Pharmacology: is a science of drugs.

- **A drug:** is a **chemical** agent which modify some functions of a biological system.

Sources of drugs

A) **Natural**

1. Plants (atropine)
2. Animals (insulin)
3. Microorganims (penicillins)
4. Minerals (iron, zinc)

B) **Synthetic (most drugs)**

1. Semi-synthetic: (e.g. penicillin derivatives)
2. Synthetic (e.g sulfonamides,…)

Names of drugs

Every drug has 3 names:

1. **Chemical group name.**
2. **Generic name or official name): It is uniform all over the world.**
3. **Trade name.**

Example:

Chemical name: Acetyl salicylic acid

Official name: Aspirin.

Trade Name: Juspirin, Ezacard, Dispirin (india), Bayer's aspirin

Types of drug action:

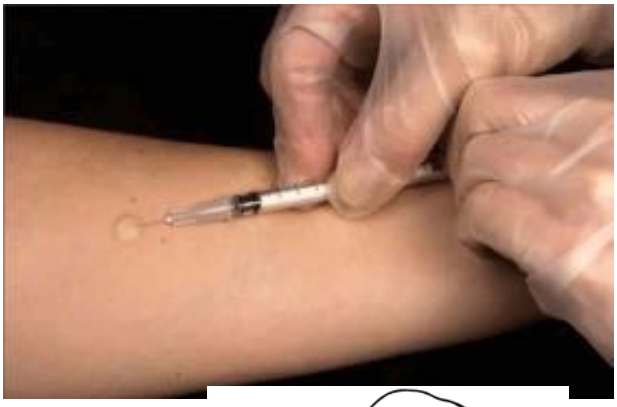
1. Local (topical): drug acts at the application site (e.g. eye drops)
2. Systemic (general): drug acts on different systems.
3. Reflex action: drug acts on one site and elicits response on another site (e.g. reflex tachycardia of vasodilators).

Routes of drug administration

A) Local B) Systemic

A) Local: If the site of drug action is surface of the body or if the site can be reached easily, i.e. by an injector needle, drugs can be applied locally.

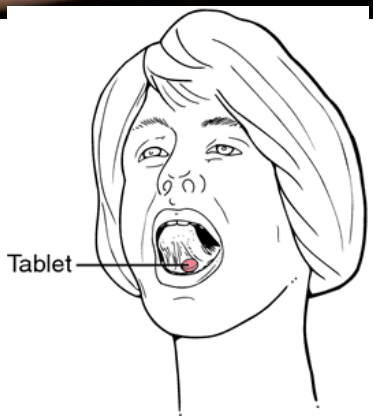
- ✓ Epidermal (percutaneous) (e.g cream,..
- ✓ Subcutaneous (e.g local anethetics, allergy test,..)
- ✓ Conjunctival
- ✓ Intranasal
- ✓ Buccal
- ✓ Intrathecal
- ✓ Intrapleural
- ✓ Intrauterine
- ✓ Intracardiac
- ✓ Intravaginal
- ✓ Intraarticula



- B) systemic:
- <u>There are 4 main routes for systemic administration of drugs</u>:
  - ✓ Enteral route
  - ✓ Parenteral route
  - ✓ Inhalation
  - ✓ Transdermal route

<u>ENTERAL ROUTE</u>

- The drug is given to GI tract and absorbed from GI tract.
- <u>There are 3 ways for enteral route</u>:
  - ❑ **Oral**
  - ❑ **Sublingual**
  - ❑ **Rectal**



<u>What are the advantages and disadvantages of every route?</u>

1) Oral route

Advantages	Disadvantages
▪ Easy	▪ Not very fast
▪ Safe	▪ Variable absorption
▪ Painless	▪ Not suitable for emergency
▪ No need for equipment	▪ Not suitable for unconscious , Vomiting
	▪ FIRST pass Metabolism

What

First f the dru

systemic circulation, occur with oral and partly rectal routes of administration.

First pass usually occurs in the liver but may be in the stomach HCL, intestinal cells or enzymes and in the portal vein.

2) Intravenous

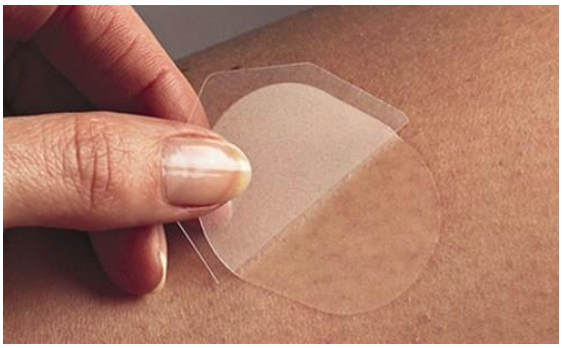
Advantages

- 1-Rapid onset of action
- 2- accurate dose adjustment
- 3-Suitable in emergency
- 4. Suitable in vomiting and diarrhea
- 5- suitable for large volume of fluids (glucose, saline,..)
- 6. bypass first pass metabolism.

Disadvantages

- 1- infection
- 2- difficult to treat verdose
- 3- needs trained professionals
- 4- Not suitable for oily substance or repository (depo) form.

3) Transdermal



Advantages

- 1- Easy
- 2- Not painful
- 3- Sustained release
- 4- Bypass GIT

Disadvantages

- 1- Can fall off
- 2- suitable for a limited number of drugs
- 3- potential toxicity to children
- 4- may cause local allergy

4) Intramuscular:.

Advantages

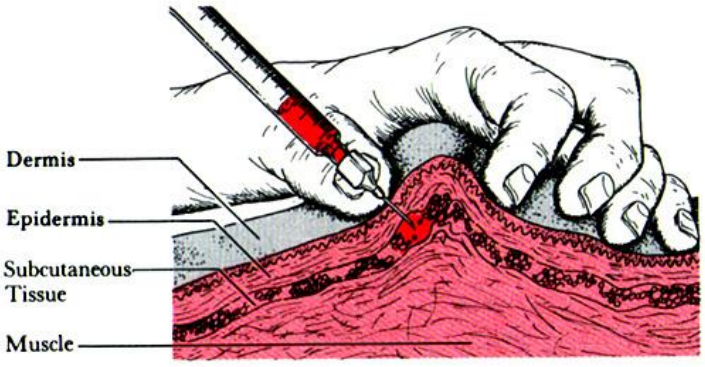
Advantages

- Suitable for aqueous and oily solutions and suspensions of insoluble drugs in water or in oil.
- Drugs in aqueous solutions are absorbed rapidly.
- If the drug is injected in

Disadvantages

- Not Suitable for large volumes

5) Subcutaneous:



Advantages
- Suitable for non-irritant drugs which may be either in aqueous solutions or in the form of fine suspensions.
- Adding a vasoconstrictor agent to a drug injected subcutaneously retards its absorption.

Disadvantages
- Not suitable for irritant drugs
- Not Suitable for large volumes

6. Sublingual administration: The drug is inserted beneath the tongue. The drug should be palatable, soluble and effective in a small dose,

Advantages
- Rapid absorption (rapid onset of action).
- Drugs are protected from the first pass effect.
- Avoids GIT enzymes and pH.

Advantages
- Not suitable for drugs that cause vasoconstriction of sublingual mucosa.

7. adr

- Advant
  1. Dru s m
  2. Avo
  3. Suit the stomach.

4. Suitable for patients who are vomiting or unconscious or when cooperation is lacking.

Disadvantages

Not suitable in presence of diarrhea.

8. Inhalation:

Absorption from the alveolar membrane is rapid. Drugs are administered in the following dosage forms:

a. Gas, e.g. oxygen and nitrous oxide.
b. Volatile liquid (vapor), e.g. halothane.
c. Solution administered as aerosol by means of nebulizer.
d. Finely micronized powder given by special inhaling device.

