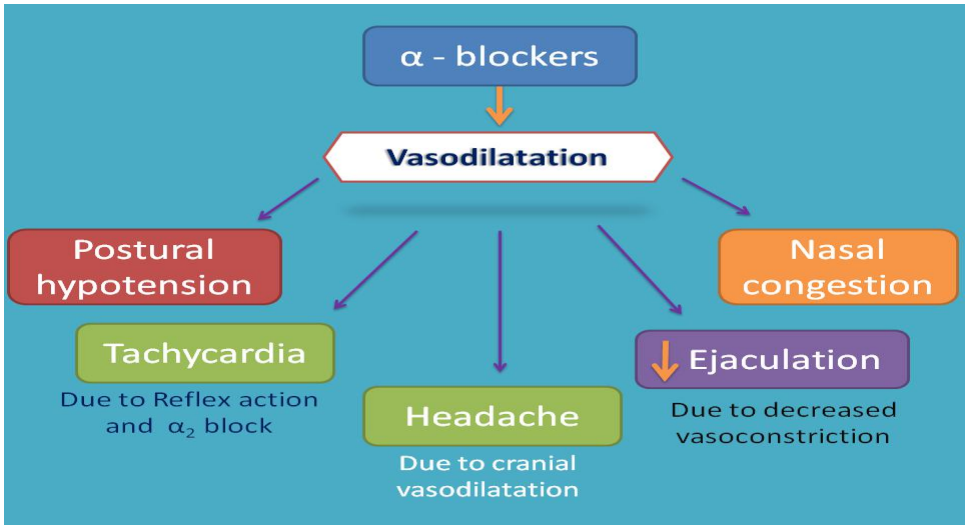
(1) These drugs may cause **modest improvement in lipid profiles** and **glucose metabolism** in hypertensive patients.
(2) The α1 receptor antagonists have been used as an *alternative to surgery* in patients with symptomatic **BPH**.
(3) *Individuals with elevated blood pressure* treated with one of these drugs do not become tolerant to its action.

> The first dose of these drugs may produce an exaggerated **orthostatic hypotensive response** that can result in syncope (fainting).
>
> This action, termed a **"first-dose" effect**, may be minimized by :
> ✓ Adjusting the first dose to *one-third* or *one-fourth* of the normal dose.
> ✓ Giving the drug at bedtime.

⋆ Note : Because of **inferior cardiovascular outcomes** as compared to other antihypertensives, α1 antagonists are ***not used as monotherapy for the treatment of hypertension***.

▪ Adverse Effects :

(1) These agents may cause "**floppy iris syndrome**" a condition in which the iris billows in response to intraoperative eye surgery.
(2) α1 antagonists may cause **inhibition of ejaculation** and **retrograde ejaculation**.
(3) An **additive antihypertensive effect** occurs when α1 antagonists are given with **vasodilators** such as nitrates or PDE-5 inhibitors (for example, sildenafil), thereby necessitating cautious dose titration and use at the lowest possible doses.
(4) α1-Blockers such as prazosin and doxazosin may cause :
✓ Dizziness .
✓ lack of energy.
✓ Nasal congestion .
✓ Headache &drowsiness .
✓ Orthostatic hypotension; to a lesser degree than that observed with phenoxybenzamine and phentolamine .



=✍ The last agent we'll discuss is →**Yohimbine**

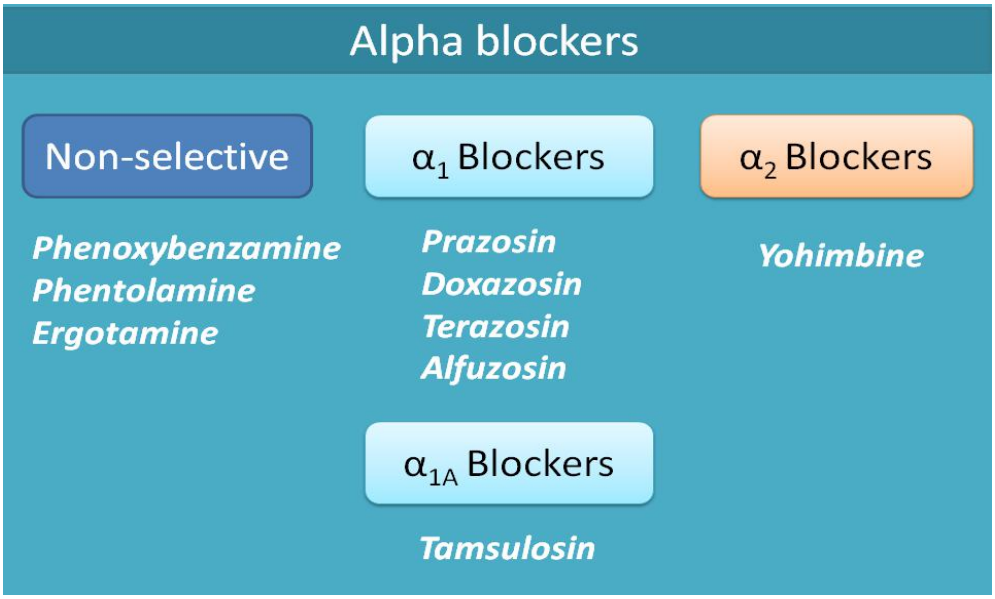
▪ Found as a component of the bark of the yohimbe tree and has been used as a sexual stimulant and in the **treatment of erectile dysfunction** , its use in the treatment of these disorders is not recommended, due to lack of demonstrated efficacy.

▪ Yohimbine works at the level of the CNS to *increase sympathetic outflow to the periphery*.

▪ It is **contraindicated in** :

✓ **Cardiovascular disease** . ✓ **Psychiatric conditions** . ✓ **Renal dysfunction** .

In a nutshell ;



✍ The second class of adrenergic blockers is :**β-Adrenergic Blocking Agents**

▪ All of the clinically available β-blockers are competitive antagonists.

▪ Nonselective β-blockers act at both β1 and β2 receptors, whereas cardioselective β antagonists primarily block β1 receptors.

⋆ These drugs also differ in:

intrinsic sympathomimetic activity, CNS effects, blockade of sympathetic receptors, vasodilation, and pharmacokinetics.

✍ Although all β-blockers lower blood pressure, **they do not induce postural hypotension**, because the α adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained.

▪ β-Blockers are effective in treating:

✓ Hypertension . ✓ Angina. ✓ Cardiac arrhythmias . ✓ Myocardial infarction.
✓ Heart failure. ✓ Hyperthyroidism . ✓ Glaucoma.
✓ They are also used for the **prophylaxis of migraine headaches**.

Propranolol

✓ A **nonselective** β antagonist .
✓ It is considered as **the prototype β-adrenergic antagonist** and blocks both β1 and β2 receptors with equal affinity.
✓ Available in **sustained release preparations** for once-a-day dosing .

▶Actions :

-Cardiovascular →

(1) Propranolol diminishes cardiac output, having both **negative** inotropic and chronotropic effects.
(2) Propranolol directly depresses sinoatrial and atrioventricular nodal activity ,the resulting **bradycardia** usually limits the dose of the drug

✍During exercise or stress, when the sympathetic nervous system is activated, β-blockers attenuate the expected increase in heart rate.

✍The β-blockers are effective in attenuating supraventricular cardiac arrhythmias, but generally are not effective against ventricular arrhythmias (except those induced by exercise).

✍Cardiac output, workload, and oxygen consumption are decreased by blockade of β1 receptors, and these effects are useful in the treatment of angina.

-Peripheral Vasoconstriction →

(1)Nonselective blockade of β receptors prevents β2-mediated vasodilation in skeletal muscles▶increasing peripheral vascular resistance.
(2)The reduction in cardiac output produced by all β-blockers leads to ▶decreased blood pressure ▶triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery.

✍In patients with hypertension, total peripheral resistance returns to normal or decreases with long term use of propranolol.

✍There is a gradual reduction of both systolic and diastolic blood pressures in those patients .

-Bronchoconstriction →

▪ Blocking β2 receptors in the lungs of susceptible patients▶contraction of the bronchiolar smooth muscle▶precipitate an exacerbation in patients with chronic obstructive pulmonary disease (COPD) or asthma.

▪ Therefore, β-blockers, particularly, nonselective ones, are **contraindicated in patients with COPD or asthma**.

-Disturbances in glucose metabolism →

▪ β blockade leads to **decreased glycogenolysis** and **decreased glucagon secretion**.

> Therefore, if propranolol is given to a diabetic patient receiving insulin, careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after insulin injection.

▪ β-blockers also **attenuate** the normal physiologic response to hypoglycemia .

-Blocked action of isoproterenol →

▪ Nonselective β-blockers, including propranolol, have the ability to **block the actions of isoproterenol** (β1, β2 agonist) on the cardiovascular system. Thus, in the presence of a β-blocker:

(1) **Isoproterenol** does not produce cardiac stimulation (**β1** mediated) or reductions in mean arterial pressure and diastolic pressure (**β2** mediated).

(2)In the presence of a nonselective β-blocker, **epinephrine** no longer lowers diastolic blood pressure or stimulates the heart, but **its vasoconstrictive action** (mediated by α receptors) **remains unimpaired**.

(3)The actions of **norepinephrine** on the cardiovascular system are mediated primarily by α receptors and are, therefore, **unaffected**.

▶Theraputic Uses :

(1)**Hypertension**

▪ Propranolol does not reduce blood pressure in people with normal blood pressure.

▪ It lowers blood pressure in hypertension by several different mechanisms of action :

> Primary Mechanism :Decreased cardiac output .

> Inhibition of renin release from the kidney, decrease in total peripheral resistance with long-term use .

> Decreased sympathetic outflow from the CNS .

(2)**Angina Pectoris**

▪ Propranolol decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing chest pain on exertion that is common in angina.Thus, it is **useful in the chronic management of stable angina**.

(3) **Myocardial Infarction**

- Propranolol reduces the incidence of sudden arrhythmic death after myocardial infarction.
- β-blockers have a **protective effect on the myocardium**. Thus, patients who have had one myocardial infarction appear to be **protected** against a second heart attack by **prophylactic use of β-blockers**.
- Administration of a β-blocker immediately following a myocardial infarction **reduces infarct size and fastens recovery**.

> The mechanism for these effects may be a **blocking of the actions of circulating catecholamines**, which would increase the oxygen demand in an already ischemic heart muscle.

(4) Migraine

- Propranolol is effective in reducing migraine episodes when used **prophylactically**.It is one of the more useful β-blockers for this indication, due to **its lipophilic nature that allows it to penetrate the CNS**.
- For the acute management of migraine, **serotonin agonists** such as sumatriptan are used, as well as other drugs.

(5) Hyperthyroidism

- Propranolol and other β-blockers are effective in **blunting the widespread sympathetic stimulation** that occurs in hyperthyroidism.
- In acute hyperthyroidism (thyroid storm), β-blockers may be lifesaving in protecting against serious cardiac arrhythmias.

▶Pharmacokinetics:

-Route of administration : Oral (almost complete absorption)
-It is subject to **first-pass effect**, and only about 25% of an administered dose reaches the circulation.

> ✍ **Recall : First-pass effect (aka first-pass metabolism)**
> **Drug metabolism whereby the concentration of a drug is greatly reduced before it reaches the systemic circulation ,It is the fraction of drug lost during the process of absorption which is generally related to the liver and gut wall.**

-The volume of distribution of propranolol is quite large (**4 L/kg**), and the drug **readily crosses the blood–brain barrier due to its high lipophilicity.**
-Propranolol is extensively metabolized, and most metabolites are **excreted in the urine.**

▶Adverse Effects

Effect	Explanation
Bronchoconstriction	Propranolol has the potential to cause significant bronchoconstriction due to **blockade of β2 receptors**. ✍ Propranolol is contraindicated in patients with COPD or asthma ; death by asphyxiation has been reported for patients with asthma whom were inadvertently administered the drug.

Arrhythmias	Long-term treatment with a β antagonist leads to **up-regulation** of the β receptor.Therefore, β-blockers must be tapered off gradually over a period of at least a few weeks but never stopped abruptly because of the risk of precipitating cardiac arrhythmias . On suspension of therapy, the increased receptors can worsen angina or hypertension.
Sexual impairment	The reasons for this are **not clear** and may be independent of β receptor blockade. Because ejaculation in the male is mediated *through α-adrenergic activation, β-blockers do not affect ejaculation or internal bladder sphincter function.* On the other hand, some men do complain of impaired sexual activity.
Metabolic disturbances	β Blockade leads to **decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia** may occur. β-blockers can prevent the counter regulatory effects of catecholamines during hypoglycemia>>The perception of symptoms of hypoglycemia such as tremor, tachycardia, and nervousness are **blunted by β-blockers** . A major role of β receptors is to mobilize energy molecules such as free fatty acids. Lipases in fat cells are activated mainly by β2 and β3 receptor stimulation, leading to the metabolism of triglycerides into free fatty acids. Patients administered nonselective β-blockers have **increased low density lipoprotein ("bad" cholesterol), increased triglycerides, and reduced high-density lipoprotein ("good" cholesterol).** These effects on the serum lipid profile may be less pronounced with the use of β1-selective antagonists such as metoprolol.
CNS effectsv	Propranolol has numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), and depression. Fewer CNS effects may be seen with **more hydrophilic β-blockers** (for example, atenolol), since they do not cross the blood–brain barrier as readily.
Drug interactions	Drugs that interfere with, or inhibit, the metabolism of propranolol , Ex : cimetidine, fluoxetine, paroxetine, and ritonavir Effect: may potentiate its antihypertensive effects. Drugs that stimulate or induce the metabolism of propranolol , Ex :barbiturates, phenytoin, and rifampin Effect : can decrease its effects

Nadolol and Timolol

▪ Nadolol and timolol block β1- and β2-adrenoceptors (**Nonselective β antagonists**) and are **more potent than propranolol**.

Nadolol	Has a **very long duration of action**.
Timolol	Reduces the production of aqueous humor in the eye. It is used **topically** in the treatment of **chronic open-angle glaucoma** and, occasionally, for **systemic treatment of hypertension**. ✍ β-blockers, such as topically applied timolol, betaxolol, or carteolol, are effective in **diminishing intraocular pressure in glaucoma**.This occurs by decreasing the secretion of aqueous humor by the ciliary body. Unlike the cholinergic drugs, these agents **neither affect the ability of the eye to focus for near vision nor change pupil size**. When administered **intraocularly**, the onset is about **30 minutes**, and the effects **last for 12 to 24 hours**. ✍ The β-blockers are **only used for chronic management of glaucoma.**In an **acute attack of glaucoma**, **pilocarpine** is still the drug of choice for emergency lowering of intraocular pressure.

The following table summarizes the classes of drugs used to treat glaucoma :

CLASS OF DRUG	DRUG NAMES	MECHANISM OF ACTION	SIDE EFFECTS
β-Adrenergic antagonists (topical)	*Betaxolol, carteolol, levobunolol, metipranolol, timolol*	Decrease of aqueous humor production	Ocular irritation; contraindicated in patients with asthma, obstructive airway disease, bradycardia, and congestive heart failure.
α-Adrenergic agonists (topical)	*Apraclonidine, brimonidine*	Decrease of aqueous humor production and increase of aqueous outflow	Red eye and ocular irritation, allergic reactions, malaise, and headache.
Cholinergic agonists (topical)	*Pilocarpine, carbachol*	Increase of aqueous outflow	Eye or brow pain, increased myopia, and decreased vision.
Prostaglandin-like analogues (topical)	*Latanoprost, travoprost, bimatoprost*	Increase of aqueous humor outflow	Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes.
Carbonic anhydrase inhibitors (topical and systemic)	*Dorzolamide* and *brinzolamide* (topical), *acetazolamide*, and *methazolamide* (oral)	Decrease of aqueous humor production	Transient myopia, nausea, diarrhea, loss of appetite and taste, and renal stones (oral drugs).

Acebutolol, atenolol, betaxolol, isoprolol, esmolol, metoprolol, and nebivolol

▪ These drugs are **selective β1 antagonists**,meaning that they preferentially block the β1 receptors.
✍ How does that help ? **minimize the unwanted bronchoconstriction** (β2 effect) seen with propranolol use in asthma patients.

Actions	Theraputic Uses
▫These drugs lower blood pressure in hypertension and increase exercise tolerance in angina . ▪ Esmolol: -Has a **very short half-life** due to metabolism of an ester linkage. -It is **only available intravenously** and is used to control blood pressure or heart rhythm during surgery or diagnostic procedures. ▪ Nebivolol : -In addition to its cardioselective β blockade, it *releases nitric oxide from endothelial cells and causes vasodilation*. ▫In contrast to propranolol, the cardioselective β-blockers have fewer effects on pulmonary function, peripheral resistance, and carbohydrate metabolism. Nevertheless, asthma patients treated with these agents must be **carefully monitored** to make certain that respiratory activity is not compromised.	▫The cardioselective β-blockers,such as acebutolol, atenolol, and metoprolol are useful in *hypertensive patients with impaired pulmonary function* and are also *first-line therapy for chronic stable angina*. ✍ This cardioselectivity is most pronounced *at low doses and is lost at high doses* (they antagonize β1 receptors at doses 50- to 100-fold less than those required to block β2 receptors) . ▫Since β1 selectivity of these agents is lost at high doses, they may antagonize β2 receptors. ▫For the management of chronic heart failure ; bisoprolol and the extended-release formulation of metoprolol are used .

▪ Because these drugs have **less effect on peripheral vascular β2 receptors**, coldness of extremities (Raynaud phenomenon), a common side effect of β-blockers, is less frequent.

Acebutolol and Pindolol

▪ Antagonists with partial agonist activity ➡**Acebutolol (β1-selective antagonist) and pindolol (nonselective β-blocker) are not pure antagonists.**

▶**Actions** :

Cardiovascular	These drugs have the ability to **weakly stimulate both β1 and β2 receptors** and are said to have ***intrinsic sympathomimetic activity*** (ISA). These partial agonists stimulate the β receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, epinephrine and norepinephrine. The result of these opposing actions is a **diminished effect on cardiac rate and cardiac output compared to that of β-blockers without ISA**.
Decreased metabolic effects	β-blockers with ISA **minimize the disturbances of lipid and**

	carbohydrate metabolism that are seen with other β-blockers. For example, these agents do not decrease plasma HDL levels.

▶Theraputic use in hypertension :

▪ β-blockers with ISA are effective in *hypertensive patients with moderate bradycardia*, **because a further decrease in heart rate is less pronounced with these drugs**.

▪ β-blockers with ISA are **not used** for stable angina or arrhythmias due to their partial agonist effect.

Labetalol and Carvedilol

▪ Antagonists of both α and β adrenoceptors → *nonselective β-blockers with concurrent α1-blocking actions* that produce peripheral vasodilation, thereby **reducing blood pressure**.

Actions	Usage in hypertension and heart failure	Adverse effacts
They contrast with the other β-blockers that produce initial peripheral vasoconstriction, and these agents are, therefore, **useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable**. Carvedilol also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in **heart failure**.	▫β-blockers should not be given to patients with an acute exacerbation of heart failure, as they can worsen the condition. ▪ Labetalol : -Employed as an alternative to methyldopa in the *treatment of pregnancy-induced hypertension*. -Intravenous labetalol is also used to treat hypertensive emergencies, because it can rapidly lower blood pressure. ▪ Carvedilol : -As well as metoprolol and bisoprolol are *beneficial in patients with stable chronic heart failure*. -These agents work by blocking the effects of sympathetic stimulation on the heart, which causes worsening heart failure over time.	**Orthostatic hypotension** and dizziness are associated with α1 blockade.

