Anticholinergic Drugs,
Cholinergic Antagonists OR **Cholinergic-Blocking Drugs**

These are drugs which can block or inhibit the actions of acetylcholine in the parasympathetic nervous system leaving the sympathetic innervation unopposed.

Classifications: Anticholinergic were classified into
1-**Antimuscarinic ;**
2- Antinicotinic ; Which subdivided into
a. Ganglionic blockers ;
b. Neuromuscular blockers (NMBs) which further classified into
i- Competitive or **N**on **D**epolarizing **N**euromuscular **B**locker**s** (**NDNMBs**)
ii- Non competitive or **D**epolarizing **N**euromuscular **B**lockers (**DNMBs**)

1-Antimuscarinic Agents:

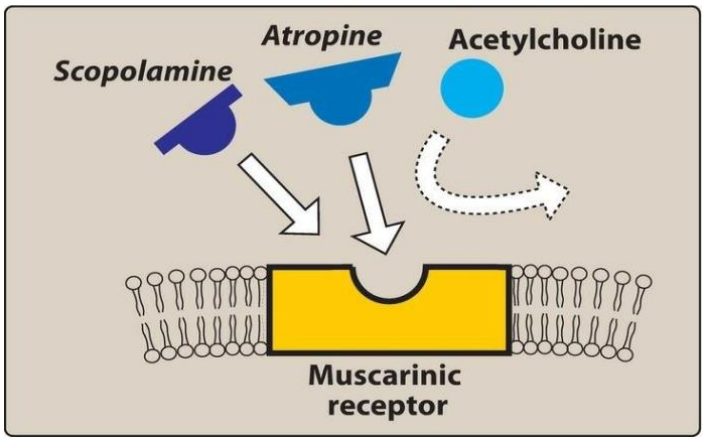
- Natural drugs; **- Atropine** (Prototype)
  - Scopolamine or **Hyoscine**

☒ **Pharmacokinetics:**

Both are natural tertiary alkaloids, well absorbed, available as oral and parenteral preparations, have central and peripheral effects. They are partly metabolized in the liver and excreted in urine. Atropine has duration of action 4 hours on all effector organs except the eye where the action of atropine that applied topically in the eye extended to several days.

Mechanism of action;

competitively antagonize the effect of Ach at all muscarinic receptors present in (smooth muscles, heart and exocrine glands), and prevent receptor activation by both endogenous Ach or other muscarinic agonists. The neuroeffector organs showed variable sensitivity to atropine. The greatest inhibitory effects are seen in bronchial secretion, salivary and sweat glands, then the heart, eye and smooth muscle of urinary bladder, GIT and bronchi. While the least sensitive is the gastric parietal cell.



Pharmacologic Effects: As atropine acts by causing muscarinic receptor blockade, so it will reverse those responses related to muscarinic activation:

1-On Exocrine Glands:

Atropine decreases secretions from all exocrine glands as salivary glands result in dryness of mouth and difficulty of swallowing, ↓ sweating (anhidrosis) result in hyperthermia and atropine flush, decrease bronchial and gastric acid secretion.

2- On Smooth Muscle:

- GIT; decrease peristaltic movement of intestine (antispasmodic effect*).* and secretions with increase in the tone of sphincter causes constipation.

- Bronchi; causes bronchodilation (relaxation of the bronchial smooth muscle) and decrease bronchial secretions.

- Urinary tract; decrease the tone of the detrusor muscle of urinary bladder result in urinary retention.

3- **On Eyes:**

Causes passive mydriasis (dilation of the pupil), *cycloplegia* (relaxation of the ciliary muscle) and loss of accommodation or far vision, decrease lachrymal secretion causes dry and sandy eyes (Xerophthalmia) and increase the intraocular pressure (IOP).

4- On Heart:

Atropine block the M2 receptors in the heart result in an increases in the heart rate, and cardiac conductivity . Therefore, atropine can be used to counteract bradycardia and Av block.

