Autonomic Pharmacology

It deals with drugs which affect autonomic nervous system or autonomic receptors on the effectors cells controlled by autonomic nervous system (cardiac, smooth muscles and exocrine glands).

Autonomic Nervous System (ANS) is divided into:

<table>
<thead>
<tr>
<th>Origin</th>
<th>Sympathetic</th>
<th>Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>From all thoracic &amp; upper 3 lumbar segments.</td>
<td>From cranial 3.7.9.10 &amp; sacral 2.3.4 segments.</td>
</tr>
<tr>
<td>Character</td>
<td>Short preganglionic &amp; long post-ganglionic fibres.</td>
<td>Long preganglionic &amp; short post-ganglionic (i.e., terminal ganglia)</td>
</tr>
</tbody>
</table>

So, isolated organs with double nerve supply contain only parasympathetic ganglia.

<table>
<thead>
<tr>
<th>* Heart:</th>
<th>Sympathetic</th>
<th>Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>. H.R.</td>
<td>Tachycardia</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>. A.V. conduction</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>. Atrial R.P.</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>. Atrial conduction</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>. Ventricular conduction and contraction</td>
<td>Increase</td>
<td>No effect</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>* Smooth muscles:</th>
<th>Sympathetic</th>
<th>Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>. Eye</td>
<td>Mydriasis</td>
<td>Miosis &amp; contraction of ciliary muscle</td>
</tr>
<tr>
<td>. Bronchi</td>
<td>Bronchodilatation (relaxation)</td>
<td>Bronchospasm (contraction)</td>
</tr>
<tr>
<td>. GIT</td>
<td>Relax wall &amp; contact sphincters</td>
<td>Contract wall &amp; relax sphincters</td>
</tr>
<tr>
<td>. Urinary bladder</td>
<td>Urine retention</td>
<td>Micturition</td>
</tr>
<tr>
<td>. Blood vessels</td>
<td>Vasoconstriction and dilatation</td>
<td>Vasodilatation of some vessels</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>* Secretions:</th>
<th>Sympathetic</th>
<th>Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>. Salivary</td>
<td>Thick viscid</td>
<td>Profuse watery</td>
</tr>
<tr>
<td>. Sweat</td>
<td>Increase</td>
<td>No effect</td>
</tr>
</tbody>
</table>

| * Sex organs           | Ejaculation                      | Ejaculation                          |

R.P. = refractory period  A.V. = atrio-ventricular conduction

-Usually each organ has double nerve supply except: most of blood vessels, sweat glands, radial muscle of iris and ventricle have sympathetic supply only, while constrictor pupillae muscle has parasympathetic supply only.

- The parasympathetic tone is usually predominating except on B.V.

-Cerebral cortex and hypothalamus control autonomic activity where ergotropic system controls sympathetic and trophotropic controls parasympathetic.
Chemical transmitters

Two chemical transmitters are identified in autonomic nerves namely acetylcholine & noradrenaline.

Steps of neurohumoral transmission:
1. Arrival of action potential at the axonal terminal causing Ca$^{2+}$ influx to destabilize the storage vesicle through interaction with special vesicle associated membrane proteins (VAMPs) to release the transmitter.
2. Combination of the transmitter with the receptor.
3. Induction of biologic change in receptor.
4. Removal of the transmitter.

1. Acetylcholine

Acetylcholine is synthesized in the cytoplasm from choline (which is transported by a membrane carried mechanism from extracellular fluid into neuronal terminal) and active acetate by choline acetyl transferase enzyme.

It is stored with ATP and proteoglycan inside vesicles near the synaptic portion of the cell membrane, some vesicles contain also a polypeptide co-transmitter (vasoactive intestinal peptide = VIP).

It is the chemical transmitter at:
1. All fibers arising from C.N.S. (preganglionic sympathetic and parasympathetic, nerve to adrenal medulla and somatic nerves).
2. All postganglionic parasympathetic and some postganglionic sympathetic (to sweat glands and some vessels).
3. Some tracts in C.N.S., e.g., basal ganglia.

Acetylcholine acts on cholinergic receptors (cholinceptors) which are two types:

<table>
<thead>
<tr>
<th>Nicotinic receptors</th>
<th>Muscarinic receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present in:</td>
<td>Present in:</td>
</tr>
<tr>
<td>- Autonomic ganglia ($N_a$)</td>
<td>- Effectors organ supplied by parasympathetic.</td>
</tr>
<tr>
<td>- Adrenal medulla ($N_h$)</td>
<td>- Sweat glands, blood vessels.</td>
</tr>
<tr>
<td>- Motor end plate ($N_m$)</td>
<td>- C.N.S. (brain mainly).</td>
</tr>
<tr>
<td>- C.N.S. spinal cord mainly ($N_b$)</td>
<td>Blocked by:</td>
</tr>
<tr>
<td>Blocked by:</td>
<td>- Atropine</td>
</tr>
<tr>
<td>- Ganglion blocker (Nicotine L.D. in ganglia).</td>
<td></td>
</tr>
<tr>
<td>- Neuromuscular blocker (as curare in skeletal muscles).</td>
<td></td>
</tr>
</tbody>
</table>

N.B.:
* Blood vessels of skeletal muscles have sympathetic cholinergic dilator fibbers.
* Some sweat glands, e.g., in palm and sole have adrenergic receptors ($\alpha_1$)
Fate of acetylcholine: Rapid hydrolysis by cholinesterase enzyme

<table>
<thead>
<tr>
<th>True cholinesterase</th>
<th>Pseudo or butyrocholinesterase</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Present at cholinergic neurons, R.B.Cs.</td>
<td>- Present in liver, plasma.</td>
</tr>
<tr>
<td>- Specific</td>
<td>- Non specific (can hydrolyse other esters).</td>
</tr>
<tr>
<td>- Regenerated in 2-3 months</td>
<td>- Regenerated in 2-3 weeks.</td>
</tr>
</tbody>
</table>

2- Noradrenaline (Norepinephrine)

- In adrenal medulla and some areas in brain noradrenaline is converted into adrenaline (epinephrine) by phenylethanolamine-N-methyl transferase (PNMT) enzyme which is induced by steroid hormones (cortisol).
- Noradrenaline is the chemical transmitter at postganglionic sympathetic (except to sweat glands & some B.V.), also inside C.N.S.
- Noradrenaline is stored inside vesicles and is released in response to nerve action potential. These vesicles contain norepinephrine, dopamine, ATP, dopamine B-hydroxylase enzyme and certain co-transmitters.
- Some drugs as amphetamine and tyramine can displace noradrenaline from vesicles but not through exocytosis or Ca^{++} influx.

Adrenergic receptors

<table>
<thead>
<tr>
<th>Heart</th>
<th>Eye</th>
<th>Bronchi</th>
<th>G.I.T.</th>
<th>Urinary tract</th>
<th>Uterus</th>
<th>B.V.</th>
<th>Insulin release</th>
<th>Other actions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decrease (α₂)</td>
<td>Increased neuromuscular transmission. Decrease renin(α₂) Increased sweat secretion from apocrine glands (α₁).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mydriasis α₁</td>
<td>Contract sphincters Contract sphincter (α₁)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>Relax wall (β)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increase all properties (β₁)</td>
<td>Bronchodilatation (β₂)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increase (β₂)</td>
<td>Glycogenolysis (β₂), Lipolysis (β₁ and β₃),</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Renin release (β₁)</td>
</tr>
</tbody>
</table>
**Fate of noradrenaline**: simple diffusion away from receptors sites then:

1. **Uptake (80%)**: which include neuronal uptake (I), vesicular or granular uptake, and extraneuronal (II).
2. **Enzymatic degradation (15%)**: by monoamine oxidase (MAO), intracellular in mitochondria, catechol-O-methyl transferase (COMT) in cytoplasm.
3. **Excretion (5%)**: in urine unchanged

**N.B.**:
* Drugs blocking uptake I as cocaine $\rightarrow$↑ sympathetic activity.
* Drugs blocking granular uptake as reserpine $\rightarrow$↓ sympathetic. activity.
* MAO enzyme is 2 types, MAO-A and MAO-B and each one has a selective inhibitor, e.g., deprenyl is MAO-B inhibitor.
* Dopamine may be released by some sympathetic. fibres to stimulate dopaminergic receptors which induces V.D. of renal and mesenteric vessels ($D_1$ receptors).
* Enteric nervous system is a collection of neurons in gut wall and it includes myenteric and submucous plexuses (Auerbach and Meissner). It receives preganglionic parasympathetic, post-ganglionic sympathetic and sensory fibres from gut wall.