▶Drugs affecting neurotransmitter release or uptake

▪ Some agents act on the adrenergic neuron, either to interfere with neurotransmitter release from storage vesicles or to alter the uptake of the neurotransmitter into the adrenergic neuron. However, due to the advent of newer and more effective agents with fewer side effects, these agents are seldom used therapeutically.

▪ **Reserpine** is one of the remaining agents in this category.

Reserpine

➞A plant alkaloid, blocks the **Mg2+/adenosine triphosphate–dependent transport of biogenic amines** (norepinephrine, dopamine, and serotonin) from the cytoplasm into storage vesicles in the adrenergic nerve terminals in all body tissues.This causes the **ultimate depletion of biogenic amines**.

➞Sympathetic function, in general, is impaired because of decreased release of norepinephrine.

➞Reserpine has a slow onset, a long duration of action, and effects that persist for many days after discontinuation.

➞It has been used for the **management of hypertension** but has largely been replaced with newer agents with better side effect profiles and fewer drug interactions.

✓ The follwoing table summarizes the theraputic uses of various B-blockers and their receptor-specificity :

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
Nadolol *Pindolol*[1]	β_1, β_2	Hypertension
Timolol	β_1, β_2	Glaucoma, hypertension
Atenolol *Bisoprolol*[2] *Esmolol* *Metoprolol*[2]	β_1	Hypertension Angina Myocardial infarction
Acebutolol[1]	β_1	Hypertension
Nebivolol	β_1, NO ↑	Hypertension
Carvedilol[2] *Labetalol*	$\alpha_1, \beta_1, \beta_2$	Hypertension

Autacoids

✍Note :

Autacoids are biological factors (molecules) which act like local hormones, have a brief duration, and act near their site of synthesis.

These are local hormones; they therefore have a paracrine effect. Some notable autacoids are: **eicosanoids**, angiotensin, neurotensin, NO (nitric oxide), kinins, **histamine, serotonin**, endothelins and palmitoylethanolamide.

✓ We'll start with '**Histamine**' :

Location :

Histamine is present in practically all tissues, with significant amounts in the lungs, skin, blood vessels, and GI tract. It is found at high concentration in mast cells and basophils.

Function :

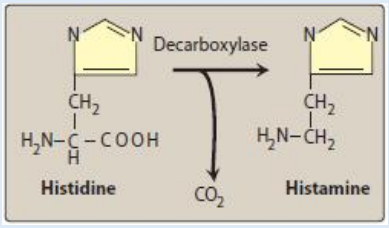
Histamine functions as a neurotransmitter in the brain. It also occurs as a component of venoms and in secretions from insect stings.

Synthesis :

Histamine is an amine formed by the **decarboxylation of the amino acid histidine** by the enzyme **histidine decarboxylase**, which is expressed in cells throughout the body, including **neurons, gastric parietal cells, mast cells, and basophils**

Degradation :

In mast cells, histamine is stored in granules. If histamine is not stored, it is rapidly inactivated by the enzyme **amine oxidase** .



Release of histamine :

Histamine is just one of several chemical mediators released in response to stimuli.The stimuli for release of histamine from tissues may include :

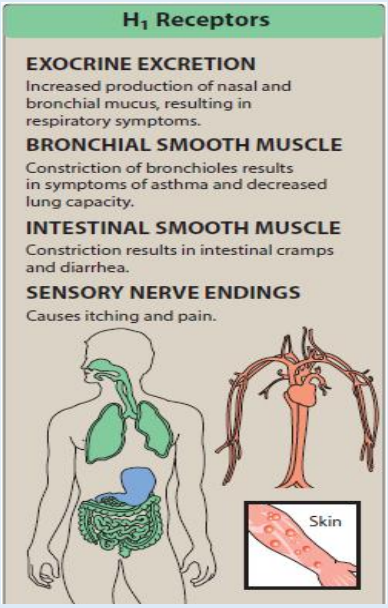
➞Destruction of cells as a result of cold, toxins from organisms, venoms from insects and spiders, and trauma.

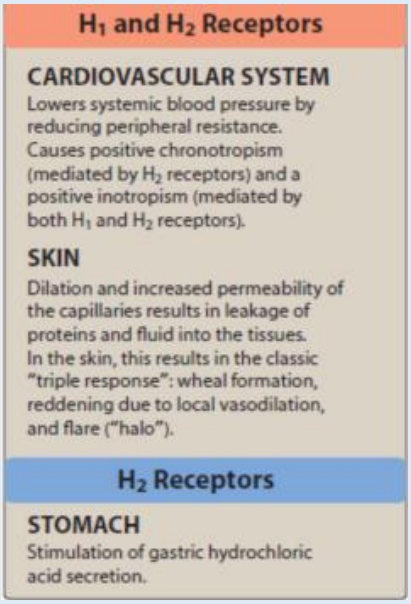
➞Allergies and anaphylaxis .

Histamine Receptors and physiological functions

Histamine released in response to certain stimuli exerts its effects by binding to various types of histamine receptors (H1, H2, H3, and H4).

Receptor	Signal transduction	Physiological Function
H1	Gq/G11	-Modulation of smooth muscle contraction. -Modulation of neurotransmission . -Vasodilation . (Check the figure below for more)
H2	Gs	Stimulation of gastric acid secretion
H3	Gi/G0	Modulation of CNS activity
H4	Gi/G0	Modulation of allergic reaction
H1 + H2	Mostly affected by drugs	-CVS : Inotropism&Chronotropism -Skin : Triple response (Flush/Wheal/Flare)





▶Role of Histamine in allergy and anaphylaxis

The symptoms resulting from intravenous injection of histamine are similar to those associated with anaphylactic shock and allergic reactions.

▪ These include:

✓ contraction of airway smooth muscle.
✓ Stimulation of secretions.
✓ dilation and increased permeability of the capillaries.
✓ stimulation of sensory nerve endings.

Symptoms associated with allergy and anaphylactic shock result from the release of certain mediators from their storage sites.

▪ Such mediators include:

✓ Histamine.
✓ Serotonin.
✓ Leukotrienes.
✓ Eosinophil chemotactic factor of anaphylaxis.

➞In some cases, these mediators cause a localized allergic reaction, producing, for example, actions on the skin or respiratory tract.Under other conditions, these mediators may cause a full-blown anaphylactic response.

It is thought that the difference between these two situations results from:

1. Differences in the sites from which mediators are released.
2. Rates of mediators release .

✍ Mast cells :

Is a type of white blood cell.

➞Specifically, it is a type of granulocyte derived from the myeloid stem cell that is a part of the immune and neuroimmune systems and contains many granules rich in histamine and heparin.

➞Mast cells play an important protective role as well, being intimately involved in wound healing, angiogenesis, immune tolerance, defence against pathogens,allergies and anaphylaxis, and blood–brain barrier function.

Antihistamines : Calssification & Differentiation

<table>
<tr><th colspan="2">H1-Antihistamine: H1-Blockers</th><th>H2-antihistamine :H2 blockers with little or no H1 affinity</th></tr>
<tr><td>1st generation</td><td>2nd generation</td><td rowspan="2">Inhibition of HCl secretion in the treatment of ulcers and heartburn .</td></tr>
<tr><td>▪ Older / widely used / effective / inexpensive .

Penetrate CNS>Sedation
▪ Interact with other receptorsm>unwanted side effects</td><td>▪ Polar form of the 1st generation by carboxyl group addition
(Hydroxyzine+carboxyl group =cetirizine)

▪ Can’t penetrate CNS>Peripheral H1 blocker

<table><tr><td>Weak-partailly sedating</td><td>Non-sedating</td></tr><tr><td>Cetirizine
Levocetirizine</td><td>Fexofenadine
loratadine .
Desloradine</td></tr></table></td></tr>
</table>

Antihistamines : Actions

✓ The action of all the H1-receptor blockers is qualitatively similar.Most of these compounds ***do not influence the formation or release of histamine***.Rather, they block the receptor-mediated response of a target tissue.

✓ They are much more effective in *preventing symptoms than reversing them* once they have occurred.

✓ However, most of these agents have **additional effects unrelated to their ability to block H1receptors**.These effects reflect binding of the H1-receptor antagonists to **cholinergic**, **adrenergic**, or **serotonin** receptors .

- Examples :

➞Cyproheptadine also acts as a **serotonin antagonist** on the appetite center and is sometimes used ***off label*** as an **appetite stimulant** and in **treating anorgasmy** associated with the use of selective serotonin reuptake inhibitors.

➞Antihistamines such as azelastine and ketotifen also have ***mast cell–stabilizing effects*** in addition to their histamine receptor–blocking effects.

- **Problems associated with Histamine, but treated by epinephrine:**
  a) Bronchial reactions ; bronchial asthma
  b) Systemic anaphylaxis

▶Theraputic Uses :

Allergic and inflammatory conditions	Mech: Prevent allergies caused by IgE antibody . Route of administration : ▪ **Oral** : for rhinitis and urticaria ▪ **Opthalmic** (azelastine, olopatadine, ketotifen) : allergic conjunctivitis
Motion sickness and nausea	▪ Prevent motion sickness symptoms along with the antimuscarnic Scopalamine e.g: Diphenhydramine/ Dimenhydrinate/ Cyclizine/ Meclizine. ▪ Prevent nausea and vomiting mediated by chemoreceptors+vestibular pathways ▪ Antiemetic action by blocking both H1 and M1 muscarnuc receptors. ▪ Vertigo that is associated with vestibular disorders e.g: Meclizine
Somnifacients	**Treat insomnia (only H1 antihistamines)** ▪ OTC ▪ Avoided when wakefulness is critical. e.g: Diphenhydramine/ Doxylomine.

▶Pharmacokinetics :

Route of Administration :

- **Oral**➞(onsets in 1-3h and lasts for 24h).
- O**phthalmic**➞Azelastine/ Olopatadine/Ketotifen/ alcaftadine/ bepotastine/ emedastine.
- I**ntranasal**➞Azelastine/ Olopatadine.

T(1/2) and metabolism :

Half life➡ **All ▶4-6h whereas Meclizine+ 2nd generation ▶12-24h**

Metabolism➡**All 1st and some 2nd generation are mediated CYP450**

e.g:Desloratadine +Loratadine.

Distribution & Elimination :

First-generation H1-receptor blockers are distributed in all tissues, including the CNS. Cetirizine and levocetirizine are excreted largely unchanged in urine, and fexofenadine is excreted largely unchanged in feces.

▶Adverse effects and drug interactions :

Adverse Effects	Drug interactions
▪ 1st generation has less specificity interacting not only with histamine receptors but also with muscarinic cholinergic receptors, α-adrenergic receptors, and serotonin receptors. ▪ CNS related➞fatigue/ Dizziness/ lack of coordination/ tremor/ blurred vision/ headache **Overdose:** Chronic is rare whereas acute poisoning is common in children, it'll cause multiple CNS effects ,including : Hallucination/ excitement/ ataxia/ convulsions if untreated it'll lead to deepening coma/ collapse of the Cardiorespiratory system .	▪ H1-receptor blockers potentiates the effects of other CNS depressants, including alcohol. ▪ MAOIs can exacerbate the anticholinergic effects of the antihistamines. ▪ The first-generation antihistamines with anticholinergic (antimuscarinic) actions may decrease the effectiveness of cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) in the treatment of Alzheimer's disease.

✓ Now , let's discuss another autacoid "**Serotonin**":

▪ It is synthesized from the **amino acid tryptophan** and acts on several types of receptors.

▪ It is widely distributed in plants and animals. Highest concentration in mammals is found in the ***pineal gland***, acting as a precursor for melatonin.

➞Actions :

▪ **CVS**:

1.Weak ino-chronotropic effect on myocardium .
2.Construction of renal/splanchnic/meningeal/pulmonary arteries and veins .
3.Dilation of skeletal/coronary/skin capillaries .

▪ **Stimulation of SM of intestines** .

▪ **CNS** : Serotonin is widely distributed in the CNS, serving as a neurotransmitter.

Altered functions may be responsible for disturbances in sleep, mood, sexual behavior, motor activity, pain perception, migraine, temperature regulation, endocrine control, psychiatric disorders and extra-pyramidal activity.

➞Serotonin Agonists :

Sumatriptan	Busirane
▪ Selective agonist of 5-HT1 receptors and is highly effective in treating acute attacks of migraine, but is not useful in the prevention. It relieves the nausea and vomiting, but the headache may recur, necessitating repeated administrations. ▪ PKs ➞ It is administered orally or by the subcutaneous route. The bioavailability of oral dose is only 14 %; thus, the oral dose is several times larger than the subcutaneous dose. ▪ Adverse effects ➞ Flushing and heat at the injection site, neck pain, dizziness, and tingling of the hands. The drug is contraindicated with symptomatic ischemic heart diseases, angina, and hypertension as it may cause coronary vasoconstriction.	Useful effective anxiolytic agent.

➞Serotonin Antagonists :

Name of the drug	**Methysergide**	**Cyproheptadine**	**Ondasertan**	**Prochlorperazine Haloperidol**
Receptor(s)	Non-selective 5-HT	Potent: 5-HT Smaller extent : Histamine & Ach	5-HT3	5-HT
ROA	----------	----------	Oral / IV	----------
Theraputic Use	Prophylactic agent for migraine	It stimulates appetite probably by acting directly on the hypothalamus. It can block the release of hydrocortisone, and the production of aldosterone. It is mainly used to relieve the itching associated with skin disorders such as allergic dermatitis	It is useful in the management of nausea and vomiting associated with cytotoxic therapy.	sometimes used for resistant acute attacks.
Adverse effect	GI irritation, drowsiness, vertigo, and psychic disturbances.	The common adverse reaction is drowsiness.	headache, constipation, and allergic reactions	_____

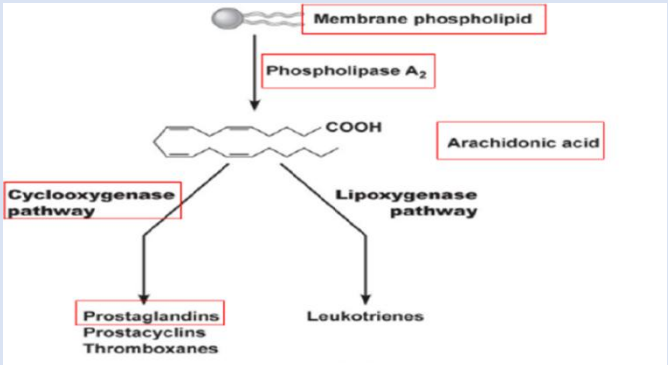
✓ The last group to be discussed is "**Prostaglandins**" :

- Prostaglandins and related compounds are produced in minute quantities by virtually all tissues.
- They generally act locally on the tissues in which they are synthesized, and they are rapidly metabolized to inactive products at their sites of action.Therefore, the prostaglandins do not circulate in the blood in significant concentrations.
- Thromboxanes and leukotrienes are related lipids that are synthesized from the same precursors as the prostaglandins

Synthesis of prostaglandins

Arachidonic acid(a component of the phospholipids of cell membranes) is the primary precursor of the prostaglandins and related compounds. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A2 via a process controlled by hormones and other stimuli.

There are two major pathways in the synthesis of the eicosanoids from arachidonic acid, the **cyclooxygenase and the lipoxygenase** pathways.



▶Actions :

Their functions vary widely, depending on the tissue and the specific enzymes within the pathway that are available at that particular site.Their action is mediated by their binding to a wide variety of distinct cell membrane receptors that operate via G-coupled proteins .

E.g. :

Thromboxane A2 (TXA2)> released from platelets during tissue injury> platelets aggregation + local vasoconstriction/ prostacyclin (PGI2)> produced by endothelial cells> has opposite effects ➞The Overall effect depends on balance between these two compounds.

▶Therapeutic uses :

✓ They have a major role in modulating pain, inflammation, and fever.
✓ They also control many physiological functions, such as acid secretion and mucus production in the gastrointestinal (GI) tract, uterine contractions, and renal blood flow.
✓ They are among the chemical mediators that are released in allergic and inflammatory processes.

▶Drugs derived from PGs :

Alprostadil	**Lubiprostone**	**Misoprostol**	**Bimatoprost Latanoprost Tafluprost Travoprost**	**Epoprostenol Iloprost Treprostinil**
▪ Nature ➞ Natural PGE_1 ▪ Produced in tissues such as seminal vesicles and cavernous tissues, in the placenta, and in the ductus arteriosus of the fetus. ▪ Therapeutically, alprostadil can be used to treat erectile dysfunction or to keep the ductus arteriosus open in neonates with congenital heart conditions until surgery is possible.	Nature➞ PGE_1 derivative ▪ Indicated for the treatment of chronic idiopathic constipation, opioid-induced constipation, and irritable bowel syndrome with constipation. ▪ MOA : It stimulates chloride channels in the luminal cells of the intestinal epithelium, thereby increasing intestinal fluid secretion. ▪ SEs: Nauseaband diarrhea are the most common side effects of lubiprostone. Nausea can be decreased if taken with food.	Nature➞ PGE_1 analogue ▪ Used to protect the mucosal lining of the stomach **during chronic NSAID treatment**. ▪ MOA: Misoprostol interacts with prostaglandin receptors on parietal cells within the stomach, reducing gastric acid secretion. ▪ Misoprostol has a GI cytoprotective effect by stimulating mucus and bicarbonate production. This combination of effects *decreases the incidence of gastric ulcers caused by NSAIDs*.	Nature➞ F2α analogs ▪ Indicated for the treatment of open-angle glaucoma. ▪ MOA : By binding to prostaglandin receptors, they increase uveoscleral outflow, reducing intraocular pressure. ▪ Administered as ophthalmic solutions once a day and are as effective as timolol or better in reducing intraocular pressure. ▪ SEs: Ocular reactions include blurred vision, iris color change (increased brown pigmentation), increased number and pigment of eyelashes, ocular irritation, and foreign body sensation.	Nature➞ PGI_2 analogs ▪ Mimic the effects of prostacyclin in endothelial cells, producing a significant reduction in pulmonary arterial resistance with a subsequent increase in cardiac index and oxygen delivery. ▪ SEs: Dizziness, headache, flushing, and fainting are the most common adverse effects. Bronchospasm and cough can also occur after inhalation of iloprost.

✍ Notes :

✓ **Misoprostol** is used **off-label** in obstetric settings for labor induction, since it increases uterine contractions by interacting with prostaglandin receptors in the uterus.

✓ Misoprostol has the **potential risk to induce abortion in pregnant women**.Therefore, the drug is ***contraindicated during pregnancy***.

✓ **Bimatoprost** increases eyelash prominence, length, and darkness and is approved for the **treatment of eyelash hypotrichosis**.

✓ **Epoprostenol** and **treprostinil** are administered as a continuous intravenous infusion, and treprostinil may also be administered orally or via inhalation or subcutaneous infusion.

✓ Inhaled **iloprost** requires frequent dosing due to the short half-life.

NSAIDs

▪ The NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities.They act by inhibiting the synthesis of prostaglandins.