5- On Central Nervous System: Antimuscarinic can cause reduce muscle rigidity and tremor.

Clinical indications

1. Preoperative use or Pre-aesthetic medication

2. Ophthalmology: (**Tropicamide**)

3. GI Disorders: Reduce Intestinal Hypermotility, secretions and bowel movement (e,g; ***Hyoscine –n-butyl bromide (librax), propantheline …….& pirenzipine***)

4. Urinary incontinence: ***Oxybutynin, Tolterodine, Darifenacin***.

5. Respiratory Disorders: ***Ipratropium, Tiotropium*** used by inhalation for acute management of bronchospasm.

6. Cardiac Disorders: Atropine used to treat bradycardia and AV block of different etiologies.

7. Parkinson's disease: treated by centrally acting antimuscarinic agent as ***Benztropine, procyclidine***

- **Atropine**: used as antidote in physostigmine toxicity, to reverse the muscarinic effects in case of poisoning with physostigmine or organophosphorous compounds.

- **Scopolamine;** It has similar action to atropine with longer duration of action and has more CNS depressant effect. It's indicated for motion sickness, and as prenesthetic medication**.**

❖ **Adverse effects**:

Body System Adverse Effects

- Cardiovascular Tachycardia (Increased heart rate)

- CNS Excitation, insomnia, irritability, disorientation, hallucinations,

- Eye (Cycloplegia**,** blurred vision and photophobia**)** Mydriasis, increased intraocular pressure

- GIT : Dryness of mouth, Difficulty in swallowing , Constipation **(**decreased secretions& motility)

- Genitourinary Urinary retention

- Glandular Hyperthermia (Anhidrosis Decreased sweating)

- Respiratory Thickening of bronchial secretions

TABLE 14.4 ▪ Relationship Between Dosage and Responses to Atropine

Dosage of Atropine	Response Produced
Low dose ↓ High dose	Salivary glands—decreased secretion Sweat glands—decreased secretion Bronchial glands—decreased secretion Heart—increased rate Eyes—mydriasis, blurred vision Urinary tract—interference with voiding Intestines—decreased tone and motility Lungs—dilation of bronchi[a] Stomach—decreased acid secretion[a]

❖ ***Contraindications:*** These drugs not used in conditions of: drug allergy, glaucoma, benign prostate hyperplasia, tachycardia, heart failure, and GI obstruction.

❖ **Drug Interactions**

Drugs like *antihistamines, Phenothiazine, & tricyclic antidepressants* have anticholinergic effects.

II-Nicotinic Blockers;

They were classified according to the type of nicotinic receptors into:

a- **Ganglionic blockers**;

They block Nn receptors present at autonomic ganglia and prevent stimulation of postsynaptic receptors. Clinically, they are the *least important* group, because of *their side effects* result from blocking of autonomic transmission through both sympathetic and parasympathetic ganglia.

e.g; **Hexamethonium, Mecamylamine and Trimethaphan**

b-**Neuromuscular blockers:**

They interfere and block the cholinergic transmission between somatic nerve endings &Nm receptors on the skeletal muscle causing skeletal muscle relaxation.

They were classified into two subtypes :

1- Competitive Non-Depolarizing Nuromuscular Blockers (NDNMBs); compete with Ach to bind with Nm receptor .

- e.g; **Tubocurarine, Gallamine, Pancoronium** .

2- Depolarizing (DNMBs); Bind to Nm receptors cause initial activation followed by blocking and muscle relaxation e.g; **Succinyl choline**

- They are quaternary compounds, have variable Onset and Duration of action where their duration depend on elimination $t_{1/2}$
- Uses: Provide complete muscle relaxation for endotracheal intubation to lower anesthetic doses and their side effects**.**

- **Adverse effect of succinylcholine**;

- Malignant hyperthermia if used with halothane in susceptible patients,
- Bradycardia , Hyperkalemia, Increase of IOP & Prolonged apnea .