**Parasympathomimetics**  
*(Cholinergic agonists)*

Drugs which stimulate muscarinic receptors (muscarinic agonists), with or without nicotinic action. They are classified into:

**A- Direct acting:**
1. Choline esters: A.Ch., methacholine, carbachol and bethanechol.
2. Cholinomimetic alkaloids: pilocarpine and muscarine.

**B- Indirect acting:**
Anticholinesterases which may be reversible or irreversible:
* Reversible as physostigmine, neostigmine, edrophonium, tacrine.
* Irreversible as parathion, isofluorophate (di-isopropyl fluorophosphate = DFP), eclothiophate, metrifonate.

![Diagram of cholinesterase inhibition]
2. Autonomic Pharmacology

1- **Muscarinic actions:**
   a. Eye:
      - Miosis due to stimulation of muscarinic receptors in the constrictor papillae muscle (M$_3$).
      - Contract ciliary muscles (M$_3$) → accommodation for near vision.
      - Increase aqueous drainage and ↓ I.O.P.
      - Lacrimation and conjunctival congestion.
   b. Secretions: ↑ salivary, bronchial, gastric and sweat secretion.
   c. Bronchi: Bronchospasm (M$_3$).
   d. C.V.S.: Bradycardia (M$_2$) and hypotension.
   e. GIT: ↑ motility (M$_3$).
   f. Urinary tract: Contract detrusor muscle, relax sphincter → micturition (M$_3$).

2- **Nicotinic actions:**
   * At neuromuscular junctions → muscle twitches.
   * At autonomic ganglia and adrenal medulla → reversal of hypotensive effect by atropine

   ![Graph](image)

   hypotension due to decreased cardiac output (COP) and total peripheral resistance (TPR). After block of these receptors by atropine, then nicotinic receptors stimulation in sympathetic ganglia and adrenal medulla will release endogenous catecholamines which produce elevation of B.P.

   **N.B.** : *The direct acting parasympathomimetics will induce hypotension due to decreased COP and TPR while anticholinesterases (indirect acting) will produce hypotension by decreasing COP only.*

   **I. Choline Esters**

   They are quaternary amines, so can not pass to C.N.S. and are distributed extracellularly.

   **1- Acetylcholine**

   **Pharmacokinetics:**
   Ineffective orally due to rapid hydrolysis by both true and pseudocholinesterase enzyme.

   **Actions:** Stimulates directly both muscarinic and nicotinic receptors.

   **Uses:** Not used due to very short duration.
2- Methacholine

It is acetyl-\(\beta\)-methyl choline.

**Pharmacokinetics:**
- Incomplete oral absorption, so oral dose is higher than parenteral dose.
- Hydrolysed by **true cholinesterase only**, so it has longer duration than ACh.

**Actions:**
Acts directly on muscarinic receptors, which are more prominent on C.V.S., and has insignificant nicotinic actions.

**Uses:** Provocative test in bronchial asthma.

3- Carbachol

**Pharmacokinetics:**
- Complete oral absorption.
- Not hydrolyzed by cholinesterase enzyme, so effective orally and has long duration, excreted in urine.

**Actions:**
- Acts directly on muscarinic and nicotinic receptors.
- It has marked action on eye, GIT, urinary tract.

**Uses:**
- Glaucoma.
- Non-obstructive urine retention and paralytic ileus (post-operative abdominal distention).
  Given oral or S.C.

4- Bethanechol (Methyl carbachol)

It is carbamoyl \(\beta\)-methyl choline. It is similar to Carbachol, but with **no nicotinic** actions and has marked effect on GIT and urinary tract.

**Uses:**
- Post-operative urine retention and paralytic ileus.
- Gastric atony after vagotomy.
  Given oral or S.C.

**Contraindications of choline esters:**
1- Bronchial asthma.
2- Peptic ulcer.
3- Coronary insufficiency, hypotension and bradycardia.
4- Hyperthyroidism (atrial fibrillation occurs).
5- Never given I.M. or I.V. (produce severe bradycardia and hypotension and atropine is the antidote).
2. Autonomic Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>ACh.</th>
<th>Methacholine</th>
<th>Carbachol</th>
<th>Bethanechol</th>
</tr>
</thead>
<tbody>
<tr>
<td>True Ch.E. enz.</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>False Ch.enz.</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Muscarinic action</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Nicotinic action</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Selectivity</td>
<td>-</td>
<td>C.V.S.</td>
<td>Eye</td>
<td>GIT &amp; urinary tract</td>
</tr>
<tr>
<td>Oral Absorption</td>
<td>Nil</td>
<td>Incomplete</td>
<td>Complete</td>
<td>Complete</td>
</tr>
<tr>
<td>Administration</td>
<td>I.V. drip</td>
<td>S.C.</td>
<td>and</td>
<td>Oral</td>
</tr>
</tbody>
</table>

II- Cholinomimetics alkaloids, pilocarpine

Alkaloid from plant origin, tertiary amine, not affected by cholinesterase enzyme.

**Pharmacokinetics:**
- Given orally, passes to CNS.
- Excreted as metabolite and unchanged.

**Actions:**
Act directly on muscarinic receptors with marked action on eye, exocrine glands and smooth muscles.

**Uses:**
- Eye drops in glaucoma, to counteract mydriatics and alternatively with mydriatics to cut recent adhesions between iris and lens.
- Sialagogue in dry mouth and diaphoretic in fever.
- Promotion of hair growth.

III- Anticholinesterases (indirect acting)

- They inhibit cholinesterase enzyme so produce accumulation of ACh. at cholinergic sites (muscarinic and nicotinic).
- They may be reversible or irreversible.

_ACh. binds to the active site of the enzyme and is hydrolyzed into free choline and acetylated enzyme which splits to free enzyme in 150 microseconds._

1- Reversible anticholinesterases:

* **Edrophonium** is a simple alcohol with a quaternary ammonium group. It binds to the active site of the enzyme for 2-10 minutes and then excreted in urine unchanged, so it is not substrate for the enzyme.

* **Carbamates** (physostigmine, neostigmine) undergo a two steps hydrolysis as ACh., but the carbamylated enzyme is resistant to hydration (prolonged to 1/2-6 hours). They are substrate for the enzyme.
2- Irreversible anticholinesterases:
They combine with the active site of the enzyme but the phosphorylated enzyme is stable (needs hundreds of hours for hydrolysis). This phosphorylated enzyme may undergo aging process which strengthens the bond and induces complete and permanent enzyme inactivation, so they have long duration until new enzyme synthesis.