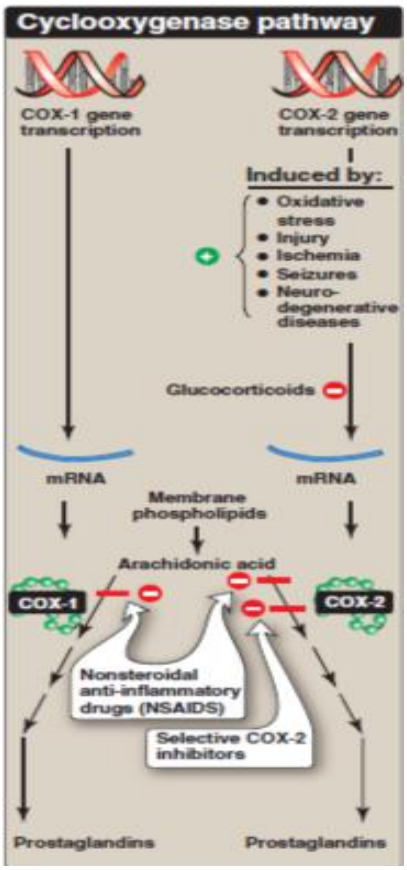
▪ NSAIDs are classified as follow :

Class	Drugs
Derivatives of salicylic acid	aspirin, diflunisal, salsalate
Propionic acid	ibuprofen, fenoprofen flurbiprofen, ketoprofen, naproxen, oxaprozin
Acetic acid	diclofenac, etodolac, indomethacin, ketorolac, nabumetone, sulindac, tolmetin
Enolic acid	meloxicam, piroxicam
Fenamates	mefenamic acid, meclofenamate
Selective COX-2 inhibitor	celecoxib

▪ MOA :

✓ They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis ▶decreased prostaglandin synthesis with both beneficial and unwanted effects.

✓ Differences in safety and efficacy of the NSAIDs may be explained by relative selectivity for the COX-1 or COX-2 enzyme ▶**Inhibition of COX-2** is thought to lead to the anti-inflammatory and analgesic actions of NSAIDs, while **inhibition of COX-1** is responsible for prevention of cardiovascular events and most adverse events



Aspirin and other NSAIDs

▪ **NSAIDs, including aspirin, have three major therapeutic actions: They reduce**:

✓ **Inflammation (anti-inflammatory)**: Cyclooxygenase inhibition diminishes the formation of prostaglandins and, thus, modulates aspects of inflammation ➞ *They neither arrest the progression of the disease nor induce remission*.

✓ **Pain (analgesic effect)**: by inhibiting COX-2, decreasing PGE2 synthesis, the sensation of pain (by nerve endings to the action of bradykinin, histamine, and other chemical mediators released) can be decreased/ used mainly for the management of mild to moderate pain arising from musculoskeletal disorders ➞ **ketorolac can be used for more severe pain but for only a short duration**.

✓ **Fever (antipyretic effect)**: by impeding PGE2 synthesis and release▶ resetting the "thermostat" toward normal▶This rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating➞NSAIDs have no effect on normal body temperature.

✍ ***The salicylates exhibit analgesic activity at lower doses. Only at higher doses do these drugs show anti-inflammatory activity***.

▪ Therapeutic uses (in general):

✓ Treatment of osteoarthritis, gout, and RA.

✓ Common conditions (for example, headache, arthralgia, myalgia, and dysmenorrhea) requiring analgesia.

✓ Combinations of opioids and NSAIDs may be effective in treating pain caused by malignancy leading to an opioid-sparing effect, allowing for lower doses of opioids to be utilized.

✓ External applications :

- •Salicylic acid is used topically to treat acne, corns, calluses, and warts.
- •Methyl salicylate ("oil of wintergreen") is used externally as a cutaneous counterirritant in liniments, such as arthritis creams and sports rubs.

▪ Pharmacokinetics (in general):

➞ROA:

Most NSAIDs are well absorbed after **oral** administration,circulate highly bound to plasma protein.

➞Metabolism:

The majority are **metabolized by the liver**, mostly to inactive metabolites .

✍ Few (for example, nabumetone and sulindac) have active metabolites .

➞Elimination :

Elimination of active drug and metabolites is primarily via the urine.

Adverse events ➡Summarized in the following table

Gastrointestinal: ranging from dyspepsia to bleeding.	Increased risk of bleeding (antiplatelet effect)	Actions on the kidney	Cardiac effects
How? Agents that inhibit COX-1 reduce: PGI2: resulting in increased gastric acid secretion. PGE2 and PGF2α: diminished mucus protection, and increased risk for GI bleeding and ulceration. ✍ **Notes:** •NSAIDs should be taken with food or fluids to diminish GI upset. •If NSAIDs are used in patients with a high risk for GI events, proton pump inhibitors or misoprostol should be used concomitantly to prevent NSAID-induced ulcers.	**How?** Aspirin irreversibly inhibits COX-1–mediated TXA2 formation, while other NSAIDs reversibly inhibit the production of TXA2> platelet aggregation (the first step in thrombus formation) is reduced **TXA2 enhances platelet aggregation, whereas PGI2 decreases it. ✍ **Notes:** •Aspirin is often held, or not given, at least 1 week prior to surgery. •NSAIDs other than aspirin are not utilized for their antiplatelet effect but can still prolong bleeding time. •Patients who take aspirin for cardioprotection should avoid concomitant NSAID use if possible. •more COX-2 selective, they are expected to have less effect	**How?** NSAIDs prevent the synthesis of PGE2 and PGI2, prostaglandins that are responsible for maintaining renal blood flow> can result in retention of sodium and water and may cause edema in some patients. ✍ **Notes:** •Patients with a history of heart failure or kidney disease are at particularly high risk. •These effects can also mitigate the beneficial effects of antihypertensive medications.	**How?** Agents such as aspirin, with a very high degree of COX-1 selectivity, have shown a cardiovascular protective effect thought to be due to a reduction in the production of TXA2. •Agents with higher relative COX-2 selectivity have been associated with an increased risk for cardiovascular events, possibly by decreasing PGI2 production mediated by COX-2. ✍ **Notes:** •For patients with cardiovascular disease in whom NSAID treatment cannot be avoided, naproxen appears to be the least likely to be harmful/ should be limited to the lowest dose possible for the shortest duration.

Asthma	Central nervous system (CNS) adverse events	hypersensitivity reactions.	Fatal anaphylactic shock
NSAIDs should be used with caution in patients with asthma, as inhibition of prostaglandin synthesis can cause a shift toward leukotriene production and, therefore, increase the risk of exacerbations of asthma.	such as headache, tinnitus, and dizziness, may occur.	•Symptoms of true allergy include urticaria, bronchoconstriction, and angioedema which is experienced with 15% of patients •Patients with severe hypersensitivity to aspirin should avoid using NSAIDs.	rare.
Drug interactions	**Toxicity**	**Pregnancy**	-
•Salicylate is roughly 80% to 90% plasma protein bound (albumin) and can be displaced from protein binding sites resulting in increased concentration of free salicylate. •Aspirin can displace other highly protein-bound drugs, such as warfarin, phenytoin, or valproic acid, resulting in higher free concentrations of these agents.	**Lower dose:** The mild form is called salicylism and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears). **Higher dose:** severe salicylate intoxication may result in Restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure may occur. **Children:** Ingestion of as little as 10 g of aspirin can cause death in children.	Most NSAIDs are pregnancy risk category C in the first two trimesters. ✍ **Notes:** •Acetaminophen is preferred if analgesic or antipyretic effects are needed during pregnancy. •Un the third trimester, NSAIDs should generally be avoided due to the risk of premature closure of the ductus arteriosus	-

Aspirine

▸ Nature :

A derivative of salicylic acid.

▸ MOA:

Irreversibly acetylates (and, thus, inactivates) cyclooxygenase .

✍ **The other NSAIDs are all reversible inhibitors of cyclooxygenase/ its antiplatelet effects persist for the life of the platelet**

▸ Theraputic Uses :

✓ Two 325-mg aspirin tablets administered four times daily produce analgesia
✓ 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity.
✓ Used acutely to reduce the risk of death in acute MI and in patients undergoing certain revascularization procedures.
✓ Treat fever.
✓ Low doses (doses less than 325 mg; many classify it as doses of 75 to 162 mg—commonly 81 mg) of aspirin are used prophylactically to:

- ▫Reduce the risk of recurrent cardiovascular events and/or death in patients with previous MI or unstable angina pectoris.
- ▫Reduce the risk of recurrent transient ischemic attacks (TIAs) and stroke or death in those who have had a prior TIA or stroke.
- ▫Reduce the risk of cardiovascular events or death in high-risk patients such as those with chronic stable angina or diabetes.

▸ Pharmacokinetics :

After **oral** administration➞aspirin is rapidly deacetylated by esterases in the body➞producing salicylate➞dissolution of the tablets (favored at the higher pH of the gut)➞Unionized salicylates are passively absorbed mostly from the upper small intestine➞converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney➞resulting in first-order elimination and a serum half-life of **3.5 hours**.

▸ The dose effects in pharmacokinetics :

✓ At ***anti-inflammatory dosages*** (more than 4 g/day), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, leading to a half-life of 15 hours or more.
✓ At low doses of aspirin (less than 2 g/day), uric acid secretion is decreased, whereas at high doses, uric acid secretion may be unchanged or increased. Therefore, aspirin is avoided in gout or in patients taking probenecid.

▸ Drug Interaction :

Aspirin can displace other highly protein-bound drugs, such as warfarin, phenytoin, or valproic acid, resulting in higher free concentrations of these agents.

Celecoxib

▸ Type: Selective COX-2 inhibitor reversibly

▸ Therapeutic use:

✓ Treatment of RA, osteoarthritis, and acute mild to moderate pain.
✓ Celecoxib has similar efficacy to NSAIDs in the treatment of pain.

▸ Pharmacokinetics:

Readily absorbed after oral administration➞extensively metabolized in the liver by cytochrome P450 (CYP2C9)➞excreted in feces and urine.

▸ The half-life: is about 11 hours, and the drug may be dosed once or twice daily.

▸ Adverse effects:

✓ Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects.
✓ Patients who are at high risk of ulcers and require aspirin for cardiovascular prevention should avoid the use of celecoxib.

✓ The dosage should be reduced in those with moderate hepatic impairment, and celecoxib should be avoided in patients with severe hepatic or renal disease
✓ Like other NSAIDs, the drug has a similar risk for cardiovascular events.
✓ Celecoxib should be used with caution in patients who are allergic to sulfonamides.
✓ Patients who have had anaphylactoid reactions to aspirin or nonselective NSAIDs may be at risk for similar effects with celecoxib.
✓ Inhibitors of CYP2C9, such as fluconazole and fluvastatin, may increase serum levels of celecoxib

Acetaminophen

▸ Nature:

(N-acetyl-p-aminophenol or APAP) inhibits prostaglandin synthesis in the CNS and has less effect on cyclooxygenase in peripheral tissues (due to peripheral inactivation). It does not affect platelet function or increase bleeding time. It is not considered to be an NSAID.

▸ Therapeutic uses:

✓ Analgesic and antipyretic effects of NSAIDs for those patients with gastric complaints/risks, in those whom a prolongation of bleeding time is not desirable, as well as those who do not require the anti-inflammatory action of NSAIDs.
✓ Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with aspirin).
✓ Acetaminophen is preferred if analgesic or antipyretic effects are needed during pregnancy.

▸ Pharmacokinetics:

▪ Rapidly absorbed from the GI tract➞A significant first-pass metabolism occurs in the luminal cells of the intestine and in the hepatocytes :

•Acetaminophen is conjugated in the liver to form an inactive glucuronidated or sulfated metabolites.

•A portion of acetaminophen is hydroxylated to form N-acetyl-p-benzoquinoneimine, or NAPQI, which could cause:

A. Toxic substance: NAPQI reacts with sulfhydryl groups and cause liver damage.
B. Nontoxic substance: NAPQI reacts with the sulfhydryl group of glutathione, which is produced by the liver, forming a nontoxic substance

▪ Acetaminophen and its metabolites are excreted in urine. The drug is also available in intravenous and rectal formulations.

▸ Adverse effects:

✓ At normal therapeutic doses, acetaminophen is virtually free of significant adverse effects.
✓ With large doses of acetaminophen, the available glutathione in the liver becomes depleted, and NAPQI reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds/ Hepatic necrosis may result..

✍ Keep in mind :
✓ Patients with hepatic disease, viral hepatitis, or a history of alcoholism are at higher risk of acetaminophen induced hepatotoxicity.
✓ Acetaminophen should be avoided in patients with severe hepatic impairment.
✓ N-acetylcysteine, which contains sulfhydryl groups to which the toxic metabolite can bind, is an antidote in cases of overdose .

Principles of Antimicrobial Therapy

✓ Brief Intro :

- Antimicrobial therapy takes advantage of the biochemical differences that exist between microorganisms and human beings.
- Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity, that is, they have the ability to injure or kill an invading microorganism **without harming the cells of the host**.
- In most instances, the selective toxicity is relative rather than absolute, requiring that the concentration of the drug be carefully controlled to attack the microorganism, while still being tolerated by the host.

✓ Selection of antimicrobial agents :

Selection of the most appropriate antimicrobial agent requires knowing :

A) Organism's identity.
B) Organism's susceptibility to a particular agent.
C) Site of the infection.
D) Patient factors.
E) Safety of the agent.
F) Cost of therapy.

▶However, some patients require **empiric therapy**

> Medical treatment or therapy based on experience and, more specifically, therapy begun on the basis of a clinical "educated guess" in the absence of complete or perfect information. Thus it is applied before the confirmation of a definitive medical diagnosis or without complete understanding of an etiology, whether the biological mechanism of pathogenesis or the therapeutic mechanism of action.

✓ 1St :Identification of the infecting organism

- Characterizing the organism is central to selection of the proper drug.
- A **rapid assessment of the nature of the pathogen** can sometimes be made on the basis of the Gram stain, which is particularly useful in identifying the presence and morphologic features of microorganisms in body fluids that are normally sterile (blood, serum, cerebrospinal fluid [CSF], pleural fluid, synovial fluid, peritoneal fluid, and urine).However, it is generally necessary to culture the infective organism to arrive at a conclusive diagnosis and determine the susceptibility to antimicrobial agents.
- Thus, it is essential to **obtain a sample culture of the organism prior to initiating treatment**. Otherwise, it is impossible to differentiate whether a negative culture is due to the absence of organisms or is a result of antimicrobial effects of administered antibiotic.
- **Definitive identification of the infecting organism may require other laboratory techniques**, such as detection of microbial antigens, DNA, or RNA, or an inflammatory or host immune response to the microorganism.

▶Empiric therapy prior to identification of the organism

Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug susceptibility established. However, in the critically ill patient, such a delay could prove fatal, and immediate empiric therapy is indicated.

(1) Timing :

Acutely ill patients with infections of unknown or a patient with meningitis require immediate treatment.

➞Therapy should be **initiated after specimens for laboratory analysis have been obtained** but **before the results of the culture and sensitivity are available**

(2) Selecting a drug :

Drug choice in the absence of susceptibility data is influenced by the site of infection and the patient's history▶for example, previous infections, age, recent travel history, recent antimicrobial therapy, immune status, and whether the infection was hospital- or community-acquired.

Broad-spectrum therapy may be indicated initially when the organism is unknown or polymicrobial infections are likely.

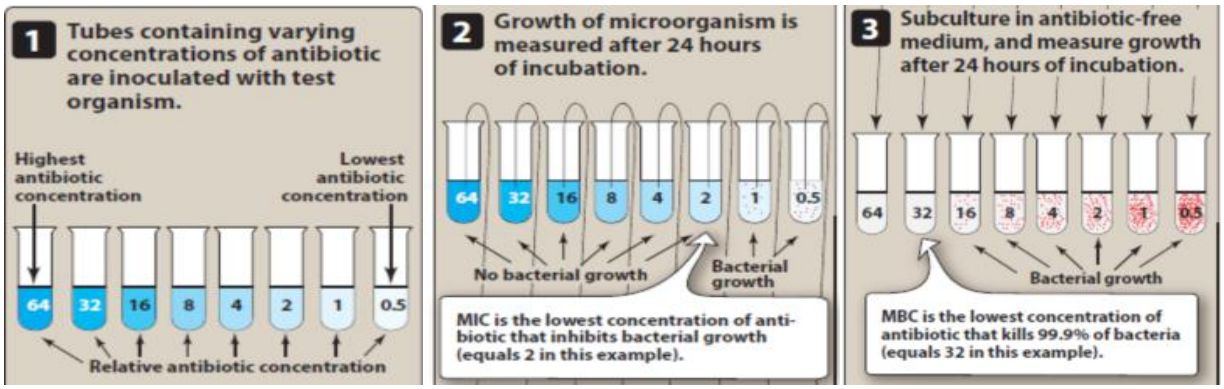
The choice of agent(s) may also be guided by known association of particular organisms in a given clinical setting.

✓ 2nd :Determining antimicrobial susceptibility of infective organisms

▪ After a pathogen is cultured, its susceptibility to specific antibiotics serves as a guide in choosing antimicrobial therapy.

➞Some pathogens, such as Streptococcus pyogenes and Neisseria meningitidis, usually have predictable susceptibility patterns to certain antibiotics.
In contrast, most gram-negative bacilli, enterococci, and staphylococcal species often show unpredictable susceptibility patterns and require susceptibility testing to determine appropriate antimicrobial therapy.

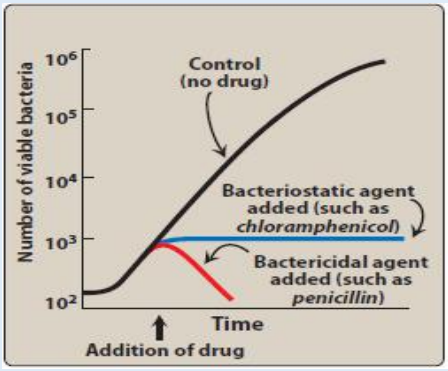
▪ The minimum inhibitory and bactericidal concentrations of a drug can be experimentally determined



✍ Recall :

▶Bacteriostatic drugs arrest the growth and replication of bacteria at serum (or urine) levels achievable in the patient, thus limiting the spread of infection until the immune system attacks, immobilizes, and eliminates the pathogen.

▶Bactericidal drugs kill bacteria at drug serum levels achievable in the patient. Because of their more aggressive antimicrobial action, bactericidal agents are often the drugs of choice in seriously ill and immunocompromised patients



▶MIC and MBC

Minimum inhibitory concentration	Minimum bactericidal concentration
MIC is the lowest antimicrobial concentration that **prevents visible growth of an organism after 24 hours of incubation**. Serves as a quantitative measure of in vitro susceptibility and is commonly used in practice to streamline therapy.	MBC is the lowest concentration of antimicrobial agent that **results in a 99.9% decline in colony count after overnight broth dilution incubations** .

✓ 3rd :Effect of the site of infection on therapy

- Adequate levels of an antibiotic must reach the site of infection for the invading microorganisms to be effectively eradicated.
- Capillaries with varying degrees of permeability carry drugs to the body tissues.
- Natural barriers to drug delivery are created by the structures of the capillaries of some tissues, such as the **prostate, testes, placenta, the vitreous body of the eye, and the central nervous system** (CNS).
- Of particular significance are the capillaries in the brain, which help to create and maintain the blood–brain barrier. This barrier is formed by the single layer of endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules, except those that are small and lipophilic.