Nursing Implications for muscarinic antagonists:

1-Preadministration Assessment

- Identify goal of therapy to assess patient condition
- Assess medication history **for *anticholinergic side effects as antihistamines, antipsychotic*, these drugs increase muscarinic blockade**
- Assess baseline of vital signs**.**
- Identify patient at risk by assessment for ***allergies, presence of BPH, glaucoma, tachycardia, HF, and GI or GU obstruction and children***

2- Administration: Medications should be taken exactly as prescribed (Dose, route and time) to have the maximum therapeutic effect **- Atropine present for (oral, IV, IM, SC and ophthalmic preparation)**

3- Minimize adverse effects;

- **Blurred vision**; used with caution, patients advised to avoid hazardous activities, driving or operating machinery.
- **photophobia:** Keep hospital room lighting low to reduce visual discomfort.

Advise patients to wear sunglasses outdoors.

- **Dry mouth *interfere with swallowing***; Patient *advised to moisten the mouth before oral administration*, or use *chewing sugar free gum*, with frequent mouth care using alcohol free mouth wash.
- **Constipation** – advise patients to increasing dietary fiber and fluids.
- **Urinary retention**– advise patients to voiding just prior to taking drugs. Or catheterization may be required.
- **Tachycardia** – monitor pulse and report significant increases.
- **Hyperthermia-**.Advise patient to avoid exertion and high temp. with adequate intake of fluids because drug reduce sweating

● Check with physician before taking any other medication, including over-the-counter medications

● Patients should report the following symptoms to their physician: urinary hesitancy and/or retention, constipation, palpitations, tremors, confusion, sedation or amnesia.

4- **Monitor for therapeutic effects**

● For patients with Parkinson's disease: fewer tremors and decreased salivation and drooling

● For patients with urologic problems: improved urinary patterns, less hypermotility, increased time between voiding.

5- Management of toxicity: Overdosing can cause life-threatening problems , treated by decrease absorption using charcoal and give **physostigmine *as Antidote* .**

Adrenergic neurotransmission

The sympathetic nervous system function to prepare the body for intense physical activity (fight or flight) result in;

1- Increase the cardiac work and BP. 2-Divert blood to skeletal muscles.
3- Bronchioles are dilated 4- Pupil dilate
5- Mobilization of stored energy to provide glucose and FA.
6- Reduce digestion and elimination.

Endogenous ligands for sympathetic receptors

The main neurotransmitter of this system is:

- **Norepinephrine (NE):**

which released from nerve terminals of adrenergic neurons.

- **Adrenaline:**

which represent **(80%)** of secretion of adrenal medulla while **Norepinephrine represent (20%) of its secretion.**

-Dopamine (D):

Dopamine is an important neurotransmitter in peripheral and central sites, it's a
precursor of both Ep. & NE and all are structurally related. They are catecholamines, can activate the adrenergic receptors.

Properties of Catechol amines

- Have high potency
- Poorly absorbed from GIT given by injection (s/c, or infusion) route
- Metabolized by COMT & MAO & have short duration
-Poor penetration into the CNS.
- Unstable & Sensitive to light & oxidizing agents.

Neurotransmission at adrenergic neurons

1- Synthesis ;

Tyrosine —(Hydroxylation)→ DOPA

DOPA —(DOPA Decarboxylase)→ Dopamine

2- Storage:

Dopamine actively enter the vesicles where its hydroxylated to NE that stored inside vesicles.

Dopamine —(dopamine beta hydroxylase)→ Norepinephrine

Within adrenal medulla NE converted to epinephrine by methyation reaction .

3- Release :

Generation of action potential result in depolarization of membrane and open voltage gated calcium channel and entry of ca which enhance exocytosis of stored NE into synaptic space. However, at adrenal medulla Epinephrine and NE released directly to circulation.