**A- Reversible anticholinesterases**

<table>
<thead>
<tr>
<th></th>
<th>Physostigmine (Eserine)</th>
<th>Neostigmine (Prostigmine)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source</strong></td>
<td>Natural (plant origin)</td>
<td>Synthetic</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td>Tertiary amine - non ionized</td>
<td>Quaternary amine - ionized</td>
</tr>
<tr>
<td><strong>Oral absorption</strong></td>
<td>Complete</td>
<td>Incomplete</td>
</tr>
<tr>
<td><strong>Passage through lipid barrier</strong></td>
<td>Passes to C.N.S.</td>
<td>Can not pass to C.N.S.</td>
</tr>
<tr>
<td><strong>Actions</strong></td>
<td>a. Muscarinic (eye bronchi, heart, gut, urinary ....).</td>
<td>a. Muscarinic</td>
</tr>
<tr>
<td></td>
<td>b. Nicotinic</td>
<td>b. Nicotinic</td>
</tr>
<tr>
<td></td>
<td>c. C.N.S. stimulation (convulsions)</td>
<td>c. Direct skeletal muscle stimulant action.</td>
</tr>
<tr>
<td><strong>Uses:</strong></td>
<td>1- Locally on eye (0.5-1%) in glaucoma, antagonize mydriatics.</td>
<td>1. Diagnosis and treatment of myasthenia gravis.</td>
</tr>
<tr>
<td></td>
<td>2- Systemically it is used in treatment of atropine poisoning but dangerous.</td>
<td>2. Antidote to non depolarizing neuromuscular blockers.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Antidote to atropine (antagonist of peripheral action).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Postoperative urine retention and paralytic ileus.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Paroxysmal atrial tachycardia.</td>
</tr>
</tbody>
</table>

**N.B.: Atropine is given before neostigmine in 1, 2.**

* **Pyridostigmine & ambenonium:** are neostigmine substitutes used in treatment of myasthenia gravis, have weak effect on GIT and have longer duration.

* **Demecarium:** miotic in glaucoma.

* **Tacrine** has anticholinesterase activity and is used in treatment of Alzheimer's disease. It produces nausea, vomiting and hepatic toxicity.

* **Donepezil, Galantamine and rivastagmine** are more selective cholinesterase inhibitor in treatment of Alzheimer’s disease and are not hepatotoxic

**Myasthenia Gravis**

Disease of neuromuscular junction characterized by weakness on repetition of movement. It is an autoimmune process which decreases the number of functioning nicotinic receptors on the post-junctional end-plate.

It is diagnosed by edrophonium test 2mg I.V.

It is treated by cholinesterase inhibitors as neostigmine (give atropine before to block muscarinic receptors), also immunosuppressants may be tried and surgical removal of thymoma if present.
* **Edrophonium:**
  
  Quaternary alcohol which has short duration due to rapid renal excretion, it is not a substrate for cholinesterase enzyme, given I.V. **Used for:**

  1. Diagnosis of myasthenia gravis and to differentiate between cholinergic and myasthenic crisis.

<table>
<thead>
<tr>
<th>Cholinergic crisis</th>
<th>Myasthenic crisis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Due to excessive cholinesterase inhibition → maintained depolarization</td>
<td>Due to ineffective or insufficient treatment by anticholinesterase drugs</td>
</tr>
<tr>
<td>Edrophonium produces more weakness</td>
<td>Edrophonium produces muscle improvement</td>
</tr>
</tbody>
</table>

**B- Irreversible anticholinesterases**

*(Organo-phosphorus compounds)*

They are non-competitive irreversible inhibitors of cholinesterase enzyme. Most of them are highly lipid soluble so can be absorbed from any site including intact skin. Ecothiophate is lipid insoluble

**They are used as:**

1. Insecticides: Parathion and malathion, which are inactive as such and should be converted into the oxygen analogs (parathion into paraoxon and malathion into malaoxon). Malathion is also rapidly metabolized by other pathways into inactive products in mammals so it is safer for public use than parathion.
2. War gas: Tabun, sarin, soman and isofluorophate (di-isopropyl fluorophosphate = DFP) which was previously used in glaucoma
3. *Ecothiophate* is a thiocholine derivative which is lipid insoluble, used in glaucoma once/3-4 weeks, but long use may produce cataract.
4. *Metrifonate* is an oral antibilharzial drug.

**Organophosphorus poisoning:** It is due to inhalation of sprays or dusts of insecticides or contamination of skin or food.

**Symptoms:**

1. **Muscarinic:** bradycardia, hypotension, nausea, vomiting, colic, diarrhea, bronchospasm, miosis, increased secretions.
2. **Nicotinic:** muscle twitches and neuro-muscular blockade of diaphragm and intercostal muscles.
3. **C.N.S.:** restlessness, insomnia, confusion, convulsions, coma and depression of R.C. and V.M.C.
   
   Death is due to respiratory failure (central or peripheral).

   -Chronic exposure to organic phosphate compounds may produce neuropathy
Protection against poisoning:
- Use gloves and spray with direction of wind
- Proper washing of vegetables and fruits
- Give reversible anticholinesterase (carbamates), if poisoning is anticipated.

*Treatment:

1. **Atropine** 2 mg, I.V. or I.M./10 minutes until pupil dilates and skin dries. It antagonizes the muscarinic effects central and peripheral.

2. Cholinesterases reactivators (oximes) as **pralidoxime** (PAM), **diacetylmonoxime** (DAM) 1-2g I.V. infusion over 15-30 mins. They combine with the poison in blood and may dephosphorylate the enzyme if given early before aging of the enzyme. They reverse muscle weakness and are used with atropine. PAM can not pass to C.N.S. but DAM crosses blood brain barrier.

3. Care of respiration by artificial respiration and suction of secretions.

4. Anticonvulsants as **diazepam**, barbiturates, or MgSO₄ injection.

5. Stomach wash if given orally and removal of contaminated clothes and washing of skin with NaHCO₃.

**Muscarinic receptor antagonists**

They produce reversible blockade of the actions of A.Ch. at muscarinic receptors by competition. They have affinity for muscarinic receptors, no efficacy and have slow dissociation rate. They are classified into:

**I. Natural belladonna alkaloids** which include **atropine** and **hyoscine** (scopolamine).

Both are tertiary ammonium alkaloid esters of tropic acid and are present in Datura stramonium, Atropa belladonna and Hyoscyamus niger.

**II. Synthetic derivatives:**

**Atropine**

**Pharmacokinetics:**
Absorbed orally, can be given by injection, metabolized in liver, distributed to all tissues, excreted in urine partly unchanged 60% and $t_{1/2}$ is 2hrs. Rabbits have atropinase enzyme which protects them against effects of atropine (they are tolerant to atropine = species tolerance).

Acquired tolerance occurs on repeated use

**Actions:** compete with Ach for muscarinic receptors

1- Eye:
2. Autonomic Pharmacology

- Mydriasis due to block of muscarinic receptors in constrictor pupillae muscle (passive mydriasis).
- Loss of reaction to light (-ve light reflex).
- Relaxation of ciliary muscle (cycloplegia) so induces loss of accommodation for near vision.
- Impairs aqueous humor drainage so \( \uparrow \) I.O.P.
- Decreases lacrimation.
  
  Local atropine application lasts for 7-10 days.

2- Secretions: Decreases salivary, bronchial, gastric, and sweat secretion.

3- Bronchi: Bronchodilatation and dryness of secretions.

4-C.V.S.: It increases heart rate and A-V conduction due to vagal block. However, low doses may produce initial bradycardia (due to block of presynaptic muscarinic receptors) followed by tachycardia.
  
  - Tachycardia is marked in healthy young adults.
  - On B.V. it has no effect in therapeutic doses as most of vessels have no parasympathetic supply. It blocks V.D induced muscarinic agonist. However, in some individuals and toxic doses cause cutaneous V.D. in the upper part of body especially face (atropine flush).

5- GIT: Decreases motility and secretions.

