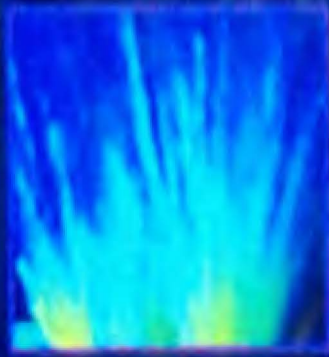


BlueprintTM

7th Edition

PHARMACOLOGY

ANIK



Edition 2017

For MBBS 3rd & 4th year, BDS 2nd year
Residency Admission Test (MD, MS, M. Phil) & FCPS Part-I

Dr. Muhammad Abdullah, MBBS (DMC)

Blueprint™

Pharmacology

**Based on new medical curriculum
Seventh edition**

For Written (SAQ), Viva, MCQ & Practical
MBBS 3rd & 4th years and BDS 2nd year
Residency admission test (MD, MS & M. Phil); FCPS- part I

Edition 2017

Agonist → Down Regulation
Antagonist → Up Regulation

↓ ↑ f r ne — ACh

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vit C increases Fe absorption

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Abbreviations:

- DU- Dhaka University
- CU- Chittagong University
- RU- Rajshahi University
- SU- Sylhet University of Science & Technology (SUST).
- NTK- Nice to know

Summative Assessment of Pharmacology & Therapeutics

Assessment Systems and Mark Distribution

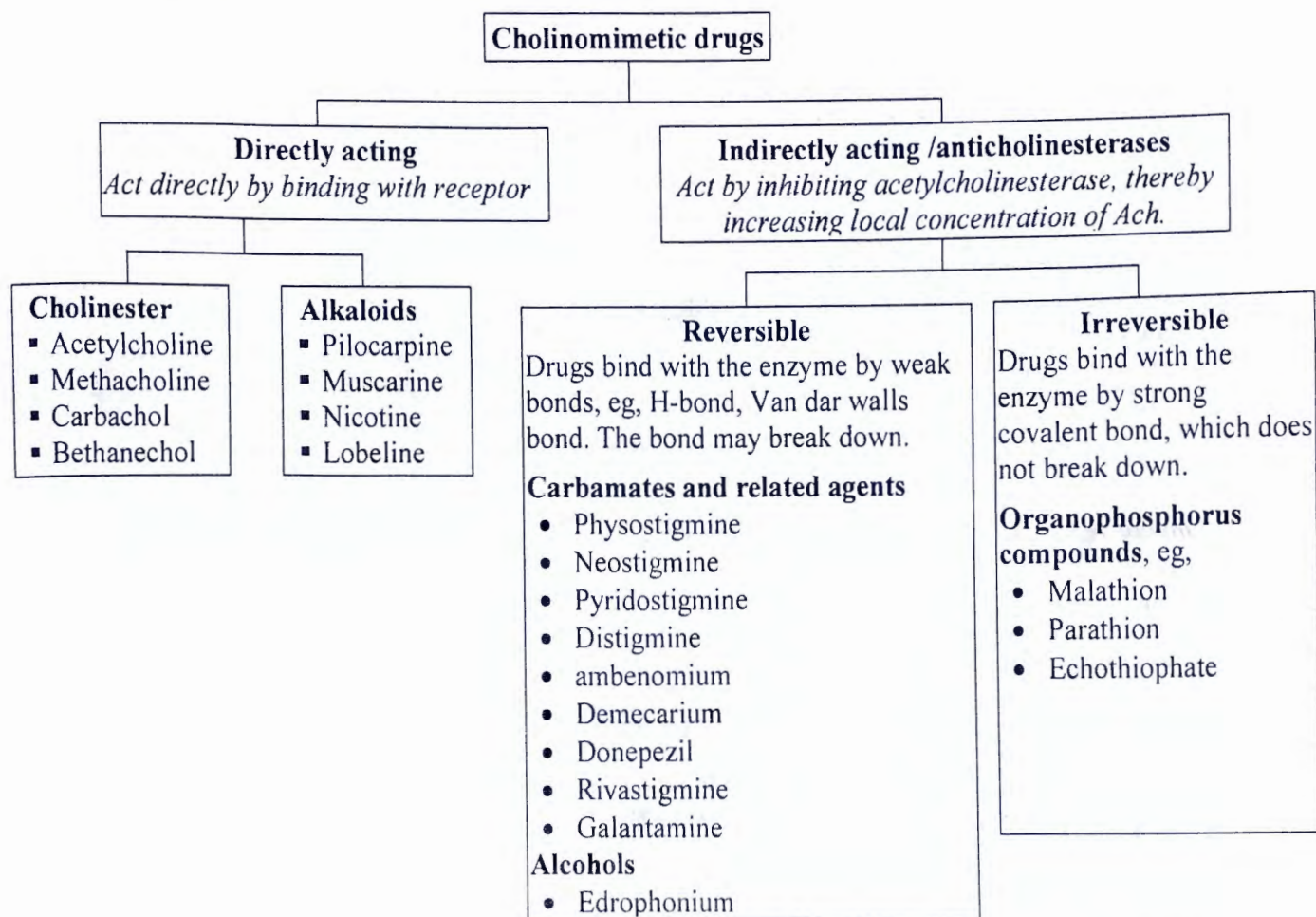
Components	Marks	Total marks
Formative assessment		10
Written examination		
• MCQ	20	90
• SAQ	70	
Practical examination		
• Traditional practical examination	60	100
• OSPE	40	
Oral examination (structured)		100
• 2 boards		
Grand total		300

There will be separate Answer Script for MCQ.

Pass marks 60 % in each of theoretical, oral and practical.

At a glance: Drugs of different systems

Cholinomimetic / cholinergic drugs:



(Ref: Katzung-13th; Lippincott's-6th; Goodman & Gilman's-12th)

Anti-cholinergic drugs: Two types-

1. Anti-muscarinic drugs: Block muscarinic receptors
 - a. Natural: Atropine, scopolamine, homatropine.
 - b. Synthetic: **Atropine substitutes-**

Quaternary amines
• Anisotropine • Clidinium • Glycopyrrolate • Isopropamide • Mepenzolate • Methantheline • Methscopolamine • Oxyphenonium • Propantheline • Tridihexethyl • Trosipium

Tertiary amines

- Darifenacin
- Dicyclomine
- Oxybutynin
- Oxyphencyclimine
- Propiverine
- Solifenacin
- Tolterodine

2. **Anti-nicotinic drugs:** Block nicotinic receptors
- a. Ganglion blocker
 - b. NMJ blocker.

Ganglion blockers:

- A. **Competitive / non-depolarizing blocker:** They compete with Ach for nicotinic receptor. So, interfere with the postsynaptic action of acetylcholine. Example—
1. Tetraethylammonium (TEA)
 2. Hexamethonium
 3. Mecamylamine
 4. Pempidine
- B. **Non-competitive / depolarizing blockers:** They prolong depolarization.
1. Nicotine
 2. Lobeline

(Ref: Katzung-13th)

Neuromuscular blocking (NMJ blocker) drugs:

1. **Non-depolarizing / competitive / reversible group:**

Isoquinoline derivatives	Steroid derivatives
• Atracurium • Cisatracurium • Doxacurium • Metocurine • Mivacurium • Tubocurarine	• Pancuronium • Pipecuronium • Rocuronium • Vecuronium

2. **Depolarizing / non-competitive / irreversible group:**

- Succinylcholine (also known as suxamethonium)
- Decamethonium

According to duration of action:

1. Short acting (5-15 minutes)	▪ Mivacurium ▪ Succinylcholine
2. Intermediate acting (20-35 minutes)	▪ Atracurium ▪ Vecuronium ▪ Rocuronium
3. Long acting (>35 minutes)	▪ Doxacurium ▪ Pancuronium ▪ Pipecuronium ▪ Tubocurarine

(Ref: Katzung-13th; Rang Dale-8th)

Sympathomimetic / adrenergic drugs: A drug that mimics stimulation of the sympathetic nervous system is called sympathomimetic / adrenergic drugs.

A. **Direct-acting adrenergic / sympathomimetic drugs:** These drugs act directly on one or more adrenergic receptors. According to receptor selectivity they are two types-

Non-selective	Drugs which act on more than one receptor	1. Adrenaline (acts on all receptors) 2. Nor-adrenaline (acts on α_1 , α_2 , β_1) 3. Isoprenaline (isoproterenol) (acts on β_1 , β_2 , β_3) 4. Dopamine (acts on α_1 , α_2 , β_1 & D_1 , D_2)	
Selective	Drugs which act on a single receptor only	α_1-selective	▪ Phenylephrine ▪ Methoxamine ▪ Oxymetazoline ▪ Midodrine
		α_2 selective	▪ α -Methyl dopa ▪ Oxymetazoline ▪ Clonidine
		β_1 selective	▪ Dobutamine
		β_2 selective	▪ Salbutamol (INN) or Albuterol (USAN) ▪ Salmeterol ▪ Formoterol ▪ Terbutaline ▪ Pirbuterol ▪ Fenoterol ▪ Reproterol ▪ Rimiterol ▪ Isoxsuprine ▪ Orciprenaline ▪ Ritodrine.

B. **Indirect-acting adrenergic / sympathomimetic drugs:**

1. **Increase release of NA from nerve ending (release promoter):**
 - a. Amphetamine
 - b. Tyramine
2. **Reuptake inhibitor:** An indirect-acting drug that increases the activity of transmitters in the synapse by inhibiting their reuptake into the presynaptic nerve ending.
 - a. Tricyclic anti-depressant (TCA)
 - b. Cocaine
 - c. Ouabin
3. **Inhibitor of enzymes COMT & MAO:**
 - a. MAO inhibitor: Pargyline
 - b. COMT inhibitor: Entacapone

C. **Mixed-action agonist** (both direct & indirect acting): Stimulate adrenoceptors directly and also increase release of NA from the nerve ending.

1. Ephedrine (α , β -agonist & release promoter)
2. Pseudoephedrine
3. Metaraminol.

(Ref: Goodman & Gilman's-12th; Katzung-13th; Lippincott's-6th, Bennett & Brown-11th)

Anti-adrenergic or sympatholytic drugs:**A. Receptor blockers**

- 1.
- α -blocker:**
- α
- blockers may be reversible or irreversible.

Reversible α-blocker (binds with receptor with weak bond, eg, H bond, van der Waals force)			Irreversible α-blocker (binds with receptor with strong covalent bond)
α_1 blocker	α_2 blocker	α_1 and α_2 blocker	α_1 and α_2 blocker
Prazosin Terazosin Doxazosin Tamsulosin	Tolazoline Yohimbine	Phentolamine	Phenoxybenzamine Dibenzamine

- 2.
- β -blocker:**
- All
- β
- blockers are competitive blockers.

Selective β-blocker (blocks either β_1 or β_2)		Non-selective β-blocker (blocks both β_1 and β_2 (cardio-nonselective))
β_1 blocker (cardioselective)	β_2 blocker	β_1 and β_2 blocker
Atenolol Bisoprolol Metoprolol Acebutolol Esmolol	Butoxamine	Propranolol Timolol Pindolol Nadolol Sotalol

(Ref: Bennet & Brown-11th)

- 3.
- Mixed antagonists: α and β blocker:**

- Labetalol
- Carvedilol

B. Neuron blockers

- **Centrally acting:** α -methyl Dopa, Clonidine
- **Peripherally acting:** Reserpine, Guanethidine

C. Ganglion blockers

- Hexamethonium
- Trimethaphan

Anti-glaucoma drugs according to their mechanism of action:

1. Anti-glaucoma drugs that act by increasing aqueous humor outflow	▪ Cholinomimetic drugs ▪ Non-selective α-agonists ▪ Prostaglandins
2. Anti-glaucoma drugs that act by decreasing aqueous secretion	▪ β-Blockers ▪ Diuretics ▪ Selective α_2-agonists

(Ref: Katzung-13th)

Sedatives & hypnotics/ Drugs for insomnia (hypnotics) & anxiety (sedatives):

A. Benzodiazepine (BDZ): (May act as both sedative & hypnotic)

According to duration of action-

Short acting (3-8 hours)	Intermediate acting (10-20 hours)	Long acting (1-3 days)
- Midazolam - Triazolam - Oxazepam	- Alprazolam - Estazolam - Lorazepam - Temazepam	- Diazepam - Clorazepate - Flurazepam - Quazepam - Nitrazepam - Parazepam - Chlordiazepoxide

B. Barbiturates: (May act as both sedative & hypnotics)

Ultra-short acting ($t_{1/2} < 15$ min)	- Thiopental sodium - Methohexital
Short acting ($t_{1/2}$ 1-3 hours)	- Pentobarbital - Secobarbital
Intermediate acting ($t_{1/2}$ 4-6 hours)	- Amobarbital - Aprobarbital - Butobarbital - Butalbital
Long acting ($t_{1/2} > 6$ hours)	- Phenobarbital / Phenobarbitone - Mephobarbital

C. Non-barbiturate sedatives:

- Antipsychotics
- Antidepressants
- Antihistamines including hydroxyzine and promethazine.
- Chloral hydrate
- Ethanol

D. Newer drugs:

- Hypnotics:** Zopiclone, eszopiclone, zolpidem, zaleplon, ramelteon (a melatonin receptor agonist).
- Sedatives:** Buspirone, meprobamate.

(Ref: Lippincott's-6th+ Katzung-13th)

Analgesic drugs:

A. Opioid / narcotic analgesics: They act in the CNS and cause drowsiness.

Low efficacy opioid for mild to moderate pain	High efficacy opioid for severe pain
- Codeine. - Dihydrocodeine. - Dextropropoxyphene. - Pentazocine. - Nalbuphine	- Morphine - Pethidine (Mepiridine) - Tramadol - Tapentadol - Fentanyl - Meptazinol - Diamorphine (heroin) - Methadone - Buprenorphin - Dexromoramide - Dipipanone - Phenazocine

(Ref: Bennett & Brown-11th)

B. Non-opioid / non-narcotic analgesics: They act chiefly peripherally, eg, NSAIDs.

Opioid / morphine antagonists:

1. Naloxone
2. Naltrexone
3. Nalmefene

Anti-depressant drugs:

1. Selective serotonin reuptake inhibitors (SSRI)	▪ Citalopram ▪ Escitalopram ▪ Fluoxetine ▪ Fluvoxamine ▪ Paroxetine ▪ Sertraline
2. Selective Serotonin-Norepinephrine reuptake inhibitors (SNRIs)	▪ Venlafaxine ▪ Desvenlafaxine ▪ Duloxetine ▪ Milnacipran
3. Tricyclic antidepressants	▪ Amitriptyline ▪ Nortriptyline ▪ Protriptyline ▪ Imipramine ▪ Desipramine ▪ Clomipramine ▪ Trimipramine ▪ Doxepin
4. 5-HT ₂ antagonists	▪ Nefazodone ▪ Trazodone
5. Tetracyclics and unicyclic	▪ Amoxapine ▪ Bupropion ▪ Maprotiline ▪ Mirtazapine
6. Monoamine oxidase (MAO) inhibitors	▪ Phenelzine ▪ Selegiline ▪ Isocarboxazid

(Ref: Katzung-13th)

Anti-psychotic drugs / drugs for schizophrenia:

- A. **Traditional or typical neuroleptic drugs** (also called **conventional** or **first-generation antipsychotics**) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of dopamine receptors.

According to chemical nature:

1. Phenothiazine derivatives	▪ Chlorpromazine ▪ Prochlorperazine ▪ Thioridazine ▪ Perphenazine ▪ Trifluoperazine ▪ Fluphenazine
2. Thioxanthene derivatives	▪ Thiothixene
3. Butyrophenone derivatives	▪ Haloperidol
4. Miscellaneous structure	▪ Pimozide ▪ Molindone

B. Atypical (or second-generation antipsychotics):

Atypical (or second-generation antipsychotics): The newer antipsychotic drugs are referred to as atypical (or second-generation antipsychotics), because they have fewer extrapyramidal adverse effects than the older, traditional agents. These drugs appear to owe their unique activity to blockade of both serotonin and dopamine (and, perhaps, other) receptors.

The "atypical" antipsychotic drugs are now the most widely used type of antipsychotic drug.

1. Loxapine
2. Clozapine
3. Asenapine
4. Olanzapine
5. Quetiapine
6. Paliperidone
7. Risperidone
8. Sertindole
9. Ziprasidone
10. Zotepine
11. Aripiprazole

(Ref: Katzung-13th; Lippincott's-6th)

Anti epileptic drugs / Anti-convulsant drugs / Antiseizure Drugs:

Mechanism of action	Drugs
1. Enhancement of GABA-ergic (inhibitory) transmission / facilitation of GABA-mediated Cl^- channel opening	▪ Barbiturate: Phenobarbitone ▪ Benzodiazepine: ☉ Diazepam. ☉ Lorazepam ☉ Clonazepam ☉ Nitrazepam ☉ Clobazam ▪ Vigabatrin ▪ Tiagabine ▪ Gabapentin ▪ Valproate
2. Blockage of voltage sensitive Na^+ -channel / prolongation of Na^+ -channel inactivation	▪ Carbamazepine ▪ Phenytoin ▪ Valproic acid ▪ Na-valproate ▪ Lamotrigine ▪ Topiramate ▪ Zonisamide
3. Blockage of T-type Ca^{2+} -channel	▪ Ethosuximide ▪ Phensuximide ▪ Methsuximide ▪ Trimethadione ▪ Valproate
4. Newer drugs	▪ Lamotrigine ▪ Levetiracetam ▪ Gabapentin ▪ Oxcarbazepine ▪ Pregabalin ▪ Topiramate

- Vigabatrin
- Lacosamide
- Zonisamide

(Ref: Tripathi-6th/404 (fig-30.2) + Katzung-13th)

Drugs used for Parkinsonism:

A. Drugs that increase central dopaminergic activity:

1. Dopamine precursor	▪ Levodopa
2. Dopamine agonists	▪ Bromocriptine ▪ Pergolide ▪ Pramipexole ▪ Ropinirole
3. Increased synthesis, release & reuptake of dopamine	▪ Amantadine
4. Decreased dopamine metabolism	MAO inhibitors: ▪ Selegiline ▪ Rasagiline COMT inhibitors: ▪ Tolcapone ▪ Entacapone

B. Drugs that decrease cholinergic activity (Anti-muscarinic drugs):

1. Procyclidine
2. Orphenadrine
3. Benztropine mesylate
4. Biperiden
5. Trihexyphenidyl

Drugs for general anesthesia:

IV or parenteral anesthetics	Inhaled anesthetics
1. Barbiturates: ▪ Thiopental sodium ▪ Methohexital	1. Halothane
2. Benzodiazepines: ▪ Diazepam ▪ Lorazepam ▪ Midazolam	2. Isoflurane
3. Opioid analgesics: ▪ Morphine ▪ Pethidine ▪ Fentanyl ▪ Sufentanil ▪ Alfentanil ▪ Remifentanyl	3. Enflurane
4. Miscellaneous: ▪ Propofol ▪ Fospropofol ▪ Ketamine ▪ Etomidate ▪ Dexmedetomidine	4. Desflurane
	5. Sevoflurane
	6. Methoxyflurane
	7. Nitrous oxide (NO)
	8. Xenon

(Ref: Goodman & Gilman's-12th & Katzung-13th)

Local anesthetics:

A. According to chemical nature:

Esters	Procaine Tetracaine Benzocaine Cocaine
Amides	Lidocaine (Xylocaine) Mepivacaine Bupivacaine Levobupivacaine Ropivacaine Articaine

(Ref: Katzung-13th)

B. According to duration of action:

Short acting	Procaine Cocaine
Intermediate acting	Lidocaine/Xylocaine/Lignocaine: Most common. Widely used. Mepivacaine Prilocaine
Long acting	Tetracaine Bupivacaine Ropivacaine

Muscle relaxants

A. Centrally acting muscle relaxants:

1. Mephenesin congeners	▪ Mephenesin ▪ Chlormezanone ▪ Carisoprodol ▪ Methocarbamol ▪ Chlorzoxazone
2. Benzodiazepine	▪ Diazepam
3. GABA derivatives	▪ Baclofen ▪ Gabapentin
4. Central α_2-agonist	▪ Tizanidine

(Ref: Tripathi-6th/348)

B. Peripherally acting muscle relaxants: (Described in the ANS chapter.)

1. Non-depolarizing / competitive / reversible group
2. Depolarizing / non-competitive / irreversible group

Anti-hypertensive drugs

According to their mechanism of action:

1. **Diuretics:** Loop & thiazide diuretics
2. **Sympatholytic drugs:**
 - a. Centrally acting: α -methyl dopa, Clonidine.
 - b. Peripherally acting:
 - Adrenergic receptor blocker
 - β -adrenoceptor blockers: Atenolol, metoprolol, bisoprolol
 - α -blockers: Prazosin
 - Mixed: Labetalol, carvedilol.
 - Adrenergic neuron blockers (α -methyl dopa, guanethidine, reserpine)

3. **Renin-angiotensin-aldosterone system inhibitor:**
 - a. **ACE inhibitors:** Captopril, lisinopril, enalapril, ramipril
 - b. **Angiotensin-II receptor blockers:** Losartan, valsartan
 - c. **Direct renin inhibitors:** Aliskiren
4. **Calcium channel blockers:** Amlodipine, nifedipine, diltiazem, verapamil
5. **Direct vasodilators:** Hydralazine, Na-nitroprusside.