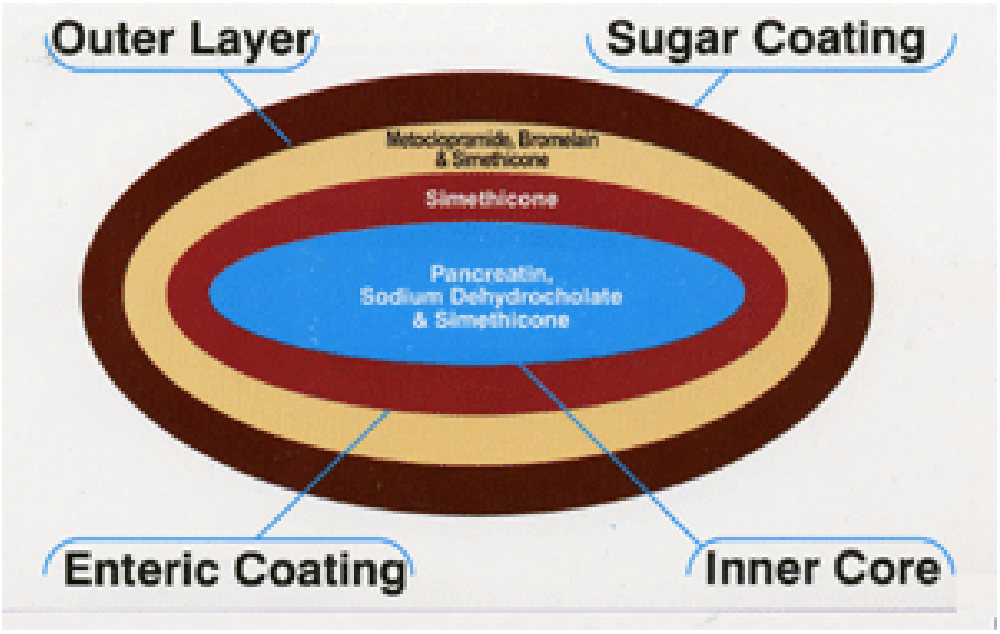
Dosage forms of drugs

Oral dosage forms:

1. Tablets:

A solid dosage form of varying weight, size and shape in which the drug is compressed with inert substances.

a. Simple.
b. Sugar coated.
c. Enteric coated: The tablet is coated with substances that resist dissolution in acid medium of the stomach but dissolve in the alkaline medium of the intestine. This protects the gastric mucosa.



Example of enteric coated tablets:

Enteric coated aspirin (prevents absorption in the stomach. Enteric coating material is a film forming polymer insoluble in gastric juices that reduces incidences of gastric bleeding from the aspirin use).

d. Sustained release (retard): This provides a prolonged duration of action and patients take them less frequently.
e. Effervescent: Improved palatability.
f. Sublingual: Small tablets to be placed under the tongue.

2. Capsules:

Gelatin shells containing individual doses of the drug.

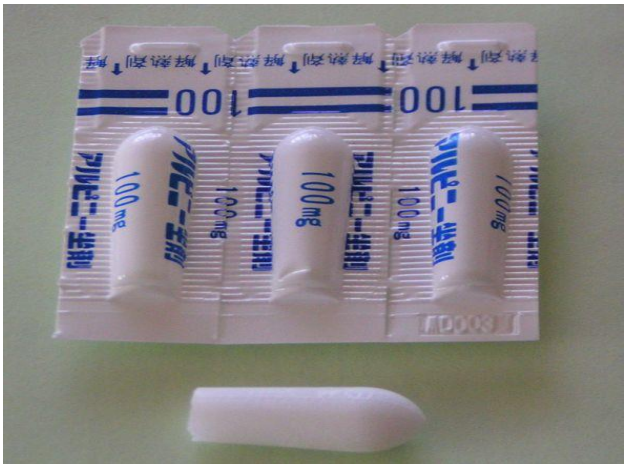
a. Hard gelatin capsules: They are packed with powdered drugs.
b. Soft gelatin capsules: They are packed with liquid drugs.

3. Liquids:

a. Mixture: A preparation in which the drug is simply dissolved in water.
b. Emulsion: Fats or oils dispersed in liquid with an emulsifier.
c. Suspension: Solid particles suspended in liquid.
d. Syrup: A concentrated sugar solution containing flavoring therapeutically active substances.

e. Elixir: Aromatic, sweetened alcohol and water solution.
f. Tincture: Alcoholic extracts of plants or vegetable substance.

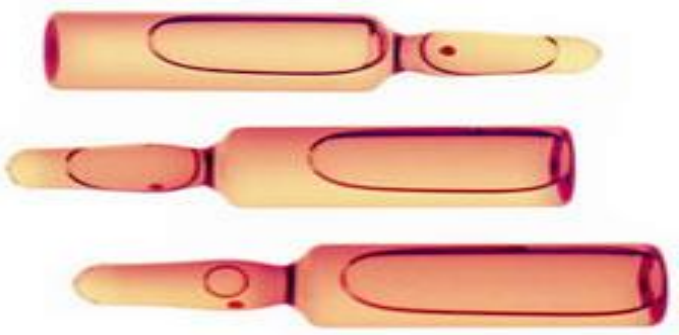
Rectal dosage forms:



a. Suppositories: Usually contain medicinal substances mixed in a firm but malleable base (cocoa butter) to facilitate insertion in rectum. Solid preparations at room temperature that melt at body temperature.
b. Enema: Fluid preparations for administration into the rectum.

Preparations for parenteral use:

- They are supplied in sterile liquid form in ampoules.



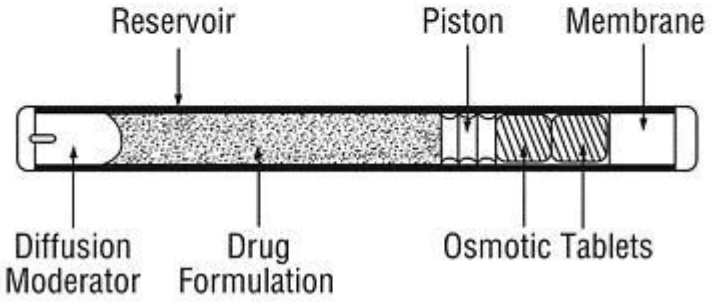
OR vials

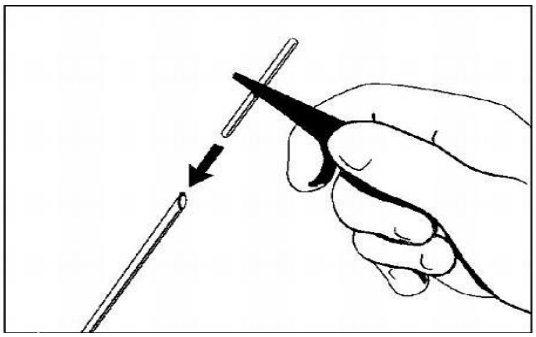
- They can also be supplied in powdered form in a sealed vial or ampule. Powdered drugs must be dissolved in sterile water or 0.9% sodium chloride prior to injection.
- Ampules: sealed glass container for liquid injectable medication.
- Vials: glass container with rubber stopper for liquid or powdered medication.
- Cartridge/Tubex: single-dose unit of parentral medication to be used with a specific injecting device.
- Glass and plastic bottles or containers are used for infusion of fluids with or without drugs.

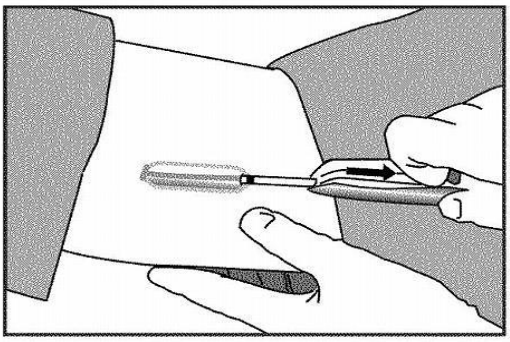
Subcutaneous implantation:

Drugs are implanted under the skin in a solid pellet form. Absorption occurs slowly over a period of several weeks or months, *e.g*. some hormones.

Figure A.
Viadur® (leuprolide acetate implant)
(diagram not to scale)



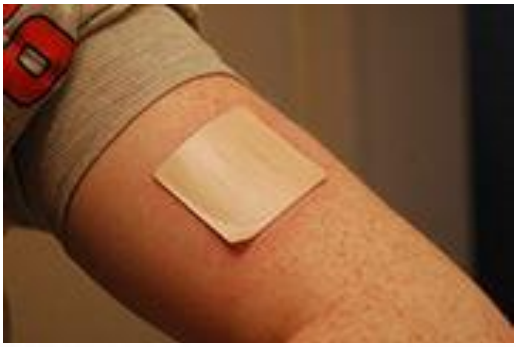




Preparations for topical use:

Linimints:	Liquid suspensions for lubrication that are applied by rubbing.
Lotions:	Liquid suspensions that can be protective, cooling or cleansing.
Ointment:	Semisolid medicine in base for local protective or transdermal application for systemic effect e.g. nitroglycerin.
Paste:	Thick ointment primary used for skin protection.
Creams:	Emulsions that contain an aqueous and an oily base.
Drops:	Aqueous solutions with or without a gelling agent to increase retention time in the eye.