➞The penetration and concentration of an antibacterial agent in the CSF are particularly influenced by the following:

Lipid solubility of the drug	E.g. ▪ **Chloramphenicol and metronidazole**, have significant penetration into the CNS. ▪ **β-lactam antibiotics**, such as penicillin, are ionized at physiologic pH and have low solubility in lipids. They therefore have limited penetration through the intact blood–brain barrier under normal circumstances.

	✍ **Imp Note :** In infections such as meningitis in which the brain becomes inflamed, the barrier does not function as effectively, and local permeability is increased. Some β-lactam antibiotics can enter the CSF in therapeutic amounts when the meninges are inflamed.
Molecular weight of the drug	A compound with a low molecular weight has an enhanced ability to cross the blood–brain barrier, whereas compounds with a high molecular weight (for example,vancomycin) penetrate poorly, **even in the presence of meningeal inflammation**.
Protein binding of the drug	A high degree of protein binding of a drug restricts its entry into the CSF. Therefore, the amount of free (unbound) drug in serum, rather than the total amount of drug present, **is important for CSF penetration**.

✓ 4th :**Patient factors**

Immune system	Alcoholism, diabetes, HIV infection, malnutrition, autoimmune diseases, pregnancy, or advanced age can affect a patient's immunocompetence, as can immunosuppressive drugs. ➞High doses of bactericidal agents or longer courses of treatment may be required to eliminate infective organisms in these individuals.
Renal dysfunction	Poor kidney function may cause accumulation of certain antibiotics. What to do ? (1)Dosage adjustment ➞prevents drug accumulation and therefore adverse effects. Serum creatinine levels are frequently used as an index of renal function for adjustment of drug regimens. (2)Direct monitoring of serum levels of some antibiotics (for example, vancomycin, aminoglycosides) is preferred to identify maximum and/or minimum values to prevent potential toxicities. (Age and kidney function?) The **number of functional nephrons decreases with age**. Thus, **elderly patients** are particularly vulnerable to accumulation of drugs eliminated by the kidneys.
Hepatic dysfunction	Antibiotics that are concentrated or eliminated by the liver (for example, erythromycin and doxycycline) must be used with caution when treating patients with liver dysfunction.
Poor perfusion	Decreased circulation to an anatomic area, such as the lower limbs of a diabetic patient, reduces the amount of antibiotic that reaches that area, making these infections **difficult to treat**.

Age	E.g. (1)Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of chloramphenicol and sulfonamides. (2)Young children should not be treated with tetracyclines or quinolones, which affect bone growth and joints, respectively. (3)Elderly patients may have decreased renal or liver function, which may alter the pharmacokinetics of certain antibiotics.
Pregnancy and lactation	Many antibiotics cross the placental barrier or enter the nursing infant via the breast milk. Although the concentration of an antibiotic in breast milk is usually low, the total dose to the infant may be sufficient to produce detrimental effects.

✓ 5th :**Safety of the agent**

- Safety is related not only to the inherent nature of the drug but also to patient factors that can predispose to toxicity.
- Antibiotics such as the penicillins are among the least toxic of all drugs because they interfere with a site or function unique to the growth of microorganisms.

Other antimicrobial agents (for example, chloramphenicol) have less specificity and are **reserved for life-threatening infections** because of the potential for serious toxicity to the patient.

✓ 6th :**Cost of therapy**

- Often several drugs may show similar efficacy in treating an infection but vary widely in cost.
- Note : Although choice of therapy usually centers on the site of infection, severity of the illness, and ability to take oral medications, it is also important to consider the cost of the medication

▶Determining of rational dosing :

Rational dosing of antimicrobial agents is based on their pharmacodynamics and pharmacokinetic properties of the drug.

- Three important properties that have a significant influence on the frequency of dosing are :

✓ **Concentration dependent killing.**
✓ **Time-dependent killing.**
✓ **Postantibiotic effect (PAE)**

Concentration-dependent killing	Increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism. E.g.➞aminoglycosides and daptomycin Giving drugs that exhibit this concentration-dependent killing by a once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.

Time-dependent (concentration-independent) killing	The clinical efficacy of antimicrobials showing this property is best predicted by the percentage of time that blood concentrations of a drug remain **above the MIC**. E.g.➞β-lactams, glycopeptides, macrolides, clindamycin, and linezolid ▪ For example, dosing schedules for the penicillins and cephalosporins that ensure blood levels greater than the MIC for 50% and 60% of the time, respectively, provide the most clinical efficacy. Therefore, extended (generally 3 to 4 hours) or continuous (24 hours) infusions can be utilized instead of intermittent dosing (generally 30 minutes) to achieve prolonged time above the MIC and kill more bacteria.
Postantibiotic effect	The PAE is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC. Antimicrobial drugs exhibiting a long PAE (for example, aminoglycosides and fluoroquinolones) often **require only one dose per day**, particularly against gram negative bacteria.

▶Chemotheraputic Spectra of antimicrobials

Generally , classified into 3 classes based on their spectra as follow :

Narrow-spectrum antibiotics	Chemotherapeutic agents acting only on a single or a limited group of microorganisms . E.g.➞ **Isoniazid** is active only against Mycobacterium tuberculosis
Extended-spectrum antibiotics	Antibiotics that are modified to be effective against gram-positive organisms and also against a significant number of gram-negative bacteria. E.g.➞ **Ampicillin** is considered to have an extended spectrum because it acts against gram-positive and some gram-negative bacteria
Broad-spectrum antibiotics	Antibiotics that affect a wide variety of microbial species. E.g.➞ **tetracycline, fluoroquinolones and carbapenems** Note: Administration of broadspectrum antibiotics can drastically alter the nature of the normal bacterial flora and precipitate a superinfection due to organisms such as Clostridium difficile, the growth of which is normally kept in check by the presence of other colonizing microorganisms.

▶Combinations of antimicrobial drugs

▪ It is therapeutically advisable to treat patients with a single agent that is most specific to the infecting organism.However, some situations require combinations of antimicrobial drugs,E.g. ➞The treatment of tuberculosis benefits from drug combinations.

Advantages of combs	Disavantages of combs
Certain combinations of antibiotics show synergism➞the combination is more effective than either of the drugs used separately. E.g.➞**β-lactams and aminoglycosides** Because such synergism among antimicrobial agents is rare, multiple drugs used in combination are only indicated in special situations ➞when an infection is of unknown origin or in the treatment of enterococcal endocarditis .	(1)A number of antibiotics act only when organisms are multiplying. Thus, coadministration of an agent that causes bacteriostasis plus a second agent that is bactericidal may **result in the first drug interfering with the action of the second**. (2)The risk of selection pressure and the development of antibiotic resistance by giving unnecessary combination therapy.

▶ Drug Resistance

Bacteria are considered resistant to an antibiotic **if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth**.

▪ Mechanisms of bacterial resistance :

(1)**Genetic alterations**

Acquired antibiotic resistance requires the temporary or permanent gain or alteration of bacterial genetic information.

Resistance develops due to the ability of DNA to undergo spontaneous mutation or to move from one organism to another

(2)**Modification of target sites**

Alteration of an antibiotic's target site through mutation can confer resistance to one or more related antibiotics.

(3)**Decreased accumulation**

(1)Decreased uptake or increased efflux of an antibiotic can confer resistance because the drug is unable to attain access to the site of its action in sufficient concentrations to injure or kill the organism.

E.g.➞gram-negative organisms can limit the penetration of certain agents, including β-lactam antibiotics, as a result of an alteration in the number and structure of porins (channels) in the outer membrane.

(2)The presence of an efflux pump can limit levels of a drug in an organism, as seen with tetracyclines.

(4)**Enzymatic inactivation**

The ability to destroy or inactivate the antimicrobial agent can also confer resistance on microorganisms.

E.g.➞

A. β-lactamases ("penicillinases") that hydrolytically inactivate the β-lactam ring of penicillins, cephalosporins, and related drugs.

B.Acetyltransferases that transfer an acetyl group to the antibiotic, inactivating chloramphenicol or aminoglycosides.

C.Esterases that hydrolyze the lactone ring of macrolides.

▶Prophylactic use of antibiotics :

Certain clinical situations, such as ***dental procedures and surgeries***, require the use of antibiotics for the prevention rather than for the treatment of infections.

✍ Imp note :

✓ Because the indiscriminate use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks.

✓ The duration of prophylaxis should be closely observed to prevent the unnecessary development of antibiotic resistance.

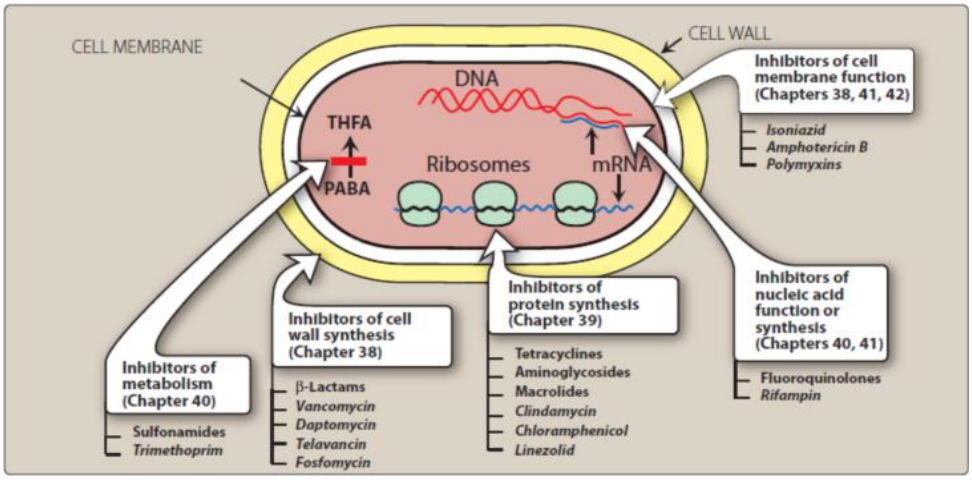
▶Complications of antimicrobial therapy :

Hypersensitivity	Hypersensitivity or immune reactions to antimicrobial drugs or their metabolic products frequently occur. Patients with a documented history of **Stevens-Johnson syndrome** (SJS) or toxic epidermal necrolysis reaction to an antibiotic should never be rechallenged, not even for antibiotic desensitization. E.g.➞ The penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock.
Direct toxicity	High serum levels of certain antibiotics may cause toxicity by directly affecting cellular processes in the host. E.g.➞ Aminoglycosides can cause ototoxicity by interfering with membrane function in the auditory hair cells.
Superinfections	Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, oral, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections usually **require secondary treatments using specific anti-infective agents**

▶Classification of antibiotics :

Antimicrobial drugs can be classified in a number of ways:

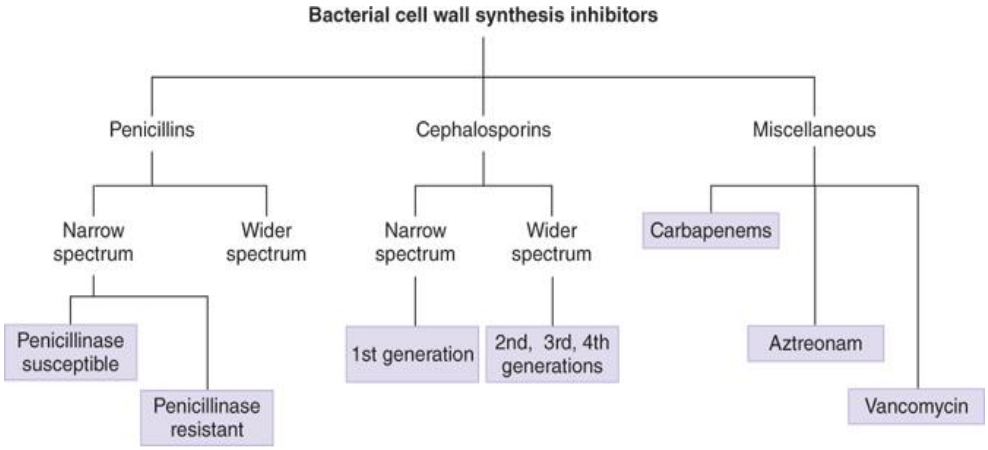
- ✓ By their chemical structure (for example, β-lactams or aminoglycosides) .
- ✓ By their mechanism of action (for example, cell wall synthesis inhibitors).
- ✓ By their activity against particular types of organisms (for example, bacteria, fungi, or viruses).



Cell Wall Inhibitors

✓ The cell wall is composed of a polymer called **peptidoglycan** that consists of glycan units joined to each other by peptide cross-links.
✓ Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall➞Cell Wall Inhibitors .
To be maximally effective, inhibitors of cell wall synthesis **require actively proliferating microorganisms**➞they have little or no effect on bacteria that are not growing and dividing.

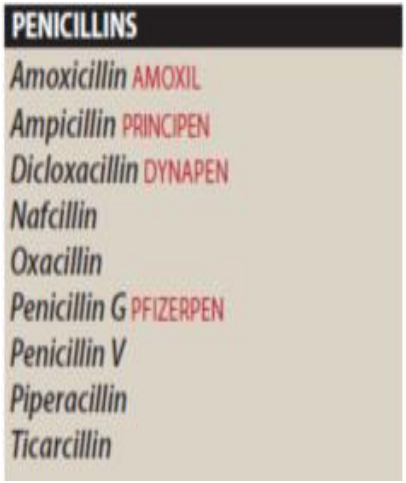
⏬ The diagram below shows major classes of cell wall inhibitors⏬

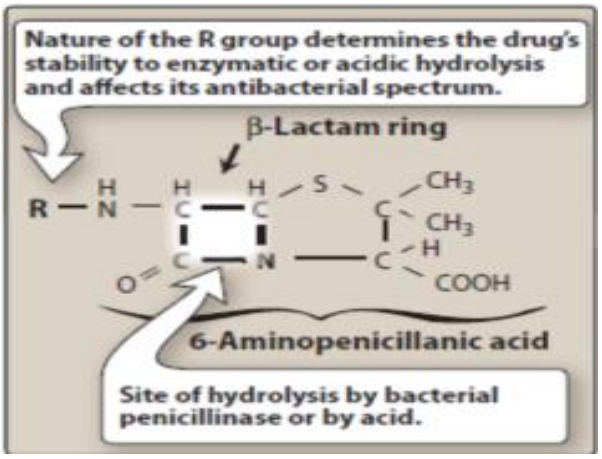


First group to be discussed is ⏩ **Penicillins**

▪ The penicillins are among the most widely effective and the least toxic drugs known, but increased resistance has limited their use.

▪ Structure :
Members of this family differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue .
The nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, crosshypersensitivity, and susceptibility to bacterial degradative enzymes (β-lactamases).





Mechanism of action

▫The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage), resulting in exposure of the osmotically less stable membrane ⏩ Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins.
▫**Bactericidal and work in a time-dependent fashion**
▫only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall ⏩ they are inactive against organisms devoid of this structure, such as mycobacteria, protozoa, fungi, and viruses.

Penicillin-binding proteins	PBPs are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium. Exposure to these antibiotics can therefore not only prevent cell wall synthesis but also lead to morphologic changes or lysis of susceptible bacteria. ✍ Alterations in some of these PBPs provide the organism with resistance to the penicillins.
Inhibition of transpeptidase	Some PBPs catalyze formation of the cross-linkages between peptidoglycan chains⏩ Penicillins inhibit this transpeptidase-catalyzed reaction ⏩ hindering the formation of cross-links essential for cell wall integrity.
Production of autolysins	Many bacteria, particularly the gram-positive cocci, produce degradative enzymes (autolysins) that participate in the normal remodeling of the bacterial cell wall. In the presence of a penicillin, the degradative action of the autolysins proceeds in the absence of cell wall synthesis⏩ the antibacterial effect of a penicillin is the result of both inhibition of cell wall synthesis and destruction of the existing cell wall by autolysins.

▶Antibacterial spectrum

Class	Spectrum
Natural penicillins	Penicillin G ⏩ cornerstone of therapy for infections caused by a number of gram-positive and gram-negative cocci, gram-positive bacilli, and spirochetes Penicillin V ⏩ similar spectrum to that of penicillin G, but it is not used for treatment of bacteremia because of its poor oral absorption. Penicillin V ⏩ more acid stable than penicillin G and is often employed orally in the treatment of infections. ✍ Penicillin remains the drug of choice for the treatment of : ✓ Gas gangrene (Clostridium perfringens) ✓ Syphilis (Treponema pallidum).
Antistaphylococcal penicillins (Methicillin, nafcillin, oxacillin, and dicloxacillin)	β-lactamase (penicillinase)-resistant penicillins. Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci, including methicillin sensitive Staphylococcus aureus (MSSA).

	Minimal to no activity against gram-negative infections. ✍ methicillin is not used clinically in the United States except in laboratory tests to identify resistant strains of S. aureus ⏩ because of its toxicity (interstitial nephritis)
Extended-spectrum penicillins (Ampicillin and amoxicillin)	Antibacterial spectrum similar to that of penicillin G but are more effective against gram-negative bacilli . Widely used in the treatment of respiratory infections . ✍ Ampicillin (with or without the addition of gentamicin) is the drug of choice for the gram-positive bacillus Listeria monocytogenes and susceptible enterococcal species. ✍ Amoxicillin is employed prophylactically by dentists in high-risk patients for the prevention of bacterial endocarditis. ✓ Combs with β-lactamase inhibitor for protection from enzymatic hydrolysis and extends their antimicrobial spectra : **Clavulanic acid + amoxicillin** **Sulbactam +ampicillin**
Antipseudomonal penicillins (Piperacillin and ticarcillin)	Available in parenteral formulations only. Called so because of their activity against Pseudomonas aeruginosa,they are effective against many gram-negative bacilli, but not against Klebsiella because of its constitutive penicillinase. ✍ Combs extends the antimicrobial spectrum of these antibiotics to include penicillinase-producing organisms (i.e.➞most Enterobacteriaceae and Bacteroides species): **Ticarcillin +clavulanic acid** **Piperacillin +tazobactam**

▶Resistance :

Natural resistance	Occurs in : ✓ Organisms that either lack a peptidoglycan cell wall (for example, Mycoplasma pneumoniae). ✓ Organisms having cell walls that are impermeable to the drugs.
Acquired resistance	Occurs by plasmid-mediated β-lactamases has become a significant clinical problem⏩ By obtaining resistance plasmids, bacteria may acquire one or more of the following properties ⏩ thus allowing survival in the presence of β-lactam antibiotics:

β-Lactamase activity	Hydrolyzes the cyclic amide bond of the β-lactam ring⏩ loss of bactericidal activity. Major cause of resistance to the penicillins and are an increasing problem. β-Lactamases can be : ✓ constitutive ➞ produced by the bacterial chromosome ✓ acquired ➞ tansfer of plasmids . Certain organisms may have chromosome-associated β-lactamases that are inducible by β-lactam antibiotics ⏩ 2nd & 3rd generation cephalosporins . ✍ Gram-positive organisms secrete β-lactamases extracellularly, whereas gram-negative bacteria inactivate β-lactam drugs in the periplasmic space.

	Decreased permeability to the drug	(1) ***Decreased penetration*** of the antibiotic through the outer cell membrane of the bacteria ⏩ prevents the drug from reaching the target PBPs. (2) ***The presence of an efflux pump*** can also reduce the amount of intracellular drug ➞Klebsiella pneumoniae
	Altered PBPs	Modified PBPs have a lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth. ⏩ Explains MRSA resistance to most commercially available β-lactams.