(Ref: Katzung-13th)

Vasodilators:**A. According to route of administration:**

Parenteral vasodilators	▪ Na-nitroprusside ▪ Diazoxide ▪ Fenoldopam
Oral vasodilators	▪ Hydralazine ▪ Minoxidil

B. Accord in to site of action:

Arterial	▪ Hydralazine ▪ Minoxidil ▪ Diazoxide ▪ Fenoldopam
Both arterial & venous	▪ Na-nitroprusside

(Ref: Katzung-13th)

C. According to nature of action:

Direct vasodilators	▪ Na-nitroprusside, Diazoxide, Hydralazine
Indirect vasodilators	▪ Ca channel blockers ▪ ACE inhibitors ▪ Angiotensin-II receptor blockers ▪ Renin release inhibitors: β-blockers

Ca²⁺ channel blockers:**A. According to degree of selectivity:**

1. Cardio-selective Ca²⁺ channel blockers: Acts on both cardiac & vascular smooth muscle	▪ Verapamil ▪ Diltiazem
2. Vessel selective Ca²⁺ channel blockers: Acts mainly on vascular smooth muscle	▪ Amlodipine (1st choice) ▪ Nifedipine ▪ Nicardipine ▪ Nimodipine

(Ref: Katzung-13th)

B. According to chemical structure:

1. Diphenylalkylamines	▪ Verapamil
2. Benzothiazepines	▪ Diltiazem
3. Dihydropyridines	First generation
	▪ Nifedipine
	Second generation
	▪ Amlodipine ▪ Felodipine ▪ Nicardipine ▪ Nimodipine ▪ Isradipine ▪ Nisoldipine

Renin angiotensin aldosterone system (RAAS) inhibitors:

A. Angiotensin converting enzyme inhibitors (ACEi)	▪ Captopril ▪ Enalapril ▪ Lisinopril ▪ Ramipril ▪ Benazepril ▪ Fosinopril ▪ Moexipril ▪ Perindopril ▪ Quinapril ▪ Trandolapril ▪ Fosinopril
B. Angiotensin-II receptor blockers (ARB)	▪ Losartan ▪ Valsartan ▪ Candesartan ▪ Eprosartan ▪ Irbesartan ▪ Telmisartan ▪ Olmesartan
C. Direct renin inhibitor	▪ Aliskiren
D. Drugs that block renin secretion	▪ Propranolol ▪ Atenolol ▪ Metoprolol ▪ Clonidine

Anti-anginal drugs:**A. Organic nitrates / nitroglycerin:**

Short acting	▪ Sublingual: Glyceryl-tri-nitrate (GTN), isosorbide dinitrate ▪ Inhalant: Amyl nitrite
Long acting	▪ GTN: Slow release tablets, 2% ointment, oral sustained action preparation ▪ Isosorbide mononitrate: Oral sustained action preparation. ▪ Isosorbide dinitrate: Chewable oral, oral.

B. Ca²⁺ channel blockers:

- Verapamil
- Diltiazem
- Nifedipine
- Nicardipine
- Amlodipine

C. β -blockers

- Propranolol
- Atenolol
- Metoprolol

D. Newer Antianginal Drugs:

Drugs or Drug Groups under Investigation for Use in Angina
• Metabolic modulators, eg, trimetazidine, ranolazine • Direct bradycardic agents, eg, ivabradine • Potassium channel activators, eg, nicorandil • Capsaicin • Amiloride

E. Antiplatelet:

- Low dose aspirin (75-150 mg)
- Clopidogrel (75 mg)

F. Anticoagulant:

- Heparin
- Low-molecular-weight heparin

Drugs for heart failure / Congestive cardiac failure (CCF):**A. According to the effect of the drug:**

1. Reduction of preload	▪ Diuretics ▪ Nitrates
2. Reduction of afterload	▪ Direct acting vasodilators (hydralazine, minoxidil, Na-nitroprusside, diazoxide)
3. Reduction of both preload and afterload	▪ ACE inhibitors (ramipril, captopril, enalapril, lisinopril) ▪ Angiotensin-II receptor blockers (losartan, valsartan, candesartan, telmisartan) ▪ Beta blockers (Metoprolol, bisoprolol, carvedilol) ▪ Spironolactone
4. Stimulation of myocardium	▪ Digoxin ▪ Digitoxin ▪ Phosphodiesterase inhibitors (enoximone and milrinone)

*(Ref: Bennett & Brown-11th)***B. According to mechanism of action:**

1. Drugs with positive inotropic effects.		
▪ Cardiac glycosides	▪ Digoxin ▪ Digitoxin ▪ Ouabain	
▪ β -agonist	▪ Dobutamine ▪ Dopamine	
▪ PDE inhibitors: Bipyridine	▪ Inamrinone ▪ Milrinone	
2. Drugs without positive inotropic effects		
▪ Diuretics	▪ Frusemide	
▪ ACE inhibitors	▪ Captopril, Enalapril, Lisinopril, Ramipril	
▪ Angiotensin-II receptor blockers	▪ Losartan, Valsartan, Telmisartan	
▪ Aldosterone antagonists	▪ Spironolactone	
▪ β -blockers	▪ Bisoprolol, Carvedilol, Metoprolol	
▪ Vasodilators	▪ Hydralazine and isosorbide dinitrate	

*(Ref: Katzung-13th)***Anti-arrhythmic drugs:****1. Class-I drugs: They are voltage sensitive Na^+ -channel blockers.**

Class IA	▪ Prolong the action potential duration (APD) by slowing phase 0 depolarization. ▪ Increase ventricular effective refractory period. ▪ Dissociate from the channel with intermediate kinetics.	• Quinidine • Procainamide • Disopyramide
Class IB	▪ Shorten the APD in some tissues of the heart by shortening phase 3 repolarization. ▪ Dissociate from the channel with rapid kinetics.	• Lidocaine • Mexiletine

Class IC	▪ Markedly slow phase 0 depolarization. ▪ Cause marked conduction slowing. ▪ Have minimal effects on the APD and ventricular effective refractory period. ▪ Dissociate from the channel with slow kinetics.	• Flecainide • Encainide • Moricizine • Propafenone
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2. **Class-II drugs:** They are **β -adrenoceptor blocker**. They suppress phase 4 depolarization, thus depressing automaticity, prolonging AV conduction, and decreasing heart rate and contractility.
 1. Esmolol
 2. Metoprolol
 3. Propranolol
 4. Pindolol
 5. Sotalol
 6. Atenolol
3. **Class-III drugs:** They are voltage sensitive **K^+ channel blocker** and thus diminish efflux of K^+ during repolarization of cardiac cells. They prolong phase-3 repolarization in ventricular muscle fiber.
 1. Amiodarone
 2. Dronedarone
 3. Sotalol
 4. Dofetilide
 5. Ibutilide
4. **Class-IV drugs:** They are voltage sensitive **Ca^{2+} channel blocker**. They decrease Ca^{2+} influx, resulting in decreased rate of phase 4 spontaneous depolarization. They slow conduction in tissues that are dependent on calcium currents, eg, SA node, AV node.
 - Verapamil
 - Diltiazem
5. **Miscellaneous Antiarrhythmic Agents:**
 - Digoxin
 - Adenosine
 - Magnesium
 - Potassium

(Ref: Lippincott's-6th, Katzung-13th edition)

Diuretics

A. According to their site of action and mechanism of action:

1. **Thiazide & thiazide-like diuretics:** Inhibit NaCl reabsorption from the **early part of distal convoluted tubule** by blocking the **Na^+/Cl^- transporter**-
 - Chlorothiazide
 - Hydrochlorothiazide
 - Chlorthalidone
 - Indapamide
 - Metolazone
 - Bendroflumethiazide
 - Hydroflumethiazide
 - Polythiazide
 - Trichlormethiazide
2. **Loop diuretics:** Inhibits **$Na^+-K^+-2Cl^-$ transporter** at the **thick ascending limb of loop of Henle**-
 - Furosemide / Frusemide
 - Torsemide

- Bumetanide
- Ethacrynic acid

3. **K⁺ sparing diuretics:** Diuretics acting over **collecting tubule-**

a. Aldosterone receptor antagonist	▪ Spironolactone ▪ Eplerenone
b. Na ⁺ channel blockers	▪ Amiloride ▪ Triamterene

4. **Carbonic anhydrase inhibitors (rarely used):** Inhibit carbonic anhydrase located in the **proximal tubular epithelium-**

- Acetazolamide
- Dorzolamide
- Methazolamide
- Brinzolamide
- Dichlorphenamide

5. **Osmotic diuretics:** Diuretics acting over **proximal convoluted tubule-**

- Mannitol
- Inulin
- Urea
- Glucose.

(Ref: Katzung-13th; Lippincott's-6th)

B. According to efficacy / potency:

1. **High efficacy diuretics/ high ceiling diuretic:** Can cause up to 25% of filtered sodium to be excreted.
 - Loop diuretics
2. **Moderate efficacy diuretics:** Can cause 5-10% of filtered sodium load to be excreted.
 - Thiazide diuretics
 - Non-thiazide
3. **Low efficacy diuretics:** Can cause 5% of the filtered sodium to be excreted.
 - Carbonic anhydrase inhibitors
 - K⁺ sparing diuretics
 - Osmotic diuretics

(Ref: Bennet & Brown & Brown-11th)

C. According to K⁺ sparing capacity:

1. **K⁺ losing diuretic:**

- a. Loop diuretics
- b. Thiazide diuretics
- c. Carbonic anhydrase inhibitors
- d. Osmotic diuretics

2. **K⁺ sparing diuretic:**

a. Aldosterone receptor antagonist	▪ Spironolactone ▪ Eplerenone
b. Na ⁺ channel blockers	▪ Amiloride ▪ Triamterene

Penicillins

1. According to source	Natural penicillins	Benzylpenicillin / penicillin G, Phenoxymethylpenicillin / penicillin V
	Semisynthetic penicillin	Ampicillin, amoxicillin, cloxacillin
2. According to spectrum coverage	Narrow spectrum	Penicillin G, Penicillin V
	Broad spectrum	Ampicillin, amoxicillin, pivampicillin, talampicillin, bacampicillin
	Extended spectrum	Ticarcillin, piperacillin, mezlocillin, azlocillin
3. According to β -lactamase sensitivity	β-lactamase sensitive	Benzylpenicillin Amoxicillin Ampicillin Ticarcillin
	β-lactamase resistant	Nafcillin Cloxacillin Methicillin Dicloxacillin Oxacillin Flucloxacillin
4. According to duration of action	Long-acting	Benzathine penicillin (7-30 days) Procaine penicillin (12-24 hours)
	Short-acting	Ampicillin, amoxicillin, penicillin V
5. According to gastric acid sensitivity	Acid labile (Can't be given orally, always in parenteral route)	Penicillin G Procaine penicillin Benzathine penicillin
	Acid stable (Can be given orally)	Penicillin V Ampicillin, amoxicillin, cloxacillin

(Ref: Katzung-13th + Bennett & Brown-11th)

Cephalosporins

	Drugs	Criteria / antibacterial spectrum
1 st generation	Oral: Cephadrine Cefadroxil Cephalexin Parenteral: Cephalothin Cephadrine Cefazolin Cephapirin	- Resistant to β-lactamase enzyme. - Very active against Gram +ve cocci: Pneumococci, streptococci, staphylococci (except enterococci & MRSA) - Moderately active against Gram -ve rods, eg, PEcK: <i>Proteus mirabilis</i>, <i>E. coli</i>, <i>Klebsiella pneumoniae</i>. Anaerobic cocci (eg, peptococcus, peptostreptococcus) are usually sensitive. - Activity against <i>P aeruginosa</i>, enterobacter, citrobacter, and acinetobacter is poor.
2 nd generation	Oral: Cefaclor Cefuroxime axetil Cefprozil Loracarbef Parenteral: Cefuroxime	- More resistant to β-lactamase enzyme. - More active against Gram -ve rods and less active against Gram +ve bacteria. - They have extended gram-negative coverage. Spectrum of Gram -ve bacteria: PEcK + HEN (<i>H. influenzae</i>, <i>Enterobacter aerogenes</i>, and some <i>Neisseria</i>).

	Cefamandole Cefotetan Cefoxitin Cefmetazole Cefonicid	As with first-generation agents, none is active against enterococci or <i>P aeruginosa</i>.
3 rd generation	Oral: Cefixime Cefdinir Ceftibuten Cefpodoxime proxetil Parenteral: Ceftriaxone Ceftazidime Cefoperazone Cefotaxime Moxalactam Ceftizoxime	- Less active against Gram +ve bacteria - They have expanded gram-negative coverage. Spectrum of Gram -ve bacteria: HENPEcK+ PSC → <i>Providencia</i>, <i>Serratia marcescens</i>, <i>citrobacter</i>. - Ceftazidime and cefoperazone are the only two drugs active against <i>P aeruginosa</i>. - Ceftizoxime and moxalactam are active against <i>B fragilis</i>. - Cefixime and ceftibuten are much less active against pneumococci and <i>S aureus</i>.
4 th generation	Only parenteral: Cefepime Cefpirome	- More resistant to β-lactamases. - Cefepime has good activity against <i>P aeruginosa</i>, Enterobacteriaceae, <i>S aureus</i>, and <i>S pneumoniae</i>. - Unlike ceftazidime, cefepime has good activity against most penicillin-resistant strains of streptococci. - It is highly active against haemophilus and neisseria. - It penetrates well into CSF.

(Ref: Katzung-13th; Lippincott's-6th)

Nice to know**5th generation cephalosporin**

- Ceftobiprole
- Ceftaroline

(Ref: Websites)

Drugs of the carbapenem group:

- Meropenem
- Imipenem
- Doripenem
- Ertapenem

Non β -lactam bacterial cell wall synthesis inhibitors:

Glycopeptide Antibiotics	Vancomycin Teicoplanin Dalbavancin Telavancin
Other cell wall or membrane active agents	Daptomycin Bacitracin Cycloserine Fosfomycin

(Ref: Katzung-13th)

Aminoglycosides

A. According to source:

Source	Drugs
Natural	1. Derived from Streptomyces: (having 'mycin' suffix) ▪ Streptomycin ▪ Neomycin ▪ Kanamycin ▪ Tobramycin 2. Derived from Micromonospora: (having 'micin' suffix) ▪ Gentamicin ▪ Sisomicin ▪ Netilmicin
Semisynthetic	Amikacin Netilmicin

(Ref: Lippincott's-6th)

B. According to route of administration:

Route of administration	Drugs
Systemic	Gentamicin Amikacin Streptomycin Tobramycin Sisomicin Netilmicin Kanamycin
Topical	Neomycin Framycetin
Oral	Neomycin Paromomycin

(Ref: Katzung-13th)

Tetracyclines

A. According to source:

Natural tetracyclines	▪ Chlortetracycline ▪ Oxytetracycline ▪ Tetracycline ▪ Demeclocycline
Semisynthetic tetracyclines	▪ Doxycycline ▪ Minocycline ▪ Demeclocycline

B. According to plasma half life:

Short acting ($t_{1/2}$ 6-8 hours)	Chlortetracycline, Oxytetracycline & Tetracycline.
Intermediate acting ($t_{1/2}$ 12 hours)	Demeclocycline, Methacycline.
Long acting ($t_{1/2}$ 16-18 hours)	Doxycycline, Minocycline & Tigecycline (36 hrs)

C. According to bioavailability:

Low bioavailability (30%)	Chlortetracycline
Intermediate bioavailability (60-70%)	Oxytetracycline, Tetracycline, Demeclocycline & Methacycline
High bioavailability (95-100%)	Doxycycline, Minocycline.

(Ref: Katzung-13th)

Macrolides:

1. Erythromycin
2. Clarithromycin
3. Azithromycin
4. Roxithromycin
5. Ketolides (Telithromycin)

(Ref: Katzung-13th)

Nucleic acid synthesis inhibitors:

Mechanism of action		Class of drug
A. Direct	DNA synthesis inhibitor	▪ Quinolones ▪ Metronidazole
	RNA synthesis inhibitor	▪ Rifampicin ▪ Rifamycin
B. Indirect	Anti-folate drugs	▪ Sulfonamide ▪ Trimethoprim ▪ Pyrimethamine

Sulfonamides:

Type		Drugs
1. Oral, absorbable: (Classified on the basis of their half-lives $t_{1/2}$)	Short acting	▪ Sulfisoxazole ($t_{1/2}$ = 6 hours) ▪ Sulfamethizole ($t_{1/2}$ = 9 hours) ▪ Sulfacytine
	Intermediate acting	▪ Sulfadiazine ($t_{1/2}$ = 10-17 hours) ▪ Sulfamethoxazole ($t_{1/2}$ = 10-12 hours) ▪ Sulfapyridine ($t_{1/2}$ = 17 hours)
	Long acting	▪ Sulfadoxine ($t_{1/2}$ = 7-9 days)
2. Oral, nonabsorbable		▪ Sulfasalazine
3. Topical (not absorbed in systemic circulation)		▪ Silver sulfadiazine (less toxic) ▪ Sodium sulfacetamide ▪ Mafenide acetate

(Ref: Katzung-13th)

FluoroquinolonesA. **Classification based on generation:** Generations of drugs are based on their antimicrobial targets.