6- Urinary tract: Relaxes detrusor muscle and contracts sphincters.

7- C.N.S.: minimal stimulant effect on CNS especially parasmpathetic medullary centers
  
  * Stimulates R.C. and C.I.C.
  * Inhibits vomiting center and basal ganglia.
  * Large doses on cortex produce excitation, agitation, hallucination and coma.

Therapeutic uses:

1- Pre-anesthetic medication to:
  
  * Decrease salivary and bronchial secretions and prevent bronchospasm.
  * Antagonize R.C. depressants.
  * Protect heart from bradycardia induced by some general anaesthetics.
  * Prevent vomiting.

  But its disadvantages are urine retention and intestinal hypomotility following surgery.

2-To measure errors of refraction in uncooperative patient (e.g., children). Also for fundus examination (derivatives are better) and to prevent synechia (adhesions) formation in iritis and iridocyclitis

3- Heart block, marked bradycardia and carotid sinus syndrome.

4-Bronchial asthma (but secretions become viscid so better use ipratropium).
5-Colics, gut hypermotility and duodenal ulcer. In traveler's diarrhea, it is combined with **diphenoxylate** (opioid anti-diarrheal drug).

6-Nocturnal enuresis and urinary urgency to reduce bladder motility.

7-Parkinsonism.

8-Motion sickness but **hyoscine** (scopolamine) is better

9-Hyperhidrosis (excessive sweating).

10-In cholinergic poisoning to antagonize muscarinic effects as in organophosphorus poisoning or physostigmine poisoning.

**Adverse effects:**
- Dry mouth, blurred vision, tachycardia, constipation, urine retention, ↑ I.O.P., flush, agitation, delirium and hyperthermia (especially in children). In acute toxicity patient is dry as a bone, blind as a bat, red as a beet and mad as a hatter.

**Treatment of toxicity:** (mainly symptomatic)
- Care of respiration and stomach wash.
- Cold fomentations to reduce hyperthermia.
- **Physostigmine** (1-4 mg) slowly I.V. to antagonize both central and peripheral effects of atropine, but it is dangerous. **Neostigmine** can be used to antagonize peripheral actions.
- Control excitation by diazepam.

**Contraindications:**
- Prostatic hypertrophy.
- Glaucoma (especially closed angle).

**Hyoscine (Scopolamine)**

* It is given orally and can be absorbed form skin, it has a shorter duration with more potent effect on eye and secretions, but less effect on heart.

* It is a tertiary amine as atropine, so stimulates R.C. and C.I.C. and inhibits vomiting centre and basal ganglia, also produces more marked CNS effects (sedation, drowsiness and amnesia).

  Toxic doses produces excitation, agitation, hallucination and coma.

* It has no local analgesic action

**Used** as atropine and preferred in preanaesthetic medication of cardiac and thyrotoxic patients, in obstetric (with meperidine to produce sedation and amnesia), in motion sickness (**Hyoscine** patch on skin), in Meniere's disease to abort vertigo, antispasmodic.
Synthetic atropine substitutes

1-Mydriatic group: Homatropine, cyclopentolate and tropicamide.

<table>
<thead>
<tr>
<th></th>
<th>Atropine 0.5-1%</th>
<th>Hyoscine 0.25%</th>
<th>Homatropine 2-5%</th>
<th>Cyclopentolate 0.5-2%</th>
<th>Tropicamide 0.5-1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>7-10 days</td>
<td>3-7 days</td>
<td>1-3 days</td>
<td>1 day</td>
<td>6 hrs.</td>
</tr>
<tr>
<td>Passive mydriasis</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cycloplegia</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

They are contraindicated in glaucoma.

2-Antisecretory antispasmodic group: They have antimuscarinic action especially on GIT, insignificant central action (quaternary amine) and in large dose they block nicotinic receptors in autonomic ganglia and motor end-plate.
* They include: Propantheline, oxyphenonium (antrenyl), atropine methyl nitrate and hyoscine butyl bromide (buscopan).
* They are used in duodenal ulcer and colics.
* They are contraindicated in glaucoma and prostatic hypertrophy.

Pirenzepine and telenzepine are selective M1 blockers, used in duodenal ulcer (limited use now).

3-Ipratropium (atrovent) and Tiotropium: are muscarinic blockers, which produce bronchodilatation without dryness of secretions. They are quaternary amine and are given by inhalation in bronchial asthma.

4-Anti-parkinsonian group: benzhexol = trihexphenidyl (artane) and benztropine (congentin).

5-Emepronium: is used to reduce bladder motility in incontinence and nocturnal enuresis.
* Oxybutynin is used to relieve bladder spasm after urological surgery and incontinence.
* Tolterodine is M3 blockers for treatment of urinary incontinence.
DRUGS affecting ganglion

1- Ganglion stimulants

- They act on nicotinic receptors (in both sympathetic and parasympathetic ganglion), so the effects will depend on the predominating tone.

**Nicotine**

**Mode of action:**
1. Stimulation of ganglion in small dose and block in large dose.
2. Stimulation of chemoreceptors in carotid and aortic bodies.
3. C.N.S. stimulation.
4. Stimulation of catecholamine release from chromaffin tissue.

**Actions:**
- C.V.S.:
  - Tachycardia, ↑COP, ↑B.P., V.C. of all vessels except coronary and skeletal vessels (which are dilated).
  - ↑ Fatty acid concentration and platelet aggregation.
  - ↑ Gut motility.
  - Stimulation of C.T.Z., ADH release, indirect R.C. stimulation and direct C.N.S. stimulation (tremors and convulsions) followed by depression.
    - Tolerance occurs on repeated use and cross tolerance with lobeline.

**Acute toxicity:**
- Nausea, vomiting, diarrhea, hypertension then hypotension, miosis then mydriasis, convulsions, and respiratory stimulation then depression.
  - Treated by stomach wash with K-permanganate and artificial respiration.

**Effect of chronic tobacco smoking:**
- Nasopharyngeal and bronchial irritation.
- Salivation and inhibition of hunger pains.
- Extrasystole, atherosclerosis, angina pectoris and Buerger's disease.
- Cancer lung and larynx.
- Spasm of retinal vessels, so ↓ acuity of vision (tobacco amblyopia).
- High incidence of abortion and neonatal mortality.

**Interactions:** Tobacco smoking is enzyme inducer so decreases the effect of itself, caffeine and theophylline.

**Contraindications:** Peripheral vascular disease-angina pectoris – hypertension – arrhythmias - respiratory diseases-peptic ulcer.

**Lobeline** is used as a respiratory stimulant (reflexly) in neonatal asphyxia, it is given intraumbilical.
2. Ganglion blockers

They are classified into:

- **a-Depolarizing blockers:** ganglion stimulants in large dose, they produce initial stimulation then block.

- **b-Non-depolarizing (competitive) blockers:**
  - Quaternary amines: *tetraethylammonium* (TEA), *hexamethonium*, *pentamethonium*, *pentolinium*, and *chlorisondamine* (*ecolid)*.
  - Secondary amine (*mecamylamine*) and tertiary amine (*pempidine*). They have C.N.S. stimulant action.
  - *Trimethaphan* (*arfonad*): which is short acting, histamine liberator and has direct V.D. effect, given by I.V. infusion. It has no C.N.S. effects.

**Action:** Normally the parasympathetic tone is predominating allover the body except on B.V., so ganglion blockers will produce effects as atropine + postural hypotension + impotence.