▶Pharmacokinetics :

Administration	Route of administration is determined by: ✓ Stability of the drug to gastric acid . ✓ Severity of the infection. ▪ **Procaine penicillin G** and **benzathine penicillin G** are administered IM and serve as **depot forms** ⏩ They are slowly absorbed into the circulation and persist at low levels over a long time period.
Absorption	Most of the penicillins are incompletely absorbed after oral administration ▪ Food decreases the absorption of all the penicillinase-resistant penicillins because as gastric emptying time increases, the drugs are destroyed by stomach acid ⏩ they should be taken on an empty stomach.
Distribution	The β-lactam antibiotics distribute well throughout the body : ✓ All the penicillins cross the placental barrier, but **none have been shown to have teratogenic effects**. ✓ penetration into bone or CSF is insufficient for therapy unless these sites are inflamed ✓ Penicillin levels in the prostate are insufficient to be effective against infections.
Metabolism	Host metabolism of the β-lactam antibiotics is usually insignificant. ▪ Some metabolism of penicillin G may occur in patients with impaired renal function.
Excretion	The primary route of excretion is : ✓ Through the organic acid (tubular) secretory system of the kidney ✓ By glomerular filtration. The penicillins are also excreted in breast milk. **Nafcillin and oxacillin** are exceptions to the rule⏩ they are primarily metabolized in the liver and do not require dose adjustment for renal insufficiency. **Probenecid** inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter⏩ can increase blood levels.

IV or IM	**Combs** : **Ampicillin with sulbactam** **Ticarcillin with clavulanic acid** **Piperacillin with tazobactam** **Nafcillin and oxacillin**
Oral only	**Penicillin V, amoxicillin, and dicloxacillin** **comb of amoxicillin with clavulanic acid**(In US)

▶Adverse reactions :

Penicillins are among the safest drugs, and blood levels are not monitored.However, adverse reactions may occur➞Summarized in the following table :

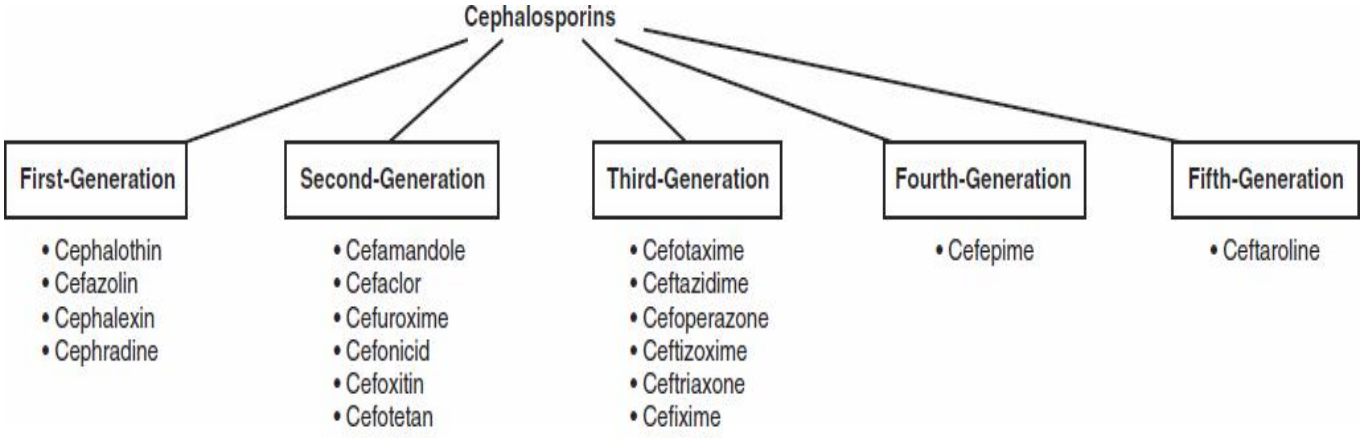
Hypersensitivity	Approximately 5% percent of patients have some kind of reaction, ranging from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis. To determine whether treatment with a β-lactam is safe when an allergy is noted, patient history regarding severity of previous reaction is essential.
Diarrhea	Common problem that is caused by a disruption of the normal balance of intestinal microorganisms. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum.
Nephritis	Penicillins, particularly methicillin, have the potential to cause acute interstitial nephritis. Methicillin is therefore no longer used clinically.
Neurotoxicity	The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk due to the ability of penicillins to cause GABAergic inhibition.
Hematologic toxicities	(1) Cytopenias have been associated with therapy of greater than 2 weeks ⏩ blood counts should be monitored weekly for such patients. (2) Decreased coagulation may be observed with **high doses of piperacillin, ticarcillin, and nafcillin** to some extent, with penicillin G .

The 2nd group to be discussed is : **Cephalosporines**

✓ The cephalosporins are β-lactam antibiotics that are closely related both structurally and functionally to the penicillins, have the same mode of action as penicillins, and they are affected by the same resistance mechanisms. However, they tend to be more resistant than the penicillins to certain β-lactamases.

✓ Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid.

✓ Cephalosporins have been classified as first, second, third, fourth, and advanced generation, based largely on their bacterial susceptibility patterns and resistance to β-lactamases .



▶Antibacterial spectrum

Commercially available cephalosporins are ineffective against MRSA, L. monocytogenes, C. difficile, and the enterococci.

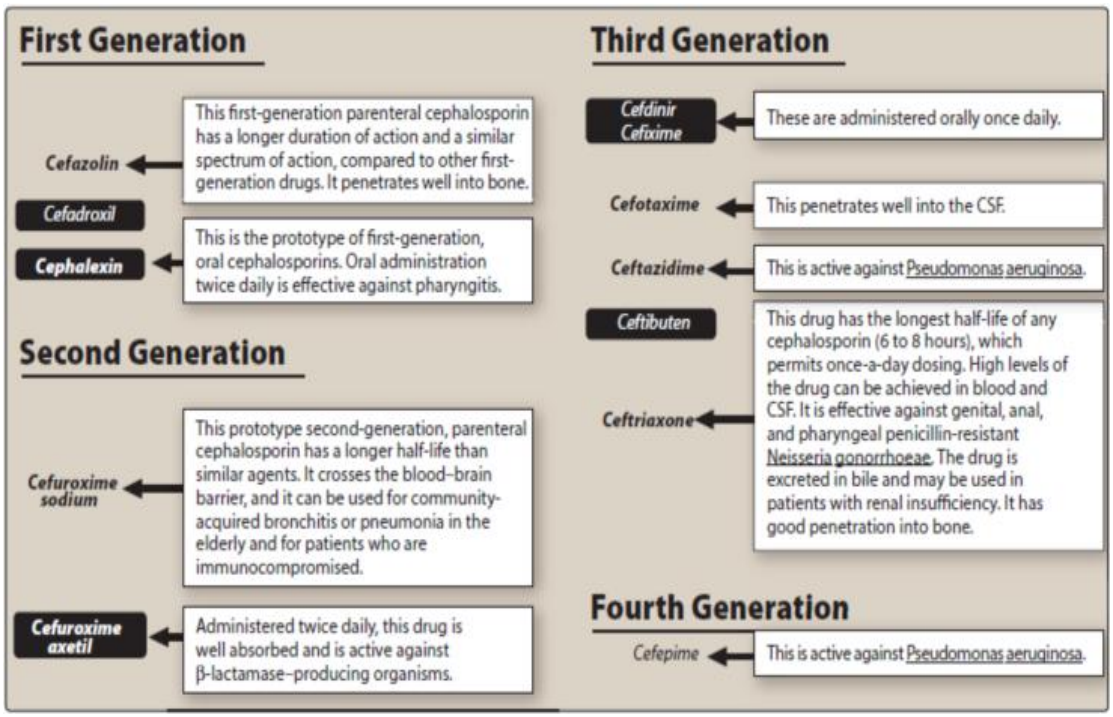
Generation	*Spectrum*
First generation	Act as **penicillin G substitutes**. ▪ They are resistant to the staphylococcal penicillinase ⏩ they **cover MSSA** ▪ Have activity against **Proteus mirabilis, E. coli, and K. pneumoniae**.
Second generation	▪ Display greater activity against three additional gram-negative organisms: H. influenzae, Enterobacter aerogenes, and some Neisseria species ▪ Activity against gram-positive organisms is weaker. ✍ Antimicrobial coverage of the cephamycins (**cefotetan and cefoxitin**) also includes anaerobes . They are the only cephalosporins commercially available with appreciable activity against gram-negative anaerobic bacteria. ➞However, neither drug is first line because of the increasing prevalence of resistance among B. fragilis to both agents.
Third generation	Have assumed an important role in the treatment of infectious diseases. ▪ Less potent than first-generation cephalosporins against MSSA ▪ Have enhanced activity against gram-negative bacilli, including those mentioned above, as well as most other enteric organisms plus Serratia marcescens. ✍ Ceftriaxone and cefotaxime have become agents of choice in the treatment of meningitis. ✍ Third-generation cephalosporins must be used with caution, as they are associated with significant "collateral damage,"& Fluoroquinolone use is also associated with collateral damage.
Fourth generation (**Cefepime**)	▪ Must be administered parenterally. ⏩ Has a wide antibacterial spectrum, with activity against streptococci and staphylococci (but only those that are methicillin susceptible). ⏩ Effective against aerobic gram-negative organisms, such as Enterobacter species, E. coli, K. pneumoniae, P. mirabilis, and P. aeruginosa.
Advanced generation (**Ceftaroline**)	▪ Administered **IV** as a prodrug, **ceftaroline fosamil**. ▪ The only commercially available β-lactam in the United States with activity against MRSA and is indicated for the treatment of complicated skin and skin structure infections and community-acquired pneumonia. ▪ In addition to its broad gram-positive activity, it also has similar gram-negative activity to the third-generation cephalosporin ceftriaxone. ✍ The unique structure allows ceftaroline to bind to PBP2a found with MRSA and PBP2x found with Streptococcus pneumoniae.

▶Resistance:

Mechanisms of bacterial resistance to the cephalosporins are essentially the same as those described for the penicillins.

▪ They are not susceptible to hydrolysis by the staphylococcal penicillinase, cephalosporins may be susceptible to ESBLs ⏩ organisms such as E. coli and K. pneumoniae are particularly associated with ESBLs.

▶Pharmacokinetics & Adverse Effects :

Administration	Many of the cephalosporins must be administered IV or IM because of their poor oral absorption. Exceptions are noted below. 
Distribution	All cephalosporins distribute very well into body fluids. However, adequate therapeutic levels in the CSF, regardless of inflammation, are achieved with only a few cephalosporins. E.g.➞**eftriaxone and cefotaxime** are effective in the treatment of neonatal and childhood meningitis caused by H. influenzae. Cefazolin is effective for most surgical procedures, including orthopedic surgery because of its ability to penetrate bone. ▪ All cephalosporins cross the placenta.
Elimination	Cephalosporins are eliminated through tubular secretion and/or glomerular filtration ⬇ Doses must be adjusted in cases of renal dysfunction to guard against accumulation and toxicity. ✍ One exception is **ceftriaxone**, which is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency.
Adverse effects	✓ Cephalosporins are generally well tolerated. However, allergic reactions are a concern. ✓ Shouldn't recieve cephalosphorines : Patients who have had an anaphylactic response, Stevens-Johnson syndrome, or toxic epidermal necrolysis to penicillins . ✓ Cephalosporins should be avoided or used with caution in individuals with penicillin allergy. ✓ Cross-reactivity between penicillin and cephalosporins is around 3% to 5% and is determined by the similarity in the side chain, not the β-lactam structure ⏭ The highest rate of allergic cross-sensitivity is between penicillin and first-generation cephalosporins.

The 3rd group to be discussed is : **Carbapenems & Monobactams**

✓ Carbapenems *(Imipenem, meropenem, doripenem, and ertapenem)*

Carbapenems are synthetic β-lactam antibiotics that differ in structure from the penicillins in that the sulfur atom of the thiazolidine ring has been externalized and replaced by a carbon atom.

⋆ Note :
Imipenem is compounded with **cilastatin** to protect it from metabolism by renal dehydropeptidase.

Antibacterial spectrum	✓ **Imipenem** resists hydrolysis by most β-lactamases, but not the metallo-β-lactamases. Plays a role in empiric therapy because it is active against β-lactamase–producing gram-positive and gram-negative organisms, anaerobes, and P. aeruginosa . ✓ **Meropenem and doripenem** have antibacterial activity similar to that of imipenem ✓ **Ertapenem** lacks coverage against P. aeruginosa, Enterococcus species, and Acinetobacter species.
Pharmacokinetics	ROA : Imipenem/cilastatin and meropenem ➞ IV Ertapenem ➞ IV or IM injection once daily . ⋆ Excretion : glomerular filtration. ⋆ Distribution : ✓ Imipenem/cilastatin and meropenem penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed. ✓ Meropenem is known to reach therapeutic levels in bacterial meningitis even without inflammation.
Adverse effects	✓ Imipenem/cilastatin can cause **nausea, vomiting, and diarrhea**. ✓ High levels of imipenem may **provoke seizures** (less common w/ other carbapenems) . ✓ **Eosinophilia and neutropenia** .

✓ Monobactams (Aztreonam)

The monobactams, which also disrupt bacterial cell wall synthesis, are unique because the β-lactam ring is not fused to another ring.

✍ The only commercially available monobactam is **Aztreonam :**

- Spectrum :
  ✓ Has antimicrobial activity directed primarily against gram-negative pathogens, including the Enterobacteriaceae and P. aeruginosa.
  ✓ It lacks activity against gram-positive organisms and anaerobes.

- ROA : It is administered either IV or IM and can accumulate in patients with renal failure.
- Adverse effects :

Aztreonam is relatively nontoxic, but it may cause phlebitis, skin rash and, occasionally, abnormal liver function tests.

- Has a low immunogenic potential, and it shows little cross-reactivity with antibodies induced by other β-lactams⏭ this drug may offer a safe alternative for treating patients who are allergic to other penicillins, cephalosporins, or carbapenems.

β-Lactamase inhibitors

✔How do they work ?

β-Lactamase inhibitors, such as **clavulanic acid, sulbactam, and tazobactam**, contain a β-lactam ring but, by themselves, do not have significant antibacterial activity or cause any significant adverse effects⏩ they bind to and inactivate β-lactamases⏩ protecting the antibiotics that are normally substrates for these enzymes⏩ therefore they are formulated in combination with β-lactamase–sensitive antibiotics.

Vancomycin - Daptomycin - Telavancin

	Vancomycin	Daptomycin	Telavancin
MOA	Inhibits : -synthesis of bacterial cell wall phospholipids. -Peptidoglycan polymerization	-Causes rapid depolarization of the cell membrane . -Inhibits intracellular synthesis of DNA , RNA and protein .	-Inhibits bacterial cell wall synthesis -Disrupts cell membrane .
Pharmacodynamics	Time-dependent bactericidal	Concentration-dependent bactericidal	Concentration-dependent bactericidal
ROA	IV ➞ ✓ In individuals with prosthetic heart valves . ✓ In patients undergoing implantation with prosthetic devices, especially in those hospitals where there are high rates of MRSA or MRSE.	IV	IV
Elimination	Renal elimination	Renal elimination	Renal elimination
Unique use	Oral formulation is limited to the treatment of severe antibiotic-associated C. difficile colitis.	treating infections caused by resistant gram-positive organisms, including MRSA and **vancomycin resistant enterococci** (VRE).	_____

✍ Notes :

✓ Daptomycin is inactivated by pulmonary surfactants; thus, it should never be used in the treatment of pneumonia.

✓ Daptomycin is indicated for the treatment of complicated skin and skin structure infections and bacteremia caused by S. aureus, including those with right-sided infective endocarditis.

✓ Telavancin is :

⏩ An alternative to vancomycin, daptomycin, and linezolid, in treating complicated skin and skin structure infections caused by resistant gram-positive organisms (including MRSA).

⏩ An agent of last choice for hospital-acquired and ventilator-associated bacterial pneumonia when alternative treatments are not suitable.

Fosfomycin - Polymyxins

Fosfomycin	✓ **Nature** ➞bactericidal synthetic derivative of phosphonic acid. ✓ **MOA**➞Blocks cell wall synthesis by inhibiting the enzyme UDP-N-acetylglucosamine enolpyruvyl transferase,which catalyzes the first step in peptidoglycan synthesis. ✓ **Use**➞indicated for urinary tract infections caused by E. coli or E. faecalis. ✍ cross resistance with other antimicrobial agents is unlikely. ✓ **PKs**➞ **ROA** : -Rapidly absorbed after **oral** administration -**Parenteral formulation** is available in select countries ⏩ used for the treatment of systemic infections **Distribution** : Distributes well to the kidneys, bladder, and prostate. **Excretion** : Excreted in its active form in the urine and feces. ✓ **Adverse effects** ➞ Diarrhea, vaginitis, nausea, and headache.
Polymyxins	✓ **Nature** ➞Cation polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria. ✓ **Pharmacodynamics** ➞Concentration-dependent bactericidal agents . ✓ **Spectrum** ➞Have activity against most clinically important gram-negative bacteria, including P. aeruginosa, E. coli, K. pneumoniae, Acinetobacter species, and Enterobacter species. ✓ **Resistance** ➞Alterations in the cell membrane lipid polysaccharides allow many species of Proteus and Serratia to be intrinsically resistant. ✍ Only two forms of polymyxin are in clinical use today, **polymyxin B** and colistin (**polymyxin E**). ✓ **PKs**➞ **ROA** : **polymyxin B** ⏩ parenteral, ophthalmic, otic, and topical **Colistin** ⏩ only available as a prodrug, colistimethate sodium, which is administered IV or inhaled via a nebulizer. ✓ **Adverse effects** ➞ The use of these drugs has been limited for a long time, due to the **increased risk of nephrotoxicity and neurotoxicity** (for example, slurred speech, muscle weakness) when used systemically. However, with the increase in gram-negative resistance, they have seen a resurgence in use and are now commonly used as salvage therapy for patients with multidrug-resistant infections.

Protein Synthesis Inhibitors

✓ Target ⏩ bacterial ribosomes and inhibit bacterial protein synthesis.
✓ Recall :
Bacterial ribosomes: 30S and 50S subunits
Mammalian cytoplasmic ribosomes: 40S and 60S subunits.
✓ Selectivity for bacterial ribosomes minimizes potential adverse consequences encountered with the disruption of protein synthesis in mammalian host cells.