Generations	Drugs	Antibacterial spectrum
1. 1 st generation	▪ Nalidixic acid	▪ Least active against Gram -ve and Gram +ve bacteria ▪ Narrow spectrum usually confined to the urinary tract.
2. 2 nd generation	▪ Ciprofloxacin ▪ Lomefloxacin ▪ Ofloxacin ▪ Norfloxacin ▪ Pefloxacin ▪ Enoxacin	▪ Excellent Gram -ve activity and moderate to good activity against Gram +ve bacteria. ▪ Active against aerobic Gram -ve bacteria and intracellular organisms eg, chlamydia, mycoplasma, legionella.
3. 3 rd generation	▪ Levofloxacin ▪ Gatifloxacin ▪ Gemifloxacin ▪ Sparfloxacin	▪ Improved activity against Gram-positive bacteria.
4. 4 th generation	▪ Moxifloxacin ▪ Trovafloxacin	▪ Active against many anaerobic as well as Gram +ve organisms.

(Ref: Lippincott's-6th)

B. According to half life:

1. Shorter half life (3-5 hours)	Ciprofloxacin, Norfloxacin
2. Intermediate half life (5-7 hrs)	Levofloxacin, Ofloxacin
3. Longer half life (>7 hours)	Gatifloxacin, Gemifloxacin, Lomefloxacin, Moxifloxacin

C. According to bioavailability:

1. Shorter bioavailability (70-90%)	Ciprofloxacin, gemifloxacin, moxifloxacin, norfloxacin
2. Longer bioavailability (> 90%)	Levofloxacin, gatifloxacin, lomefloxacin, ofloxacin

(Ref: Katzung-6th)

Anti-tubercular drugs:

First line drugs: (in approximate order of preference)- These drugs have high antitubercular efficacy as well as low toxicity & are used routinely.

1. Isoniazid (H)
2. Rifampicin (R)
3. Pyrazinamide (Z)
4. Ethambutol (E)
5. Streptomycin (S)

Second line drugs: These drugs have either low antitubercular efficacy or high toxicity or both & are used in special circumstances.

1. Amikacin
2. Aminosalicic acid
3. Capreomycin
4. Ciprofloxacin
5. Clofazimine
6. Cycloserine
7. Ethionamide
8. Levofloxacin
9. Rifabutin
10. Rifapentine

(Ref: Katzung-13th)

Modified WHO-recommended multidrug therapy regimens in leprosy:

Type of leprosy	Monthly supervised drug treatment	Daily self-administered drug treatment	Duration of treatment
Paucibacillary	Rifampicin 600 mg	Dapsone 100 mg	6 months
Multibacillary	Rifampicin 600 mg Clofazimine 300 mg	Clofazimine 50 mg Dapsone 100 mg	12 months
Paucibacillary single-lesion	Ofloxacin 400 mg Rifampicin 600 mg Minocycline 100 mg		Single dose

Antimalarial drugs:

Classes	Definition	Drugs
1. Tissue schizonticides	- Drugs that eliminate developing or dormant liver forms. - They cause a radical cure by acting on the parasites in the liver. - These drugs also destroy gametocytes and thus reduce the spread of infection.	Primary tissue schizonticides: Drugs for causal prophylaxis / chemoprophylaxis. - Proguanil - Mefloquine - Pyrimethamine - Doxycycline - Dapsone

		Latent tissue schizonticides: Drugs for radical cure - Primaquine - Tafenoquine
2. Blood schizonticides	- Drugs that act on erythrocytic parasites. - They are used to treat the acute attack. - They are also known as drugs for suppressive or clinical cure.	Highly efficacious: fast acting & can be used singly. - Chloroquine - Mefloquine - Quinine - Quinidine - Atovaquone - Artemisinins - Lumefantrine - Halofantrine Less efficacious: slow acting & always used in combination. - Pyrimethamine - Sulfadoxine - Proguanil
3. Gametocides	Drugs that kill sexual stages and prevent transmission to mosquitoes.	- Primaquine: For <i>P. falciparum</i> - Chloroquine: For <i>P. vivax</i>, <i>P. malariae</i>, <i>P. ovale</i>.
4. Causal prophylactic drugs	- Drugs that are capable of preventing erythrocytic infection. - They block the link between the exoerythrocytic stage and the erythrocytic stage and thus prevent the development of malarial attacks.	- Chloroquine - Mefloquine - Proguanil - Pyrimethamine - Dapsone - Doxycycline

(Ref: Katzung-13th; Rang & Dale's-8th)

Anti-leishmanial drugs:

Leishmaniasis	Drug of choice	Alternative drugs
Visceral leishmaniasis	Sodium stibogluconate	- Miltefosine - Amphotericin B - Paromomycin - Meglumine antimonite - Pentamidine
Cutaneous leishmaniasis	Sodium stibogluconate	- Meglumine antimonite - Amphotericin - Pentamidine - Topical or intralesional therapies - Ketoconazole - Itraconazole

(Ref: Katzung-13th + Davidson's Medicine-22nd)

Anti-amoebic drugs:

1. Luminal amoebicides in large gut: Act on the ameba (cyst) in the lumen of the bowel	- Diloxanide furoate - Iodoquinol - Paromomycin
2. Systemic / Tissue amoebicides: Effective against ameba (trophozoite) in the intestinal wall and tissues eg, liver. These drugs are useful for treating liver abscesses or intestinal wall infections caused by amebas.	- Chloroquine - Dehydroemetine

3. **Mixed type of amoebicides:** Effective against both luminal (cyst) and systemic forms (trophozoite) of the disease.

- Metronidazole
- Tinidazole
- Nitazoxanide
- Secnidazole
- Omidazole

(Ref: Lippincott's-6th)

Anthelmintic drugs

Anthelmintic drugs according to mode of action:

1. Inhibits ATP synthesis by inhibiting glucose uptake	▪ Albendazole ▪ Mebendazole ▪ Thiabendazole
2. Paralysis of worm and expel in feces	
▪ Neuromuscular blocker	▪ Pyrantel pamoate
▪ Increased influx of Cl^- by activating GABA receptor	▪ Ivermectin
▪ Increased permeability of cell membrane of worm to Ca^{2+}	▪ Praziquantel
3. Destroy scolex	▪ Niclosamide

(Ref: Lippincott's-6th + Katzung-13th + Rang & Dale's-8th)

Antifungal drugs

A. *On the basis of site of administration:*

Site of administration	Drugs
1. Systemic antifungal drugs for systemic infections (oral or parenteral)	▪ Amphotericin-B ▪ Flucytosine ▪ Echinocandins: ➤ Caspofungin ➤ Micafungin ➤ Anidulafungin ▪ Azoles: ➤ Imidazole groups: Ketoconazole ➤ Triazole groups: Itraconazole, Fluconazole, Voriconazole & Posaconazole.
2. Systemic antifungal drugs for mucocutaneous infections (oral)	▪ Griseofulvin ▪ Terbinafine
3. Topical antifungal drugs for mucocutaneous infections	▪ Nystatin ▪ Amphotericin-B ▪ Topical azoles: Miconazole, Clotrimazole & Ketoconazole. ▪ Topical allylamines: Terbinafine, Naftifine.

(Ref: Katzung-13th)

B. *On the basis of mechanism of action:*

Mechanism of action	Drugs
1. Drugs that disrupt the fungal cell membrane	▪ Polyenes: e.g. amphotericin ▪ Azoles: imidazoles, e.g. ketoconazole, fluconazole ▪ Allylamines: terbinafine
2. Drug that inhibits mitosis	▪ Griseofulvin
3. Drug that inhibits DNA synthesis	▪ Flucytosine

(Ref: Bennet & Brown-11th)

Antiviral drugs:

Mechanism of action	Drugs
A. Early event inhibitors	
1. Viral entry inhibitors / fusion inhibitor	• Enfuvirtide
2. Viral uncoating inhibitors	• Amantadine • Rimantadine
B. Viral nucleic acid synthesis inhibitors	
1. Inhibitors of herpes viruses (HSV)	
▪ Nucleoside viral DNA polymerase inhibitors	• Acyclovir • Ganciclovir • Famciclovir • Valacyclovir • Cidofovir • Vidarabine • Iododeoxyuridine • Trifluorothymidine
▪ Non-nucleoside viral DNA polymerase inhibitors	• Foscarnet
2. Inhibitors of retroviruses	
▪ Nucleoside reverse transcriptase inhibitors	• Azidothymidine • Dideoxyinosine • Dideoxycytidine • Lamivudine • Stavudine • Abacavir • Tenofovir
▪ Non-nucleoside reverse transcriptase inhibitors	• Nevirapine • Delavirdine • Efavirenz
3. Inhibitors of other viruses	• Ribavirin • Adefovir
C. Protease inhibitors	• Saquinavir • Nelfinavir • Indinavir • Amprenavir • Ritonavir • Atazanavir
D. Viral protein synthesis inhibitors	• Interferon • Fomivirsen • Methisazone
E. Viral release inhibitors / neuraminidase inhibitor	• Zanamivir • Oseltamivir

(Ref: LANGE Microbiology-12th; Katzung-13th)

Anti-histamine / Histamine antagonist:

A. Physiological antagonist	▪ Adrenaline
B. Histamine release inhibitors	▪ Cromolyn, Nedocromil-sodium ▪ β_2 -agonist: Salbutamol, Terbutaline
C. Histamine receptor antagonists	▪ H_1 -receptor antagonists ▪ H_2 -receptor antagonists ▪ H_3 & H_4 -receptor antagonist

(Ref: Katzung-13th)

H₁ receptor antagonists:**A. According to their generation:**

1. 1 st generation H ₁ -receptor antagonists	Ethanolamines • Carbinoxamine • Dimenhydrinate • Diphenhydramine
	Piperazine derivatives • Hydroxyzine • Cyclizine • Meclizine
	Alkylamines • Brompheniramine • Chlorpheniramine
	Phenothiazine derivative • Promethazine
	Miscellaneous • Cyproheptadine
2. 2 nd generation H ₁ -receptor antagonists	Piperidine • Fexofenadine
	Miscellaneous • Loratadine • Cetirizine

(Ref: Katzung-13th)

B. According to degree of sedative effect:

1. Highly sedative	▪ Diphenhydramine ▪ Dimenhydrinate ▪ Promethazine ▪ Hydroxyzine
2. Moderately sedative	▪ Pheniramine ▪ Cyproheptadine ▪ Meclizine ▪ Buclizine
3. Mildly sedative	▪ Chlorpheniramine ▪ Dexchlorpheniramine ▪ Cyclizine ▪ Dimethindene ▪ Triprolidine
4. Least or non-sedative	▪ Cetirizine ▪ Levocetirizine ▪ Fexofenadine ▪ Loratadine ▪ Desloratadine ▪ Azelastine ▪ Mizolastine ▪ Ebastine ▪ Rupatadine

(Ref: Tripathi-6th/156)**Oxytocic / ecbolics in obstetrics:**

1. Oxytocin
2. Ergot derivatives
3. Prostaglandins (E & F)

NSADs:**A. According to their chemical nature & structure:**

1. **Salicylates:** Aspirin
2. **Propionic acid derivatives:** Ibuprofen, Naproxen, fenoprofen, ketoprofen, flurbiprofen and oxaprozin.
3. **Acetic acid derivatives:** Indomethacin, sulindac, and etodolac.
4. **Fenamic acid derivatives:** Mefenamic acid and meclofenamate.
5. **Heteroaryl acetic acids:** Diclofenac, aceclofenac and tolmetin.
6. **Oxicam derivatives:** Piroxicam, tenoxicam and meloxicam.
7. Nabumetone
8. **Pyrrolo-pyrrolo derivative:** Ketorolac.
9. **Pyrazolone derivatives:** Phenylbutazone, Oxyphenbutazone.
10. **Benzoxazocine derivatives:** Nefopam.
11. **COX-2 inhibitors:** Celecoxib, Rofecoxib.
12. **Para-aminophenol derivative:** Paracetamol (acetaminophen)

(Ref: Lippincott's-6th; Tripathi-6th/184)**B. According to efficacy/ degree of anti-inflammatory effect:**

1. Weak anti-inflammatory / Low efficacious	▪ Para-aminophenol derivative: Paracetamol
2. Moderate anti-inflammatory/ Moderate efficacious	▪ Propionic acid derivatives: Ibuprofen, Naproxen, ketoprofen, flurbiprofen. ▪ Fenamic acid derivatives: Mefenamic acid.
3. Strong anti-inflammatory/ High efficacious	▪ Salicylates: Aspirin ▪ Heteroaryl acetic acids: Diclofenac, Aceclofenac. ▪ Oxicam derivatives: Piroxicam, Tenoxicam. ▪ Pyrrolo-pyrrolo derivative: Ketorolac. ▪ Acetic acid derivatives: Indomethacin. ▪ Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone.

C. According to COX isoenzyme selectivity:

1. **COX-2 selective NSAIDs**, whose selectivity for inhibiting COX-2 is at least 5 times that for COX-1. The group includes
 - Rofecoxib
 - Celecoxib
 - Meloxicam
 - Etodolac and
 - Nabumetone
2. **Non-COX-2 selective NSAIDs**, which comprise all other NSAIDs. These drugs inhibit COX-1 as much as, or even more than, COX-2.

(Ref: Bennett & Brown-11th edition)**D. According to plasma half-life:**

1. Short acting NSAIDs ($t_{1/2}$ <6 hrs)	▪ Aspirin ▪ Diclofenac ▪ Ibuprofen ▪ Fenoprofen ▪ Indomethacin ▪ Ketoprofen
2. Intermediate acting NSAIDs ($t_{1/2}$ 6-26 hours)	▪ Celecoxib ▪ Rofecoxib ▪ Naproxen ▪ Ketorolac ▪ Etodolac

- | | |
|---|--|
| 3. Long acting NSAIDs ($t_{1/2} > 26$ hours) | <ul style="list-style-type: none"> ▪ Nabumetone ▪ Piroxicam ▪ Oxaprozin |
|---|--|

Anti-platelet drugs:

1. Cyclooxygenase inhibitors: Inhibition of prostaglandin synthesis	▪ Aspirin
2. ADP receptor inhibitors: Inhibition of ADP induced platelet aggregation.	▪ Clopidogrel ▪ Prasugrel ▪ Ticlopidine
3. Inhibitor of glycoprotein IIb/IIIa receptors inhibitors on platelets (intravenous use only)	▪ Abciximab ▪ Eptifibatide ▪ Tirofiban
4. Additional antiplatelet-directed drugs	
• Phosphodiesterase inhibitor	▪ Cilostazol
• Inhibitor of adenosine uptake and cGMP phosphodiesterase	▪ Dipyridamole

(Ref: Katzung-13th)

Anticoagulant drugs:

A. Anticoagulants acting in vitro:

1. Heparin
2. Ca chelating agents: 3.8% Na citrate, Na^+ -oxalate

B. Anticoagulants acting in vivo:

1. Parenteral anticoagulant drugs	
▪ Indirect thrombin inhibitors	1. Unfractionated heparin (UFH) / standard heparin / regular heparin 2. Low-molecular weight (LMW) heparin / fractionated heparin / irregular heparin: • Enoxaparin • Dalteparin • Tinzaparin 3. Synthetic pentasaccharide • Fondaparinux
▪ Parenteral direct thrombin inhibitors	• Hirudin • Lepirudin • Bivalirudin • Argatroban
2. Oral anticoagulant drugs	
▪ Coumarin anticoagulants	• Warfarin • Dicumarol
▪ Oral direct thrombin inhibitors	• Ximelagatran (<i>withdrawn from the market because of hepatic toxicity</i>) • Dabigatran

C. Anticoagulants acting in vivo & vitro: Heparin.

Fibrinolytic / thrombolytic drugs: Agents that hydrolyze fibrin and, thus, dissolves clots.

1. Streptokinase
2. Alteplase
3. Urokinase
4. Tissue plasminogen activator (t-PA)
5. Reteplase
6. Tenecteplase

Drugs used to stop bleeding/ Fibrinolytic inhibitors/ Anti-fibrinolytic drugs:

1. Aminocaproic acid / epsilon aminocaproic acid (EACA)
2. Tranexamic acid (*an analog of aminocaproic acid*).
3. Protamine sulfate (*antidote of heparin*)
4. Vitamin K₁ / phytonadione (*antidote of warfarin*)
5. Aprotinin (*serine protease inhibitor*)

(Ref: Lippincott's-6th)

Lipid lowering agents:**A. Predominantly cholesterol lowering agents:**

1. HMG-CoA reductase inhibitors (Statins): (↓cholesterol synthesis & ↑LDL catabolism)	▪ Lovastatin ▪ Atorvastatin ▪ Fluvastatin ▪ Pravastatin ▪ Simvastatin ▪ Rosuvastatin
2. Cholesterol absorption inhibitors	▪ Ezetimibe
3. Bile acid-binding resins	▪ Colestipol ▪ Cholestyramine ▪ Colesevelam
4. Niacin (Vit-B3)	

B. Predominantly TG lowering agents:

1. Fibrates / fibric acid derivatives	▪ Gemfibrozil ▪ Fenofibrate ▪ Bezafibrate
2. Highly poly-unsaturated long-chain n-3 fatty acids	▪ Eicosapentanoic acid ▪ Docosahexanoic acid

(Ref: Davidson's medicine-20th/450; Lippincott's-6th)**Iron preparations**

A. Oral iron preparations	Tablet form	• Ferrous sulfate • Ferrous fumarate • Ferrous gluconate • Ferrous succinate • Ferrous glycine-SO₄
	Liquid form	• FeSO₄ pediatric mixture • Polysaccharide iron complex
	Sustained release form	• Slow-Fe • Sytron • Na-Fe edetate
B. Parenteral iron preparations	IV iron	• Iron dextran • Iron sucrose
	IM iron	• Iron dextran • Iron sorbitol citric acid

(Ref: Katzung-13th)

Drugs for peptic ulcer diseases (PUD):

Types of anti-ulcerant drugs	Name of drugs
A. Acid neutralizers	
1. Antacids	• Sodium bicarbonate, NaHCO_3 • Calcium carbonate, CaCO_3 • Magnesium hydroxide, $\text{Mg}(\text{OH})_2$ • Aluminium hydroxide, $\text{Al}(\text{OH})_3$
B. Antisecretory: Agents that reduce HCl secretion	
1. H_2 -receptor blockers	• Ranitidine • Famotidine • Nizatidine • Cimetidine
2. Proton pump inhibitors (PPI)	• Omeprazole • Esomeprazole • Pantoprazole • Lansoprazole • Rabeprazole
3. Anti-muscarinic drugs	• Dicyclomine • Pirenzepine • Telenzepine
C. Agents that kill the causative bacteria (<i>Helicobacter pylori</i>)	
1. Antibiotics	• Metronidazole • Amoxicillin • Tetracycline • Clarithromycin
D. Agents that enhance mucosal resistance (ulcer healing drugs)	• Sucralfate • Prostaglandin analog (Misoprostol) • Colloidal bismuth compounds.

(Ref: Katzung-13th & Goodman & Gilman's-12th)

Prokinetic agents:

1. D_2 -receptor antagonists:
 - Metoclopramide
 - Domperidone
2. Cholinomimetic agents:
 - Bethanechol
 - Neostigmine
3. Macrolides: Erythromycin, azithromycin
4. Chloride channel activator: Lubiprostone.