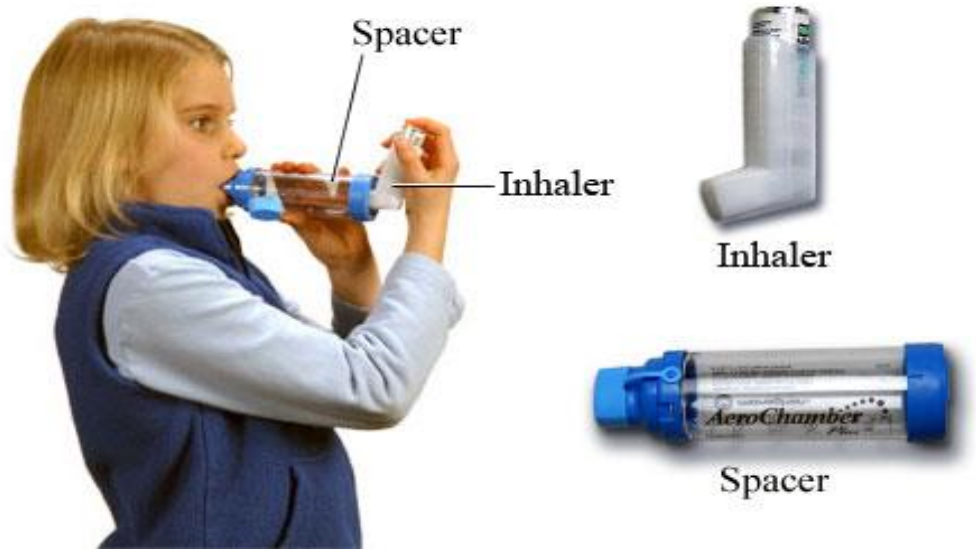
Transdermal patches: Patches containing medication that is absorbed continuously through the skin and acts systemiclly. Consists of a disk or patch that contains a day's to a week's supply of medication. After being applied to the skin, the drug is absorbed at a steady state. Examples are nitroglycerin and scopolamine.



Topical administration:

a. Eye: Eye drops, ointments and lotions (powder in water suspension).
b. Ear: Ear drops.
c. Vagina: Vaginal tablet and vaginal pessary .
d. Nose: Nasal drops, nasal spray and nasal inhaler.
e. Mouth: Mouth wash, gargle and lozenge (medicated tablets that dissolve slowly in mouth) .
f. Skin: Ointment, cream, lotion and dusting powder.

Inhalation dosage forms:



- A **metered dose inhaler (MDI)** delivers a specific amount of medicine in aerosol form. This makes it possible to inhale the medication.
- MDI's are commonly used to treat asthma, COPD, and other respiratory conditions.
- How to use an MDI:
  - Take off the cap and shake the inhaler hard.
  - Breathe all the way
  - Hold the inhaler 1 to 2 inches in front of your mouth (about the width of two fingers).
  - Start breathing in slowly through your mouth, and then press down on the inhaler one time. Breathe in slowly, as deeply as you can.
  - Slowly count to 10 while you hold your breath. This lets the medicine reach deep into the lungs.
  - Rinse mouth to reduce side effects

- **Spacers** are very important because:
  - They make aerosol inhalers easier to use and more effective.
  - The patient gets more medicine into their lungs than when just using the inhaler on its own.
  - They are convenient and compact and work at least as well as nebulisers at treating most asthma attacks in children and adults.
  - They help to reduce the possibility of side effects from the higher doses of preventer medicines by reducing the amount of medicine that is swallowed and absorbed into the body.

- **Nebulizers**

A.D.A.M.

- Convert a solution of a drug into an aerosol mist for inhalation.
- Nebulisers are used to deliver higher doses of drug to the airways than is usual with standard inhalers.
- To use a nebuliser, the nebuliser hose is attached to an air compressor. Most jet nebulisers require an optimum gas flow rate of 6-8 liters/min and in hospital can be driven by piped air or oxygen.
- The drug is be placed in a small cup. Air from the compressor converts the drug into an aerosol mist that the patient inhales through a mouth piece. Children can wear a mask.
- The medicine is delivered into the lungs by taking slow deep breaths.
- A nebuliser requires that the patients sit down and relax for 5-30 minutes while he inhales the drug.

Fate of drugs (Pharmacokinetics)

Definition: Pharmacokinetics means the effect of body on the drug.

It includes:

1. Absorption
2. Distribution
3. Metabolism (Biotransformation)
4. Elimination

Absorption is the transportation of the drug across the biological membranes

- Mechanisms of drug absorption
  - ✓ **Passive (simple) diffusion**
  - ✓ **Active transport**
  - ✓ **Pinocytosis**
  - ✓ **Facilitated diffusion**

Bioavailability

- Definition: it is the ***fraction*** of unchanged drug that reaches the systemic circulation following administration by any route.
- Example: If 100 mg of a dose are administered orally and 70 mg of this drug are absorbed unchanged, the bioavailability is 70 %.

Distribution: It is the process by which a drug moves freely between different body compartments.

- Half life ($t_{1/2}$): it is the time required for the plasma concentration to fall to one half its original value.

Biotransformation: it is a chemical transformations that occur to drugs inside the body.

- Aims:

1. **Reducing lipid solubility**

2. **Alteration of biological activity**

Eliminations: the drug is eliminated mainly by

1) Kidney: In the urine
2) Liver: In the faces
3) Lung: Volatile gases

Side effects of drugs (Adverse drug reactions)

Types:

Type A: Predictable: extension of pharmacological effects e.g. hypoglycemia by insulin.

Type B: Non predictable: allergy of penicillin,…

Autonomic nervous system

The autonomic nervous system is distributed throughout the body and regulates autonomic functions that occur without conscious control.

It contains sympathetic and parasympathetic nervous system.

Sympathetic nervous system

Neurotransmitters: adrenaline and noreadrenaline

Receptors:

- ***Alpha receptors:*** alpha-1 (postsynaptic) ***and*** alpha-2 (presynaptic and postsynaptic). Stimulation of presynaptic alpha-2 receptors inhibits the release of noradrenaline, while stimulation of vascular alpha-2 receptors results in vasoconstriction.
- ***Beta receptors:*** **Beta-1** receptors: they are found mainly in the heart and kidneys.**Beta-2** receptors: found mainly in blood vessels, bronchi and uterine smooth muscles.**Beta-3** receptors: they are found mainly in adipose tissue.

Responses of organs to autonomic nerve impulse

Organ	Sympathetic		Parasympathetic (M Receptors)
	Receptor	Response	
Eye Iris: Radial muscle Circular muscle Ciliary muscle	 α_1 β	 Mydriasis 	 Miosis
Heart	β_1	↑heart rate ↑contractility ↑conductivity	↓heart rate ↓contractility ↓conductivity
Blood vessels: Skin and mucosa Skeletal muscle	 α_1 β_2	 constriction dilatation	
Bronchi	β_2	relaxation	contraction
GIT: Motility Sphincters Secretion	 α&β α_1	 ↓contraction 	 ↑relaxation ↑
Urinary bladder: Bladder wall Sphincter	 β_2 α_1	 Relaxation of the wall and contraction of sphincter	 Contractio of the wall and relaxation of the sphincter
Metabolic effects Liver Kidney	 β_2 β_1	 ↑Glycogenolysis ↑renin release	
Sweat glands	α_1	localized secretion	Generalized secretion

Catecholamines and Sympathomimetics

- ✓ Drugs produce effects similar to stimulation of sympathetic postganglionic nerves called sympathomimetics.
- ✓ Catecholamines are inactivated by MAO & COMT and poorly penetrated into CNS.
- ✓ Catecholamines include endogenous catecholamines as epinephrine, norepinephrine & dopamine and exogenous as isoproterenol and dobutamine.
- ✓ Non catecholamines compounds have longer half-lives and better CNS penetration.