✍ Note :
High concentrations of drugs (**chloramphenicol or the tetracyclines**) ➞toxic effects (interaction with mitochondrial mammalian ribosomes)

✔The following table summarizes the major groups of this class of antimicrobials:

Group	MOA	Antibacterial Spectrum	PKs	Adverse effects	Resistance
Tetracyclines	Bind reversibly to the 30s subunit of the bacterial ribosome⏩ prevent binding of tRNA to mRNA-ribosome complex ⏩ inhibit bacterial protein synthesis Bacteriostatic	G+ve, G-ve, Protozoa, Mycobacteria, Spirochetes, atypical species. ▪ Treatment of : 1) Acne 2)chlamydia infections 3)Lyme disease, Cholera (doxycycline) 4)rocky mountain spotted fever 5) Mycoplasma pneumonia (doxycycline or macrolide)	✓ Absorption ROA⏩ Orally Doxycycline and minocycline ⏩ orally and IV ✍ Divalent and trivalent ions⏩ decreases absorption (esp : tetracycline). ✓ Distribution: ▫Only minocycline, doxycycline ⏩ CSF ▫Minocycline⏩ saliva, tears ▫All of them cross the placental barrier ✓ Elimination ▫Tetracycline⏩ urine (unchanged) ▫Minocycline⏩ hepatic metabolism and is eliminated to a lesser extent via the kidney ▫Doxycycline⏩ bile into feces	▪ Gastric discomfort ▪ Effects of calcified tissues ▪ Hepatotoxicity ▪ Photo-toxicity ▪ Vestibular dysfunction ▪ Pseudotumor cerebri ✓ Contraindicated in: pregnant women breast feeding women Children under 8	1)efflux pumps 2) enzymatic inactivation of the drug 3) Reduction of bacterial proteins. No cross resistance

Glycylcyclines (**Tigecycline**)	Bind reversibly to the 30S ribosomal subunit⏩ inhibit protein synthesis	✓ MRSA , VRE ✓ Multidrug resistant streptococci ✓ ESBL producing G-ve bacteria ✓ A. baumanii ✓ Anaerobic organisms ▪ Isn't active against: 1)Morganella 2) proteus 3) Providencia 4) Pseudomonas spp. ✍ Used for treatment of : ▪ complicated skin and soft tissue infections. ▪ intraabdominal infections	✓ ROA : IV infusion ✓ Elimination : Biliary/fecal elimination (not renal) ✍ Poor option for BS infections (Large volume of distribution)	▪ Acute pancreatitis. ▪ Increases liver enzymes and serum creatinine ▪ Photosensitivity ▪ pseudotumor cerebri ▪ fetal harm during pregnancy ▪ Decreases the clearance of warfarin	Overexpression of efflux pumps
Aminoglycosides	-Diffuse through porin channels -Transported by an O2 dependent system 1) interferes with assembly of the functional ribosomal apparatus 2) causes the 30S of the completed ribosome to misread the genetic code ✍ bactericidal and PAE ✍ Concentration dependent	✓ Aerobic G- bacilli ⏩ P. aeruginosa, K. pneumonia, Enterobacter spp. ✓ synergistic effects with B-lactam ⏩ tx of E.faecalis and E.farcium infective endocarditis	✓ Absorption : Highly polar ⏩ not orally All parenterally except neomycin ✓ Distribution : -In fatty tissues ⏩ lean body mass For CNS infections ⏩ Intrathecal route -Crosses the placental barrier ✓ Elimination : More than 90% unchanged in urine	Nephrotoxicity Ototoxicity Neuromuscular paralysis Allergic reactions	1.efflux pumps. 2.decreased uptake 3.modification and inactivation by plasmid-associated synthesis of enzymes. ✍ No cross resistance ✍ Amikacin is the least vulnerable

Macrolides and ketolides	Bind irreversibly to 50s subunit of the bacterial ribosome ⏩ inhibits translocation steps of protein synthesis ✍ Bacteriostatic	✓ Erythromycin: like penicillin G ✓ Clarithromycin : Like erythromycin but also H. influenzae and intracellular pathogens ✓ Azithromycin: against respiratory infections due to H.influenzae and Moraxella catarrhalis & urethritis caused by C.trachomatis & Also for mycobacterium avium ✓ Telithromycin: similar to azithro. But modifications neutralize the most common resistance mechanisms (methylase and efflux mediated) that make macrolides ineffective	✓ ROA : All⏩ orally Erythro&Azithro ⏩ Oral / IV ✍ Food increases the absorption of clarithromycin ✍ Erythro.⏩ dest royed by gastric acid ✓ Distribution : ▪ Erythromycin ⏩ all except CSF(also cross the prostatic fluid) ▪ All of them accumulates in the liver ✓ Excretion : •Erythromycin and azithromycin ⏩ bile as active drugs. <Partial reabsorption occurs through the enterohepatic circulation> •clarithromycin and its metabolites⏩ eliminated by the kidney as well as the liver⏩ should be adjusted in patients with renal impairment.	▫Gastric distress and motility . ▫Cholestatic jaundice ▫Ototoxicity ✍ Cont.Ind : ✓ Patients with hepatic dysfunction ✓ Should be used with caution in those patients with proarrhythmic conditions or concomitant use of proarrhythmic agents.	1)Inability of the organism to take up the antibiotic 2) Efflux pumps 3) Decreased affinity of the 50s 4) The presence of plasmid mediated erythromycin estrases in G-ve ✍ Note : clarithromycin and azithromycin share some cross-resistance with erythromycin, but telithromycin may be effective against macrolide resistant organisms.
Chloramphenicol	Binds reversibly to 50s ⏩ inhibits protein synthesis at peptidyl transferase rxn	chlamydiae, rickettsiae, spirochetes, and anaerobes. ✍ Bacteriostatic ⏩ may be bactericidal depends on the dose and organism.	✓ ROA : IV and reaches CSF ✓ Metabolism : Hepatic metabolism to inactive glucuronide which is ✓ Elimination: eliminated in urine	✓ Anemias : •Dose-related anemia. •Hemolytic anemia •Aplastic anemia. ✓ Gray baby syndrome	1)presence of enzymes that inactivate chloramphenicol 2)decreased ability to penetrate the organism 3)ribosomal binding site alterations.

			✓ Secretion : Secreted in breast milk		

✍MISC. Notes :

✓ Tetracycline should be taken on an empty stomach.

✓ The use of tetracyclines is limited in pediatrics :

Deposition in the bone and primary dentition occurs during the calcification process in growing children ⏩ discoloration and hypoplasia of teeth and a temporary stunting of growth.

✓ Tetracylcines **hepatotoxicity** may occur with high doses in :

- Pregnant women
- Preexisting hepatic dysfunction or renal impairment.

✓ Severe sunburn may occur in patients receiving a tetracycline who are exposed to sun or ultraviolet rays ⏩ Patients should be advised to wear adequate sun protection.

✓ Tigecycline may decrease the clearance of warfarin and increase prothrombin time. Therefore, the international normalized ratio should be monitored closely when tigecycline is coadministered with warfarin.

✓ Prompt administration of **calcium gluconate or neostigmine** can reverse the block that causes neuromuscular paralysis which can occur with use of aminoglycosides .

✓ Higher doses of erythromycin lead to smooth muscle contractions that result in the movement of gastric contents to the duodenum, an adverse effect sometimes used therapeutically for the treatment of gastroparesis or postoperative ileus.

✓ Drug-Drug interactions associated with Macrolides and ketolides :

(1)Erythromycin, telithromycin, and clarithromycin inhibit the hepatic metabolism of a number of drugs⏩ accumulation of these compounds.

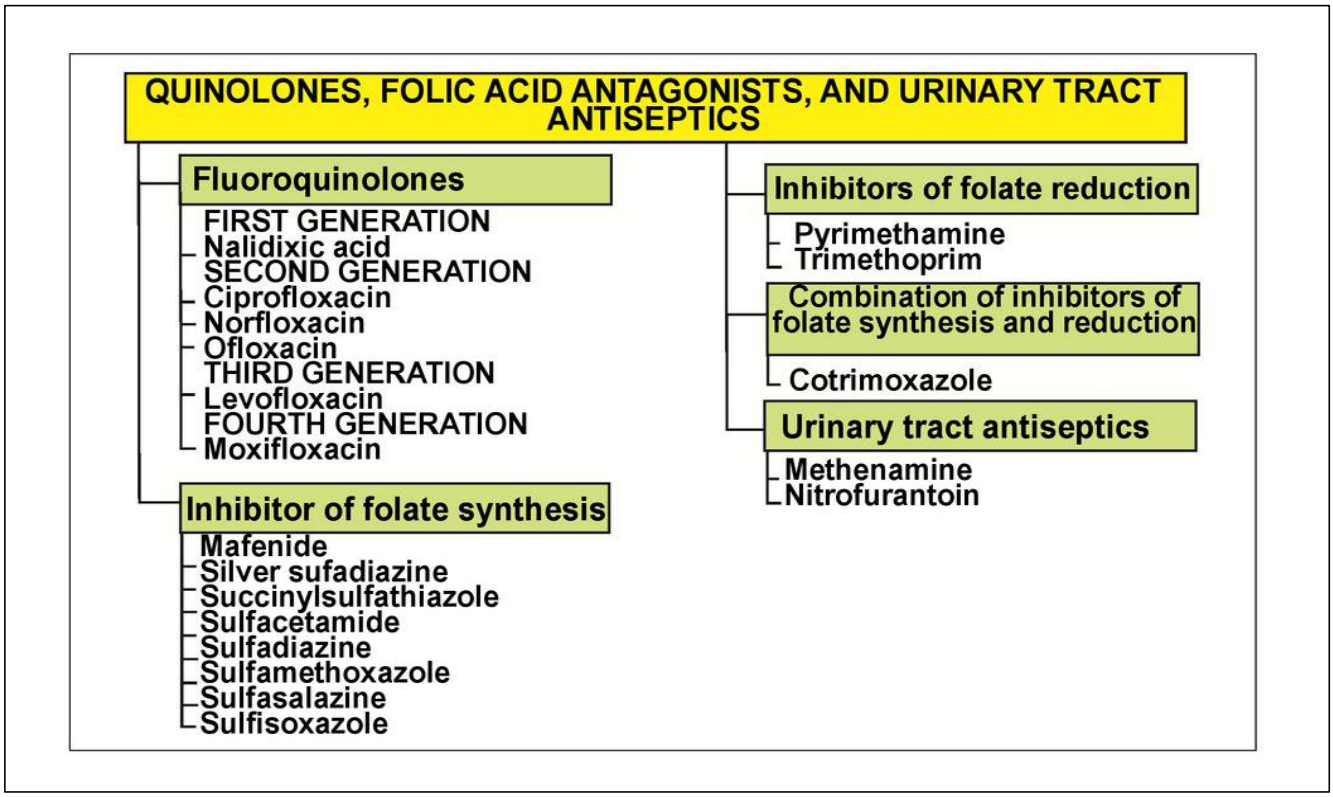
(2)An interaction with digoxin may occur. In this case, the antibiotic eliminates a species of intestinal flora that ordinarily inactivates digoxin, thus leading to greater reabsorption of the drug from the enterohepatic circulation.

(3)Interference with the metabolism of theophylline, statins, and numerous antiepileptics, has been reported for clarithromycin.

✓ Drug-Drug interactions associated with chloramphenicol use :

Inhibits some of the hepatic mixed-function oxidases and, thus, blocks the metabolism of drugs such as warfarin and phenytoin, thereby elevating their concentrations and potentiating their effects.

Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics



▶Fluoroquinolones

The predecessor to all fluoroquinolones ⏩ **Nalidixic acid**

- Fluoroquinolones in use today typically offer greater efficacy, a broader spectrum of antimicrobial activity, and a better safety profile than their predecessors.
- **Unfortunately, fluoroquinolone use has been closely tied to Clostridium difficile infection and the spread of antimicrobial resistance in many organisms** (for example, methicillin resistance in staphylococci).

✍ Recall :
The unfavorable effects of fluoroquinolones on the induction and spread of antimicrobial resistance are sometimes referred to as "collateral damage," which is also associated with third-generation cephalosporins .

MOA	Fluoroquinolones enter bacteria through porin channels and exhibit antimicrobial effects on: ✓ **DNA gyrase (bacterial topoisomerase II) .** ✓ **bacterial topoisomerase IV .** ✍ Note : In g-ve organisms (e.g.> Pseudomonas aeruginosa), the inhibition of DNA gyrase is more significant than that of topoisomerase IV In g+ve organisms (e.g.>Streptococcus pneumoniae), the opposite is true.

Antibacterial Spectrum

Effective against:
✓ G-ve organisms (Escherichia coli, P. aeruginosa, Haemophilus influenzae).
✓ Atypical organisms (Legionellaceae, Chlamydiaceae).
✓ G+ve organisms (streptococci), and some mycobacteria (Mycobacterium tuberculosis).
✍ Notes :
⋆ Levofloxacin and moxifloxacin are sometimes referred to as "respiratory fluoroquinolones," ➞ they have excellent activity against S. pneumoniae, which is a common cause of community-acquired pneumonia .
⋆ Fluoroquinolones are typically not used for the treatment of Staphylococcus aureus or enterococcal infections.
⋆ Fluoroquinolones are not effective against syphilis and have limited utility against Neisseria gonorrhoeae due to disseminated resistance worldwide.

Classified into "generations" based on their antimicrobial targets:

First generation	**Nonfluorinated quinolone >nalidixic acid ➞narrow spectrum of susceptible organisms**
Second generation	**Ciprofloxacin and norfloxacin ➞Effective against aerobic gram-negative and atypical bacteria**
Third generation	**Levofloxacin ➞increased activity against gram-positive bacteriax**
Fourth generation	**Moxifloxacin ➞Effective against anaerobic and gram-positive organisms Has excellent activity against many anaerobes**

Clincal uses

Norfloxacin	**Infrequently prescribed due to poor oral bioavailability and a short half-life . Effective in treating nonsystemic infections, such as UTIs, prostatitis, and infectious diarrhea (unlabeled use).**
Ciprofloxacin	**▪ Effective in the treatment of many systemic infections caused by gram-negative bacilli. ▪ Has the best activity against P. aeruginosa and is commonly used in cystic fibrosis patients for this indication. ▪ Traveler's diarrhea caused by E. coli as well as typhoid fever caused by Salmonella typhi can be effectively treated with ciprofloxacin. ▪ Used as a second-line agent in the treatment of tuberculosis.**
Levofloxacin	**Utilized in a wide range of infections, including prostatitis, skin infections, CAP, and nosocomial pneumonia. ▪ Has excellent activity against S. pneumoniae respiratory infections. ▪ Has 100% bioavailability and is dosed once daily.**

	Moxifloxacin — **It has poor activity against P. aeruginosa.** **Moxifloxacin does not concentrate in urine and is not indicated for the treatment of UTIs.**
PKs	✓ Absorption : Only 35% to 70% of orally administered norfloxacin is absorbed, compared with 80% to 99% of the other fluoroquinolones. ▪ Ingestion of fluoroquinolones with sucralfate, aluminum- or magnesium containing antacids, or dietary supplements containing iron or zinc can reduce the absorption. ▪ Calcium and other divalent cations also interfere with the absorption of these agents. ✓ ROA : Intravenous and ophthalmic preparations of ciprofloxacin, levofloxacin, and moxifloxacin are available. ✓ Distribution : Distribute well into all tissues and body fluids, which is one of their major clinical advantages. ✓ Elimination : Most fluoroquinolones are excreted renally⏩ dosage adjustments are needed in renal dysfunction. ▪ Moxifloxacin is excreted primarily by the liver, and no dose adjustment is required for renal impairment.
Resistance	1. Altered target: Chromosomal mutations in bacterial genes have been associated with a decreased affinity for fluoroquinolones at their site of action. Both topoisomerase IV and DNA gyrase may undergo mutations. 2.Decreased accumulation: Reduced intracellular concentration is linked to : 1) porin channels >involves decreased number of porin proteins in the outer membrane of the resistant cell, thereby impairing access of the drugs to the intracellular topoisomerases. 2)efflux pumps > pumps drug out of the cell.
Adverse rxns	1)nausea, vomiting, and diarrhea &Headache and dizziness or lightheadedness may occur⏩ patients with CNS disorders, such as epilepsy, should be treated cautiously with these drugs. 2)Peripheral neuropathy and glucose dysregulation (hypoglycemia) 3)phototoxicity⏩ patients taking these agents should be advised to use sunscreen and avoid excess exposure to sunlight. ▪ If phototoxicity occurs, discontinuation of the drug is advisable. 4)Articular cartilage erosion (arthropathy)⏩ these agents should be avoided in pregnancy and lactation and in children under 18 years of age. 5)Careful monitoring is indicated in children with cystic fibrosis who receive fluoroquinolones for acute pulmonary exacerbations. 6)An increased risk of tendinitis or tendon rupture may also occur with systemic fluoroquinolone use. 7)fluoroquinolones should not be used in patients who are predisposed to arrhythmias or those who are taking other medications that cause QT prolongation. ▪ **Drug-Drug interactions** : ✓ Ciprofloxacin can increase serum levels of theophylline by inhibiting its metabolism. ✓ Quinolones may also raise the serum levels of warfarin, caffeine, and cyclosporine.

▶Folate Antagonists

Enzymes requiring folate-derived cofactors are essential for the synthesis of purines and pyrimidines (precursors of RNA and DNA) and other compounds necessary for cellular growth and replication. Therefore, in the absence of folate, cells cannot grow or divide.

✓ To synthesize the critical folate derivative, tetrahydrofolic acid, humans must first obtain preformed folate in the form of folic acid from the diet. In contrast, many bacteria are impermeable to folic acid and other folates and, therefore, must rely on their ability to synthesize folate de novo.

The two types to be discussed are :
⏩ **The sulfonamides (sulfa drugs)** ➞inhibit de novo synthesis of folate.
⏩ **Trimethoprim** ➞ prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid, with minimal effect on the ability of human cells to make this conversion.

Sulfonamides

MOA	✓ In many microorganisms, dihydrofolic acid is synthesized from p-aminobenzoic acid (PABA), pteridine, and glutamate⏩ All the sulfonamides currently in clinical use are synthetic analogs of PABA. ✓ Because of their structural similarity to PABA, the sulfonamides compete with this substrate for the bacterial enzyme, dihydropteroate synthetase⏩ inhibit the synthesis of bacterial dihydrofolic acid ⏩ the formation of its essential cofactor forms. ▪ The sulfa drugs, including cotrimoxazole, are bacteriostatic.
Spectrum	Sulfa drugs are active against : ✓ select Enterobacteriaceae in the urinary tract and Nocardia infections. ✓ **Sulfadiazine in combination pyrimethamine** is the preferred treatment for toxoplasmosis. ✓ **Sulfadoxine in combination with pyrimethamine** is used as an antimalarial drug .
PKs	✓ Absorption & ROA : ▪ After oral administration, most sulfa drugs are well absorbed. An exception is sulfasalazine .It is not absorbed when administered orally or as a suppository⏩ is reserved for treatment of chronic inflammatory bowel disease . ▪ Intravenous sulfonamides are generally reserved for patients who are unable to take oral preparations. ✓ Local intestinal flora split sulfasalazine into sulfapyridine and 5-aminosalicylate, with the latter exerting the anti-inflammatory effect⏩ Absorption of sulfapyridine can lead to toxicity in patients who are slow acetylators. ✓ Applied topically (Only in cases of burns): In burn units, creams of silver sulfadiazine or mafenide acetate have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria. Silver sulfadiazine is preferred because mafenide produces pain on application and its absorption may contribute to acid–base disturbances. ✓ Distribution : ▫Sulfa drugs distribute throughout the bodily fluids and penetrate well into cerebrospinal fluid even in the absence of inflammation. ▫They can also pass the placental barrier and enter fetal tissues. ✓ Metabolism : Acetylated and conjugated primarily in the liver.