(Ref: Katzung-13th)

Anti-emetic drugs:

1. Serotonin 5HT_3 -receptor antagonists	• Ondansetron • Granisetron • Dolasetron • Palonosetron
2. Prokinetic agents (D_2 -receptor antagonists)	• Domperidone
3. Corticosteroids	• Dexamethasone • Methylprednisolone
4. Neurokinin receptor antagonists	• Aprepitant • Fosaprepitant

5. Phenothiazines	• Prochlorperazine • Promethazine • Thiethylperazine
6. Butyrophenone	• Droperidol • Haloperidol
7. Substituted benzamides	• Metoclopramide • Trimethobenzamide
8. H ₁ -receptor antagonists	• Diphenhydramine • Dimenhydrinate • Meclizine • Cyclizine
9. Anticholinergic drugs	• Hyoscine
10. Benzodiazepines	• Lorazepam • Alprazolam • Diazepam
11. Cannabinoids	• Dronabinol • Nabilone

(Ref: Katzung-13th; Lippincott's-6th)

Anti-asthmatic Drugs:**A. Bronchodilator:** Reverses bronchoconstriction and provides short-term relief (short-term reliever).

1. Selective β_2 -agonists	a. Short acting (2-6 hours) • Salbutamol • Albuterol • Terbutaline • Metaproterenol • Pirbuterol b. Long acting (>12 hours) • Salmeterol • Formoterol
2. Anti-muscarinic agent	• Ipratropium bromide • Tiotropium • Atropine
3. Methylxanthines	• Aminophylline • Theophylline • Enprophylline • Pentoxifylline (used in intermittent claudication) • Theobromine • Caffeine

B. Anti-inflammatory drugs: Suppress chronic inflammation of bronchial asthma (long-term controller).

1. Corticosteroids / Glucocorticoids	• Hydrocortisone (Inj) • Prednisolone (tablet) • Beclomethasone (inhaler) • Betamethasone (inhaler) • Triamcinolone (inhaler) • Budesonide • Ciclesonide • Flunisolide • Fluticasone • Mometasone
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2. Leukotriene receptor antagonists: These drugs also competitively prevent bronchoconstriction caused by leukotrienes (C4, D4 and E4)	• Zafirlukast • Montelukast
3. Leukotriene synthesis inhibitor	• Zileuton
4. Mast cell stabilizers: Prevents mast cell degranulation.	• Cromolyn sodium • Nedocromil sodium
5. Anti-IgE monoclonal antibody: Inhibits the binding of IgE to mast cells & prevents mast cell degranulation.	• Omalizumab

(Ref: Katzung-13th)

Oral antidiabetic / hypoglycemic agents (OHA):

A. **Insulin secretagogues:** Increase insulin release.

1. Sulfonylureas	1 st generation sulfonylureas	• Tolbutamide • Chlorpropamide • Tolazamide
	2 nd generation sulfonylureas	• Glibenclamide (in USA) or Glyburide (outside USA) • Glipizide • Gliclazide • Glimepiride
2. Meglitinides		• Repaglinide
3. D-phenylalanine derivatives		• Nateglinide

B. **Biguanides:** (insulin sensitizer, euglycaemic agents)

- Metformin
- Phenformin (*not used now a days*)

C. **Thiazolidinediones:** (insulin sensitizer) Two thiazolidinediones are currently available:

- Pioglitazone
- Rosiglitazone

D. **α -glucosidase Inhibitors:**

- Acarbose
- Miglitol

E. **Synthetic Amylin Analog:**

- Pramlintide

F. **Incretin-based therapies**

1. **Incretin mimetics / Synthetic analog of glucagon-like-polypeptide 1 (GLP-1):**

- Exenatide

2. **Dipeptidyl Peptidase-IV (DPP-IV) Inhibitors:**

- Sitagliptin

(Ref: Katzung-13th; Lippincott's-6th)

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Chapter 1

General Pharmacology

Introducing Pharmacology

The word *pharmacology* is derived from the Greek words *pharmakon* (which means drug) and *logos* (which means a study).

Q. Define pharmacology. (RU-14J, 09J, CU-05S)

Ans.

Pharmacology

Definition: Pharmacology can be defined as the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes.

(Ref: Katzung-13th/1)

Definition: Pharmacology can be defined as a branch of science that includes history, source, physio-chemical properties, dosage forms, methods of administration, absorption, distribution, mechanism of action, pharmacological effects, biotransformation, excretion, clinical uses, and adverse effects of drug.

(Ref: Misbahuddin-5th/01)

Definition: Pharmacology can be defined as the study of the effects of drugs on the function of living systems.

(Ref: Rang & Dale's-6th/3)

Q. Define medical pharmacology? (RU-11Ju, 08Ju, 05J/S, CU-05S)

Q. Define therapeutics? (RU-14J, SU-11J)

Ans.

Medical pharmacology/ therapeutics: Medical pharmacology is often defined as the science of substances used to prevent, diagnose, and treat disease.

PDT

(Ref: Katzung-13th/01)

Q. What do you mean by clinical pharmacology? (RU-08Ju)

Q. Define clinical pharmacology. (SU-11J, RU-11J, CU-05S)

Ans.

Clinical pharmacology: It is a branch of pharmacology which deals with the scientific study of drugs in the patients and also in healthy persons for the safe and effective use of drugs (therapy). It has two parts:

1. Pharmacology
 - a. Pharmacodynamics
 - b. Pharmacokinetics
2. Therapeutic evaluation

Q. What are the branches of pharmacology? (RU-10J, 08Ju, 05J/S)

Q. Define pharmacodynamics. (DU-10Ju, 06S, RU-15Ju, 07Ju)

Q. Define pharmacokinetics. (DU-10Ju, SU-06M, RU-07Ju)

Q. Define pharmacognosy. (RU-09J)

Q. Define therapeutics. (SU-11J)

Q. Define pharmaco-therapeutics. (SU-11J)

Q. Define pharmacogenetics. (RU-15Ju)

Ans.

Branches of pharmacology:

1. **Pharmacy / Pharmaceutics:** It is the branch of pharmacology which deals with the preparation, quality control and dispensation of drugs. Pharmacy includes —

- a. **Pharmacognosy:** Pharmacognosy deals with the source, identification, isolation, purification and standardization of drug. *Identification of botanical source of drug*
- b. **Pharmaceutical chemistry:** It deals with the synthesis of new drug.
- c. **Biopharmaceutics:** It deals with the formulation of drug.

(Ref: Misbahuddin-5th/3)

2. **Pharmacokinetics:** The study of absorption, distribution, biotransformation (metabolism) & excretion of drug is called pharmacokinetics. Simply pharmacokinetics means "what the body does to the drug."
(Ref: Misbahuddin-5th/03)
3. **Pharmacodynamics:** This is the branch of pharmacology which deals with the biochemical and physiological effect of drugs and their mechanism of action.
(Ref: Goodman & Gilman's-11th/22)
Pharmacodynamics: Pharmacodynamics is the study of biological effects produced by the drug". Simply pharmacodynamics means "what the drug does to the body."
(Ref: Misbahuddin-5th/03)
4. **Therapeutics:** Therapeutics is a branch of pharmacology which deals with the use of drugs in human body to detect, protect, control and cure of the diseases.
5. **Pharmaco-therapeutics:** It deals with practical application of drugs for treatment or prevention of diseases.
6. **Toxicology:** Toxicology is that branch of pharmacology which deals with the undesirable effects of chemicals on living systems, from individual cells to humans to complex ecosystems.
(Ref: Katzung-13th/01)
7. **Pharmacogenomics:** Pharmacogenomics (or **pharmacogenetics**) is the study of the relation of the individual's genetic makeup to his or her response to specific drugs.
The study of genetic influence on response to drugs (Ref: Katzung-13th/2)
8. **Immunopharmacology:** It deals with the immunological aspects of drug action, including the effects of drug in immune response and development of antibodies in response to drug.
9. **Behavioral pharmacology:** Refers to the study of how drug affects the behavior of a patient.
10. **Pharmacoeconomics:** This branch of health economics aims to quantify in economic terms the cost and benefit of drugs used therapeutically. It arose from the concern of many governments to provide for healthcare from tax revenues, raising questions of what therapeutic procedures represent the best value for money.
It is the study of cost of medicine. (Ref: Rang & Dale's-6th edition)
11. **Pharmacoepidemiology:** It is the study of both the beneficial and the adverse effects of a drug on a large number of people.
(Ref: Misbahuddin-5th/4)
12. **Chemotherapy:** It is the branch of pharmacology which deals with the effects of drugs upon micro-organisms, parasites & cancer cells.

Nice to know

Materia medica: *Materia medica is the science of drug preparation and medical use of drugs. It is a Latin medical term for the body of collected knowledge about the therapeutic properties of drugs. In Latin, the term literally means "medical material/substance". The term was used from the period of the Roman Empire until the twentieth century, but has now been generally replaced in medical education contexts by the term pharmacology.*

(Ref: Katzung-13th/2+others)

Q. How does clinical pharmacology differ from therapeutics? (RU-10J,06J)

Ans.

Clinical pharmacology	Therapeutics
It is a branch of pharmacology which deals with the scientific study of drugs in the patients and also in healthy persons for the safe and effective use of drugs (therapy). It has two parts: 1. Pharmacology a. Pharmacodynamics b. Pharmacokinetics 2. Therapeutic evaluation	Therapeutics is a branch of pharmacology which deals with the use of drugs in human body to detect, protect, control and cure of the diseases.

Drug

Drug originates from Old French "drogue" which means *medicinal plants (dry herbs)*.

Q. Define drug with example. (DU-13Ju, RU-16J, 15J, 11J, 10J, 08Ju, 06J; SU-15J, 10J, 06J)

Q. Define drug according to WHO. (DU-17J)

Ans.

Drug: According to WHO, 1992:

Any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient is called a drug.

(Ref: Bennett & Brown-10th/5)

Example: Paracetamol, ciprofloxacin, omeprazole etc.

Q. Write down the properties of ideal drug.

Ans.

Properties of an ideal drug

1. A drug must have-
 - a. Appropriate size, shape, electrical charge & atomic composition.
 - b. Appropriate properties to be transported from the site of administration to the site of action to exert physiological response.
2. A drug should be inactivated or excreted from the body at a reasonable rate so that its action will be stopped after an appropriate duration of action.
3. It must have good efficacy and potency.
4. It must have least adverse effects.

Nice to know

Information on DRUG

1. A drug can be defined as a chemical substance of known structure, other than a nutrient or an essential dietary ingredient, which, when administered to a living organism, produces a biological effect.
2. Drugs may be synthetic chemicals, chemicals obtained from plants or animals, or products of genetic engineering.
3. To count as a drug, the substance must be administered as such, rather than released by physiological mechanisms. Many substances, such as insulin or thyroxine, are endogenous hormones but are also drugs when they are administered intentionally.
4. Many drugs are not used in medicines but are nevertheless useful research tools.
5. In everyday parlance, the word drug is often associated with addictive, narcotic or mind-altering substances-an unfortunate negative connotation that tends to bias opinion against any form of chemical therapy. To use the word 'drug' intending only a harmful, dangerous or addictive substance is to abuse a respectable and useful word.
6. Poisons fall strictly within the definition of drugs.

(Ref: Rang & Dale's-8th)

Q. What are the uses of drugs- give one example of each (RU-16J)

Q. What are the benefits of the recipient of drug? (SU-10J)

Q. What are the rational uses of drugs/ aim of drug use/ purpose of drug?

Ans.

Rational uses of drugs/ aim of drug use/ purpose of drug/ benefit of the recipient

1. **Diagnosis of disease:** eg,
 - Barium salt for diagnosis of GIT lesions by barium meal x-ray.
 - Edrophonium for diagnosis of myasthenia gravis.
 - Histamine for diagnosis of pernicious anemia.
2. **Prevention of disease:** eg,
 - Vaccines prevent communicable diseases, e.g. tetanus toxoid for prevention of tetanus.
 - Contraceptives prevent unwanted pregnancy (X) - *Drugs*

3. **Control or suppression of diseases:** eg,
 - Insulin is used for the control of diabetes.
 - Anti-hypertensive drugs control hypertension.
4. **Treatment of diseases:** eg,
 - Antibiotics are used for treatment of infections.
 - Antipyretic for pyrexia (fever).
 - Analgesics for pain.
 - Diuretics for edema.

Q. What are the types of drugs?

Ans.

Types of drugs:

1. **Over the counter drug (OTC):** The drugs which are available without prescription are called OTC drugs. They are highly safe producing least toxic effects, eg. paracetamol, laxatives, iron tab, vitamin tab, antiemetic.
2. **Prescription drugs:** The drugs which are available only on prescription are called prescription drugs. They include majority of drugs which are prescribed by registered physician & are sold by registered pharmacist.
3. **Control drug:** The drugs which can never be dispensed with prescription are called control drugs. eg. narcotics, hallucinogens (LSD, pethidine, heroine) etc. They produce addiction.
4. **Experimental drug:** The drugs which are on trial are called experimental drugs. eg. Newer, better, safer drugs.
5. **Official drug:** The drugs which are included in pharmacopoeia.

Q. Short note: Over the counter drug (OTC).

Ans.

Over the counter (OTC) drugs

Definition: The drugs which are available without prescription are called OTC drugs. They are highly safe producing least toxic effects.

Synonym: Non-prescription drug.

Examples:

Systemic OTC drugs	Topical OTC drugs
1. Paracetamol	1. Ketoconazole
2. Ranitidine	2. Miconazole
3. Omeprazole	3. Clotrimazole
4. Antacid	4. Xylometazoline
5. Loratadine	
6. Chlorpheniramine	
7. Naproxen sodium	
8. Ketoprofen	
9. ORS	
10. Vitamin tablet	

Advantages of OTC drugs:

1. They are easily available & comparatively cheap.
2. Decrease the load to the hospitalization.

3. Sometimes greatly affect the improvement of the community health; e.g. ORS decreases the childhood mortality rate. The more the availability of ORS is, the less the death in diarrhoeal disorder.
4. Treatment of minor illness can be done easily.

Disadvantages of OTC drugs:

1. Increased chance of maltreatment / wrong treatment.
2. More chance of complication of diseases.
3. May misguide or delay the right diagnosis of the disease.
4. Chance of drug induced disease; e.g. chronic renal failure in paracetamol abusers who chronically uses the drug for mild to moderate pain.
5. Chance of acute overdose or suicidal attempt; e.g. Paracetamol poisoning.

Nice to know**Characteristics of the drug:****1. Molecular weight (MW) and size:**

- a. **MW usually:** 100 – 1000 dalton.
- b. **Low MW (100-150 D):** Can easily pass through epithelial lining, eg, ethanol (46 D), N₂O (44 D).
- c. **High MW (7000 D):** Cannot pass through epithelial lining, eg, insulin (5800 D), dextran (40,000D).
- d. **MW < 300:** Eliminate through kidney.
- e. **MW > 300:** Eliminate through bile.
- f. **MW < 600:** Can cross blood placental barrier.
- g. **Microsized particle:** Well absorbed (eg, griseofulvin).
- h. **Ultra microsized:** Absorbed 2 fold than microsized.

2. Physical nature:

- a. **Solid:** Paracetamol, azithromycin.
- b. **Liquid:** Nicotine, ethanol, ceftriaxone.
- c. **Gas:** Nitrous oxide.

3. Chemical nature of drug:**1. Acidic:**

- Acetazolamide
- Levodopa
- Aspirin
- Phenytoin
- Cloxacillin
- Phenobarbitone

2. Basic:

- Amphetamine
- Atropine
- Isoprenaline
- Morphine
- Pilocarpine

3. Neutral:

- Ethanol

4. Stereoisomerism:

- (+) Sotalol: Antiarrhythmic
- (-) Sotalol: Beta blocker
- (+) Dobutamine: α 1 antagonist
- (-) Dobutamine: α 1 agonist.

5. **Ionization constant:** It depends on pKa of drug and pH of media.

In acidic pH:

- Acidic drug in acidic urine → Less ionization → More lipid soluble → More reabsorbed.
- Alkaline drug in acidic urine → More ionization → Less lipid soluble → More excreted.

In alkaline pH:

- Alkaline drug in alkaline urine → Less ionization → More lipid soluble → More reabsorbed.
- Acidic drug in alkaline urine → More ionization → Less lipid soluble → More excreted.

6. **Partition co-efficient:**

- **Lipid : water partition co-efficient:** Relative solubility of drug in lipid as compared to water.
- **Higher lipid : water partition co-efficient** → More lipid soluble → More reabsorbed, (eg, phenobarbitone, thiopental Na).
- **Low lipid : water partition co-efficient** → Less lipid soluble → More excreted.

7. **Salt preparation:**

- Theophylline (100%) → Insoluble.
- Aminophylline (Theophylline 80% + Ethylene diamine 20%) → More solubility (can be given in IV route).

8. **Affinity to bind with others:**

- Bind with food particle.
- Bind with plasma protein (mainly albumin).
- Bind with receptor.
- Bind with tissues (liver, retina, bone)
- Binds with drugs, eg,
 - Fe + Tetracycline
 - Antacid + Iron
 - Fe + Desferrioxamine

9. **SAR (Structure activity relationship):** Study of variation of drug effects in relation to their chemical structure is known as SAR. Affinity and efficacy both are related to SAR. Eg,

Acetylcholine	Methacholine
Rapidly hydrolyzed by plasma cholinesterase.	Slowly hydrolyzed by plasma cholinesterase.
Short duration of action.	Prolong duration of action.
Non-selective in action.	Only muscarinic in action.

Importance:

1. **Synthesis of newer compound:**

- To increase duration of action: Procaine → Procainamide.
- To decrease duration of action: Atropine (7 days) → Homatropine (1 day)
- To synthesize more potent drug: Polythiazide → chlorothiazide
- To restrict the drug action on a particular system
Chlorpromazine (Antihistamine/antipsychotic/Anticholinergic) → Trifluoperazine (CNS only)
- To decrease adverse effects & Toxicity: Nicotinic Acid → Nicotinamide
- To increase drug absorption:
Chlorotetracycline (30% absorb) → tetracycline (60-80% absorb)

2. **Synthesis of competitive antagonism:** Morphine by Nalorphine

3. **Understanding basic chemical group responsible for drug action:**

- Adrenaline → stimulates α & β .
- Isoprenaline → stimulates only β receptor.

Q. Define medicine.

Ans.

Medicine: A *medicine* is a chemical preparation, which contains one or more drugs and usually other substances (excipients, stabilisers, solvents, etc.) besides the active drug to make them more convenient to use.

Medicine = Drug + Additional substances (excipients, stabilisers, solvents, etc.)

(Ref: Rang & Dale's-8th)

Example: Paracetamol is the drug and Napa (brand name of paracetamol) is the medicine.

Q. What are the differences between drug & medicine? (RU-11J)

Ans.

Differences between drug & medicine

Drug	Medicine
1. Drug is the <u>active ingredient</u> of medicine.	1. Medicine = Drug + additional substances (<u>excipients, stabilisers, solvents, etc.</u>)
2. Drugs may not be <u>stable</u> .	2. Medicine is made more stable by adding stabilisers.
3. It <u>may not have a suitable form & dose</u> .	3. It has a suitable form & dose. Eg, Tab. Pantoprazole 20 mg.
4. It has <u>chemical and generic name</u> .	4. It has <u>brand or trade name</u> .
5. All drugs are not medicine.	5. All medicines are drugs.
6. It <u>does not have a suitable form and dose</u> .	6. It has suitable form and dose. Eg, Cap. Omeprazole 20 mg. Here capsule is form and 20 mg is dose.