Natural direct acting catecholamines

Adrenaline	**Noreadrenaline**	**Dopamine**
Actions Epinephrine (adrenaline) is a potent stimulant of both α and β adrenergic receptors. It is the major constituent of adrenal medullary secretions (80%). ***Cardiovascular actions:*** ***Heart:*** Epinephrine is a powerful cardiac stimulant through β_1 receptor. ***Blood pressure****:* epinephrine increases the systolic blood pressure (vasoconstriction, direct myocardial stimulation, and increased heart rate) but the diastolic pressure usually falls (due to decreased peripheral resistance as a result of dilation of skeletal muscle β 2. ***Metabolic actions:***It has catabolic effect ***Actions on muscles:*** Bronchi: Epinephrine has a powerful bronchodilator action (β_2), inhibition of antigen-induced release of inflammatory mediators from mast cells (β2) and decreased bronchial secretion and congestion (α). Eye: Mydriasis , Skeletal muscles tremors U. T.: It relaxes the wall and contracts the sphincters (retention of urine) . Uterus: During last month of pregnancy and at parturition, adrenaline inhibits contractions (β 2)	**Actions:** It is the chemical transmitter released by postganglionic adrenergic nerves. (α1, α 2, β1) Constitutes10–20%of catecholamine of human adrenal medulla. ↑ HR, ↑ contractility, increase stroke volume, increase Cardiac output and Systolic, diastolic pressure and mean arterial pressure and vasoconstriction	**Actions:** It is the immediate precursor of noradrenaline and central neurotransmitter. It acts as an agonist at D1,α, β1 Responses in human depend on the dose of dopamine **In low dose** it acts mainly on D1 receptors (vasodilatation of the renal and mesenteric arteries with increase in GFR & renal blood flow). **In moderate dosages,** dopamine acts directly on the beta-1 receptors of the myocardium and increase myocardial contractility and stroke volume. **In higher dosages,** α-receptors are stimulated with increase peripheral resistance and blood pressure.

Pharmacokinetics: Subcutaneous injection occurs slowly because of its local vasoconstriction. Rapidly inactivated in the body by MAO and COMT.		**Pharmacokinetics:** Given only by I.V. infusion and absorbed poorly after s.c. injection and metabolism is similar to that of epinephrine	**Pharmacokinetics:** Half-life: 2 min. thus it is given only by i.v. infusion and metabolism by MAO &COMT.
Therapeutic uses: 1- **Allergy and anaphylactic shock**. Adrenaline is the physiological antagonist of histamine. 2- **Cardiac resuscitation**. 3- Relieves **respiratory distress** due to bronchospasm. 4- **Glaucoma:** Dipivefrin eye drops. 5- Prolongation of the duration of action of local anesthetics. **6- Local homeostatic**		**Therapeutic uses:** **Shock** because it increases vascular resistance and therefore increases BP. **Low blood pressure cases** as in spinal anesthesia. *N.B. Blood pressure should be monitored. Drug should be stopped gradually.*	**Therapeutic uses:** **Shock** (cardiogenic and septic shock) and chronic refractory congestive heart failure. **Precautions during use:** Rate of infusion monitoring heart rate, blood pressure and urine flow.
Side effects: Fear, anxiety, tremor, dizziness, palpitation, restlessness. Cardiac arrhythmias and Anginal pain, Severe v.c or even gangrene.	Large dose increase blood pressure and can cause cerebral hemorrhage.	**Side effects:** As epinephrine. In addition, norepinephrine may cause blanching and sloughing of skin along injected vein (due to extreme vasoconstriction).	**Side effects:** Nausea, vomiting.Tachycardia,anginal pain, arrhythmia, hypertension, vasoconstriction, headache. Extravasation leads to ischemia and necrosis.

Sympatholytics:

Types: Alpha blockers and beta blockers

Beta blockers: selective and non selective

Selective Beta-2 agonists

- It is short acting used for COPD and asthma.

Formoterol & Salmeterol

- They are long acting bronchodilators (up to 12 hours).
- Their major advantage is prolonged duration which makes them useful for nocturnal asthma.
- salmeterol has relatively slow onset of action than formeterol after inhalation.
- Used as a uterine relaxant.
- Administered intravenously to selected patients to arrest premature labour.

Side effects of selective Beta-2agonists:

- Selectivity is not absolute and it is lost at sufficiently high concentration of these drugs.
- Feeling of restlessness and anxiety.
- **3T:** Tremors, Tachycardia and Tolerance.

Non-selectiveAlpha agonist

Oxymetazoline

- Oxymetazoline is a direct-acting synthetic agonist that stimulates both α-1 and α-2.
- It is primarily used locally in the eye or the nose as a vasoconstrictor used as decongestant.
- Side effects: nervousness, headaches, and trouble sleeping, burning of the nasal mucosa and sneezing may occur and ***Rebound congestion*** is observed with long-term use.

Alpha-1selective agonists

Phenylephrine

- Is a direct-acting, synthetic adrenergic drug that binds primarily to α and favors α1 over α2.
- It is not a catechol derivative and not a substrate for COMT.

- Phenylephrine is a vasoconstrictor that raises both systolic and diastolic blood pressures.
- It induces reflex bradycardia when given parenterally.
- It is used topically on the nasal mucous membranes and in ophthalmic solutions for mydriasis.
- Phenylephrine acts as a nasal decongestant and produces prolonged vasoconstriction.
- The drug is used to raise blood pressure and to terminate episodes of supraventricular tachycardia (rapid heart action arising both from the atrioventricular junction and atria).
- Large doses can cause hypertensive headache and cardiac irregularities.

Selective alpha-2agonists

Clonidine

- Stimulates central alpha-2 adrenoceptors, reduce sympathetic outflow from the CNS.
- Reduce blood pressure results from ↓COP due to (decreased HR & relaxation of capacitance vessels) and reduction in peripheral vascular resistance.
- It is lipid-soluble and rapidly enters the brain from the circulation.
- Oral or transdermal preparation
- Side effects include dry mouth, sedation (frequent) and depression.
- Withdrawal of clonidine after prolonged use leads to life threatening hypertensive crisis (stopped gradually). Treatment of hypertensive crisis consists of reinstitution of clonidine therapy or administration of α- and β-adrenoceptor blocking agents.

Beta-Blockers

classification:

Non-selective blocker e.g. Propranolol

Beta1 selective blockers e.g: Atenolol, Acebutolol and Metaprolol.

Actions

- They have a negative effect on heart.
- hypoglycemia
- Non selective beta-antagonists ↓HDL, ↑LDL, and ↑triglycerides.
- Blockade of beta 2 receptors in the bronchi cause bronchoconstriction in asthmatics.

- Beta-receptor antagonists block catecholamine-induced tremor.
- Decrease IOP by blocking Beta-adrenoceptors on the ciliary epithelium that facilitate the secretion of aqueous humor, (e.g. timolol).

Therapeutic uses

- ***Angina pectoris, Myocardial infarction, Hypertension, Heart Failure,Cardiac tachyarrhythmias***
- ***Hepatic portal hypertension & esophageal variceal bleeding***: reduction of portal pressure.
- ***Hyperthyroidism***
- ***Pheochromocytoma:*** Tumor of Adrenal Medulla with increased Adrenaline.
- ***Anxiety, Essential tremor, Migraine headache***, ***Alcohol and opioids acute withdrawl symptoms, Glaucoma***

Side effects

- ***Cardiac failure***, ***Bronchoconstriction***, ***Hypotension***, ***Bradycardia and heart block.***
- ***Hypoglycemia, Cold extremities***, ***CNS side effect:*** sedation, fatigue, nightmares and depression. ***Hyper sensitivity reaction, Withdrawal phenomenon:*** Abrupt withdrawal leads to up regulation of B-receptors ***Intrauterine growth retardation, Hyperlipidemia and impotence***

Mixed α and β adrenergic blocking drugs:

Labetolol and Carvedilol

- **Labetolol** is used in treatment of hypertension.
- **Carvedilol** has both antioxidant and vasodilator activity and used in treatment of hypertension, congestive heart failure and improve metabolic abnormalities associated with diabetes.