<table>
<thead>
<tr>
<th>Predominant tone</th>
<th>Ganglion block</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Eye *</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td></td>
<td>Passive mydriasis, cycloplegia, ↑ I.O.P.</td>
</tr>
<tr>
<td>* Salivation</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td>* Bronchi</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td></td>
<td>Bronchodilatation</td>
</tr>
<tr>
<td>* H.R.</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
</tr>
<tr>
<td>* Gut motility</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td>* Urinary tract</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td></td>
<td>Urine retention</td>
</tr>
<tr>
<td>* Erection</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td></td>
<td>Impotence</td>
</tr>
<tr>
<td>* Ejaculation</td>
<td>Sympathetic</td>
</tr>
<tr>
<td></td>
<td>Impotence</td>
</tr>
<tr>
<td>* Sweat</td>
<td>Sympathetic</td>
</tr>
<tr>
<td></td>
<td>Anhidrosis</td>
</tr>
<tr>
<td>* B.V.</td>
<td>Sympathetic</td>
</tr>
<tr>
<td></td>
<td>Dilate arterioles, ↓ TPR, Dilate veins, ↓ COP, So ↓ B.P.</td>
</tr>
</tbody>
</table>

**Uses:** Trimethaphan can be used in hypertensive emergency, and to induce controlled hypotension in surgery
2. Autonomic Pharmacology

**Sympathomimetics**

- **Catecholamines**
  - contain catechol nucleus
  - Natural: Dopamine, noradrenaline, adrenaline.
  - Synthetic: Isoprenaline (isoproterenol), dobutamine, isoetharine.

- **Non-catecholamines**
  - as ephedrine, amphetamine, ... etc

**Mechanism of action:**
1. Direct action on adrenergic receptors as catecholamines, phenylephrine, salbutamol.
2. Indirect acting by releasing noradrenaline as tyramine, amphetamine and ephedrine or by blocking uptake-1 (cocaine).
3. Mixed acting (dual mechanism) as ephedrine.

**N.B.:**
- Following sympathectomy or depletion of catecholamine stores the effect of indirect acting sympathomimetics is diminished, while direct acting induce exaggerated effect.
- Indirect acting drugs stimulate $\alpha$ and $\beta_1$ receptors.
- Tachyphylaxis (acute acquired tolerance) is observed with indirect acting sympathomimetics.
Signal transduction mechanism of adrenergic agonist:

- \( \beta \)-receptor stimulation results in activation of adenyl cyclase through Gs protein so increase cAMP.
- \( \beta \)-receptor stimulation results in smooth muscle relaxation (may be through phosphorylation of myosin light chain kinase into inactive form). It may also act by increasing \( Ca^{++} \) influx and activation of voltage sensitive \( Ca^{++} \) channels.
- \( \alpha_1 \) receptor stimulation through Gq protein activates phospholipase C (PLC) leading to release of IP\(_3\) and DAG. IP\(_3\) increases cytoplasmic Ca concentration which activates Ca dependent protein kinases and DAG activates protein kinase C.
- \( \alpha_2 \) receptor activation inhibits adenyl cyclase through Gi protein and decreases cAMP.

![Diagram](image)

Adrenaline (Epinephrine)

Natural in adrenal medulla, it is unstable in aqueous or alkaline solution and in presence of light (oxidized into adrenochrome which is pink in colour, so it is put in dark bottles and reducing agent is added). It is more stable in blood due to ascorbic acid and glutathione (reducing agents).

Pharmacokinetics:

- Ineffective orally (due to V.C. and destruction by gut juices and metabolism in liver).
- Slowly absorbed if given S.C. (V.C.), rapidly absorbed after I.M. injection (V.D.).
- It is inactivated by tissue uptake (80%), enzymatic degradation by MAO and COMT and small part is excreted unchanged in urine.

Action: direct agonist on \( \alpha \) and \( \beta \) receptors.

Local actions:
- Decongestant and hemostatic.
- Delay absorption of drugs when given S.C.
- Inhalation in bronchial asthma.
- On eye: decongestion with little effect on size of pupil due to V.C., destruction by alkaline tears and metabolism by enzymes.
  I.O.P. is decreased due to reduced aqueous formation, increased drainage.

**Systemic actions:**
- C.V.S.: Heart (β₁): +ve inotropic, chronotropic, increased excitability, conductivity (+ve dromotropic), ↑ COP
- B.V.: V.C. of skin and mucous membrane vessels (α₁), V.D. of skeletal muscle vessels (β₂)
- B.P.: Increases systolic due to ↑COP while diastolic is usually decreased. But large dose ↑ peripheral resistance.
  The hypertensive effect is reversed by α-blocker.

[Diagram showing B.P. changes with Adr., α-blocker, and Adr.]

- Respiration: Bronchodilatation (β₂) decongestion (α₁), reflex apnea due to ↑B.P.
- GIT: Decreases tone and motility (α & β)
- Urinary: Relaxes wall (β₂) contracts sphincter(α₁).
- Uterus: Variable with species, phase of sexual cycle and gestation. In human it contracts non pregnant uterus (α-effect), but relaxes in late pregnancy (β₂)
- Eye: Active mydriasis (α₁).
- Increases sweat secretion from apocrine sweat glands located on the palms of hands and other areas (α). These glands are non-thermoregulatory glands usually associated with psychologic stress. Other sweat glands contain muscarinic receptors.

**Metabolic actions:**
1. Hyperglycemia due to enhanced liver glycogenolysis (β₂) and inhibition of insulin release (α₂).
2. Increases blood lactate level.
3. Increases fatty acid concentration (β₁), ↑ lipolysis in fat cells (β₃).

**Antiallergic action:** It is the physiological antidote to histamine on B.P and bronchi (act on different receptors).

**Increased blood coagulation** by activating factor V.

**Weak C.N.S. action:** anxiety and tremors.
Skeletal muscles: Facilitates transmission and antifatigue.

Hypokalemia: due to increase $K^+$ uptake in cells

Therapeutic uses:
1. Allergy, angioneurotic oedema and anaphylactic shock.
2. With local anaesthetic to decrease absorption, prolong duration, hemostatic and decrease toxicity.
3. In nasal bleeding (epistaxis) locally.
4. Cardiac arrest (intracardiac).
5. In open (wide) angle glaucoma. The dipivaloyl derivative (dipivefrin) which is a prodrug of adrenaline is better.
6. Acute bronchial asthma.
7. Insulin hypoglycemia.

Adverse effects:
- Restlessness, tremors, anxiety, headache.
- Tachycardia, palpitation, anginal pain.
- Cardiac arrhythmia with halothane and digoxin (treated by $\beta_1$-blocker).
- Sudden rise of B.P. leading to cerebral hemorrhage.
- Gangrene if used with local anaesthetics in fingers and toes.
- Repeated use produces necrosis of B.V. and myocardium which can be prevented by $\alpha + \beta$ blockers and $Ca^{++}$ channel blockers.
- Long use on eye $\rightarrow$ blurred vision, conjunctival hyperaemia and pigmentation.

Contraindications:
- Coronary heart disease.
- Hypertension.
- Hyperthyroidism.
- With cardiac glycosides (digitalis) or halothane.
- With local anaesthetics in fingers, toes and circumcision.
- With non selective B-blockers.
- With MAO inhibitors (MAOIs)
Noradrenaline (Norepinephrine)

It is the chemical transmitter at postganglionic sympathetic except to sweat glands, present also in brain and adrenal medulla (20% of its secretion).

**Pharmacokinetics:** Ineffective orally, due to strong V.C., it is given only by I.V. infusion.

It has the same fate as adrenaline.