(Ref: Bennett & Brown-11th+ Rang & Dale's-8th)

Nice to know

Compare between Drug and Food

Drug	Food
Foreign substance for body.	Ingredient (essential for body)
Generally does not provide energy (vitamin, Iron provide energy).	Provide energy
Drug modifies or explores physiological system or pathological state.	Food maintains physiological system of the body.
Must be excreted out from the body.	Retain in the body as ingredient or essential component of the body.
It may produce addiction or habituation.	It may produce habituation.
It may produce tolerance.	It does not produce tolerance.

Q. Short note: Excipient.

Ans.

Excipient: Additional chemical substances that are used in drug production having no drug property are called excipient.

Components of excipient:

1. **Diluents:** Form bulk of drug (shape, size); e.g. Dextrose, lactose, starch, sucrose etc.
2. **Binder:** They bind several drug molecules to prevent autobreakdown, e.g. Methyl cellulose.
3. **Disintegrating agent:** To break the drug molecule before absorption is called disintegration. e.g. Starch, vee gum.
4. **Lubricant:** To lubricate drug molecule, e.g. stearic acid, Ca-stearate, Mg-stearate, talc.
5. **Colouring substances:** To color drug for identification, attraction etc. e.g. brilliant blue, caramel etc.
6. **Sweetening agent:** To make a drug sweet taste, e.g. saccharin, lactose, mannitol etc.
7. **Flavoring agent:** Orange flavor, peppermint oil etc. are the flavoring substances.

Q. What is placebo?

Ans.

Placebo / dummy medicine: Latin: *placebo*, I shall be pleasing or acceptable.

Definition: A placebo is any component of therapy that is without specific biological activity for the condition being treated.

(Ref: Bennett & Brown-11th edition)

Definition: "Placebo are inactive substances (having no pharmacological effect) given to satisfy patient's demand for medicine (mental satisfaction)".

Substances used as placebo: Starch, glucose, sucrose, lactose, dextrose, etc.

Purpose of using placebo:

1. **As a control in scientific evaluation of drugs.** The placebo medicine is given to a group of patients and the drug being tested is given to a similar group; then the results obtained in the two groups are compared (double blind trial).
2. To benefit or please a patient, not by any pharmacological actions, but by psychological means.
3. To prevent habituation and addiction.

(Ref: Bennett & Brown-11th edition)

Nice to know

Explanation of placebo: All treatments have a psychological component, whether to please (placebo effect) or, occasionally, to vex (negative placebo). A placebo medicine is a vehicle for 'cure' by suggestion, and is surprisingly often successful, if only temporarily. All treatments carry placebo effect: physiotherapy, psychotherapy, surgery, entering a patient into a therapeutic trial, even the personality and style of the doctor.

A placebo-reactor is an individual who reports changes of physical or mental state after taking a pharmacologically inert substance.

Negative reactors, who develop adverse effects when given a placebo, exist but, fortunately, are fewer.

Comments

1. Some 35% of the physically ill and 40% or more of the mentally ill respond to placebos.
2. Placebo reaction is an inconstant attribute; a person may respond at one time in one situation and not at another time under different conditions.
3. It is of great importance that all who administer drugs should be aware that their attitudes to the treatment may greatly influence the result. Undue scepticism may prevent a drug from achieving its effect and enthusiasm or confidence may potentiate the actions of drugs.

(Ref: Bennett & Brown-11th edition)

Sources of drugs

Q. Describe briefly the sources of drugs with example. (DU-10Ju, RU-11J, 07Ju, 06S, SU-16Ju, 06J)

Q. What are the common present sources of drugs? Give examples. (RU-09J)

Q. Name the different sources of drugs. (RU-15J)

Ans.

Sources of drugs:

Sources	Examples
1. Natural sources	
▪ Plant	• Alkaloids, glycosides, atropine, morphine, <i>Oil, Gummy</i>
▪ Animal	• Bovine pancreas- Insulin • Liver- Heparin • Liver of cod fish- Vitamin A • Pituitary gland- Gonadotropin.
▪ Microorganisms	• Penicillin, kanamycin, polymyxin-B, chloramphenicol, tetracycline, bacitracin.
▪ Mineral	• I ₂ , iron (FeSO ₄), MgSO ₄ .7H ₂ O

*Mucilage
CHO*

2. Synthetic sources	• Aspirin, paracetamol, antimalarial drugs, sulfonamides, hormones.
3. Semi-synthetic sources	• Ampicillin, tetracycline, pethidine
4. Biotechnology & genetic engineering (By recombinant DNA)	• Human insulin, growth hormone

Q. Name the plant sources of drug. (SU-10J)

Ans.

Types of plant sources

1. Alkaloids- Atropine, cocaine, morphine, *quinine*
2. Glycosides- Digoxin
3. Oil- Olive oil, castor oil *Edible oil = castor oil*
4. Gum & mucilage- Agar & psylum
5. Tannins- Tannic acid
6. Carbohydrate- Dextrose
7. Antibiotics

Nice to know

Demerits of plant source

1. Expensive
2. Less & slow action
3. Less amount of drug are found at a time.

Oil $\left\{ \begin{array}{l} \text{Fixed Oil} \\ \text{Volatile Oil} \end{array} \right.$

Q. Define alkaloids. (RU-09J)

Q. Mention the characteristics of alkaloids.

Ans.

Alkaloids:

Definition: The word alkaloid literally means alkali like substance. Alkaloid is defined as basic nitrogenous compound of plant origin that produces salt when combines with acid and is physiologically active in plant and animal.

Properties of alkaloids:

1. They are basic nitrogenous compounds.
2. They are non-volatile, white crystalline substances.
3. Taste is bitter
4. Reaction is alkaline. They form salt with acid. Acid + Alkaloid = Salt.
5. Insoluble in water, less soluble in alcohol but their salts are soluble in water.
6. Their names always end with "ine", eg, atropine, morphine.

(Ref- Misbahuddin-5th/11)

Example

Alkaloids	Sources
Plant source	
• Atropine, scopolamine	Atropa belladonna
• Quinine, quinidine	Cinchona <i>(cinchona)</i>
• Morphine, codeine	Seed capsule of poppy plant
• Reserpine	Rauwolfia serpentina
• Theophylline, caffeine	Tea, coffee plant
• Ergot alkaloid	Claviceps purpurea
• Cocaine	Erythroxylon Cocae
Synthetic	Homatropine Vincristine Vinblastine

(Ref- Misbahuddin-5th/11)

Q. Define glycosides? (DU-04J, RU-08J)

Q. Mention the characteristics of glycosides. (DU-04J, RU-08J)

Ans.

Glycosides:

Definition: Glycosides are compounds formed from condensation between monosaccharide or monosaccharide residue and -OH group of a second compound that may or may not be another monosaccharide.

Monosaccharide + Substance containing -OH group (phenol, alcohol, sterol, glycerol) = Glycoside.

Properties of glycosides:

1. Plant origin.
2. Non-nitrogenous substance.
3. Colourless and crystalline.
4. They consist of sugar (glycone) and non-sugar (aglycone or genin) parts.
5. Soluble in organic solvent but insoluble in water.
6. Reaction with acids: Breaks after reaction.
7. Their names end with 'in', e.g. Digoxin, Streptomycin etc.

(Ref- Misbahuddin-5th/13)

Examples:

1. Cardiac Glycosides (eg, Digoxin, Digitoxin etc.).
2. Aminoglycosides (eg, Streptomycin).
3. Sennoside, salicin.

Classification / types: According to type of sugar present:

1. Glucoside
2. Galactoside
3. Fructoside

(Ref- Misbahuddin-5th/13)

Chemical structure & their function

1. Sugar part

- a. Easy absorption and neutralization.
- b. Increases potency and duration of action of glycosides.
- c. It facilitates the attachment of glycoside to myocardium that is why 70% of administered digitalis is taken up by the myocardium.
- d. It protects the aglycon part from enzymatic destruction.

2. Non-sugar / genin / aglycon:

a. Steroid nucleus

- Causes immediate but brief action on force of the heart.
- Responsible for mineralocorticoid activity, eg, hypokalemia.

b. Lactone ring

- Responsible for cardiotonic action, if removed → no cardiotonic action.
- 5 membered and attach at 17 position of steroid nucleus.
- It is always unsaturated.

c. -OH group:

- Responsible for absorption.
- Prolongs cardiotonic action.

(tonicity of heart muscle)

Clinical importance

1. Cardiac Glycosides (eg, digoxin, digitoxin etc.) are used in heart failure.
2. Aminoglycosides (eg, streptomycin) acts as an antibiotic.
3. Glycosides are found in many drug species and in the constituents of animal tissues.

Q. Give the difference between alkaloids & glycosides. (DU-16Ju)

Ans.

Differences between alkaloids & glycosides:

Alkaloids	Glycosides
1. Nitrogenous organic substances.	1. Non- nitrogenous sugar containing substances.
2. Basic in nature.	2. Neutral or acidic in nature.
3. It forms salt with acid.	3. No such kind of reaction.
4. It is bitter in taste.	4. It is not bitter.
5. Devoid of glycosidic linkage.	5. Contains glycosidic linkage.
6. Insoluble in water, less soluble in alcohol but their salts are soluble in water.	6. Soluble in organic solvent but insoluble in water.
7. Their names always end with "ine", eg, atropine, morphine.	7. Their names end with "in", e.g. Digoxin, Streptomycin etc.
8. Exception: Adrenaline	8. Exception: Gentamicin.

Q. Describe animal sources of drugs. (SU-07J)

Ans.

Animal sources of drug:

1. **Vitamin-A** → obtained from cod liver oil.
2. **Insulin** → extracted from bovine or porcine pancreas.
3. **Immunoglobulin G** → prepared by injecting antigen into the animal body.
4. Hepatitis B immunoglobulin, rabies immunoglobulin, tetanus immunoglobulin are prepared by pooling the plasma of selected donors with high level of specific antibody.
5. **Human menopausal gonadotropin (hMG)** → isolated from the urine of postmenopausal women.
6. **Human chorionic gonadotropin (hCG)** → prepared from placenta & may be isolated from the urine of pregnant women.

I know

Animal sources of antibiotics:

1. **Microorganisms:**

- a. Actinomycetes (58%): eg,
 - Erythromycin
 - Kanamycin
 - Chloramphenicol
- b. Fungus (18%): eg,
 - Penicillin from *Penicillium notatum*
 - Cephalosporin
- c. Bacteria (9%)
 - Polymixin B
 - Bacitracin

2. **Higher plant (12%)**

3. **Algae, Lichens & Animals (3%)**

Advantages of synthetic sources

1. Huge amount of drug can be found quickly at a time.
2. Low price in pure form.

Minerals & their uses:

1. **Mg, Al-** Antacid (in peptic ulcer)
2. **FeSO₄**- In iron deficiency anemia

3. **I₂**- In goiter
4. **Au**- In arthritis
5. **Hg**- As diuretics.
6. **K**- After using diuretics
7. **Milk of magnesia (MgSO₄)**- as purgatives
8. **NaHCO₃**- to alkalize the urine.

Q. What is biological drug? Name some biological drugs.

Ans.

Biological drugs: The drugs that are obtained from living sources, mostly animal, are called biologic drugs.

Examples of biological drugs:

Drugs	Sources
1. Insulin	Human, pig
2. Heparin	Beef lung, porcine intestine
3. Different vaccines	Microorganisms
4. Immunoglobulins	Horse serum
5. Histamine	Mast cell
6. Vitamin A	Liver of Cod fish
7. Toxin, toxoids	Microorganism

Characteristics of biologic drugs:

1. Obtained from living sources.
2. **Chemistry:** Protein & polypeptide in nature.
3. **Route:** Not suitable for oral route as they are metabolized in the stomach & GIT by proteolytic enzymes. So, must be given in parenteral route.
4. **Antigenicity:** As they are protein in nature & biological products, they may cause hypersensitivity reaction.
5. **Storage:** They must be kept below 4°C. Otherwise the protein will be denatured.
6. Comparatively costly.
7. They have a manufacturer date, expiration date before which they should be used.

Q. What are the active constituents of plants?

Ans.

Active constituents of plants

1. Alkaloid
2. Glycoside
3. Oil (Volatile + Fixed)
4. Gum & Mucilage.
5. Antibiotic
6. Tannin.
7. Carbohydrate

Q. Explain recombinant DNA technology. (SU-07J)

Ans.

Recombinant DNA technology

Definition: The genetic manipulations in the laboratory involving the isolation and cloning of a specific DNA are collectively referred to as recombinant DNA technology.

(Ref: Satyanarayana-2nd/577)

Procedure

1. **Isolation of a target DNA by restriction endonuclease enzymes.**

2. **Selection of vectors:** plasmid, phages, cosmids etc.
3. **Preparation of recombinant DNA:** Now, the target DNA (eg, gene for human insulin) and the vector DNA (eg, plasmid) are ligated by **DNA ligase enzyme**. The hybrid combination of two fragments of DNA is called **recombinant DNA** (hybrid plasmid).
4. **Cloning of recombinant DNA:** The recombinant DNA is then introduced into the host (eg, *E. coli*). As the host cell multiplies, it forms a clone in which every cell carries copies of the same inserted DNA fragment. Bacteria are lysed and the hybrid plasmids are isolated. The cloned DNA is eventually released from its vector by cleavage using appropriate restriction endonuclease and is isolated and used for various purposes.

(Ref: Lippincott's-6th; Satyanarayana-2nd/577-81)

Medically important human proteins produced by RDT:

1. Human insulin
2. Erythropoietin
3. Interferons
4. Factor VIII
5. Hepatitis B vaccine
6. Tissue plasminogen activator
7. Calcitonin.

Drug discovery & development

Q. What are the steps of drug development? (NTK)

Ans.

Steps of drug development:

1. **Drug discovery:** Most new drugs or drug products are discovered or developed through one or more of six approaches:
 - a. identification or elucidation of a new drug target;
 - b. rational drug design of a new drug based on an understanding of biologic mechanisms, drug receptor structure, and drug structure;
 - c. chemical modification of a known molecule;
 - d. screening for biologic activity of large numbers of natural products, banks of previously discovered chemical entities, or large libraries of peptides, nucleic acids, and other organic molecules;
 - e. biotechnology and using genes to produce peptides, proteins and information useful as targets, drugs or diagnostics; and
 - f. combinations of known drugs to obtain additive or synergistic effects or a repositioning of a known drug for a new therapeutic use.
2. **Preclinical development:** during which a wide range of non-human studies (e.g. toxicity testing, pharmacokinetic analysis and formulation) are performed
3. **Clinical development / clinical trial:** during which the selected compound is tested for efficacy, side effects and potential dangers in volunteers and patients.

(Ref: Rang & Dale's-8th+ Katzung-13th/11)

Q. Short note: Clinical trial.

Q. Short note: Post marketing surveillance. (DU-10J)

Ans.

Clinical trial: A carefully designed and executed investigation of the effect of a drug when it is administered to human subject is called clinical trial.

Phases of clinical trial: It has four phases:

Phase I	▪ Subject: Healthy human volunteers (20 to 100 persons). ▪ Observed finding: 1. Safety 2. Tolerability 3. Pharmacokinetic measurement (absorption, distribution, metabolism, excretion). ▪ Performed in: Research centre. ▪ Performed by: Specially trained clinical pharmacologist. ▪ Type of study: These trials may be nonblind or "open"; that is, both the investigators and the subjects know what is being given. Alternatively, they may be "blinded" and placebo-controlled.
Phase II	▪ Subject: A modest number of patients (100 to 200) with target disease. ▪ Observed finding: 1. Efficacy ("proof of concept") in the clinical situation 2. Dose 3. Toxicities ▪ Phase 2 trials have the highest rate of drug failures, and only 25% of innovative drugs move on to phase 3. ▪ Performed in: Special clinical centers (eg, university hospitals). ▪ Performed by: Clinician. ▪ Type of study: A single-blind design may be used, with an inert placebo medication and an established active drug (positive control) in addition to the investigational agent.
Phase III	▪ Subject: Large number of patients (1000-6000). ▪ Observed finding: 1. To further establish and confirm safety and efficacy. 2. To compare the new drug with commonly used alternatives. 3. Certain toxic effects, especially those caused by immunologic processes. ▪ Performed in: 3 to 4 clinical centers. ▪ Performed by: Specialists in the disease being treated. ▪ Type of study: Double-blind randomized trials. ▪ At the end of phase III, the drug will be submitted to the relevant regulatory authority for licensing.
Phase IV	▪ Once approval to market a drug has been obtained, phase IV begins. ▪ Phase IV studies consists of post-marketing surveillance. It is a recently introduced phase of clinical trial which refers to long term observation by clinicians regarding adverse reaction, safety and efficacy of new drug under actual condition in large number of patients. Example: Nimesulide, celecoxib and many other drugs are withdrawn from market after post-marketing surveillance. ▪ Phase 4 has no fixed duration.

(Ref: Rang & Dale's-8th + Katzung-13th/11-12)

Q. Short note: Bio-assay.

Ans.

Bio-assay / biological assay:

Definition: Bioassay is defined as the estimation of the concentration or potency of a substance by measurement of the biological response that it produces.

(Ref: Rang & Dale's-8th)

Definition: Biological assay (bioassay) is the process by which the activity of a substance (identified or unidentified) is measured on living material: e.g. contraction of bronchial, uterine or vascular muscle.

(Ref: Bennett & Brown-11th)

Uses of bioassay: The uses of bioassay are:

1. **To measure the pharmacological activity of new or chemically undefined substances.** Bioassay plays a key role in the development of new drugs. In the past, bioassay was often used to measure the

concentration of drugs and other active substances in the blood or other body fluids, an application now superseded by analytical chemistry techniques.

2. **To investigate the function of endogenous mediators.** Bioassay is useful in the study of new hormonal or other chemically mediated control systems. For example, the ability of extracts of the posterior pituitary to produce a rise in blood pressure and a contraction of the uterus was observed at the beginning of the 20th century. By the bioassay, it was shown that two distinct peptides-*vasopressin* and *oxytocin* - were responsible.
3. **To measure drug toxicity and unwanted effects.**

(Ref: Rang & Dale's-8th)

Q. Short note: Biological standardization.

Ans.

Biological standardization: Biological *standardization* is a specialized form of bioassay. It involves matching of material of unknown potency with an International or National Standard with the objective of providing a preparation for use in therapeutics and research. The results are expressed as *units* of a substance rather than its weight, e.g. insulin, vaccines.

(Ref: Bennett & Brown-11th)

Posology: The study of dose

Q. Define posology.

Q. Define dose. (SU-06S)

Ans.

Posology: It is the science of dosages or a system of dosage. (Ref: Dorland's dictionary)

Dose: This is the amount of drug to be administered at one time. (Ref: Taber's dictionary)

Or,

Dose is the amount of drug or medicinal preparation that are to be administered in a particular time, in a single administration to get biological response.

Dosage: (Dose in multiple times) Determination of the amount, frequency and number of doses of drug for a patient is called dosage.

Q. Define different doses with example. (SU-06S)

Ans.

Types of doses:

1. Therapeutic dose or effective dose (ED)
2. Booster dose
3. Toxic dose
4. Lethal dose
5. Loading dose
6. Maintenance dose
7. Adult dose
8. Test dose
9. Ceiling dose
10. Maximum dose
11. Minimum dose

■ **Therapeutic dose or effective dose (ED):** The amount of drug that produces the optimum / expected therapeutic effect is called therapeutic dose.

■ **Median effective dose (ED₅₀):** A dose that produces the desired effect in half of a population is called ED₅₀.