Drugs acting on parasympathetic nervous system

The parasympathetic division of ANS maintains essential body functions, such as digestive processes and elimination of wastes, and is required for life. It usually acts to oppose or balance the actions of the sympathetic division "Rest and Digest".

Parasympathomimetics

The parasympathomimetics are also called the Cholinomimetic drugs and they stimulate mainly the muscarinic receptors.

Classification: Direct acting and Indirect acting

A - Direct Parasympathomimetics:

Choline Esters*:* a. natural: Acetylcholine b. synthetic: Methacholine, carbachol, Bethanechol.

Natural Alkaloids: a. Pilocarpine

B- Indirect Parasympathomimetics (Anti-Cholinesterases):

1- *Reversible Anti-Cholinesterases:*Edrophonium (rapidly acting) *and* Neostigmine, physostigmine &pyridostigmine (slowly acting).
2- *Irreversible Anti-Cholinesterases* as Insecticide

Acetylcholine

Acetylcholine is the **postganglionic** neurotransmitter in the parasympathetic nervous system. It is also the **preganglionic** neurotransmitter for ***both*** the sympathetic and parasympathetic nervous system. **Ach** at neuromuscular junction, brain and spinal cord.

Pharmacological actions: **A-muscrinic**

1-Eye: miosis, fix the accommodation for near vision,↑lacrymation& ↓IOP.

2-C.V.S: *Heart:* ↓ HR and SAN-conduction-*Blood Vessels:* Vasodiltation and Hypotension through the stimulation of muscrinic receptors in the endothelial cells.

3-GIT (↑motility, tone, and relax the sphinctors) 4-Urinary Tract (↑motility, tone, and relaxes the sphinctors), 5-Bronchi (↑tone & secretion) 6-Exocrine Glands (profuse and watery secretions e.g. sweating) ,7-Uterus: contract non pregnant uterus.

B- Nicotinic actions: Twitches + Hypertension, Motor end plate→ skeletal muscle twitches (N_m). **Synthetic Choline Esters**

	Methacholine	***Bethanechol***	***Carbachol***
1-Kinetic: aadministration b-Metabolism	 S.C. True CE only	 S.C. Eye drops Not	 S.C. Eye drops Not
2-Dynamic: a-Muscarinic b-Nicotinic	 +++ +	 +++ No	 +++ +++
3-Specificity	C.V.S.	GIT and U.B.	Eye, GIT and U.B.
4-uses	✓ Treatment of paroxysmal atrial tachycardia ✓ Peripheral vascular disease	✓ Post-operative paralytic ileus. ✓ Urinary retention	✓ Glaucoma ✓ Post-operative paralytic ileus. ✓ Urinary retention

Organophosphorus Poisoning:

Causes: It is may be accidental or as a result of homicidal or suicidal intention.

Manifestations: 1- Muscarinic as: Pin point pupil- ↑Secretions- Bronchospasm- vomiting and abdominal cramps- ↓B.P & H.R.

2- Nicotinic as: Ms weakness and paralysis of intercostal Ms and diaphragm.

3- CNS as: Restlessness- Confusion- Coma- Depression of VMC and R.C.

Death may occur due to respiratory depression and secondary circulatory failure within minutes or reach to 24 h depending on: the agent type, duration of exposure, route….etc.

Treatment of Organophosphorus Poisoning:

1- Endotracheal intubation and artificial respiration.

2-Avoid further exposure, clean: skin- cloths- stomach wash, and care of vital systems.

3-Atropine: i.v. or i. m repeated every 5-10 min till atropine toxic signs appear as: mydriasis, dry mouth, tachycardia. It affects only the muscarinic, CNS but not nicotinic symptoms.

4-Cholinesterases (Oximes):*e.g.*Paralidoxime

5-Anticonvulsants as diazepam.

Parasympatholytics

Anticholinergic drugs may be:

1. Antimuscarinic drugs - atropine, scopolamine
2. Ganglionic blocking drugs
3. Neuromuscular blocking drugs

Antimuscarinic are classified into two groups:

1. Belladona alkaloids as Atropine and Scopolamine (hyosine).
2. Synthetic atropine substitute

Parasympatholytics

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SHOCK

Definition: Shock is a state of peripheral circulatory failure characterized by hypotension, impaired tissue perfusion.

Types

1. Hypovolemic
2. Anaphylactic
3. Septic.

I. HYPOVOLEMIC (OLIGEMIC) SHOCK

- **Etiology:**
  1. Blood loss as in hemorrhage.
  2. Plasma loss as in burn & peritonitis.
  3. Fluid loss as in dehydration & diarrhea.

- **Clinical picture:**
  1. **Rapid weak pulse** ("thready, low pulse volume").
  2. **Hypotension** and **low pulse pressure**.
  3. **Subnormal temperature** (due to ↓ basal metabolic rate).
  4. ↑ **Rate & depth of respiration** (tachypnea & air hunger): due to stimulation of the respiratory center (by hypoxia, ↓ vagal inhibition and the catecholamines action on the CNS).
  5. **Pale cold clammy skin** of extremities & nose due to sympathetic overactivity.
  6. **Collapsed veins & ↓ CVP.**
  7. **Oliguria & thirst sensation.**
  8. In the early post-hemorrhagic state the patient is **restless** but later on the patient is **lethargic**.

- **Treatment**

Anti-Shock Measures

- **First Aid Measures:**

1. **Stop** external bleeding if present.
2. **Respiratory support**: Ensure good ventilation, aspiration of bronchial and salivary secretions as well as artificial respiration to correct the hypoxia.
3. **Analgesics:** Morphine 10 mg is given slowly i.v. (since s.c. absorption is poor in shocked patients).
4. ***Posture:*** Recumbent position with moderate (30 degrees) elevation of the lower limbs.
5. ***Temperature:*** Keep the patient comfortably warm.
   - ⇨ Avoid chilling (to prevent heat loss).
   - ⇨ Avoid excessive externally applied heat, which causes cutaneous vasodilatation & excessive sweating with fluid loss.

6. ***Start i.v. fluids*** through a venous line by veni-puncture & if difficult venous cut down.
7. ***Restore Blood Volume***
   - ⇨ If there is blood loss; blood transfusion is necessary.
   - ⇨ If there is plasma loss, plasma should be given.

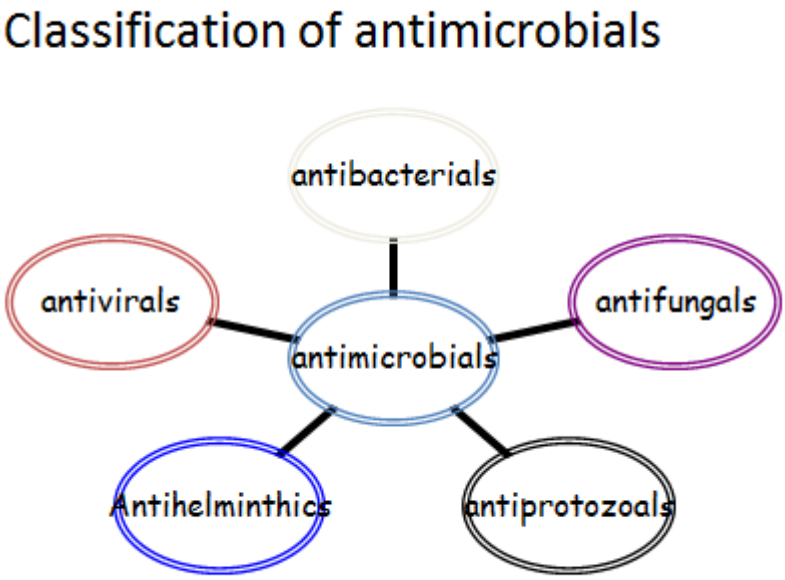
B. Anaphylactic Shock

- **Etiology:**
- It may follow the administration of antibiotics, anesthetics, foreign sera or dextran.
- **Pathophysiology:**
- It is due to capillary paralysis from histamine release with pooling of blood in the open capillary bed.
- **Clinical picture:**
- Hypotension.
- Laryngeal edema, bronchospasm & respiratory distress.
- **Treatment:**
  1. ***First line of treatment:*** administration of ***sympathomimetics*** (epinephrine, 0.5 mg i.m. or s.c.) to improve blood pressure and a physiological antagonist for histamine. Dopamine may also be administrated.
  2. Administration of ***corticosteroids*** (*e.g.*, hydrocortisone, 50-100 mg, i.m. or i.v.) to relieve laryngeal edema and to restore distribution of body fluids into tissues.
  3. ***Tracheostomy*** if there is severe laryngeal edema and ***oxygen inhalation***.
  4. ***Aminophylline*** (0.25-0.5 g, i.v.) to relieve bronchospasm (if there is any).
  5. ***Antihistaminics*** can be also used.