**Actions:** Direct on $\alpha$ and $\beta_1$ receptors.

- **C.V.S.:**
  - Heart ($\beta_1$): $\uparrow$ H.R. (masked by reflex bradycardia).
  - B.V.:
    - V.C. of skin, mucous membrane and skeletal muscle vessels so $\uparrow$ TPR $\rightarrow$ elevate both systolic and diastolic B.P. $\rightarrow$ reflex bradycardia mediated through vagus nerve which masks the $\beta_1$ stimulant effect.
    - Stroke volume is increased but COP is little affected or decreased.
    - It stimulates isolated heart ($\beta_1$ effect), also stimulates the heart after vagotomy or atropine.

  **Other actions:** as adrenaline but with predominant $\alpha$-effect.

**Uses:** Used as hypertensive agent, e.g., in spinal anaesthesia, after sympathectomy or overdose with ganglion blockers. Given by I.V. drip (0.2% sol., 4 ml, with 1 liter glucose or saline, 0.5 ml/minute) with recording of B.P. every 10 minutes and infusion should be stopped gradually.

**Adverse effects:**
- Anxiety, headache, bradycardia.
- Excessive hypertension.
- Extravasation $\rightarrow$ necrosis and sloughing.

Dopamine (Intropin)

Natural, precursor of noradrenaline. It is present in brain and act as chemical transmitter in basal ganglia. It can't pass B.B.B. (but L-dopa can pass).

**Pharmacokinetics:**
- Ineffective orally, it is given by I.V. infusion.
- Small part is converted into noradrenaline and adrenaline but the main part is metabolized by MAO and COMT to be excreted in urine as homovanillic acid.

**Actions:** Acts as agonist on $\alpha$ and $\beta_1$ receptors and specific dopaminergic receptors (in renal and mesenteric vessels).
- Low rate of infusion ($D_1$ effect) $\rightarrow$ V.D. of renal, mesenteric, coronary and intracerebral vessels which can be antagonized by dopaminergic blocker as haloperidol. $D_2$ presynaptic receptor stimulation decreases noradrenaline release.
2. Autonomic Pharmacology

- Moderate rate of infusion $\rightarrow \uparrow$ contraction, COP and H.R. Action mediated by $\beta_1$-receptor and noradrenaline release. So $\uparrow$ systolic pressure and diastolic is unchanged or slightly increased.
- High concentrations through ($\alpha_1$ effect) produce V.C., which can be antagonized by $\alpha$-blocker.

**Uses:** Cardiogenic, endotoxic and hypovolemic shock with correction of hypovolemia.

**Adverse effects:** Nausea, vomiting, arrhythmia, angina, headache, hypertension and extravasation may occur leading to necrosis.

**Administration:**
I.V. infusion 2.5 ug/kg/min., with monitoring of H.R., B.P. and urine flow.
The dose is reduced in patients taking MAO inhibitors.

**Fenoldopam**

It is a $D_1$ receptor agonist which decreases TPR by dilating arterioles.
It is given by I.V. drip in emergency hypertension.
It is rapidly metabolised by conjugation and $t_{1/2}$ is 5 minutes.

**Side effects:** headache, flushing, tachycardia and $\uparrow$ I.O.P

**$\beta$-adrenergic agonists**

**Isoprenaline (Isoproterenol)**
Synthetic catecholamine.

**Pharmacokinetics:**
- Not effective orally, can be given sublingual, inhalation, and parenterally.
- Inactivated by tissue uptake (mainly II), enzyme degradation by COMT and by MAO to less extent.

**Actions:** direct agonist on $\beta$ receptors

* **C.V.S.:**
  - Heart: ($\beta_1$) increase all properties, so $\uparrow$ COP
  - B.V.: V.D. of skeletal muscle and coronary vessels ($\beta_2$) so $\downarrow$ TPR
  - B.P.: Increases systolic and decreased diastolic pressure $\rightarrow \downarrow$ mean pressure $\rightarrow$ reflex tachycardia.
* Bronchi: relaxation ($\beta_2$).
* Uterus: relaxation ($\beta_2$).
* Metabolic: $\uparrow$ Lipolysis, hyperglycemia, (less than adrenaline), it $\uparrow$ insulin release, $\uparrow$ glycogenolysis.
Uses:  - Acute bronchial asthma.
       - Heart block.

Administration: Inhalation, injection, or sublingual (rapid onset, bypass liver metabolism and is easily removed).

Adverse effects:
- Palpitation, tachycardia, arrhythmia, anginal pains, flushing, headache and tremors.

Selective $\beta_1$-agonists
Dobutamine (Dobutex)
Sympathomimetic synthetic catecholamine
Pharmacokinetics: Given by I.V. infusion, metabolized by COMT.
Actions:
- Selective $\beta_1$ agonist and to some extent $\alpha$.
- +ve inotropic more than chronotropic (affects contractility > H.R.).
- It has little effect on peripheral resistance.
- Does not stimulate dopaminergic receptors.
Uses: For short-term treatment of cardiac decompensation after cardiac surgery or myocardial infarction (cardiogenic shock).
- Given by I.V. infusion (2.5 - 10 ug/kg/min.).
Side effects: Tachycardia, palpitations, arrhythmia, headache, nausea, anginal pains and hypertension.

Selective $\beta_2$ receptor agonists
(stimulate $\beta_2$$\beta_1$)
* Catecholamines: isoetharine (metabolized by COMT).
* Non-catecholamines: They are not affected by MAO and COMT.
  Short acting (4hrs duration): salbutamol, terbutaline.
  Long acting (12hrs duration): formoterol and salmeterol.
Actions:
1-Bronchodilation, reduce bronchial secretion, increase mucociliary activity and inhibit release of allergotoxins from mast cells. This is mediated through activation of adenylcyclases so $\uparrow$ cAMP.
2-V.D. of skeletal muscle vessels $\rightarrow \downarrow$ B.P.
3-Uterine relaxation.
4-Mild tachycardia (reflex and weak $\beta_1$ effect).
5-$\uparrow$ Glycogenolysis and increase insulin release.
Uses: - In bronchial asthma (acute attack and prophylaxis).
2. Autonomic Pharmacology

- Given by inhalation (which provides drug directly to site of action and minimizes systemic effects). Some of them can be given oral and parenteral.

**Adverse effects:** Skeletal muscle tremors. Dose dependent effects include tachycardia and hypokalemia, which are mild, if drug is given by inhalation.

**Ritodrine** is selective $\beta_2$ stimulant, used in premature labour, dysmenorrhoea, and contraction ring of uterus.

### $\alpha$-Adrenergic agonists

* **Selective $\alpha_1$ agonists:**
  - **Phenylephrine** and **methoxamine**, which are given by injection and phenylephrine, can be used orally or locally on eye.
  - **Midodrine** is a prodrug given orally and is enzymatically hydrolyzed into desglymidodrine ($\alpha_1$ selective agonist)
    - It is used mainly in treatment of postural hypotension.

**Actions:**
- Decongestion of mucous membrane.
- Active mydriasis, no cycloplegia.
- V.C. of all vessels so increase the TPR and elevate both systolic and diastolic B.P. $\rightarrow$ reflex bradycardia.
- H.R. is reflexly decreased (blocked by atropine or ganglion blocker).

**Uses:**
- **Phenylephrine** is used as a decongestant and active mydriatic. Also used to treat hypotension and paroxysmal atrial tachycardia (PAT).
- **Methoxamine** is given parenterally (usually I.V.) in treatment of hypotension and in treatment of PAT ($\uparrow$ B.P. $\rightarrow$ $\downarrow$ H.R. reflexly, but don't exceed 160 mmHg systolic pressure).

* **Nasal decongestants:**
  a) **Local**: Naphazoline (privine), xylometazoline (otrivin) and tetrahydrozoline (tyzine). There is no rebound congestion, but produce drowsiness in infants.
  b) **Oral**:
    - **Pseudoephedrine** relieves congestion, it has wide safety margin
    - **Phenylpropanolamine** (norephedrine): is similar to ephedrine with less C.N.S. actions. Used as a decongestant orally in cold medication. It is withdrawn due to haemorrhagic strokes.