- **Booster dose:** The amount of drug given some times (months / years) after the initial dose to enhance the effect is called booster dose.
Booster dose is commonly used in vaccines of some communicable disease; e.g. the booster dose of vaccines for HBV is given 10 months after the 3rd dose (schedule of HBV vaccines is 0, 1, 2 & 12 months)
- **Toxic dose:** It is the excess dose which will produce serious toxic effect.
- **Median toxic dose (TD₅₀):** It is the dose which will produce toxic effect in 50% of test animal.
- **Lethal dose:** The amount of drug that causes death of certain percent (it may or may not be 100%) of experimental animals is called lethal dose.
- **Median lethal dose (LD₅₀):** It is the dose which will cause death in 50% of test animals.
- **Fatal dose:** The amount of drug which causes death of 100% of the test animals is called fatal dose.
- **Loading dose:** The loading dose is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly. Because this requires filling the volume of distribution (V_d), the calculation uses the volume of distribution (V_d) equation as:
Loading dose = V_d x Target plasma concentration
- **Maintenance dose:** It is the dosing rate at fixed dosing interval which is required to maintain target concentration for optimum therapeutic effect.

$$\begin{aligned} \text{Maintenance dose} &= \text{Dosing rate} \times \text{Dosing interval} \\ \text{Dosing rate} &= \text{Rate of elimination} \\ &= \text{Clearance of drug} \times \text{Target concentration} \end{aligned}$$
- **Adult dose:** According to British pharmacopoeia, the dose in between 20-60 years of age is known as adult dose. If age is below 20 years, or above 60 yrs, the dose should be reduced.
- **Test dose:** Amount of drug given initially (before giving full therapeutic dose) to see sensitivity/ response of tissue to the drug is called a test dose.
- **Importance of test dose:**
 1. To see the sensitivity of tissue to the drug, eg, penicillin is given as test dose to detect presence of any penicillin hypersensitivity.
 2. To see the potency of the drug.
 3. To see the nature of response.
- **Maximum dose:** The maximum amount drug within which drug cannot produce any toxic effects is called maximum dose.
- **Minimum dose:** The minimum amount of drug that is required for any desired therapeutic effect is called minimum dose.
- **Ceiling effect & ceiling dose:** When the dose of a drug is increased progressively, the effect of drug also increases progressively and ultimately reaches a steady level. If the dose of the drug is again increased, there will be no more increase of drug effect. So, this is the maximum effect that can be produced by that particular drug. This maximum effect of a drug is called ceiling effect and the dose which produces the ceiling effect is called the ceiling dose.

Q. Short note: Loading dose. (DU-13Ju,12Ju)

Ans.

Loading dose: The loading dose is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly.

For example, the use of a loading dose of lidocaine in the coronary care unit to prevent arrhythmia in myocardial infarction is standard.

(Ref: Goodman & Gilman-12th edition)

Calculation: Because this requires filling the volume of distribution (V_d), the calculation uses the volume of distribution (V_d) equation as:

$$\text{Loading dose} = V_d \times \text{Target plasma concentration}$$

Indication of loading dose:

1. When $t_{1/2}$ of the drug is short. Eg, $t_{1/2}$ of dopamine is 2 mins.
2. To provide rapid therapeutic effect in critically ill patient by IV route.
3. For long term safety, eg,
 - a. Dopamine
 - b. Lidocaine.

Nice to know**Indications of monitoring plasma concentration of drugs:**

1. When the TI of drug is low. Eg, digoxin, phenytoin.
2. If individual variation of drug response is large, eg, TCA, lithium.
3. Potentially toxic drug when given in presence of renal failure, eg, aminoglycoside.
4. In case of poisoning.
5. In case of failure of response without any apparent reason, eg, antimicrobials.

Pediatric dose (PD): Rough calculation of pediatric dose-**Young's formula: (mostly used)**

$$PD = \text{Adult dose} \times \frac{\text{Age (in years)}}{\text{Age} + 12}$$

Clerk's formula (most accurate):

$$PD = \text{Adult dose} \times \frac{\text{Weight (Kg)}}{70}$$

$$PD = \text{Adult dose} \times \frac{\text{Weight (lb)}}{150}$$

Body surface area (BSA) estimates are more accurate for calculation of pediatric doses than body weight since many physiologic phenomena correlate better to body surface area. The average body surface area of a 70 Kg human is about 1.8 m^2 . Thus, to calculate the dose for a child, the following formula may be used:

$$\text{Approximate PD} = \frac{\text{Surface area of the patient (m}^2\text{)} \times \text{Adult dose}}{1.8}$$

Dosage forms of drugs

Dosage forms: Dosage form is the preparation of a drug for delivering or applying into the body through a particular route.

Selection of the proper dosage form: Before a medicinal agent is formulated into one or more dosage forms, following factors may be considered —

1. Nature of illness
2. The manner in which it is treated generally (e.g. locally or systemically)
3. The age & anticipated condition of the patient.

Importance of dosage forms:

1. To provide the mechanism for the safe & convenient delivery of accurate dosages.
2. For the protection of a drug substance from the destructive influences of atmospheric oxygen or humidity (e.g. coated tablets, sealed ampoules).
3. For the protection of a drug substances from the destructive influences of gastric acid after oral administration (enteric coated tablet).
4. To conceal the bitter, salty or offensive taste or odour (capsules, coated tablets, flavoured syrups)

5. To provide liquid preparations that are either insoluble or unstable in the desired vehicle (e.g. suspensions).
6. To provide clear liquid preparation (e.g. syrup, solutions).
7. To provide "time-controlled" drug action (e.g. various controlled release tablets, capsules & suspensions).
8. To provide optimum drug action from topical administration sites (e.g. ointments, cream, transdermal patches, ophthalmic ear & nasal preparations).
9. To provide for the insertion of a drug into one of the body's orifices (e.g. rectal or vaginal suppositories).
10. To provide for the placement of drugs directly into the blood-stream or into body tissues (e.g. I/V injection).
11. To provide optimal drug action through inhalation therapy (e.g. inhalants & inhalation aerosols).

Q. Mention the different dosage forms of drugs & give examples. (RU-08Ju,06S,04S)

Q. Write down the different drug dosage formulations with few examples. (RU-04S)

Q. What are the solid preparations? (SU-04J)

Q. What are the liquid preparations? (SU-04S)

Ans.

Different dosage forms:

A. Solid preparations:

1. **Tablets:** Uncoated, coated, soluble, dispersible, gastro-resistant, modified release, sublingual, effervescent tablets etc.
2. **Capsules:** Hard capsules, soft capsules, implant capsules, modified release capsules.
3. **Powders:** For external and internal uses.
4. **Granules:** Coated granules, gastro-resistant, modified-release, effervescent granules etc.
5. **Suppositories**
6. **Others:**
 - Ocular insert
 - Intrauterine device
 - Transdermal patch

B. Semi-solid preparations:

1. Ointment
2. Paste
3. Creams
4. Gels

C. Liquid preparations:

1. Oral liquid preparations:
 - Solutions
 - Suspensions
 - Emulsion
 - Drops
2. Injections
3. I/V infusions
4. Drops or liquid sprays (Nasal / Ear / Eye)
5. Shampoos
6. Lotions.

D. Gaseous preparations:

1. Aerosol
2. Gas
3. Nebuliser
4. Metered-dose inhaler

Tablet

Definition: Tablet is a solid dosage form in which powder, crystalline, or granular form of drug is compressed in a disk or molded with pharmacologically inert substances (excipients).

Composition of a tablet:

1. Active ingredients of drug

2. Excipient:

- Diluents:** Form bulk of drug (shape, size); e.g. Dextrose, lactose, starch, sucrose etc.
- Binder:** They bind several drug molecules to prevent autobreakdown. It is known as shelf life. e.g. Methyl cellulose.
- Disintegrating agent:** To break the drug molecule before absorption, e.g. Starch, vee gum.
- Lubricant:** To lubricate drug molecule, e.g. stearic acid, Ca-stearate, Mg-stearate, talc.
- Colouring substances:** To color drug for identification, attraction etc. e.g. brilliant blue, caramel etc.
- Flavoring agent:** Orange flavor, peppermint oil etc. are the flavoring substances.
- Sweetening agent:** To make a drug sweet taste, e.g. saccharin, lactose, mannitol etc.

(Ref: Misbahuddin-5th/49-50)

Types of tablet:

1. Uncoated tablet:

- Chewable tablet: Antacid, vitamin C.
- Effervescent tablet: Vitamin C. - Releases CO_2 in the presence of H_2O (guzn 50)
- Lozenge tablet
- Sublingual tablet: Nitroglycerine

2. Coated tablet:

- Enteric-coated tablet: Aspirin - Coat is insoluble in gastric content but dissolves in intestine
- Film-coated tablet: Metronidazole - Covered with thin layer of a polymer film (H_2O sol / insol)
- Sugar-coated tablet
- Modified released tablet: Analgesics
- Pills - This term is now used in conjunction

(Ref: Misbahuddin-5th/50-53)

Characteristics of tablet:

- Solid structures & sufficiently hard.
- May be circular, ovoid, triangular, flat or any other suitable shape.
- May have lines or breaking marks on the surface.
- Usually onset is slow.
- Needs disintegration after reaching in the GIT
- Comparatively cheaper than parenteral routes
- Not suitable for hospitalized / unconscious / non-cooperative patients including children.

Capsule

Definition: Capsule is a solid dosage form in which one or more active ingredients with or without inert substances are enclosed within a small shell or container generally prepared from gelatin. They are intended for oral administration.

Composition of capsule:

- Capsule shell:** Composed of gelatin or other materials.
- Active ingredient**

3. **Diluent** — Lactose
4. **Lubricant** — Magnesium stearate
5. **Preservative** — Soft gelatin shell may contain a preservative to prevent the growth of fungi. Commonly used preservatives are methyl- and propylparabens, and sorbic acid.

Types of capsule:

1. **Hard capsule:** The active ingredient is usually in solid form (powder, granule). Eg. antibiotic capsules.
2. **Soft capsule:** Liquid may be enclosed directly. Eg. high potency vitamin A capsule (VAC-HP), adalat (antihypertensive).
3. **Modified-release capsule** — Capsule is coated with a variety of substances that are designed to dissolve at different times.
4. **Coated capsule**, eg, gastro-resistant capsules.
5. **Implant capsule**, eg, norplant.

(Ref: Misbahuddin-5th/53-55)

Purpose of using capsule

1. Bypasses disintegration
2. Provides stability of drugs
3. Avoids unwanted taste.

Parenteral = 2nd intestine
2nd rectum

Powder

Definition: It is a mixture of finely divided drugs and/or chemicals in dry form.

Types of powder:

1. **Powder for external uses:** Is also known as dusting powder. They are applied to various parts of the body as lubricants, protective absorbents, antiseptics, and antipruritics.
2. **Powder for internal uses:** Is designed for oral or parenteral administration.

Advantages of powder:

1. Flexibility in compounding.
2. Relatively good chemical stability.

(Ref: Misbahuddin-5th/56)

Suppository

It is a solid medicated preparation designed for insertion into the rectum (or vagina, when it may be called a pessary); it may be designed to dissolve or it may melt at body temperature; the vehicle in which the drug is carried may be fat, glycerol with gelatin, or macrogols (polycondensation products of ethylene oxide) with gelatin.

(Ref: Bennett & Brown-11th)

Ointment

Ointment is a semisolid greasy preparation which is normally anhydrous and insoluble in water. It is more occlusive than cream. It is used over the skin and mucus membrane.

Types:

1. Greasy ointment: Petroleum jelly.
2. Absorbent ointment
3. Paste

Example:

1. Antibiotic ointment (chloramphenicol, neomycin)
2. Antifungal ointment (clotrimazole)

Other dosage forms

■ **Granule:** Granule is small irregular particle ranging from 0.5 to 2 mm in diameter.

✓ ■ **Paste:** Paste is a semisolid preparation to be intended for external application to the skin. It differs from ointment primarily in that it generally contains a larger percentage of solid material and as a consequence is thicker and stiffer than ointment. Paste is generally more absorptive and less greasy than ointment prepared with the same component. (Thicker than ointment)

✓ ■ **Cream:** Cream is a semisolid preparation consisting of opaque emulsion system and is essentially miscible with the skin secretion.

■ **Solution:** Solution is a homogenous liquid preparation containing one or more dissolved ingredients.

✓ ■ **Suspension:** A suspension is a heterogeneous system of liquid dosage form of drug in which the finely divided solid particles ranging from 0.5 to 5.0 μm are suspended or dispersed in a liquid vehicle. (Liquid + Solid)

✓ ■ **Emulsion:** An emulsion is a two phase system prepared by intimate mixture of two immiscible liquids, one of which is uniformly dispersed as globules throughout the other. The system is stabilized by the presence of an emulsifying agent. (Liquid + Liquid)

✓ ■ **Elixir:** It is an aqueous preparation containing active ingredients, flavoring agents and 5-10% alcohol. Example: Elixir Pyperazine, Phenargan syrup.

■ **Parenteral preparation:** Parenteral preparations are sterile preparations intended for administration by injection, infusion or implantation into the human or animal body.

■ **Topical semi-solid preparation:** Topical semi solid preparations are intended to be applied to the skin or to certain mucous surfaces for local action or percutaneous penetration of active ingredients, or for their emollient or protective action. They are of homogeneous appearance.

■ **Inhaler:** Preparation for inhalation are liquid or solid preparations intended for administration as vapour, aerosols or powders to the lower respiratory tract in order to obtain a local or systemic effect. They contain one or more active ingredients dissolved or dispersed in a suitable vehicle.

■ **Nasal preparation:** Nasal preparations are liquid, semi-solid or solid preparations intended for administration to the nasal cavities to obtain a systemic or local effect. They contain one or more active ingredients. Nasal preparations are as far as possible non-irritating & do not adversely affect the functions of the nasal mucosa & its cilia. Aqueous nasal preparations are usually isotonic.

■ **Ear preparation:** Ear preparations are liquid, semi-solid or solid preparations intended for instillation, for spraying, for insufflation, for application to the auditory meatus or as an ear wash.

■ **Eye preparation:** Eye preparations are sterile, liquid, semi-solid or solid preparations intended for administration upon the eyeball &/or to the conjunctiva or to be inserted in the conjunctival sac.

■ **Rectal preparation:** Rectal preparations are intended for rectal use in order to obtain a systemic or local effect, or they may be intended for diagnostic purposes.

■ **Vaginal preparation:** Vaginal preparations are liquid, semi-solid or solid preparations intended for administration to the vagina usually in order to obtain a local effect. They contain one or more active ingredients in a suitable basis.

✓ ■ **Syrup:** The drug is provided in a concentrated sugar (fructose or other) solution.

✓ ■ **Linnetus:** A viscous liquid formulation, traditional for cough.

Suspension: Oral antibiotic syrup, antacid

Emulsion: Lotion (Benzyl benecate), Castor oil

Oil in water
Water in oil

Q. How does ointment differ from cream? (RU-08Ju)

Ans.

Difference between ointment and cream:

Traits	Cream	Ointment
1. Nature	Water-based and has capability to spread uniformly. (water soluble)	Oil-based and not able to spread. (water insoluble)
2. Composition	Oil- 50% and water- 50%	Oil- 80% and water- 20%
3. Appearance	Less greasy and has lighter consistency.	More greasy and has thicker consistency.
4. Absorption	Quickly absorbed by the skin.	Slowly absorbed and stays longer over the skin.
5. Function	Suitable to use both in small and large areas of skin.	Suitable to use in small skin lesions.
6. Application on dry skin	Cream promotes skin dryness and therefore not suitable for use. (dry skin)	Best used in dry skin.

miscible with skin secretion

Pharmacopoeia & Formulary

Q. Enumerate the potential sources of information on drugs. (CU-07J)

Q. List the drug information sources that can be consulted for rational prescribing. (SU-07J)

Ans.

Sources of drug information:

- Pharmacopoeia:**
 - United states Pharmacopoeia
 - British Pharmacopoeia
 - British Pharmaceutical Codex
 - Indian Pharmacopoeia
 - The International Pharmacopoeia (Ph. Int.) by WHO etc.
- Formulary:**
 - British National Formulary (BNF)
 - Bangladesh National Drug Formulary (BDNF) etc.
- Textbooks:**
 - Goodman & Gilman's The Pharmacological Basis of Therapeutics,
 - Basic & Clinical Pharmacology (By Bertram G. Katzung) etc.
- Medical journals:**
 - New England Journal of Medicine
 - British Medical Journal
 - Biochemical Pharmacology
 - Molecular Pharmacology
 - European journal of pharmacology
 - Japanese journal of pharmacology
- Pharmaceutical companies:** But their information sometimes may be biased.
- Computer based information:** Single comprehensive source of drug information. Data base software for pharmacokinetic designing, drug-dose includes PCONLINE, PHARMAKIN & MINSQ. Online authentic information about drug can be obtained from the "food & drug administration" or FDA; using <http://www.fda.gov/>
- Unbiased information about drug is proved by —**
 - Martindale's Extra Pharmacopoeia
 - American Drug Index
 - WHO drug information

(Ref: Misbahuddin-5th/6-8)

Q. Define pharmacopoeia. (DU-15Ju)

Q. Name some important drug compendia. (RU-08Ju)

Q. Short note: Pharmacopoeia. (DU-17J)

Ans.

Pharmacopoeia / drug compendia

Definition: A book containing a list of products used in medicine with description, chemical tests for determining identity & purity & formulas for certain mixtures of these substances. It also generally contains a statement of average dosage.

(Ref: Dorland's medical dictionary-31st/1446)

Definition: Pharmacopoeia is an official book published by legally authorized body which deals with details about drug such as name, sources, chemical nature, and test for identification, physic-chemical properties, pharmacology, dosage, indication, contraindication and drug specification.

Example:

1. United states Pharmacopoeia (USP)
2. British Pharmacopoeia (BP)
3. British Pharmaceutical Codex (BPC)
4. Indian Pharmacopoeia (IP)
5. The International Pharmacopoeia (Ph. Int.) by WHO

(Note: There is no Bangladesh pharmacopoeia or formulary. Pharmacopoeia means **drug compendium**. A compendium is a concise, yet comprehensive compilation of a body of knowledge. The word compendium comes from the Latin word "compenso", meaning "to weigh together or balance".)

Q. Define is formulary?

Ans.

Formulary: Formulary is a book that contains a list of drugs with descriptions, tests and formulas for preparing the same.

Q. How does pharmacopoeia differ from formulary? (RU-08J)

Ans.

Difference between pharmacopoeia & formulary:

Pharmacopoeia	Formulary
1. Published by authorized body.	1. Published by drug administration authority.
2. Contains descriptions of all drugs <u>individually including structure chemistry</u> etc.	2. May contain all nationally licensed drugs prescribed by the health professionals or lists only preferred drugs.
3. Trade names are not included.	3. Trade names are included
4. Can be followed by doctors of all over the world as there is generic name.	4. Can't be followed by all doctors of the world as there is trade name here. Used only by doctors of the same country.
5. Published less frequently (<u>5 yearly or more</u>)	5. More frequently (<u>Yearly / Two yearly</u>)
6. Example: United states Pharmacopoeia, British Pharmacopoeia	6. Example: British National Formulary (BNF), Bangladesh National Drug Formulary (BDNF).

Drug nomenclature

Q. Nomenclate the drugs with example. (SU-04S, CU-01S)

Q. What are the usual names of drugs? (RU-04J)

Q. How the nomenclature of drug is done? (RU-14J)

Q. Write down the drug nomenclature, its advantages & disadvantages. (SU-16Ju)

Ans.