C. Septic shock: due to sever infection

Treated by empirical antibiotics.

Antimicrobials



Classification of antibacterials

Mechanism of action	Drug
Inhibition of folic acid synthesis (metabolic)	Sulfonamides, trimethoprim,
Inhibition of bacterial cell wall synthesis	Penicillins, cephalosporins, vancomycin
Inhibition of bacterial protein synthesis	Aminoglycosides, chloramphenicol, macrolides, tetracyclines
Inhibition of nucleic acid synthesis	Fluoroquinolones, rifampin

Sulfonamide

Adverse reactions:

1- GIT disturbance (nausea, vomiting, diarrhea, abdominal colics).

2- Urinary tract: Crystalluria and nephrotoxicity

3- Blood (hemolytic anemia, aplastic anemia, agranulocytosis, porphyria), especially in G6PD deficiency people.

4- Hypersensitivity (may present as erythema multiforme of Stevens-Johnson syndrome)

5- New-born: (hyperbilirubinemia and kernicterus)

6- CNS: headache, convulsions, depression, ataxia.

7- Liver: hepatitis and hepatocellular necrosis.

II- Inhibitors of cell wall synthesis

All inhibitors of cell wall synthesis are bactericidal. They are divided into:

1. Beta-Lactam group	**2. Non Beta-Lactam group**
Penicillins, cephalosporins	Vancomycin

Spectrum:

It is mainly active against **gram positive** bacteria.

Note: Penicillins are ineffective against organisms that lack a cell wall (e.g mycobacteria).

- Penicillins kill bacterial cells only when they are actively growing and synthesizing cell wall.

Types of penicillin:

1. Natural penicillin (Narrow spectrum) as penicillin G & penicillin V
2. Anti-staph penicillin (Very narrow spectrum) as oxacillin, Cloxacillin, fluclocacillin, and nafcillin
3. Broad spectrum penicillin as ampicillin & amoxicillin

4. Extended Antipsudomonal penicillin as carbincillin & ticarcillin

Clinical uses of penicillin:

- Penicillin G is a drug of choice in streptococci, meningococci, enterococci infection.
- Penicillin V, the oral form of penicillin, is indicated only in minor infection because of relatively poor bioavailability.
- Benzathine penicillin (1.2 million units, im/3weeks), long acting form, is effective in treatment and prophylaxis of pharyngitis caused by β-hemolytic streptococci. It is used also in treatment of syphilis (2.4 million units / week for 1-3 weeks).
- Broad spectrum penicillins (usually used with β-lactamase inhibitors; Sulbactam & clavulanic acid) used in chest & urinary tract infections.

Adverse reactions:

A. Penicillin hypersensitivity: severe penicillin hypersensitivity with anaphylactic shock is very rare and occurs mostly in connection with parenteral administration (5 to 10 cases on 10000 treated subjects). The emergency treatment is based primarily on adrenaline (and, in addition, may be intravenous corticosteroids, antihistamine, and aminophylline). However, hypersensitive skin reactions (skin rashes, urticaria) are frequent (1 to 7% of the treated subjects).

Note: A simple skin allergy test can be performed to determine if you are allergic to penicillin.

B. GIT disturbances (nausea, vomiting, diarrhea, with oral penicillins)
C. Hepatitis (oxacillin and some other anti-staph)
D. Non allergic skin rash (ampicillin & amoxicillin specially in patients with viral infection)
E. Psudomembraneous colitis with ampicillin.
F. Neutropenia with nafcillin.

Cephalosporins

Mechanism of action:

Similar to penicillin, but more stable against many bacterial β-lactamases and therefore have a broader spectrum of activity.

Classification:

Based on differences in their antimicrobial spectrum, they have been classified into four generations.

1- First generation

Examples: Oral [cefadroxil (durecief)]. Parenteral [cefazolin (totacef)]. Both oral and parentetal [Cephalexin (ceporex), cephradine (velosef)].

General characteristics:

- Good activity against gram-positive bacteria and relatively modest activity against gram-negative microorganisms.

Clinical uses: They are rarely the drug of choice of any infection.

1. May be used for the treatment of non complicated UTI and surgical prophylaxis.

2-Second-generation

Examples: Oral [cefaclor (ceclor), cefprozil (cefzil)]. Pareneral [cefamandol (mandole)]. Oral & parenteral [cefuroxime (zinnat)]

General characteristics:

- They have broader spectrum than the first-generation agents
- Cefuroxime, the only member of second generation that crosses blood brain barrier

Clinical uses:

1- Upper & lower respiratory tract infection

2- Peritonitis in mixed infection caused by aerobic and anaerobic bacteria.

3- Third-generation

Examples: Parenteral [cefotaxime (cefotax); cefoperazone (cefobid); ceftazidime (fortum); ceftriaxone (rocephin)], Oral [cefpodoxime (orelox); cefixime (suprax)]

General characteristics:

- Some are able to cross BBB (Cefotaxime, ceftriaxone).

Clinical uses:

1. The drugs of choice for serious infections caused by Klebsiella, Enterobacter, Proteus, Serratia, and Haemophilus spp
2. Cefotaxime, ceftriaxone are approved for treatment of meningitis cused by pneumococci, meningococci, H. influenza, ...
3. Cefixime can be given orally in respiratory and urinary tract infections.
4. Ceftriaxone is the therapy of choice for all forms of gonorrhea.

4- Fourth-generation

Examples: Parenteral (Cefepime (maxipime), cefpirome)

General characters:

- Good activity against Pseudomonas aeruginosa, Enterobacteriaceae, S aureus, and S pneumonia, Haemophilus and neisseria.
- Good activity against most penicillin-resistant strains of streptococci.
- Cefepime penetrates well into CSF.

Particularly useful for the empirical treatment of serious infections in hospitalized patients.

General adverse effects of cephalosporins:

Generally, the cephalosporins have an excellent safety record. However, they may cause:

3- Allergy (ranges from skin rash, anaphylaxis, nephritis, granulocytopenia, hemolytic anemia). There is some cross-antigenicity with penicillins.
4- Local irritation & thrombophelebitis at site of injections
5- Renal toxicity
6- Hypoprothrombinemia and bleeding disorders (with some drugs e.g cefoperazone, cefamandole) (can be prevented by Vitamin K, 10 mg twice weekly)

III- Nucleic acid inhibitors:

Flouroquinolones (Inhibitors of DNA)

Mechanism of action

- The quinolone antibiotics inhibit DNA synthesis

Note: Nucleic acid Inhibitors of RNA e.g.: rifampicin: see anti-TB drugs)

Spectrum of activity

Generally, flouroquinolons were developed because of their excellent activity against gram-negative aerobic bacteria. They can be classified into:

- First group: (e.g. Norfloxacin). It is the least active against both gram negative and gram positive organisms..
- Second group: (Ciprofloxacin, ofloxacin, levofloxacin, pefloxacin). It has excellent activity against gram -ve and moderate to good activity against gram +ve organisms.
- Third group: (Gemifloxacin, gatifloxacin, moxifloxacin, sparafloxacin). This group is more active than other groups against gram positive organisms. However, none of these members is as active as ciprofloxacin against gram negative organisms.

Note: Antibacterial activity of quinolones is concentration dependant and has post antibiotic effect (see "Introduction to chemotherapy")

Clinical uses:

1) urinary Tract Infections
2) Gastrointestinal Infections caused by shigella, salmonella (e.g. Typhiod fever)
3) Respiratory quinolons [Levofloxacin, gatifloxacin, gemifloxacin, sparafloxacin] used in treatment of respiratory Tract Infections
4) Genital, Bone, Joint, and Soft Tissue Infections.