	✍ Note : The acetylated product is devoid of antimicrobial activity but retains the toxic potential to precipitate at neutral or acidic pH⏩ causes crystalluria "stone formation" ⏩ potential damage to the kidney. ✓ Excretion : ▫By glomerular filtration and secretion⏩ require dose adjustments for renal dysfunction. ▫In breast milk.
Resistance	Resistance is generally irreversible and may be due to: 1) An altered dihydropteroate synthetase. 2) Decreased cellular permeability to sulfa drugs . 3) Enhanced production of the natural substrate, PABA.
Adverse Effects	1)Crystalluria 2)Hypersensitivity reactions, such as rashes, angioedema or Stevens-Johnson syndrome 3)Hematopoietic disturbances: ▪ Hemolytic anemia is encountered in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. ▪ Granulocytopenia and thrombocytopenia 4) Kernicterus ✍ Drug-Drug interactions : 1) Transient potentiation of the anticoagulant effect of warfarin results from the displacement from bind in sites on serum albumin. 2) Serum methotrexate levels may also rise through its displacement. ✍ Cont.Ind : ✓ Avoided in newborns and infants less than 2 months of age ✓ Avoided in pregnant women at term. ✓ Should not be given to patients receiving methenamine, since they can crystallize in the presence of formaldehyde produced by this agent .

Trimethoprim -Cotrimoxazole

✍**Note: The combination of trimethoprim with sulfamethoxazole is called Cotrimoxazole**

	Trimethoprim	Cotrimoxazole
MOA	The active form of folate is the tetrahydro derivative that is formed through reduction of dihydrofolic acid by dihydrofolate reductase⏩ This enzymatic reaction is inhibited by trimethoprim⏩ decreased availability of the tetrahydrofolate cofactors required for purine, pyrimidine, and amino acid synthesis.	Inhibition of two sequential steps in the synthesis of tetrahydrofolic acid : ⋆ Sulfamethoxazole inhibits the incorporation of PABA into dihydrofolic acid precursors. ⋆ Trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate.
Spectrum	Similar to that of sulfamethoxazole. However, trimethoprim is 20- to 50-fold more potent than the sulfonamides. ⋆ May be used alone in the treatment of UTIs and in the treatment of bacterial prostatitis(fluoroquinolones are preferred).	It is effective in treating: ⋆ UTIs and respiratory tract infections. ⋆ Pneumocystis jirovecii pneumonia (PCP). ⋆ Toxoplasmosis. ⋆ ampicillin- or chloramphenicol-resistant salmonella infections.

		It has activity against MRSA and can be particularly useful for community-acquired skin and soft tissue infections caused by this organism. The drug of choice for infections caused by susceptible Nocardia species and Stenotrophomonas maltophilia.
Resistance	⋆ Resistance in gram-negative bacteria is due to the presence of an altered dihydrofolate reductase that has a lower affinity for trimethoprim. ⋆ Efflux pumps and decreased permeability to the drug may play a role.	Less frequently encountered than resistance to either of the drugs alone, because it requires that the bacterium have simultaneous resistance to both drugs. ✓ Significant resistance has been documented in a number of clinically relevant organisms, including E. coli and MRSA.
PKs	✓ ROA : Orally ✓ Distribution : ▪ Higher concentrations of trimethoprim are achieved in the relatively acidic prostatic and vaginal fluids. ▪ Widely distributed into body tissues and fluids, including penetration into the cerebrospinal fluid. ✓ Excretion : Undergoes some O-demethylation, but 60% to 80% is renally excreted unchanged.	✓ ROA : Generally ⏩ Orally In pts w/ severe pneumonia caused by PCP ⏩ IV ✓ Distribution : ▪ Both agents distribute throughout the body. ➞Trimethoprim concentrates in the relatively acidic milieu of prostatic fluids, and this accounts for the use of trimethoprim–sulfamethoxazole in the treatment of prostatitis. ▪ Cotrimoxazole readily crosses the blood–brain barrier. ✓ Excretion : Both parent drugs and their metabolites are excreted in the **urine**.
Adverse effects	Produce the effects of folic acid deficiency ,include : megaloblastic anemia, leukopenia, and granulocytopenia, especially in pregnant patients and those having very poor diets. These blood disorders may be reversed by the simultaneous administration of folinic acid, which does not enter bacteria.	✓ Reactions involving the skin are very common and may be severe in the elderly. ✓ Nausea and vomiting are the most common gastrointestinal adverse effects. ✓ Glossitis and stomatitis . ✓ Hyperkalemia, especially with higher doses. ✓ Megaloblastic anemia, leukopenia, and thrombocytopenia ⏩ The hematologic effects may be reversed by the concurrent administration of folinic acid, which protects the patient and does not enter the microorganism. ✓ Hemolytic anemia may occur in patients with G6PD deficiency due to the sulfamethoxazole component. ✓ Immunocompromised patients with PCP frequently show drug-induced fever, rashes, diarrhea, and/or pancytopenia. ✍ Drug-Drug interactions : 1)Prolonged prothrombin times (increased INR) in patients receiving both sulfamethoxazole and warfarin have been reported, and increased monitoring is recommended when the drugs are used concurrently.

		2)The plasma half-life of phenytoin may be increased due to inhibition of its metabolism. 3)Methotrexate levels may rise due to displacement from albumin-binding sites by sulfamethoxazole.

Urinary Tract Antiseptics:

- UTIs are prevalent in women of child-bearing age and in the elderly population.
- E. coli is the most common pathogen, causing about 80% of uncomplicated upper and lower UTIs.
- Staphylococcus saprophyticus is the second most common bacterial pathogen causing UTIs.

✓ In addition to cotrimoxazole and the quinolones previously mentioned, UTIs may be treated with any one of a group of agents called urinary tract antiseptics, including **methenamine, nitrofurantoin**, and the quinolone nalidixic acid (not available in the United States). These drugs do not achieve antibacterial levels in the circulation, but because they are concentrated in the urine, microorganisms at that site can be effectively eradicated.

Methenamine

- **MOA** :

⋆ Methenamine decomposes at an acidic pH of 5.5 or less in the urine⏩ producing formaldehyde, which acts locally and is toxic to most bacteria⏩ Bacteria do not develop resistance to formaldehyde, which is an advantage of this drug.
⋆ Methenamine is frequently formulated with a weak acid (for example, mandelic acid or hippuric acid) to keep the urine acidic⏩ The urinary pH should be maintained below 6.
✍ Antacids, such as sodium bicarbonate, should be avoided.

- **Antibacterial spectrum**:

⋆ Primarily used for chronic suppressive therapy to reduce the frequency of UTIs.
⏩ Routine use in patients with chronic urinary catheterization to reduce catheterassociated bacteriuria or catheter-associated UTI is not generally recommended.
⋆ Methenamine should not be used to treat upper UTIs (for example, pyelonephritis).
⋆ Resistant to the action of methenamine⏩ Urea-splitting bacteria that alkalinize the urine, such as Proteus species .

- **PKs** :

ROA	Oral
Cont.Ind	▫In patients with hepatic insufficiency, as ammonia can accumulate⏩ because the liver rapidly metabolizes ammonia to form urea ▫ In patients with renal insufficiency, because mandelic acid may precipitate.
Distribution	Distributed throughout the body fluids, but no decomposition of the drug occurs at pH 7.4⏩ systemic toxicity does not occur
Elimination	In urine

- **Adverse effects** :

✓ Major side effect ⏩ gastrointestinal distress, although at higher doses, albuminuria, hematuria, and rashes may develop.

Nitrofurantoin

- **MOA**:

Nitrofurantoin sensitive bacteria reduce the drug to a highly active intermediate that inhibits various enzymes and damages bacterial DNA

- **Antibacterial Spectrum** :

✓ Useful against E. coli, but other common urinary tract gram-negative bacteria may be resistant.
✓ Gram-positive cocci (e.g.⏩ S. saprophyticus) .

▪ **Adverse effects**:

✓ Hemolytic anemia may occur with nitrofurantoin use in patients with G6PD deficiency.
✓ Gastrointestinal disturbances, acute pneumonitis, and neurologic problems.
✓ Interstitial pulmonary fibrosis has occurred in patients who take nitrofurantoin chronically.

✍ **Cont.Ind :**
The drug should not be used in patients with significant renal impairment or women who are 38 weeks or more pregnant.

Anthelmintic and Antiprotozoal drugs

1st ⏩ Anthelmintic drugs

Worms that infect humans :
✓ Nematodes (roundworms)
✓ Trematodes (flukes)
✓ Cestodes (tapeworms)

Most anthelmintics target:
✓ Eliminating the organisms from the host.
✓ Controlling spread of infections.

CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR NEMATODES
Diethylcarbamazine BANOCIDE
Ivermectin STROMECTOL
Mebendazole VERMOX
Pyrantel pamoate PIN-X
Thiabendazole MINTEZOL

CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR TREMATODES
Praziquantel BILTRICIDE

CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR CESTODES
Albendazole ALBENZA
Niclosamide

Drugs for the treatment of nematodes

▪ Nematodes cause infections of the:
✓ Intestine
✓ Blood
✓ Tissues

The next table summarizes basic concepts of drugs used for tx of nematodes :

	MOA/Use	Adverse effects
Mebendazole	Acts by: ✓ Inhibiting the assembly of the microtubules in the parasite. ✓ Irreversibly blocking glucose uptake. ⏩ Affected parasites are expelled in the feces.	Abdominal pain and diarrhea. ✍ Cont.Ind: Should not be used in pregnant women.
Pyrantel pamoate	Depolarizing, neuromuscular-blocking agent⏩ release of acetylcholine and inhibition of cholinesterase leading to paralysis of the worm⏩ paralyzed worm releases its hold on the intestinal tract and is expelled.	Mild and include nausea, vomiting, and diarrhea.

Ivermectin	Targets the glutamate-gated chloride channel receptors⏩ Chloride influx is enhanced, and hyperpolarization occurs⏩ paralysis and death of the worm. ✍ Given orally and does not readily cross the blood–brain barrier.	The killing of the microfilaria in onchocerciasis can result in a dangerous Mazzotti reaction (fever, headache, dizziness, hypotension). The severity of this reaction is related to parasite load Antihistamines or steroids may be given to ameliorate the symptoms. ✍ Cont.Ind: Should not be used in pregnancy
Diethylcarbamazine	It kills the microfilariae and has activity against adult worms. ✓ The drug of choice for filariasis. ✍ Rapidly absorbed following oral administration with meals . ✍ Excreted mainly in the urine.	Fever, nausea, vomiting, arthralgia, and headache, can accelerate blindness and ✍ Cont.Ind: Causes severe Mazzotti reactions in patients with onchocerciasis. ⏩ It should be avoided in patients with this disorder.

Drugs to treat trematodes

- Trematodes are characterized by the tissues they infect:

✓ liver.
✓ lung.
✓ Intestine.
✓ Blood.

Praziquantel

✓ **Use** :
Agent of choice for the treatment of :
⭑ All forms of schistosomiasis, other trematode infections.
⭑ Cestode infections such as taeniasis.

✓ **MOA** :
Permeability of the cell membrane to calcium is increased, causing contracture and paralysis of the parasite.

✓ **PKs** :

ROA&Absorption	-Oral administration -Should be taken with food and not chewed due to a bitter taste.
Metabolism	Extensively metabolized, and the inactive metabolites
Excretion	Excreted primarily in the urine
Cont.Ind	Contraindicated for the treatment of ocular cysticercosis, because destruction of the organism in the eye may cause irreversible damage.
Distribution	Distributes into the CSF

✓ **Adverse Effects** :
Dizziness, malaise, and headache as well as gastrointestinal upset.

Drugs to treat cestodes

Niclosamide	✓ **MOA**: ⋆ It inhibits the mitochondrial phosphorylation of adenosine diphosphate (ADP) in the parasite, making it lethal. ⋆ Anaerobic metabolism may also be inhibited. ✍ Note : A laxative is administered prior to oral administration ⏩ purge the bowel of all dead segments ⏩ enhance digestion and liberation of the ova.
Albendazole	✓ **MOA** : Inhibits microtubule synthesis and glucose uptake in nematodes and is effective against most nematodes known. ✓ **Use**: Its primary therapeutic application ⏩ treatment of cestodal infestations, such as cysticercosis and hydatid disease ✓ **PKs**: ▪ **ROA** ⏩ Oral ▪ **Absorption** ⏩ Enhanced by a high-fat meal. ▪ **Distribution** ⏩ Distributes widely, including the CSF. ▪ **Metabolism**⏩ Extensive first-pass metabolism, including formation of an active sulfoxide.

2nd ⏩ Antiprotozoal Drugs

✍ Keep in mind :
Because they are unicellular eukaryotes, the protozoal cells have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens⏩ protozoal diseases are less easily treated than bacterial infections, and many of the antiprotozoal drugs cause serious toxic effects in the host, particularly on cells showing high metabolic activity.

✍ IMP :
Most antiprotozoal agents have not proven to be safe for pregnant patients.

The group to be discussed ⏩ Antiprotozoal drugs used for tx of Amebiasis

✓ Amebiasis (also called amebic dysentery) ⏩ infection of the intestinal tract caused by Entamoeba histolytica.

⋆ Can be acute or chronic, with varying degrees of illness, from no symptoms to mild diarrhea to fulminating dysentery.

⋆ Dagnosis is established by isolating E. histolytica from feces.

⭐ Therapy is indicated for acutely ill patients and asymptomatic carriers, since dormant E. histolytica may cause future infections in the carrier and be a potential source of infection for others.

✓ Therapeutic agents for amebiasis are classified according to the site of action as:

⭐ **Luminal amebicides**: act on the parasite in the lumen of the bowel.

⭐ **Systemic amebicides**: are effective against amebas in the intestinal wall and liver.

⭐ **Mixed amebicides**: are effective against both the luminal and systemic forms of the disease, although luminal concentrations are too low for single-drug treatment.

Mixed Amebicides (Metronidazole)

✓ Mixed amebicide of choice for treating amebic infections.
⏩ The drug of choice for the treatment of pseudomembranous colitis caused by the anaerobic, gram-positive bacillus Clostridium difficile.

MOA	PKs	Adverse Effects
Amebas possess ferredoxin-like, low-redox-potential, electron transport proteins that participate in metabolic electron removal reactions. The nitro group of metronidazole is able to serve as an electron acceptor⏩ forming reduced cytotoxic compounds that bind to proteins and DNA⏩ death of the E. histolytica trophozoites.	⭐ **ROA** : Orally ✍ For the treatment of amebiasis, it is usually administered with a luminal amebicide, such as iodoquinol or paromomycin. (combination provides cure rates of greater than 90%) ⭐ **Distribution**: Distributes well throughout body tissues and fluids ⏩ therapeutic levels can be found in vaginal and seminal fluids, saliva, breast milk, and CSF. ⭐ **Metabolism:** Depends on hepatic oxidation of the metronidazole side chain by mixed-function oxidase, followed by glucuronidation⏩ drug accumulates in patients with severe hepatic disease. ⭐ **Excretion**: The parent drug and its metabolites are excreted in the urine	✓ Nausea ✓ GI disturbance ✓ Metallic Taste

Luminal Amebicides

(Iodoquinol, diloxanide furoate, paromomycin)

✓ Should be administered after treatment of invasive intestinal or extraintestinal amebic disease is complete ⏩ for treatment of the asymptomatic colonization state

✓ Iodoquinol:
⋆ mebicidal against E. histolytica .
⋆ Effective against the luminal trophozoite and cyst forms.

✓ Paromomycin:
⋆ Aminoglycoside antibiotic.
⋆ Only effective against the intestinal (luminal) forms of E. histolytica⏩ because it is not significantly absorbed from the gastrointestinal tract.
⋆ Directly amebicidal and also exerts its antiamebic actions by reducing the population of intestinal flora.

Systemic Amebicides

✓ These drugs are useful for treating liver abscesses and intestinal wall infections caused by amebas.

Chloroquine	Dehydroemetine
✓ **Theraputic Use**: ⋆ In combination with metronidazole treat amebic liver abscesses. ⋆ Effective in the treatment of malaria. ✓ **MOA**: It eliminates trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis ⏩ should be followed with a luminal amebicide.	✓ **Theraputic Use** : Alternative agent for the treatment of amebiasis. ✓ **MOA**: Inhibits protein synthesis by blocking chain elongation. ✓ **PKs**: **ROA** ⏩ Intramuscular injection is the preferred route, since it is an irritant when taken orally. ✍ The use of this ipecac alkaloid is limited by its toxicity, and it has largely been replaced by metronidazole. ✓ **Adverse Effects** : Pain at the site of injection. Nausea. Cardiotoxicity ⏩ arrhythmias and congestive heart failure. Neuromuscular weakness. Dizziness, and rash.

Antifungal Drugs

✍Recall :

✓ Fungi are eukaryotic, With rigid cell walls composed largely of chitin rather than peptidoglycan. The fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes.

✓ Fungal infections (Mycoses): Often chronic in nature, can be either:
- ⋆ Superficial and involve only the skin (cutaneous mycoses extending into the epidermis)
- ⋆ Penetrate the skin, causing subcutaneous or systemic infections.

✓ The incidence of fungal infections such as candidemia has been on the rise for the last few decades for many reasons:
- ⋆ Increased number of patients with chronic immunosuppression due to organ transplantation
- ⋆ Cancer chemotherapy
- ⋆ Infection with human immunodeficiency virus (HIV).