Drug nomenclature: Any drug may have all the following 4 names:

1. **Code name:** Is the first name that is given to a drug by the pharmaceutical manufacturer. After the synthesis of a lot of chemical compounds, some code names are given before screening its role in physiological processes done in the laboratory. It may be an abbreviation, a numerical, or combination of both.
2. **Chemical name:** Chemical name is the name used by the organic chemist to indicate the chemical structure of the drug. It is obviously unsuitable for prescribing.
3. **Generic (non-proprietary/official/approved) name:** This non-proprietary or generic name is given by an official (pharmacopoeia) agency, e.g. WHO. Three principles remain supreme and unchallenged in importance:
 - a. the need for distinction in sound and spelling, especially when the name is handwritten.
 - b. the need for freedom from confusion with existing names.
 - c. the desirability of indicating relationships between similar substances.

The generic names **diazepam**, **nitrazepam**, **flurazepam** are all of benzodiazepines. The WHO chooses recommended International Nonproprietary Names (rINN). Most countries have used rINNs for many years. The USA is an exception, but even here most USA National Names are the same as their rINN counterparts. In the UK, the British Approved Name (BAN) system is being progressively modified such that the rINN name is adopted. Eg, adrenaline is the BAN, epinephrine is the rINN name.

4. **Trade (proprietary/commercial/brand) name:** The proprietary name is a trade mark applied to particular formulation(s) of a particular substance by a particular manufacturer. E.g. Napa or Ace is the brand name of Paracetamol. Losectil is the commercial name of omeprazole. Manufacture is confined to the owner of the trademark. It is designed to maximize the difference between the names of similar drugs marketed by rivals for obvious commercial reasons. To add confusion, some companies give their proprietary products the same names as their generic products in an attempt to capture the prescription market.

(Ref: Misbahuddin-5th/21-23; Bennett & Brown-11th)

Nice to know

Example of drug with 3 types of name:

Chemical name	Generic name	Trade name
3, 4-dihydroxy-phenyl- ethyl amine.	Noradrenalin	Lephophed
Acetylsalicylic acid	Aspirin	Dispirin
Acetaminophen	Paracetamol	Napa
1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazine-1-ylquinoline-3-carboxylic acid	Ciprofloxacin	Ciprocin

Q. Write down the advantages and disadvantages of non-proprietary and proprietary name of drug. (DU-15Ju)

Q. List advantages of proprietary and non-proprietary name. (SU-03S)

Q. Write down the differences between non-proprietary and proprietary name of drug. (DU-16Ju)

Ans.

Drug name	Advantages	Disadvantages
1. Chemical name UPAC system: international union of pure & applied chemistry.	Describes the chemical structure of drug.	- Quite long and difficult to remember - Not suitable for routine usages.
2. Generic (non-proprietary) name: Is chosen by official agencies. Before entering in Pharmacopoeia, the name is approved. INN- International non-proprietary name council (WHO recommended) USAN- United states approved names (council) BAN- British approved names (council)	- Short, easy to pronounce, recall and recognize; so doctors need not memorize all the manufacturing products. - Useful primarily to health practitioners and it is worldwide recognized. - Reflects chemical, pharmacological or other characteristics. - Free of conflicts with other drug names. - Pharmacist can supply any brand of drug and can run his business at a low cost investment. - The same name is pronounced everywhere in the world, eg, aspirin, penicillin.	- Quality control is impossible - Variation of formulation is done by different companies. - Patient can receive preparation of inferior quality or of uncertain bioavailability. - Biological half-lives vary. - More difficult to remember than the trade name. - It is not suitable for prescribing drugs with low TI.
3. Trade (proprietary) name: It refers to a name given by a particular company.	- Shorter, simpler, easier to remember & write. - Medical practitioners can prescribe the best one from the different formulation of the same drug. - The use of proprietary name reduces the problem of quality. - It reduces the problem of quality, ie, bioavailability is ensured. - Drugs with low TI (digoxin) are generally suitable for prescribing in trade name.	- Different pharmaceutical companies market the same drug with different trade names which produce a lot of confusion. - It differs from country to country. - It does not provide the information about class of drug. - Drugs sold under trade name are usually costly. - Sometimes drugs of different classes have closely similar names & cause confusion. - Pharmacist is obliged to supply the prescribed drug under trade name. - Multiple companies can run their business easily. - For different formulation of the same drug, the investment of pharmacist is much more.

Routes of drug administration

Q. What are the routes of administration of drugs? Give examples. (DU-10J, CU-11Ju, 09Ju, RU-12J, SU-16J, 06M)

Q. Enumerate common routes of administration of drugs with example. (DU-17M, 14J, 12J, RU-12J)

Q. Name the commonly used injectable routes of drug administration? (DU-00S)

Ans.

Different routes of drug administration

A. **Local route:** The drugs are applied to a localized area & the action is confined to that area.

a. **Topical:** External application of drugs to the surface of skin & mucus membrane for localized action. The formulations for these drugs are ointment, paste, creams, drops, powder, patch, lotion etc.

1. **Skin:** Cream / ointment.
2. **Eye:** Drop / ointment
3. **Ear:** Drop / cream
4. **Nose:** Drops / spray
5. **Oropharyngeal mucosa**
6. **Vagina:** Suppositories, jelly, cream.
7. **Anus:** Cream.

b. **Deeper tissues:** Certain deep areas can be approached by using a syringe & needle.

1. **Intra-articular injections** (hydrocortisone acetate) (joint)
2. **Infiltration** (around a nerve)
3. **Intrathecal injection** (medication / local anaesthesia) (Subarachnoid space)
4. **Retro-bulbar injection** (hydrocortisone acetate)
5. **Intra-cardiac injection:** Adrenaline (in cardiac arrest)
6. **Intra-peritoneal:** Hypertonic solution for dialysis in patients with chronic renal failure.

c. **Inhalational:**

1. Steroid inhalation
2. Bronchodilator inhalation
3. Inhalation anaesthesia

d. **Selective arterial:**

1. Closed intra-arterial injection is used as contrast media in angiography
2. Anticancer drugs can be infused on femoral / brachial artery to localize the effects for limb malignancies.

B. **Systemic routes:** Drugs go to the site of action through circulation.

a. **Enteral route:** (Alimentary route for 20 2m)

1. **Oral:** Most of the drugs.
2. **Sublingual:** Drugs to be absorbed by the lingual vein, eg, GTN.
3. **Buccal:** Tetracycline, GTN.
4. **Rectal:** Suppositories, eg, diclofenac suppository, (parenteral)
5. **Colonic route:** Enema
6. **Nasogastric route:** Desmopressin (in treatment of diabetes insipidus), Salmon calcitonin (in treatment of osteoporosis).

b. **Parenteral route:** The parenteral route introduces drugs directly across the body's barrier defenses into the systemic circulation or other vascular tissue.

1. **Intramuscular (IM):** Benzylpenicillin, diazepam, iron-dextran complex.
2. **Intravenous (IV):** Thiopental Na, heparin, infusion of fluid, transfusion of blood.
3. **Subcutaneous (SC):** Insulin, adrenaline.
4. **Transdermal:** Norplant, Nitroglycerine, Scopolamine.

(Ref: Tripathi-6th/6-10; Bennett & Brown-11th)

Nice to know

Sublingual: Placement *under the tongue* allows a drug to diffuse into the capillary network and, therefore, to enter the systemic circulation directly.

(Ref: Lippincott's-6th/2)

Intramuscular (IM): Drugs administered IM can be aqueous solutions or specialized depot preparations. Absorption of drugs in an aqueous solution is fast, whereas that from depot preparations is slow. An example is sustained-release haloperidol decanoate, which slowly diffuses from the muscle and produces an extended neuroleptic effect.

(Ref: Lippincott's-6th/3)

Many drugs are well absorbed when administered intramuscularly. The rate of absorption is governed by muscle blood flow, and this varies from site to site (deltoid > vastus lateralis > gluteus maximus).

The drug must be sufficiently water soluble to remain in solution at the injection site until absorption occurs. This is a problem for some drugs, including **phenytoin**, **diazepam** and **digoxin**, as crystallization and/or poor absorption occur when these are given by intramuscular injection, which should therefore be avoided.

(Ref: A Textbook of Clinical Pharmacology and Therapeutics by Ritter & Lewis-5th/ & 21)

Subcutaneous (SC): This route of administration is somewhat slower than the IV route. Examples of drugs utilizing SC administration include epinephrine along with local anesthetic, norplant, LMW heparin and programmable mechanical pumps that can be implanted to deliver insulin in diabetic patients.

(Ref: Lippincott's-6th/3)

Oral Inhalation: Inhalation provides the rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium, producing an effect almost as rapidly as with IV injection. This route of administration is used for drugs that are **gases** (for example, some anesthetics) or those that can be dispersed in an aerosol. This route is particularly effective and convenient for patients with **respiratory complaints** (such as asthma, or chronic obstructive pulmonary disease) because the drug is delivered directly to the site of action and systemic side effects are minimized. Examples of drugs administered via this route include **sulbutamol**, and **corticosteroids**, such as **fluticasone**.

(Ref: Lippincott's-6th/4)

Nasal inhalation: This route involves administration of drugs directly into the nose. Agents include nasal decongestants such as the anti-inflammatory corticosteroid mometasone furoate. Desmopressin is administered intranasally in the treatment of diabetes insipidus; salmon calcitonin, a peptide hormone used in the treatment of osteoporosis, is also available as a nasal spray. The abused drug, cocaine, is generally taken by intranasal sniffing.

(Ref: Lippincott's-6th/4)

Intrathecal/intraventricular: This route provides access to the CNS for drugs that are normally excluded by the blood-brain barrier. This inevitably involves very high risks of **neurotoxicity**, and this route should never be used without adequate training. The possibility of causing death or permanent neurological disability is such that extra care must be taken in checking that both the drug and the dose are correct. Examples of drugs used in this way include-

1. **Methotrexate**
2. Local anesthetics (e.g. **levobupivacaine**)
3. Opiates, such as **morphine** and **fentanyl**.
4. **Amphotericin B** used in treating cryptococcal meningitis.
5. **Aminoglycosides** are sometimes administered by neuro-surgeons via a cisternal reservoir to patients with Gram negative infections of the brain.
6. The antispasmodic **baclofen** is sometimes administered by this route.

(Ref: A Textbook of Clinical Pharmacology and Therapeutics by Ritter & Lewis-5th/ & 22)

Topical: The topical route includes application to the skin or to the mucous membrane of the eye, ear, nose, throat, airway, or vagina for local effect. The rate of absorption varies with the area of application and the drug's formulation.

(Ref: Katzung & Trevor-9th edition)

Transdermal: The transdermal route involves **application to the skin** via a **transdermal patch** for **systemic effect**. Absorption usually occurs **very slowly** (because of the thickness of the skin), but the first-pass effect is avoided. This route is most often used for the **sustained delivery of drugs**, such as the antianginal drug **nitroglycerin**, the antiemetic **scopolamine**, and the **once-a-week contraceptive patch** that has an efficacy similar to oral birth control pills.

(Ref: Lippincott's-6th/4+Katzung & Trevor-11th edition)

Q. Write down the advantages & disadvantages of oral route. (DU-12J, CU-11Ju, RU-04S, SU-06M)

Q. Write down the advantages & disadvantages of sublingual route. (SU-03J, DU-17J)

Q. Write down the advantages & disadvantages of intravenous route. (DU-16J, 12J, RU-04J, SU-13J)

Q. Write down the advantages & disadvantages of intramuscular route. (RU-04J)

Q. What are the advantages rectal route over oral route? (SU-05M)

Q. Mention the advantages of oral route & disadvantages of intravenous route. (DU-14J)

Q. What are the advantages of sublingual & rectal route? (CU-06J, SU-16J)

Q. Short note: Rectal route of administration. (RU-13J)

Q. Describe the importance of rectal administration of Diclofenac Sodium. (CU-17M)

Ans.

Advantages & disadvantages of different routes:

Routes	Advantages	Disadvantages
Oral	1. Oral drugs are easily self-administered. 2. Safe, cheap, most convenient, painless. 3. No disturbance of daily activity 4. Ambulatory patients can utilize this route 5. Strict sterilization is not necessary. 6. Toxicities or overdose by the oral route may be overcome with antidotes such as activated charcoal. 7. Least chance of hypersensitivity reaction 8. Self satisfaction & patient compliance is mostly ensured.	1. Unconscious, non-cooperative patients, patients with vomiting, diarrhea, malabsorption cannot be given. 2. Cannot be given in emergency condition due to delayed onset of action. 3. Ingested drugs are subject to the first-pass effect. 4. Variable bioavailability (5 to < 100%) 5. May cause severe nausea & vomiting. 6. Certain drugs cannot be given orally- ▪ Foul smelling, irritating, bitter, hypertonic drugs. ▪ Drugs destroyed by gastric HCl, proteolytic & carbohydrate splitting enzymes (insulin, oxytocin, heparin, testosterone). ▪ Polyionic drugs (more water soluble) due to less absorption ▪ Drugs that undergo extensive first pass hepatic metabolism.
Sublingual	1. Rapid onset of action 2. Bypass 1st pass hepatic metabolism 3. Drugs can be split out after optimum action. Thus less toxic effect. 4. Not destroyed by gastric HCl. 5. Also useful, if the patient is vomiting. 6. Low incidence of infection.	1. Foul smelling & irritating drugs cannot be given. 2. Water soluble drugs cannot be given. — <i>soluble to</i> 3. Frequent administration is not possible, because the drug will cause excessive salivation and the drug may be swallowed. <i>2nd 2nd</i> 4. Large volume of drug cannot be given.
Intravenous (IV)	1. Rapid onset of action, so suitable for emergency condition. 2. 100% bioavailability, so more action of drug. 3. Can be given to unconscious & uncooperative patient. 4. Drugs that are not absorbed orally, such as the neuromuscular blocker atracurium, can be given IV. 5. No first-pass metabolism of drug by the liver. 6. Large volume of drug can be given. 7. Drugs of large molecular weight can be given. 8. Water soluble drugs can be given. 9. Intravenous delivery permits a maximal degree of control over the circulating levels of the drug.	1. Increased risk of hypersensitivity reaction. 2. Chance of complications like thromboembolism, air embolism, thrombophlebitis, infection at the site of injection. 3. Drugs that are injected cannot be returned. So mistakes are unreturnable. 4. Ambulatory patients cannot utilize this route. 5. Self medication may not be possible. 6. Strict aseptic measures are necessary. 7. Special technique & skilled hand is required. 8. Expensive 9. IV injection may also induce hemolysis or cause other adverse reactions by the too-rapid delivery of high concentrations of drug to the plasma and tissues.

Routes	Advantages	Disadvantages
Intramuscular (IM)	1. Rapid onset of action 2. Uniform absorption, so prolonged duration of action 3. Significant bioavailability (75 to $\leq$ 100%) 4. Administration of moderate volume of drugs.	1. Painful 2. Large volume of drug cannot be given. (Injected volumes should usually be no greater than 5mL) 3. Hematoma formation. 4. Expensive 5. Self medication not possible. 6. Sterile abscesses at the injection site (e.g. paraldehyde). 7. There is no way of stopping absorption of the drug. So mistakes are unreturnable. 8. Sciatic nerve palsy following injection into the buttock = this is avoided by injecting into the upper outer gluteal quadrant;
Subcutaneous (S/C)	1. Prolonged duration of action. 2. Foul smelling & irritating drugs can be given. 3. Significant bioavailability (75 to $\leq$ 100%) 4. Self medication may be possible.	1. Painful 2. Hypersensitivity reaction may occur. 3. Large volume of drug cannot be given. 4. Discoloration of skin may occur. 5. Irritation, infection, tissue necrosis to the site of injection may occur.
Inhalation	1. Rapid onset of action 2. Bypass hepatic first hepatic metabolism 3. Less or no systemic toxicity 4. Can be used on demand. 5. Dose can be adjusted 6. Drug is directly delivered to the site of action.	1. Special apparatus is required. 2. May produce systemic toxicity (in heart & lungs). 3. Drugs can cause irritation in the airway. 4. Variable bioavailability (5 to $<100\%$)
Rectal (Suppository)	1. Suitable for- - Patients who cannot swallow, eg, unconscious patient. - Extreme of ages, eg, infant & old. - Patients with vomiting, motion sickness & migraine. 2. Significant avoidance of 1st pass hepatic metabolism. 3. Irritant drugs (bad smell & taste) drugs can be given. 4. Avoid gastric irritation. 5. Not destroyed by gastric acid or intestinal enzymes.	1. Embarrassing process. It hampers the privacy of the patient. 2. Cannot be given in diarrhea. 3. Fecal material may interfere with absorption of drug. 4. Rectal inflammation or irritation can occur with repeated use.
Transdermal	1. Prolonged duration of action 2. Avoid 1st pass hepatic metabolism. 3. Significant bioavailability (80 to $\leq$ 100%)	1. Need minor surgical procedure. only a small number of drugs can be used

Q. List four emergency routes of drug administration. (DU-16J)

Ans.

Emergency routes of drug administration

1. Intravenous
2. Intramuscular
3. Rectal (Suppository)
4. Inhalation

Nice to know

Some characteristics of common routes of drug administration

Traits	Oral	SC	IM	IV
Absorption Pattern	Variable; depends upon many factors	Same as IM route	Prompt from aqueous solution, slow and sustained from repository preparation	Absorption circumvented potentially immediate effect
Process of absorption	Passive processes (eg. simple diffusion)	Simple diffusion	Simple diffusion	Not applicable
Special utility	Most convenient and economical; usually more safe	Suitable for some insoluble suspensions and for implantation of solid pellets	Suitable for moderate volumes, oily vehicles and some irritating substances	Valuable for emergency use. Permits titration of dosages suitable for large volumes and for irritating substances, when diluted
Limitations	Requires patient co-operation; availability; potentially erratic, and incomplete for drugs that are poorly soluble, slowly absorbed, unstable or extensively metabolized by the liver.	Not suitable for large volumes; possible pain and necrosis from irritating substances	Precluded during anticoagulant medication	Increased risk of adverse effects. Not suitable for oily solutions or insoluble substances.

Key points

- **Oral** – generally safe and convenient
- **Buccal/sublingual** – circumvents presystemic metabolism
- **Rectal** – useful in patients who are vomiting
- **Transdermal** – limited utility, avoids presystemic metabolism
- **Lungs** – volatile anesthetics
- **Nasal** – useful absorption of some peptides (e.g. DDAVP)
- **Intramuscular** – useful in some urgent situations (e.g. behavioral emergencies)
- **Subcutaneous** – useful for insulin and heparin in particular
- **Intravenous** – useful in emergencies for most rapid and predictable action, but too rapid administration is potentially very dangerous, as a high concentration reaches the heart as a bolus
- **Intrathecal** – specialized use by anesthetists.

(Ref: A Textbook of Clinical Pharmacology and Therapeutics by Ritter & Lewis-5th / 22)

Viva Q. Why there are so many routes?

Ans.

1. **Due to physicochemical property:** Antacids will do well in gastric environment whereas benzylpenicillin will get inactivated in gastric environment.
2. **Due to site of action:**
 - Vapor (anesthetic) is suitable in inhalational administration only.