Adverse effects:

1. GIT (nusea, vomiting, and diarrhea): the most common side effects.
2. CNS: headache, delerium, hallucination
3. Photosensitivity has been reported with lomefloxacin and pefloxacin.
4. Abnormal liver function tests
5. Damaging growing cartilage and causing arthropathy (so, it is not routinely recommended in patients below 18 years). However, the arthropathy is reversible and there is a growing consensus that flouroguinolons may be used in children in some cases (e.g for psudomonal infection in patients with cystic fibrosis).
6. Gatifloxacin (Tequin) has been associated Hyperglycemia in diabetic patients and hypoglycemia in patients receiving oral hypoglycemic drugs.

IV- Inhibitors of protein synthesis

Include tetracyclines, aminoglycosides, chloramphenicol, and macrolides

All are bacteriostatic, except aminoglycosides which are bactericidal

1- Tetracyclines

Spectrum of antimicrobial activity:

Bateriostatic broad spectrum against gram-positive and gram-negative bacteria,

Members:

- Short acting ($t_{1/2}$ 6-8 hr): oxytetracycline.
- Intermediate acting ($t_{1/2}$ 12 hr): demeclocycline.
- Long acting ($t_{1/2}$ 16-18 hr): doxycycline & minocycline.
- Very long acting ($t_{1/2}$ 36 hr): tigecycline.

Notes: Distribution: to all tissues including CNS, placenta, milk, so, may affect the development of tooth and bone in growing child.

Drug interactions:

Pharmacokinetic interactions:

- Absorption: Inhibited by dairy foods, calcium, Al and Fe
- Metabolism: Induced by (carbamazepine, phenytoin, barbiturates, chronic alcohol), especially with doxycycline and tigecycline.

Pharmacodynamic interactions:

- Antagonistic effect with bactericidal-Penicillin

Adverse effects:

- GIT: the most common adverse effect (nausea, vomiting, diarrhea)
- Bone and teeth: discoloration, abnormal growth (not used in young children and pregnant or nursing mother).
- Liver: rise in liver enzymes and fatal hepatotoxicity has been reported in pregnant women who received high doses of tetracyclins and had impaired renal functions.

2- Aminoglycosides

Antimicrobial activity:

- Active against aerobic gram-negative bacteria; streptomycin is used for the treatment of tuberculosis.

Members: gentamicin, tobramycin, amikacin, netilmicin, kanamycin, streptomycin, and neomycin.

Pharmacokinetics:

Absorption

- All are are very poorly absorbed orally. However, gentamicin oral absorption may be increased in case of ulcers or inflammatory bowel disease.
- Intoxication may occur when aminoglycosides are applied topically for long periods to large wounds, burns, or cutaneous ulcers, particularly if there is renal insufficiency.

Distribution

- Because of their polar nature, the aminoglycosides do not penetrate into most cells, the central nervous system (CNS), and the eye.

Adverse effects:

1. Ototoxicity
2. Nephrotoxicity (usually reversible), especially gentamicin and tobramycin.
3. Neuromuscular blockade:
4. In pregnancy: Administration of aminoglycosides to women pregnancy may result in accumulation of drug in fetal plasma and amniotic fluid. Streptomycin and tobramycin can cause hearing loss in children born to women who receive the drug during pregnancy.

Clinical uses:

- Treatment of infection caused by gram-negative enteric bacteria.
- Used in combination with Beta-lactam antibiotic to extend the spectrum as in endocarditis. They have synergestic effects.

- Streptomycin used in TB, brucellosis, plague, tularemia.
- Gentamycin and neomycin can be used topically in skin infection.
- Neomycin can be used orally in GIT infection, preoperative, hepatic coma.

3- Chloramphenicol

Antimicrobial Actions:

- Chloramphenicol possesses a broad spectrum of antimicrobial activity against aerobic and anaerobic gram positive and gram negative organisms.
- Chloramphenicol is bacteriostatic against most species, although it may be bactericidal against H. influenzae, Neisseria meningitidis, and S. pneumoniae.

Pharmacokinetics:

Distibution: Chloramphenicol is widely distributed in the body, including CNS, where the drug may accumulate in the brain. It passes to bile, milk, and placental fluid.

Therapeutic uses:

Chloramphenicol is only used for treatment of life-threatening infections (e.g., meningitis, rickettsial infections) in patients who cannot take safer alternatives.

1- Typhoid fever (replaced by third generation cephalosporins and quinolons)
2- Bacterial meningitis (replaced by third generation cephalosporins)
3- Anaerobic or mixed infection
4- Used topically in eye infection.

Adverse effects:

1) Hematological: The most important adverse effect of chloramphenicol is on the bone marrow. Chloramphenicol affects the hematopoietic system in two ways:

- anemia, leukopenia, or thrombocytopenia

2) Gray baby syndrome: Appears about 4 days after treatment and manifested by vomiting, flaccidity, cyanosis, respiratory irregularities, hypothermia, loose green stool, gray color. This occurs especially in neonate or premature baby because of

- Insufficient metabolizing enzymes

- In adequate renal excretion.

3) GIT: Nausea and vomiting, unpleasant taste, diarrhea, and perineal irritation may follow the oral administration of chloramphenicol.

4) Hypersensitivity: Skin rash, fever, angionueurotic oedema.

5) Others as blurring of vision and digital paresthesias.

4- Macrolides

Mechanism of Action

Macrolide antibiotics are generally bacteriostatic agents

Antimicrobial activity: Mainly against gram positive organisms, in addition to infections by Mycoplasma, legionella, Chlamydia trachomatis.

Members: Erythromycin, Azithromycin (Zithromax), Clarithromycin (Claribiotic), Clindamycin (clindacine), Spiramycin (Spirex), Roxithromycin (Rulid)

A- Erythromycin

Pharmacokinetics

Absorption the drug is administered as enteric-coated tablets, as capsules containing enteric-coated pellets that dissolve in the duodenum. Food, which increases gastric acidity, may delay absorption.

Distribution Distributed widely except to the CNS. It traverses the placenta and reaches the fetus.

Clinical uses

- It is used as an alternative to in penicillin-allergic individual with infection caused by streptococci, or pneumococci.

Adverse Reactions

1- GIT: Anorexia, nausea, vomiting, and diarrhea (due to direct stimulation of gut motility; it acts as motilin receptor agonist). It is the most common reason for discontinuing oral erythromycin

2- Liver Toxicity: Cholestatic hepatitis (probably due to allergic reaction)

B- Clarithromycin:

Pharmacokinetics: Acid stability and oral absorption increased by food.

Less frequent GIT adverse effects than erythromycin

Clinical uses: Alternative to erythromycin. It may be used in combination with amoxicillin and proton pump inhibitors in treatment of Helicobacter pylori associated with peptic ulcer. It is the first line therapy in the treatment of M. Avium and other infections associated with Aids (e.g. Toxoplasmosis).

C- Azithromycin

- Azithromycin's unique pharmacokinetic properties include extensive tissue distribution and high concentrations within cells (including phagocytes), resulting in much greater concentrations in tissue or secretions compared to simultaneous serum concentrations.
- It doesn't have drug interaction as of erythromycin and clarithromycin
- It is used in combination with amoxicillin and proton pump inhibitors in treatment of Helicobacter pylori associated with peptic ulcer.

D- Clindamycin (clindacine)

Similar to erythromycin

Clinical uses

- For anaerobic infection
- Used in combination with aminoglycosides in treatment of intraabdominal infection
- Used in combination with pyrimethamine in treatment of some infections affecting AIDS-patients (e.g toxoplasmosis).

Adverse reactions

1- GIT: Diarrhea (2-20 %), Psudomembraneous colitis (0.01- 10%)

2- Skin rashes (10 %); rarely Steven-Johnson syndrome

3- Cholestatic hepatitis

Chemotherapy of Tuberculosis (TB)

- TB is caused by infection with Mycobacterium tuberculosis, M. bovis and M africanum.
- It is the number one cause of death from infectious disease worldwide.
- Multidrug-resistant TB is a growing problem in many parts of the world.

Drugs used in treatment of TB include:

First line drugs (more effective and less toxic):

1- Isoniazide (INH)

2- Rifampin

3- Ethambutol

4- Pyrazinamide

5- Streptomycin

Second line drugs

- Aminosalicylic acid (GIT irritation, hypersensitivity)
- Ethionamide (gastric irritation, neurological and hepatological toxicities)
- Capreomycin (ototoxicity and nephrotoxicity)
- Cycloserine (CNS toxicity)
- Others (ciprofloxacin, amikacin)

Note: Second line drugs (used only in case of resistance to first line drugs because they are less effective and more toxic).