**N.B.:** Ephedrine and phenylephrine can be used locally or orally as decongestant.

**Ephedrine**
- Non catecholamine, plant origin or synthetic.
Pharmacokinetics: Effective orally (not metabolized by MAO or COMT) and excreted in urine. It is a weak base so acidic urine increases its excretion.

Actions: Stimulates α, β receptors by dual mechanism.

* Local actions:
  - Hemostatic and decongestant.
  - Active mydriatic (weak in heavy pigmented iris which is racial tolerance).

* Systemic:
  - As adrenaline but with slow onset, long duration and more α-effect.

C.V.S.:
  - Stimulates heart, increases systolic and diastolic B.P. which is blocked by α-blocker, tachyphylaxis occurs.

Smooth muscles:
  - Bronchi, intestine, urinary and uterus as adrenaline.

C.N.S.:
  - Stimulates cortex, vital medullary centers and reticular activating system → insomnia.
  - Facilitation of the transmission in neuro-muscular junction.

Uses:
  - Inbetween attacks in bronchial asthma (prophylaxis).
  - Prevent fall of B.P. during spinal anaesthesia.
  - Myasthenia gravis (with neostigmine).
  - Nocturnal enuresis.
  - Nasal decongestant (rebound congestion).
  - Heart block - Narcolepsy-Mydriatic.

Adverse effects: As adrenaline + insomnia, tolerance, retention of urine in prostatic hypertrophy.

Amphetamine

- Synthetic non-catecholamine.
- It acts indirectly with prominent C.N.S. action.
- Absorption and fate as ephedrine.
- Excretion is increased in acidic urine (base drug).

Actions:

1. C.N.S. actions: It stimulates cortex, reticular activating system, midbrain and spinal cord manifested by:
   - Euphoria, wakefulness and ↑ mental activity.
   - Analeptic action (stimulates vital medullary centers).
   - Enhances analgesia of morphine.
   - Facilitates mono- and polysynaptic transmission.
   - Decreases appetite.
2. Sympathomimetic action:
As ephedrine but usually with bradycardia and little effect on bronchi.

Tolerance: Occurs to anorexigenic and psychic action.

Addiction: On prolonged use.

Uses:
- Narcolepsy
  - Attention-deficit hyperkinetic disorder in children (ADHD).
  - Obesity - psychic depression - nocturnal enuresis - mydriatic - nasal decongestant

Adverse and toxic effects:
- Palpitation, hypertension, arrhythmia, mydriasis, anxiety, anorexia, loss of weight, insomnia, hallucination, convulsions, coma, psychosis (schizophrenia), and addiction.

Contraindications:
- As adrenaline + insomnia, prostatic hypertrophy and with MAO inhibitors.

Amphetamine derivatives:
- Methamphetamine: more C.N.S. action with less peripheral action.
- Phenmetrazine (Preludin) - diethylpropion (Tenuate), Diphenmetrazine are used in obesity.

N.B.:
- **Methylphenidate** is amphetamine variant which is used in Attention-deficit hyperkinetic disorder in children (ADHD).

Tyramine
Indirect acting sympathomimetic which is present in cheese, youghourt, and is metabolized by MAO.

In patients taking MAO inhibitors a hypertensive crisis may be precipitated (treated with α-blocker).
**Sympathetic depressants**  
*(Sympatholytic drugs)*

1- Adrenoceptor blockers alpha and beta - blockers.
2- Adrenergic neuron blockers which inhibit noradrenaline release (guanethidine, bretylium) or deplete noradrenaline stores (reserpine).
3- Inhibitors of noradrenaline synthesis (α-methyl dopa, α-methyl tyrosine).
4- Ganglion blockers.
5- α₂ stimulants (clonidine, guanfacine, guanabenz and α-methyl dopa).

---

*N.B.*:

*α –Methyl-tyrosine inhibits conversion of tyrosine into Dopa by inhibiting tyrosine hydroxylase enzyme.*

**Adrenoceptor Blocking Drugs**  
*(1) α-Blockers*

- They can prevent the pressor effect of α-agonists, but convert the pressor effect of adrenaline (epinephrine) into a depressor response.
- α₁ adrenergic antagonists decrease B.P. due to decreased TPR.
  The fall in B.P. will ↑ H.R. and COP & produce fluid retention.
- Block of α₂ receptors will ↑ noradrenaline release.
- Most of them produce tachycardia, which is reflex due to hypotension and also due to block of α₂ receptors.
- They produce nasal stuffiness and decrease adrenergic sweating.
- They are reversible competitive except phenoxybenzamine which is irreversible and non-competitive.

α -blockers are classified into:

1- Non selective α blockers (block both α₁ and α₂)
  - Imidazoline derivatives: **tolazoline, phentolamine**.
2. Autonomic Pharmacology

- B-haloalkylamines: **phenoxybenzamine**.

2- Selective $\alpha_1$ blockers **prazosin, trimazosin, tamsulosin, indoramin**.

3- $\alpha_1$ and $\beta$ receptors blockers : **labetolol, carvedilol**.

4-Selective $\alpha_2$ blockers **yohimbine** (aphrodisiac, ↑ADH release).

**Therapeutic uses of alpha-blockers**:

1-Hypertension due to excess catecholamines as pheochromocytoma, excessive sympathomimetic administration and sudden clonidine withdrawal.

2-Selective $\alpha_1$ blockers in primary hypertension.

3-Peripheral vascular diseases (Ca$^{++}$ blockers can be used).

4-To reverse severe V.C. caused by leakage of noradrenaline during I.V. infusion.

5-Benign prostatic hyperplasia (BPH) to antagonise smooth muscle contraction in enlarged prostate by selective $\alpha_1$ antagonists as prazosin, doxazosin. Tamsulosin (selective $\alpha_1$-A antagonist) is more selective and has less effect on BP.

6-Erectile dysfunction: phentolamine is injected intracavernous with papaverine (non specific dilator) to induce erection in male sexual dysfunction. Systemic absorption, priapism and fibrotic changes may occur on repeated use.

**N.B.: Most of $\alpha$ blockers (except selective $\alpha_1$ blockers as prazosin) are not effective alone in treatment of essential hypertension because they block $\alpha_1$ and $\alpha_2$. The block of $\alpha_2$ will increase noradrenaline release and so increase B.P. again.**

1-**Phentolamine**: Potent competitive $\alpha$-receptors antagonist.

- It reduces peripheral resistance through $\alpha$-blocking effect and additional non-adrenergic action.
- It stimulates heart so produces tachycardia.
- It has agonistic effect on muscarinic, H$_1$ & H$_2$ receptors and has antiserotonin action.
- It stimulates heart and gut.

**Uses:**

1-In peripheral vascular diseases.

2- Control hypertension resulting from pheochromocytoma, overdose of sympathomimetic drugs or clonidine withdrawal.

3- It was used in diagnosis of sustained pheochromocytoma (greater than average drop occurs), but it is a dangerous test.

**Adverse effects:** Tachycardia, arrhythmia, angina pectoris and gastrointestinal stimulation causing diarrhea and increased gastric acidity.

**Contraindications:** Peptic ulcer – cardiac arrhythmia.

**Tolazoline**: is similar to phentolamine but better absorbed orally and is less potent. It is used in peripheral vascular diseases.
2. Autonomic Pharmacology

2-Phenoxybenzamine:
Given orally but bioavailability is low.

**Actions:**
- α-blocking action with slow onset long duration. It is irreversible non-competitive antagonist.
- Blocks uptake I and II of norepinephrine.
- Blocks H₁, muscarinic and serotonin receptors.