4- Binding:

The released neurotransmitters bind to adrenergic receptors producing a biological
response

5- Fate of NE: The action of NE terminated by

1-Neuronal uptake 2-Vesicular uptake 3- Tissue or Non neuronal uptake

6- Metabolism: Both epinephrine and, NE metabolized by two enzymes mono amine
oxidase (MAO) and Catechol-o-methyl transferase (COMT).

Adrenergic receptors:

They were classified into two main types depending on the specific *physiologic responses* caused by
their stimulation.

1-**alpha-adrenergic receptors** 2- **beta-adrenergic receptors**

Each type subdivided into subtypes as ;

- The alpha receptors are excitatory receptor present in two subtypes α1 and α2
- The **beta- receptors** subdivided into three subtypes (β1,β2, β3) . All of these receptors are stimulatory receptors.

Adrenergic receptors have variable sensitivity to endogenous ligands ;

Epinephrine can activate all receptors**.**

Norepinephrine α1=α2 > β 1>>>>>>> β 2

Dopamine D > β 1 >>>α1

- **Locations of different adrenergic receptor subtypes and the response produce by their activation;**

Location	Receptor	Response
Cardiovascular		
○ Blood vessels	α_1	Constriction
	β_2	Dilation
○ Cardiac muscle	β1	Increased cardiac work [HR, conductivity, force of contraction, COP and oxygen need]
Gastrointestinal		
- Muscle	β2 and α	Decreased motility
Genitourinary		
○ Bladder	α1	Constriction sphincter
○ Uterus	α1	Contraction
	β2	Relaxation
Respiratory		
○ Bronchial	β_2	Bronchodilation
Eye Pupils	α_1	Dilation (active mydriasis)
Liver , skeletal muscle	β2	Increase glycogenolysis Increase uptake of potassium
Adipose tissue	β 3	Increase lipolysis
Pancreas	β 2	Increase insulin release
	α2	Decrease insulin release
Kidney	β 1	Increase renin release
	α2	decrease renin release
Male sex organs	α1	Ejaculation
Skin	α 1	constriction of B.V (cold extremities)
Sweat gland	α1	Increase secretion

Sympathomimetics or adrenergic agonists

▪ Classifications:

1-According to their chemistry they fall into two chemical classes:

o Catecholamines: Epinephrine, Norepinephrine, Dopamine, Isoprenaline & Dobutamine

o Non-catecholamines: Phenylephrine, ephedrine.

- Non catechole drugs are of lower potency, given orally, have longer duration of action, Not metabolized by COMT & MAO, Have CNS effect and chemically stable.

2- Classification according to mechanism

• **Direct acting drugs;** They are directly bind and activate adrenergic receptors. Including All catechol amines (Ep., NE, Dopamine, isoprenaline & dobutamine) + non catechol drugs as phenylephrine, **…. Etc**

• **Indirect-acting sympathomimetics**: Include adrenergic drugs that act either by enhancing the release of norepinephrine from nerve terminal to bind and activate the receptors or by inhibit the neuronal uptake of NE
e.g: **Amphetamine**, **Metamphetamine**, **Tyramine and Cocaine**.

• **Mixed-acting sympathomimetic:** They act by both direct stimulation of the receptor and indirect effect through the release of neurotransmitter.
e.g; **Ephedrine** and **Pseudoeohedrine**.

3- Classification according to receptor selectivity:

	Receptor	Drug	
1-Non selective	alpha1, alpha2,beta1,beta2	Adrenaline	Ephedrine
	alpha1, alpha2,beta1	Noradrenaline	
	Dopamine, beta1, alpha	Dopamine (dose dependent)	
2-Less selective	Beta1, Beta2	Isopretrenol	
	alpha1, alpha2	Xylometazoline	
3- Selective	alpha1	phenylephrine	
	alpha2	Clonidine	
	Beta1	Dobutamine	
	Beta2	Salbutamol	
	D1	Fenoldopam	