✓ Cellular Targets of Antifungal Drugs:
- ⋆ Nucleus
- ⋆ Cell wall
- ⋆ Cell membrane
- ⋆ DNA synthesis
- ⋆ Mitotic spindle
- ⋆ Endoplasmatic spindles

Drugs For Subcutaneous and Systemic Mycotic Infections

	Amphotericin B	**Azole antifungals:** **✓ Imidazoles** **✓ Triazoles** ⏬ **fluconazole** **itraconazole** **Posaconazole** **voriconazole**	**Echinocandins** **Caspofungin** **micafungin** **anidulafungin**	**Antimetabolite antifungals:** **Flucytosine (5-FC)**
Nature	Naturally occurring polyene antifungal produced by Streptomyces nodosus.	⋆ Itraconazole: synthetic triazole ⋆ Posaconazole: synthetic triazole ⋆ Voriconazole: synthetic triazole related to fluconazole		Synthetic pyrimidine antimetabolite
MOA	Amphotericin B binds to ergosterol in the plasma membranes hydrophobically⏭ It forms pores ⏭ potassium and other small molecules are lost	Inhibit C-14 α-demethylase [CYP450] enzyme)⏭ blocking the demethylation of lanosterol to ergosterol⏭ disrupts membrane structure		Flucytosine enters the cell by the permease enzyme⏭ it'll turned to 5-fluorouracil by cytosine deaminase⏭ it'll then form 5-fdUMP

	through the pores ⏩ cell death ✍ fungicidal or fungistatic depending on the organism and the concentration of the drug	and function ⏩ inhibits fungal cell growth. ✍ Fungistatic (both)		that inhibits the thymidylate synthase⏩ decreasing dTMP levels and so the DNA synthesis ✍ Fungistatic
Spectrum	Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, and many strains of Aspergillus.	*Imidazoles for cutaneous infections. *Fluconazol: is used for prophylaxis against invasive fungal infections in recipients of bone marrow transplants./ the drug of choice for Cryptococcus neoformans after induction therapy with amphotericin B and flucytosine/ most forms of mucocutaneous candidiasis/ a single-dose oral treatment for vulvovaginal candidiasis. *Posaconazole: the treatment and prophylaxis of invasive Candida and Aspergillus infections in severely immunocompromised patients. *Voriconazole has replaced amphotericin B as the drug of choice for invasive aspergillosis.	*Caspofungin: is a first-line option for patients with invasive candidiasis, including candidemia, and a second-line option for invasive aspergillosis in patients who have failed or cannot tolerate amphotericin B or an azole. *Micafungin and anidulafungin: first-line options for the treatment of invasive candidiasis, including candidemia. **Micafungin :for the prophylaxis of invasive Candida infections in patients who are undergoing hematopoietic stem cell transplantation.	It's used in combination with other drugs due to high resistance: 1-Itraconazole 2-Fluconazole 3-Amphotericin B⏩ treatment of systemic mycoses and for meningitis caused by C. neoformans and C. albicans as it'll increase its cell permeability, allowing more 5-FC to penetrate the cell

PKs	✓ **ROA:** Slow IV infusion or topically ✓ **Distribution**: Extensively bound to plasma proteins and is distributed throughout the body. ✓ **Elimination**: Bile and urine ✍ Coformulated with either sodium deoxycholate (conventional) or a variety of artificial lipids to form liposomes⏩ reduced renal and infusion toxicity. ✍ High cost, liposomal preparations are reserved mainly as salvage therapy for patients who cannot tolerate conventional amphotericin B.	✓ **ROA:** *Imidazoles are given topically for cutaneous infections. *Fluconazol: oral or IV dosage formulations. *Posaconazole: oral suspension, oral tablet, or IV formulation/ should be given with food. *Voriconazole:IV and oral dosage forms ✓ **Distribution**: *Itraconazole: including bone and adipose tissues ✓ **Elimination** : *fluconazole: Drug is excreted unchanged via the urine. *Itraconazole: metabolized by the liver, and excreted in the feces and urine. *Voriconazole: metabolism through the CYP450 enzymes. ✍ *Itraconazole: two oral dosage forms, a capsule (taken with food, and ideally an acidic beverage). and an oral solution (on an empty stomach).	✓ **ROA**: Available for IV administration once daily, but only Micafungin does not require a loading dose.	✓ **ROA** ⏩ Oral ✓ **Distribution** : Penetrates well into the CSF . ✓ **Elimination** : Glomerular filtration

Resistance	Fungal resistance, although infrequent, is associated with decreased ergosterol content of the fungal membrane.			Resistance due to: 1-Decreased levels of any of the enzymes in the conversion of 5-FC to 5-fluorouracil (5-FU). 2-Increased synthesis of cytosine can develop during therapy.
Adverse effects	✓ Fever, chills. ✓ kidney failure. ✓ hypotension ✓ Anemia	*fluconazole: ✓ nausea, vomiting, headache, and skin rash. ✓ Hepatotoxicity can also occur, and the drug should be used with caution in patients with liver dysfunction. *Itraconazole: ✓ nausea, vomiting, rash (especially in immunocompromised patients). ✓ Hypokalemia. ✓ Hypertension ✓ edema. ✓ headache, ✓ Hepatotoxicity, ✓ negative inotropic effect. *Posaconazole: ✓ Gastrointestinal disturbances (nausea, vomiting, and diarrhea). ✓ Headaches, ✓ Elevation in serum hepatic transaminases. *Voriconazole: increase the serum concentration of: warfarin, phenytoin, Trizolam, Cyclosporine.	*All: Well tolerated, with the most common adverse effects being: ✓ fever, rash, nausea, and phlebitis at the infusion site ✓ histamine-like reaction (flushing) when infused too rapidly.	✓ Dose-related bone marrow depression. ✓ Gastrointestinal disturbances

Dose adjustment	Dosage adjustment is required in patients with renal dysfunction, the total daily dose is decreased by 50%. ✍ Amphotericin B has a low therapeutic index.		*Caspofungin: adjustment with moderate hepatic dysfunction/ Concomitant administration with certain CYP450 enzyme inducers (for example, rifampin) may require an increase in the daily dose/ should not be coadministered with cyclosporine due to a high incidence of elevated hepatic transaminases with concurrent use. *Micafungin and anidulafungin do not need to be adjusted in renal impairment or mild to moderate hepatic dysfunction/ Anidulafungin can be administered in severe hepatic dysfunction, but micafungin has not been studied in this condition / are not substrates for CYP450 enzymes and do not have any associated drug interactions.	The dose must be adjusted in patients with compromised renal function.

✍ Notes:

✓ **Fluconazole:** It is the least active of all triazoles. Resistance is a concern.

✓ **Itraconazole:**

- Hepatotoxicity when given with other drugs that affect the liver.
- Should be avoided in patients with evidence of ventricular dysfunction, such as heart failure

✓ **Posaconazole:**

- Affect the gastric pH which may decrease the absorption of oral posaconazole and should be avoided if possible.

Antiviral drugs

Structure and Properties Review:

Obligate intracellular/ lack (cell wall + membrane)/ do NOT carry out metabolic process unless they are in a living cell using its metabolic machinery.

Why their therapy is complicated?

1-Used prophylactically.
2-Symptoms appears late in the course of the disease.
3-Few drugs are selective enough to prevent host injury.
4-It blocks viruses replication and then depends on the host immune system to eradicate them.

How and when to use?

Firstlly , we immunize the patients since birth unless the patient is allergic or if a outbreaks occur we tend to use antiviral drugs.

▶Tx of respiratory viral infections :

Category/ Name	Neuraminidase inhibitors (oseltamivir / zanamivir)	Adamantane antivirals (amantadine/rimantadine)	Ribavirin
Structure	-	-	Synthetic Guanosine analog
spectrum	Type A,B influenzae.	Type A influenza	Broad RNA and DNA viruses
Therapeutic use	✓ Prophylically ✓ Lowering symptoms until eradicated by immune system. ✍ It doesn't interfere with the immune system response to vaccines)	-	✓ Immunocompromised patients/infants/children with RS infection ✓ Combined with interferon-alfa for chronic hepatitis (c) infections
PKs	✓ ROA ⋆ Osel⏩ orally as a prodrug hydrolyzed by the liver ⋆ Zana⏩ inhalation ✓ Elimination⏩ with urine	✓ ROA orally ✓ Distribution: AMA⏩ Higher CNS RIM⏩ lower CNS ✓ Elimination⏩ with urine	✓ ROA oral and aerosol (Safe). ✓ Absorption: increases with Fatty meals. ✓ Elimination⏩ with urine.
MOA	Prevent the release of new viruses by interfere with host cell neuraminidase	Interfere with viral uncoating prolien M2	Inhibit guanosine triphosphate from forming⏩ prevent viral RNA capping⏩ block RNA-dependent RNA polymerase
Adverse effect	Osel⏩ Gi discomfort + nausea. Zana⏩ RS irritation	1-CNS problems 2-GI discomfort 3-Cross-resistance between the two drugs	1-Dose-diaper transient anemia⏩ increase bilirubin

	✍ NEVER use zana with patients with asthma or chronic obstructive diseases / symptoms increase with food intake	✍ Cont.Ind: ✓ patients with CNS problems. ✓ Pregnancy Nnursing mothers	✍ Cont.Ind: ✓ Infants as it cause RS problems. ✓ Pregnant women
resistance	Mutation in neuraminidase enzyme	Cross-resistance between the two drugs	-

▶Tx of herpesvirus infection :

Herpes viruses are associated with:

1. cold sores 2. viral encephalitis 3. genital infection.

✍ Note:

These drugs exert their actions during the acute phase of viral infections and are without effect during the latent phase .

Category/ Name	Acyclovir	Cidofovir	Foscarnet	Ganciclovir/ alganciclovir (valyl ester of ganciclovir)
Structure	Prototypic, guanosine analog	Nucleotide analog of cysteine	Phosphonoformate (a pyrophosphate derivative)	analogue of acyclovir
spectrum	1-Herpes simplex viruses type 1 &2 (HSV-1/2) 2-varicella zoster virus/chickenpox/ HHC-3 3-Epstein-Barr-virus/ HHV-4	-	-	Has greater activity against CMV than Acyclovir.
Therapeutic use	1- Drug of choice⏩ HSV⏩ encephalitis 2-Common use ⏩ genital infection 3-Prophylactic to seropositive patients before bone marrow & heart transplant	cytomegalovirus (CMV) rhinitis in patients with AIDS. ✍ The introduction of highly active antiviral therapy (HAART)⏩ reduce cidofovir and CMV infection.	1-CMV retinitis in immunocompromised patient. 2-Acyclovir-resistant HSV infection	1-CMV retinitis in immunocompromised patients. 2-CMV prophylaxis in transplant patient
pharmacokinetics	✓ ROA: Topical/ IV=oral (due to high bioavailability in a form of Valyl Ester-valacyclovir) ✓ Distribution: all + CSF.	✓ ROA: IV/ intravitreal injection. ✓ Elimination: by permanent venous access/ slow/ require high	✓ Distribution: 10% interbone matrix and slowly leaves. ✓ Elimination: glomerular filtration and tubular secretion	✓ ROA: Ganciclovir⏩ IV Alganciclovir⏩ oral

	✓ Elimination: with urine(by glomerular filtration and tubular secretion)	dosage intervals		✍ High bioavailability, because rapid hydrolysis in the intestine and liver) ✓ Distributes: all & CSF. ✓ Excretion: urine.
mechanism	Competitive inhibitor to viral DNA polymerase (note: monophosphorylated by viral thymidine kinase and di/tri phosphorylated by host cell kinases)	Phosphorylation is independent from viral and host Kinases	Reversible inhibition of viral RNA/DNA polymerase	Inhibits viral DNA polymerase and can be incorporated into the DNA, resulting in chain termination
Adverse effect	1-If orally⏩ ✓ headache. ✓ nausea ✓ vomiting ✓ diarrhea. 2-If IV⏩ transient renal dysfunction with high dose or dehydration.	1-Renal toxicity neutropenia metabolic acidosis⏩ reduced by oral probenecid/ IV normal saline 2-hypotony/uveitis when used intravitreal injection ✍ Cont.Ind: ✓ Patients taking neutronephratics drugs . ✓ Patients with renal impairment	1-Nephrotoxicity/ anemia/ nausea/ fever 2-hypo-calcemia/magnesemia /kalemia. 3-hypo/hyperphosphatemia (due to chelation with divalent cations. 4-Relapse when levels get low (must be given frequently)	1-accumulates in patients with renal failure 2-include severe, dose-dependent neutropenia. 3-Ganciclovir is carcinogenic as well as embryotoxic and teratogenic in experimental animals
resistance	1- lower thymidine kinase and DNA polymerases in immunocompromised patients. 2-cross-resistance to other agents in the family 3-accumulation in a patient with renal failure.		By polymerase structure mutations	have lower levels of ganciclovir triphosphate

Clinical Toxicology

✓ Toxins can be:
⋆ Inhaled.
⋆ Insufflated (snorted).
⋆ Orally ingested .
⋆ Injected.
⋆ Absorbed dermally.

✓ Once in the body, some of the common targets of toxicity include :

⋆ CNS ⋆ Lungs ⋆ Kidneys ⋆ Heart ⋆ liver ⋆ The blood
⋆ The intricate acid/base and electrolyte balance of the body.

Emergency tx of the poisoned patient

treat the patient, not the poison	✓ ABC : **A**irway , **B**reathing , **C**irculation ✓ **Lifethreatening toxic effect**: Profound increases or decreases in blood pressure. Heart rate. Breathing. Body temperature. Dangerous dysrhythmias. ✓ **Further assessed as laboratory results are obtained**: Acid/base and electrolyte disturbances Acetaminophen and salicylate blood level ✓ After administering oxygen, obtaining intravenous access, and placing the patient on a cardiac monitor, the poisoned patient with altered mental status should be considered for administration of the **"coma cocktail"** ⏩ The "coma cocktail" consists of : (ROA➞ IV) ⋆ Dextrose to treat hypoglycemia, a possible toxicological cause of altered mental status ⋆ Naloxone to treat possible opioid or clonidine toxicity ⋆ Thiamine for ethanol-induced Wernicke encephalopathy.
Decontamination	✓ When ?Once the patient is stabilized . ✓ Includes ? ⋆ Ocular Exposure ⏩ flushing of the eyes with saline or tepid water to a neutral pH ⋆ Dermal Exposuee⏩ rinsing of the skin ⋆ GIT⏩ Gastric lavage, activated charcoal, or whole bowel irrigation (utilizing a polyethylene glycol electrolyte balanced solution) for selected ingestions. ✍ The following substances limits the use of activated charcol (unless there are coingested products): lead and other heavy metals, iron, lithium, potassium, and alcohols

Elimination enhancement		
	Hemodialysis	✓ Effective in elimination of substances with these properties: 1) Low protein binding substances . 2) Small Volume of Distribution 3) Water solubility 4) Small molecular weight substances ✓ The following can be removed by hemodialysis: Methanol Ethylene glycol Salicylates Theophylline + phenobarbital . Lithium .
	Urinary alkalinization	✓ Elimination of substances like ⏩ ***phenobarbital , salicylates*** . ✓ Achieved by → administration of IV sodium bicarbonate . ✓ **Goal** urine pH→ 7.5-8 ✓ Serum pH must not exceed → 7.55 (7.6)
	Multiple-dose activated charcoal	✓ Elimination of substances like⏩ *phenobarbital , theophylline , digoxin , carbamazepine , valproic acid* ✓ Bowel sounds must be present prior to each activated charcoal dose,why ? 1) To ensure movement of GIT . 2) Prevent obstruction .

▶Selected pharmaceutical and occupational toxicities :

Acetaminophen	✓ Toxic when → its usual metabolic pathways are saturated . ✓ Acetaminophen metabolism : 1) Sulfation 2) glucuronidation 3)N-hydroxylation ⬇ ⬇ Get overwhelmed When toxic amount of Acetaminophen is ingested ⏬ ⬆ **production of NAPQI** (hepatotoxic metabolite) ✓ Normally , NAPQI is detoxified by Glutathione (here we have increase NAPQI production , so glutathione we have won't be enough → toxicity result) ✓ Antidote of Acetaminophen → NAC(N -acetylcysteine) ⏩ MOA → precursor of glutathione, and may function as antioxidant , this aid in recovery . ⏩ Most effective → when initiated 8h-10h postingestion
Alcohols	1st : **Methanol + ethylene glycol** ⭐ They are primarily nontoxic and cause CNS sedation ⭐ Oxidized to toxic products : Methanol→ **formic acid** Ethylene glycol → **glycolic acid + glyoxylic acid + oxalic acid** . ⭐ **Antidote → Fomepizole** MOA → inhibition of their oxidative pathway of metabolism by blocking alcohol DH⏩ prevent formation of toxic metabolites .

	✍ Cofactors that encourage metabolism of these alcohols to nontoxic metabolite : ✓ Methanol → **folate** ✓ Ethylene glycol → **thiamine + pyridoxine** ⋆ If untreated , several problems arise , the most important thing → they both cause Metabolic acidosis 2nd : **Isopropanol (isopropyl alcohol)** ⋆ It is : 1) CNS depressant 2) GI irritant ⋆ Oxidized to **Acetone** , by the action of alcohol DH . ➞Acetone can't further be converted to COO- acid → explaining why **no metabolic acidosis occurs in case of isopropyl toxicity** . ✓ No antidote available .
Carbon monoxide	✓ Highly toxic , why ? 1) The binding affinity of CO to Hb is much higher than that if O2 . 2) Bound CO ⬆ Hb affinity for O2 at other oxygen -binding sites→ this high affinity binding of O2 prevents the unloading of O2 at the tissues → reducing O2 delivery . ⋆ **Cherry red skin**→ due to presence of high concentration of oxygenated blood . ⋆ CO toxicity associated with → ✓ Inhalation ✓ Ingestion of methylene chloride⏩ it gets metabolized by the liver to CO . ⋆ **Symptoms** → ✓ hypoxia ((most affected organs are : brain + heart)) ✓ Headache , confusion , coma , dyspnea . ⋆ **Treatment** → 1) Prompt removal from the source of CO . 2) Institution of 100% oxygen by nonbreathing face mask / endotracheal tube 3) Oxygenation in hyperbaric chamber → in cases of severe intoxication
Cyanide	✓ Produced from ⏩ Cyanide salts (in electroplating) , hydrogen cyanide , house fires ✓ What does it do → binds to Metalloenzymes rendering them inactive , primarily to Cytochrome a3 ⏩ inhibition of cellular metabolism ✓ Death may occur due to → Respiratory arrest of oxidative phosphorylation and production of ATP . ✓ Antidote → **hydroxocobalamin** (B12) → **IV** , to bind to cyanide and produce cyanocobalamin .
Iron	✓ Factors affect potential toxicity produced by iron : Patient weight Quantity ingested Elemental iron concentration ✓ Patient may experience a latent period or progress quickly to hypovolemia , metabolic acidosis , hypotension and coagulopathy→ depending on the amount ingested . ✓ Antidote → **Deferoxamine** ⋆ **IV** usually; but hypotension may occur if it was given as rapid boluses instead of continuous infusion .

Lead	Sources of exposure : 1) Old paint 2) Drinking water 3) Industrial pollution 4) Contaminated dust ✓ Age-dependant differences in absorption of ingested lead are known to occur: Adults absorb about 10% of an ingest dose . Children do absorb about 40% → Children are at higher risk for lead intoxication ✓ Inorganic forms of lead distributed to → soft tissues ⏩ Redistributed to → bone, teeth , hair . ✓ **Lead in bone** → 1) Impairs new bone formation 2) Increases calcium deposition in long bones . ✓ Lead half life differs between different body sites → ⭐ **1 -2 months → blood** . ⭐ **20-30 years → bone** . ✓ Treatment : 1) **>45 microgram and < 70 microgram in children** → succimer (DMSA acid) → orally . 2) **> 70 micrograms or if encephalopathy is present**→ dual parenteral therapy ⭐ Dimercaprol → IM . ⭐ Calcium disodium edetate → IV . ✍ Dimercaprol is usually suspended in peanut oil → so,is not given to patient with peanut allergy .
Organophosphate and carbamate insecticides	Insecticides toxicity is due to : Inhibition of AchE ⬇ Accumulation of excess Ach ⏬ Producing nicotinic and muscarinic effects. ✓ **Carbamate Insecticides vs Organophosphates** ⭐ Carbamates ⏩ reversibly bind to AchE. ⭐ Organophosphates ⏩ cause irreversible inactivation of AchE (and have much more rapid effect than insecticides) ✓ Treatment : 1) Muscarinic effects → Atropine (IV or IM). 2) Nicotinic effects → pralidoxime (IV or IM) .

▶Summary of poisions and their antidotes

Drug	Therapeutic uses
Muscarinic blockers	
Trihexyphenidyl *Benztropine*	● Treatment of Parkinson's disease
Darifenacin *Fesoterodine* *Oxybutynin* *Solifenacin* *Tolterodine* *Trospium*	● Treatment of overactive urinary bladder
Cyclopentolate *Tropicamide* *Atropine**	● In ophthalmology, to produce mydriasis and cycloplegia prior to refraction
*Atropine**	● To treat spastic disorders of the GI tract ● To treat organophosphate poisoning ● To suppress respiratory secretions prior to surgery ● To treat bradycardia
Scopolamine	● To prevent motion sickness
Ipratropium *Tiotropium*	● Treatment of COPD
Ganglionic blockers	
Nicotine	● Smoking cessation

اللهمَّ تقبل العَمل مع قلتِه ، والجُهد مع ضالته والسَّعي مع شوائبه

وَآخِرُ دَعْوَاهُمْ أَنِ الْحَمْدُ لِلَّهِ رَبِّ الْعَالَمِينَ