**Uses:** see before.

**Adverse effects:** postural hypotension - tachycardia - nasal stuffiness - failure of ejaculation - fatigue - sedation and nausea.

3-Prazosin (minipres):
- It blocks postsynaptic α-receptors (α₁)
- It produces V.D. of both arterioles and veins so reduces both afterload and preload. It decreased B.P. with little effect on H.R.
- It is given orally, extensively metabolized and oral bioavailability is 50%.

**Uses:**
Treatment of essential hypertension, peripheral vascular diseases, pheochromocytoma.
Benign prostatic hyperplasia (BPH).

**Adverse effects:** Postural hypotension with first dose (so start with small dose at bedtime), salt retention and sexual dysfunction.

(2) β-Adrenoceptor Blockers

**Pharmacokinetics:** They are given orally or I.V. and sustained release preparations are available (e.g., propranolol).
- **Propranolol** is extensively metabolized in liver (first pass), so it has low oral bioavailability which is increased by giving large doses. There is great individual variability in plasma concentration after oral propranolol.
- Most of β-blockers are rapidly eliminated with half-lives of 2-5 hours due to hepatic metabolism mainly as they are lipophilic so enter liver cells and pass to brain inducing C.N.S. actions (sedation, sleep disturbances). Elimination of these drugs may be impaired in liver disease, reduced hepatic flow or by hepatic enzyme inhibitors. They are given t.d.s.
- **Nadolol, atenolol** and **sotalol** are less lipid soluble and so have poor C.N.S. actions. They are eliminated mainly unchanged in urine particularly nadolol and so half-life is prolonged in renal failure. They have long duration so given once daily.
Classification:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Partial agonist activity (ISA)</th>
<th>Membrane stabilizing action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Non selective (block $\beta_1$ &amp; $\beta_2$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Propranolol</td>
<td>O</td>
<td>+</td>
</tr>
<tr>
<td>* Oxprenolol</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>* Pindolol (potent)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>* Timolol (potent)</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>* Nadolol (long)</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>* Sotalol (long)</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>2) Cardioselective (block $\beta_1$&gt;$\beta_2$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Atenolol (long)</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>* Bisoprolol</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>* Acebutolol</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>* Celiprolol</td>
<td>+ ($\beta_2$)</td>
<td>O</td>
</tr>
<tr>
<td>* Metoprolol</td>
<td>O</td>
<td>+</td>
</tr>
<tr>
<td>* Betaxolol</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>* Esmolol (ultrashort)</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>3) $\beta +\alpha_1$ blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Labetalol</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>* Carvedilol (antioxidant)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4) Butoxamine is selective $\beta_2$ blocker, not used clinically.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-Esmolol is an ultrashort acting $\beta$ blocker given by I.V. infusion. It is used to control cardiac arrhythmia and emergency intraoperative or postoperative hypertension. It is hydrolyzed by esterase enzyme in RBCs and $t_{1/2}$ is 10 minutes.

**N.B.:**

- **$\beta$-blockers may be classified into:**
  * Antagonists: propranolol, timolol, atenolol and metoprolol.
  * Partial agonist: oxprenolol, pindolol, acebutolol and labetalol.

- **According to pharmacokinetics, we have:**
  * Lipophilic as propranolol, oxprenolol, timolol.
  * Hydrophilic as nadolol, sotalol, atenolol (long acting).

**Actions of $\beta$-blockers:**

1- C.V.S.:
- -ve inotropic, chronotropic action, so decrease COP and B.P. thus decrease myocardial work and myocardial $O_2$ requirements.
- Antiarrhythmic action (class II). They decrease H.R., conduction, excitability and automaticity.
- Induce hypotensive effect on prolonged use in hypertensive patients due to:
  a-Inhibition of renin release.
  b-Reduction in COP (initially).
  c-Resetting of baroreceptor mechanism.
d-Block of presynaptic $\beta$-receptors central and peripheral so decrease noradrenaline release and $\downarrow$ sympathetic outflow.

e-Decrease TPR (late, although they may increase it initially).

- Block the hypotensive effect of isoprenaline and $\beta_2$ stimulant, but augment the hypertensive effect of adrenaline.

2-Respiration: Blockade of $\beta_2$ receptors in bronchi may $\uparrow$ airway resistance particularly in asthmatic patients. $\beta_1$-blockers are less liable to induce bronchospasm.

3-Metabolic actions.

- Inhibit lipolysis induced by sympathetic stimulation.
- They may increase the hypoglycemic effect of insulin in diabetic patients and mask hypoglycemic manifestations except sweating.
- Chronic use $\uparrow$ VLDL and $\downarrow$ HDL which is less likely to occur with partial agonist $\beta$-blockers.
- Block hypokalemia of adrenaline.

4-Reduce I.O.P. most probably due to reduced aqueous formation, but have no effect on pupil size or ciliary muscle.

5-Antianxiety action particularly propranolol.

6-Decrease portal pressure in liver cirrhosis

7-Other actions (with some blockers).

- Partial agonistic action (intrinsic sympathetic activity = ISA).
- Local anaesthetic action (membrane stabilizing action = quinidine like), due to inhibition of $\text{Na}^+$ channels. This effect is unlikely after systemic use due to low concentration achieved.

Uses:

A-CVS

1-Ischemic heart diseases. In prophylactic treatment of angina (stable and unstable), but not in variant angina.

Long-term use in acute myocardial infarction may prolong survival and limit size of infarction.

2-Arrhythmias either auricular (as paroxysmal atrial tachycardia) or ventricular due to myocardial infarction, general anaesthesia, thyrotoxicosis during surgery and in digitalis toxicity.

3-Hypertension (no postural hypotension occurs).

4- Pheochromocytoma (combined with $\alpha$-blockers) and in dissecting aortic aneurysms (with sodium nitroprusside).

5-Obstructive hypertrophic cardiomyopathy (chronic hypertrophic subaortic stenosis) and some cases of heart failure (see C.V.S).

N.B.: Carvedilol has antioxidant and is used in treatment of heart failure
6. Thyrotoxicosis to control symptoms and in thyrotoxic crisis (thyroid storm). Use β-blockers with no I.S.A. They may inhibit conversion of T₄ into T₃.

7. Portal hypertension in alcoholic cirrhosis

B. Others

1. Glaucoma particularly open angle glaucoma by timolol locally which has no local anaesthetic action, but sufficient amount may be absorbed. Betaxolol, carteolol and levobunolol are newer agents in glaucoma.

2. Prophylactic treatment for migraine headache.

3. To control essential tremors and anxiety.

Adverse effects:

1. Sudden cessation of therapy after chronic use may be followed by sympathetic overactivity (angina, infarction or arrhythmia). This may be due to increased number (up-regulation) of beta receptors.

2. Precipitation of heart failure when COP is dependent on sympathetic drive in patient with abnormal myocardial function.

3. Heart block and severe bradycardia (treated with atropine).


5. Hypotension.

6. Cold extremities and exacerbation of Raynaud’s phenomenon (due to reduced peripheral blood flow).

7. Fatigue, depression and sleep disturbances.

8. Enhance the hypoglycemic effect of insulin in diabetic patient and mask clinical signs of hyperthyroidism.


10. Increased VLDL and decrease HDL.

Contraindications:

1. Partial heart block.

2. Heart failure (except certain cases), see CVS.

3. Hypotension.

4. Peripheral vascular diseases.

5. Alone in pheochromocytoma.

6. Variant (Prinzmetal’s) angina.

7. Bronchial asthma (β₂-blockers).

8. Never stopped suddenly.

9. Not combined with verapamil or diltiazem.

10. Care in diabetic patients.