Analgesics

Definition: analgesia means diminished ability to perceive pain impulses without loss of consciousness.

Classes of Analgesics:

A) **Narcotic (Opioid) –analgesics**: Act mainly in the CNS. Morphine is the prototype.

B) **Non-narcotic –analgesics**: It includes:

a. Non steroidal anti-inflammatory drugs (NSAIDs): Act mainly in the periphery as anti-inflammatory with some CNS activity as well. e.g. aspirin, ibuprofen, etc.

b. Paracetamol

OPIOID ANALGESICS

Morphine

- Is well absorbed from the gastrointestinal tract. The analgesic effect is greater when drug is administered intramuscularly or intravenously because it has a significant first-pass effect.
- It distributes to all tissue and it passes to placental barrier → neonatal asphyxia during labor

Pharmacological effects and Mechanisms

CNS effects

- **Analgesi**a
- **Euphoria**
- **Respiration:** respiratory depression and suppression of cough
- **Nausea and vomiting**
- **Miosis**

Cardiovascular effects:

- Only large dose may produce orthostatic hypotension

Gastrointestinal effect:

- Constipation and relieving diarrhea.
- Increase in biliary pressure.

Urinary tract: It may cause urine retention

Labor: Prolong second stage of labor

Therapeutic Uses:

1. Analgesia, such as the relief of pain from myocardial infarction, terminal illness, surgery, biliary colic and renal colic (combined with atropine).
2. Dyspnea due to pulmonary edema because of sedative, vascular dilatation and inhibition of the respiratory centers responsiveness to CO_2.
3. Treating severe diarrhea because of its constipating effects.
4. Treating cough (usually replaced by codeine)

Precautions & Contraindications:

1. During labor. It prolongs labor and causes neonatal asphyxia.
2. In asthmatic patients. (Release of histamine)
3. In cases of head injuries
4. Sever hepatic and/ or renal failure.

Side Effects and toxicity of morphine:

1. Respiratory depression is the most important effect.
2. Nausea and dysphoria can occur.
3. Increase biliary tract pressure.
4. Increased intracranial pressure, particularly in head injury.
5. Allergic reactions and bronchoconstriction.
6. Constipation and urine retention (especially in prostatic hyperplasia).
7. Tolerance and Dependence.

Non-narcotic analgesics

1) Non steroidal Anti-Inflammatory Drugs (NSAIDs)

The NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities.

Classification:

I. <u>Non selective COX Inhibitors: They inhibit both COX-1 and COX-2</u>

1. Salicylates: Aspirin, salicylate salt, and diflunisal.
2. Acetic Acid Derivatives: Indomethacin, Sulindac, Diclofenac.
3. Propionic Acid Derivatives: Ibuprofen, Ketoprofen, Naproxen, Fenoprofen.
4. Oxicam Derivatives: Piroxicam, Meloxicam
5. Fenamic Acid derivatives: Mefenamic Acid.

II. ***Selective COX-2 Inhibitors: They selectively inhibit COX-2 only*** e.g. **Celecoxib.**

Aspirin

Mechanism of action:

- Inhibition of Cyclooxygenase that promotes the formation of prostaglandins.

Pharmacological Actions:

1. **Anti-inflammatory actions**
2. **Analgesic action**
3. **Antipyretic action**

Therapeutic uses:

1. Antipyretic.
2. Analgesic: for some kinds of pain (as before).
3. Anti-inflammatory:
4. Antiplatelet: As treatment or prophylaxis of cerebral and coronary thrombosis and postoperative DVT (325mg/day or lower).

Side effects and Toxicity:

1. **Gastrointestinal:** The most common GI effects of the salicylates are epigastric distress, nausea, vomiting, and bleeding by inhibiting the cytoprotective PGs.
2. **Blood:** Bleeding tendency
3. **Renal**: analgesic nephropathy.
4. **Respiration**: In toxic doses, salicylates cause respiratory depression and a combination of uncompensated respiratory and metabolic acidosis.

5. **Metabolic processes**: hyperthermia caused by salicylates when taken in toxic quantities.
6. **Hypersensitivity**: Approximately 15 percent of patients taking aspirin experience hypersensitivity reactions.
7. **Reye's syndrome**: Aspirin and other salicylates given during viral infections has been associated with an increased incidence of Reye's syndrome, which is an often fatal, fulminating hepatitis with cerebral edema. This is especially encountered in children, who therefore should be given acetaminophen instead of aspirin when such medication is required to reduce fever. Ibuprofen is also appropriate.

Other non-selective NSAIDs (All are reversible inhibitors of COX)

Group	Properties
Propionic acid derivatives Examples: Ibuprofen, ketoprofen	➢ Used in the chronic treatment of RA and osteoarthritis.
Acetic acid derivatives Example: **indomethacin**, sulindac, etodolac, **declofenac**, ketorolac	• Antiinflammatory, Analgesic, Antipyretic. **Uses:** - In rheumatoid and osteoarthritis, ankylosing s. - In patent Ductus Arteiosus because patensy is depending on PGs. **Diclofenac**: accumulates in synovial fluid and the primary route of excretion for the drug and its metabolites is the kidney.
<u>Oxicams</u> Examples: Piroxicam and meloxicam.	They have the same pharmacological actiond uses, side effects as other NSAIs except that they have long half-life due to the enterohepatic recycling, so it is used once/ day. Meloxicam has a high COX-2 selectivity reducing its GIT side effects

Selective COX-2 Inhibitors: e.g Celecoxib

- Unlike aspirin, celecoxib does not inhibit platelet aggregation and does not increase bleeding time.
- Celecoxib has similar efficacy to NSAIDs in the treatment of pain and the risk for cardiovascular events.
- Celecoxib is approved for treatment of RA, osteoarthritis, and pain.
- Celecoxib has less GI bleeding and dyspepsia.

Paracetamol (Acetaminophen):

Mechanism of action:

- It inhibits prostaglandin synthesis in the CNS. This explains its antipyretic and analgesic properties.
- Acetaminophen has less effect on cyclooxygenase in peripheral tissues, which accounts for its weak anti-inflammatory activity.
- Acetaminophen does not affect platelet function or increase blood clotting time.

Pharmacokinetics

- Under normal circumstances, acetaminophen is conjugated in the liver to form inactive glucuronidated or sulfated metabolites.
- A portion of acetaminophen is hydroxylated to form N-acetylbenzoiminoquinone, a highly reactive and potentially dangerous metabolite that reacts with sulfhydryl groups. At normal doses of acetaminophen, the N-acetylbenzoiminoquinone reacts with the sulfhydryl group of glutathione, forming a nontoxic substance. Acetaminophen and its metabolites are excreted in the urine.

Uses:

1. Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of aspirin for those patients with gastric complaints.

2. Those in whom prolongation of bleeding time would be a disadvantage or those who do not require the anti-inflammatory action of aspirin.
3. Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox (recall that aspirin increases the risk of Reye's syndrome).

Side effects:

1. With normal therapeutic doses, acetaminophen is virtually free of any significant adverse effects.
2. Allergy: Skin rash and minor allergic reactions occur infrequently.
3. Kidney: Renal tubular necrosis and hypoglycemic coma are rare complications of prolonged, large-dose therapy.
4. Hepatic necrosis: With large doses of acetaminophen [Note: Administration of N-acetylcysteine, which contains sulfhydryl groups can be lifesaving if administered within 10 hours of the overdose.] This agent should be avoided in patients with severe hepatic impairment. Periodic monitoring of liver enzymes tests is recommended for those on high-dose acetaminophen.

Corticosteroids

Examples: dexamethasone, Prednisone

Uses

1) **Anti-inflammatory**
2) **Anti-allergic**
3) **Auto-immune diseases**

Side effects and contraindications

1) **Salt and water retention…..hypertension**
2) **Hyperglycemia……diabetes**
3) **Hypocalcemia…..osteoporosis**
4) **Peptic ulcer**
5) **Increased risk of infection**

Sedative hypnotics: e.g diazepam

Antihistamines: H1-blockers (e.g. loratadine) used in allergy.

H2-blockers: (e.g. ranitidine) used in peptic ulcer.