- *Anthelmintics are only active in oral administration.*

3. *Due to onset of action: Intravenous or inhalation for emergency case.*

4. *Due to prolong effect: Transdermal or S/C route is chosen for sustained action.*

5. *To avoid adverse effect:*

- *Oral salbutamol- Cardiac arrhythmia*
- *Inhalation salbutamol- no cardiac arrhythmia*

Q. Why certain drugs cannot be given orally? Explain with examples. (DU-03M)

Ans.

Certain drugs cannot be given orally-

1. Foul smelling, irritating, bitter, hypertonic drugs.
2. Drugs destroyed by gastric HCl, proteolytic & carbohydrate splitting enzymes (insulin, oxytocin, heparin, testosterone).
3. Polyionic drugs (more water soluble) due to less absorption
4. Drugs that undergo extensive first pass hepatic metabolism.

Q. Name three drugs that cannot be given orally with reasons. (DU-17M,09J)

Q. Drugs like nitroglycerine, oxytocin, dobutamine, heparin & methicillin are not administered orally. Explain with reason in each case. (DU-04M)

Q. Why certain drugs cannot be given orally? Explain with examples. (DU-03M)

Ans.

Drugs that cannot be given orally

1. **Nitroglycerine:** If it is given orally, it undergoes an extensive first-pass metabolism. In liver, there is a high capacity hepatic organic nitrate reductase that removes nitrate groups in a step-wise fashion from the parent molecule and ultimately inactivates the drug. Therefore, the bioavailability of nitroglycerine is very low (<10-20%).
2. **Oxytocin:** It becomes inactive if swallowed, because it is destroyed in the stomach and intestine.
3. **Dobutamine:** If administered orally, it is metabolized in the liver.
4. **Heparin:** Must be given parenterally because the drug does not readily cross membranes.
5. **Methicillin:** It is acid labile, and will be destroyed by gastric acid if given orally. So not suitable for oral administration.

Q. Name some drugs which are given through sublingual route. (DU-17J)

Ans.

Some drugs which are given through sublingual route

1. Nitroglycerine
2. Ondansetron

Q. How will you administer drugs directly into the human systemic circulation? (RU-09Ju)

Ans. By intravenous, intra-arterial and intra-cardiac routes.

Q. What factors modify selection of drug routes? (CU-09Ju)

Q. What factors should you consider before selecting the route of administration of drug?

Q. Explain with examples why we administer the drugs in different routes. (DU-07Ju,CU-07J,RU-04S)

Ans.

Factors considered before selection of route of administration

1. Physiochemical properties of the drug:

a. **Consistency:**

- **Solid drugs:** Oral, rectal, sublingual routes
- **Liquid drugs:** Enteral & parenteral routes
- **Gaseous drugs:** Inhalation

- b. **Solubility:**
 - Water-soluble drugs are given intravenously.
 - Lipid-soluble drugs are given in any route.
 - c. **pH of drugs:**
 - **Acidic drugs:** Any route
 - **Basic drugs:** intravenous route
 - d. **Chemical nature of drugs:**
 - Protein & polypeptide drugs (eg, insulin): Cannot be given orally
 - Non-protein drugs: Can be given orally.
 - e. **Gastric acid stability:**
 - **Acid stable:** Can be given orally
 - **Acid labile:** Cannot be given orally
 - f. **Hepatic first pass metabolism:** Some drugs are destroyed by hepatic first pass metabolism. So, other routes are used, eg, nitroglycerine by sublingual route.
 - g. **Irritating drugs:**
 - Not suitable for oral route or inhalation.
 - Suitable for parenteral route.
 - h. **Molecular size of drug:**
 - **Large molecular size:** Intravenous route.
 - **Small molecular size:** Any route.
 - **Aerosol:** Inhalation
2. **Site of action:**
 - **Eye, ear, nose, skin:** Local route.
 - **Intestine (eg, antihelminthic drugs):** Oral route
 - **Airways and lungs:** Inhalation route.
 3. **Onset of action:** When rapid onset of action is required, most of the drugs are administered parenterally.
 4. **Desired duration of action of drug:**
 - **Prolonged action:** Transdermal (eg, norplant), Subcutaneous (eg, insulin).
 - **Slow and sustained:** Subcutaneous and intramuscular (eg, streptomycin).
 5. **Severity of disease:**
 - **Severe condition:** Intravenous route
 - **Stable condition:** Any route
 6. **Condition of the patient:**
 - **Unconscious patient:** IV / Rectal route.
 - **Conscious patient:** Any route.
 - **Infant or old patient:** IV / Rectal route.
 - **Vomiting, diarrhea:** Parenteral route.
 7. **Adverse effects:** The route selection sometimes prevents or reduces the adverse effects. For example, salbutamol is well tolerated inhalationally than oral route.
 8. **Bioavailability:**
 - **High expectation of bioavailability:** Intravenous route
 - **Low bioavailability:** Oral.

Q. What is enema? What are the types of enema?

Ans.

Enema: Administration of liquid drugs per rectum is called enema.

Types:

1. Evacuant enema.
2. Retention enema.

-
3. Diagnostic enema.
 1. **Evacuant enema:** Warm soap water to remove the fecal matter & flatus. H₂O stimulates the rectum and soap lubricates.
 - **Use:** Before surgical operation, delivery, radiological investigation of GIT.
 - **Amount:** 600 ml at a time.
 2. **Retention enema:**
 - Prednisolone enema- in ulcerative colitis.
 - Glycerine vegetable oil enema- in constipation
 - Normal saline glucose- Nutrient enema
 - Amount: 100-200 ml at a time
 3. **Diagnostic enema:** BaSO₄ suspension or emulsion is administered into rectum for x-ray examination of colon.
-

Pharmacokinetics

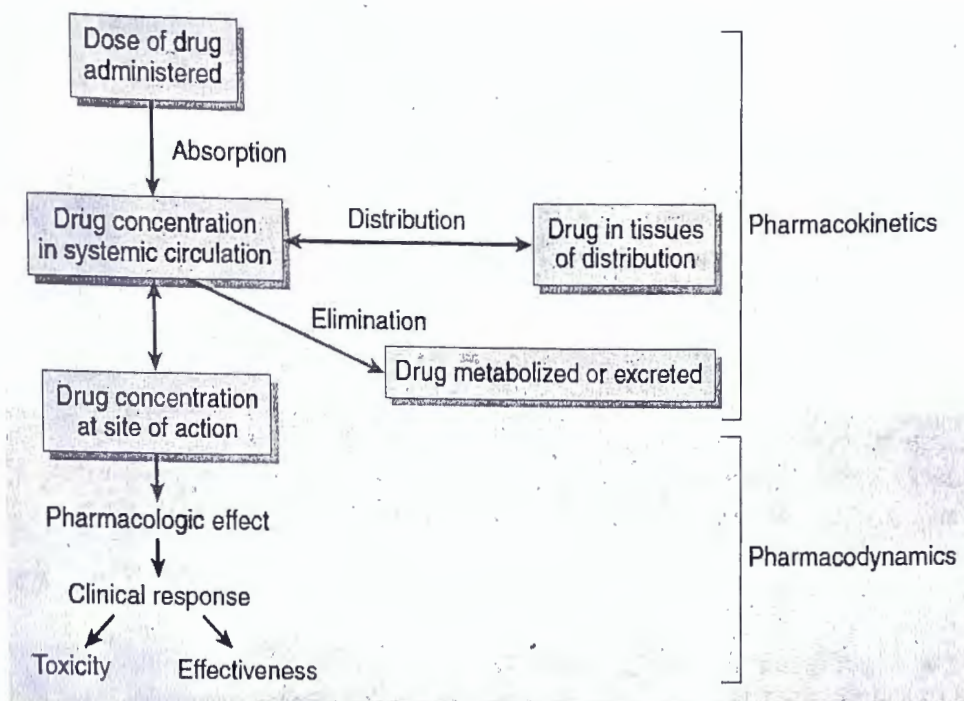


Fig. The relationship between dose and effect can be separated into pharmacokinetic (dose-concentration) and pharmacodynamic (concentration-effect) components. Concentration provides the link between pharmacokinetics and pharmacodynamics and is the focus of the target concentration approach to rational dosing.

(Ref: Katzung-13th/42)

Q. Define pharmacokinetics. (DU-10Ju, SU-06M, RU-07Ju)

Ans.

Pharmacokinetics: The study of absorption, distribution, biotransformation (metabolism) & excretion of drug is called pharmacokinetics. Simply pharmacokinetics means "what the body does to the drug."

(Ref: Misbahuddin-5th/03)

Q. Define pharmacodynamics.

Ans.

Pharmacodynamics: This is the branch of pharmacology which deals with the biochemical and physiological effect of drugs and their mechanism of action.

(Ref: Goodman & Gilman's-12th/22)

Pharmacodynamics: Pharmacodynamics is the study of biological effects produced by the drug". Simply pharmacodynamics means "what the drug does to the body."

(Ref: Misbahuddin-5th/03)

Q. Name the pharmacokinetic processes.

Ans.

Pharmacokinetic process:

1. Absorption of drug
2. Distribution of drug
3. Biotransformation / Metabolism of drug
4. Excretion / Elimination of drug

Remember: ADME

Drug absorption

Q. Define drug absorption. (DU-11Ja,04J, CU-07J, RU-02M, SU-16Ju)

Ans.

Drug absorption:

Definition: It is a process by which a drug enters into the circulation (systemic or portal or pulmonary) from its site of administration (except intravenous & intra-arterial) across the biological membrane. *barrier*

Definition: Absorption is the transfer of a drug from its site of administration to the bloodstream.

(Ref: Lippincott's-6th/6)

Information

■ In case of **intravenous & intra-arterial** administration, the drug needs not to be absorbed; rather all the drug enter into the circulation directly.

■ There are instances, such as **inhalation** of a bronchodilator aerosol to treat asthma, where absorption as just defined is not required for the drug to act, but in most cases the drug must enter plasma / circulation before reaching its site of action.

(Ref: Rang & Dale's-8th)

Q. Enumerate the processes of drug absorption with example. (CU-05S, RU-11/10J,06S, SU-14Ju,13J,11J,08J/Ju,07J,06M/J)

Q. How does a drug cross cell membrane? (SU-10J)

Q. Briefly outline different processes by which drugs can cross the biological membrane. (SU-09Ju)

Ans.

Processes of drug absorption

1. <u>Simple transport / Passive process</u>	1. Simple diffusion/ Lipid diffusion <i>Passive diffusion</i> 2. <u>Filtration/ Aqueous diffusion</u>
2. <u>Specialized transport</u> <i>Active Process</i> <i>Carrier mediated</i>	1. <u>Active transport</u> . 2. <u>Facilitated diffusion</u> 3. Bulk flow 4. <u>Endocytosis</u> ▪ Phagocytosis ▪ Pinocytosis 5. <u>Exocytosis</u> 6. <u>Ion-pair transport</u> .

(Ref: Modern Pharmacology With Clinical Applications by Charles & Robert-6th/22)

Q. Name the sites of absorption. (SU-08J)

Ans.

Sites of drug absorption:

1. Alimentary tract:

- Oral cavity:** Less drug absorption occurs due to less surface area and short time of absorption. Absorption occurs by simple diffusion *(First pass met. liver)*
- Stomach:** Less drug absorption occurs due to less surface area and short time of absorption. Absorption occurs by simple diffusion *Aspirin, Alcohol*
- Small intestine:** More drug absorption occurs due to more surface area and greater blood supply than stomach.

• **Non-ionized drugs:** Absorption occurs by simple diffusion *(Upper part of SI)*

• **Ionized drugs:**

- ✓ By filtration (eg, methyl dopa, levodopa, fluorouracil).
- ✓ By active transport (eg, Fe-specific carrier, Ca²⁺ by vitamin D dependant carrier).

↑↑ Vascular Supply

Def. - mis 87

Vascular Supply

d. Rectum:

- Absorption occurs by simple diffusion.
- Slow and incomplete absorption.
- **In lower 2/3rd of rectum:** Drug bypasses liver & enters systemic circulation → No first pass metabolism (FPM).
Drug → Absorb through middle & inferior rectal vein → hypogastric vein → inferior vena cava not portal vein → No hepatic FPM.
- **In upper 1/3rd of rectum:** Drug → Absorb through superior rectal vein → portal circulation → Liver → First pass metabolism.
Eg, aminophylline, indomethacin, paracetamol, diclofenac, magnesium sulphate, anti-hemorrhoidal drug, aspirin.

2. Subcutaneous tissue:

- By simple diffusion through capillary wall.
- Less absorption than IM route due to less blood supply to subcutaneous fat.
- Eg, insulin, adrenaline, steroid, progesterone, levonorgestrel.

3. Muscle:

- By simple diffusion through capillary wall.
- More absorption than S/C route due to more vascularity.
- Eg, depot preparation, vaccine, injection.

4. Skin:

- Absorption occurs by passive process.
- Eg, silver sulphadiazine, gentamycin, OPC, steroid.

Simple diffusion

Rate: Slow

5. Respiratory tract

- Rapid absorption due to more vascularity and more surface area. Eg,
 - ✓ Salbutamol- aerosol (bronchodilator)
 - ✓ General anesthetic – (Volatile gas) NO
 - ✓ Na. Chromoglycate- inhaled vapour.
 - ✓ Lignocaine (Local anesthetic) – spray during intubations.

Diffusion
High lipid
water partition
co-efficient

mainly Abs →
cell lining sweat
& sebaceous
glands, hair
follicles
(canon multilayer
keratin and
cell fragility)

6. Eye

- Absorption occurs by simple diffusion.

Q. Briefly discuss simple diffusion of drug absorption with examples. (CU-00S, RU-01J)

Q. What are the criteria of simple diffusion of a drug? (DU-05J, CU-05S; RU-04S)

Q. What are the criteria of passive diffusion? (RU-06S)

Ans.

Simple diffusion of drug:

Definition: Simple diffusion may be defined as movement of drug molecules across the biological membrane along the concentration gradient (from higher conc. to lower conc.) without the help of energy & carrier.

Criteria of simple diffusion:

1. **Commonest process** of drug absorption. About 70% drugs are absorbed by this process. Lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane bilayers. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores.
2. Energy is not needed.
3. Carrier is not needed.
4. Occurs along the concentration gradient.
5. Slow process
6. Bi-directional process
7. Obeys Fick's law of diffusion and law of mass action.
8. No selectivity & saturability
9. Shows a low structural specificity

10. Temperature can modify the process
11. Diffusion shows first order kinetics
12. The rate of diffusion depends on-
 - Conc. Gradient
 - Lipid:water partition co-efficient
 - pKa of a drug
 - pH of surrounding fluid.

Drugs absorbed by simple diffusion:

1. Most drugs follow this.
2. Lipid soluble drugs follow this.
3. Low MW drugs follow this.
4. Eg, Aspirin, morphine, pethidine, paracetamol, barbiturates, glucose in liver.

Permeability or diffusion co-efficient: The extent to which a drug is soluble in lipid membrane/biological membrane is called its permeability co-efficient. It is determined by solubility of drug to the lipid phase than water phase.

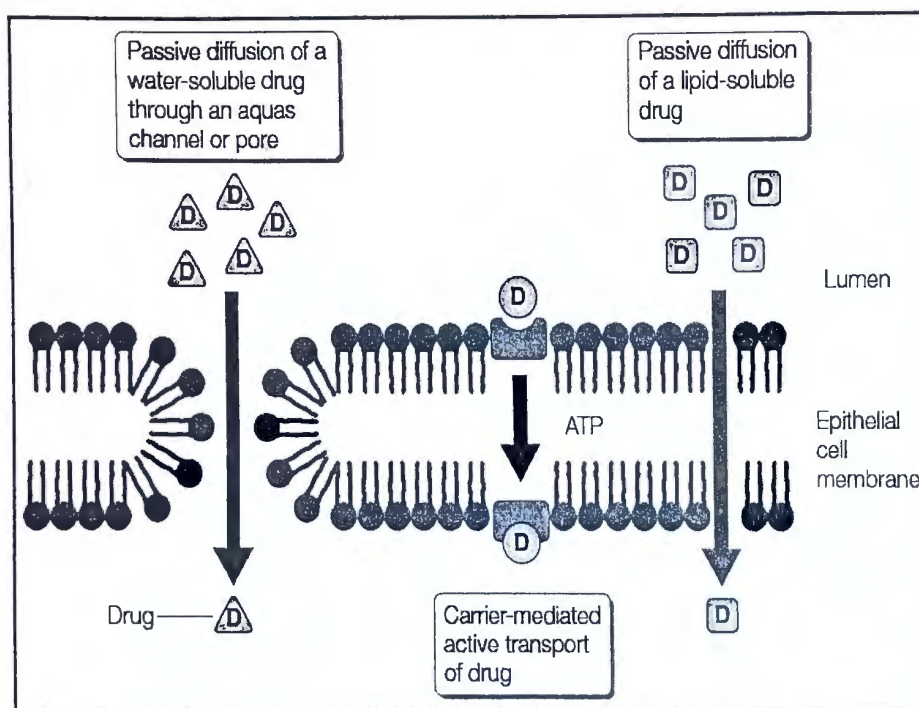


Fig. Modes of absorption of drugs from the gut.

Q. What is filtration?

Q. Short note: Aqueous diffusion.

Ans.

Filtration / Aqueous diffusion: Diffusion of drug molecule through aqueous pores formed by special proteins (aquaporins) present in the lipid bilayer by the filtration pressure, is called aqueous diffusion or filtration.

Criteria of aqueous diffusion / filtration:

1. In biological systems, the passage of many small water-soluble solutes through aqueous channels in the membrane is accomplished by filtration.
2. No energy is needed.
3. No carrier is needed.
4. Majority of the cells (including intestinal mucosa) have aqueous pores. The hypothetical diameter of these pores is about 7 Å, a size that generally limits passage to compounds of molecular weight less than 100 (e.g., urea, ethylene glycol).

5. The rate of filtration depends both on the-
 - a. Existence of a pressure gradient as a driving force and
 - b. Size of the compound relative to the size of the pore through which it is to be filtered.
6. This can be accelerated if hydrodynamic flow of the solvent occurs under hydrostatic or osmotic pressure gradient, e.g. across most capillaries including glomeruli.

Sites of filtration

1. GIT
2. Glomerular membrane: urea, glucose, ethyl glycol.
3. Capillary endothelium, eg, urea, insulin.

(Ref: Tripathi-6th/13; Modern Pharmacology With Clinical Applications by Charles & Robert-6th/24)

Nice to know

Carrier Mediated Transports: When carrier protein is mandatory for drug transport, it is called carrier mediated transport.

- Without expenditure of energy: Facilitated diffusion
- With expenditure of energy: Active transport
- With making a pseudopod: Endocytosis.

Q. Mention the criteria of active transport.

Q. Narrate with examples the active process.

Ans.

Active transport

Definition: The movement of drugs across the biological membrane against chemical or electrical gradient with the active expenditure of energy by the help of carrier protein is called active transport.

(Ref: Ganong-24th, modified)

Criteria:

1. Transport occurs against chemical or electrical gradient. (Uphill transport process)
2. Membrane must be present.
3. Energy is necessary
4. Carrier protein is necessary
5. Very rapid process
6. Metabolic inhibitor can block this process (eg, cyanide, fluoride, anaerobic condition → ↓ATP synthesis).
7. Competitive in nature
8. Exhibits saturability: Saturation of carrier protein or exhaustion of energy occurs.
9. Exhibits selectivity: Show specificity for ions, sugars and amino acids.
10. There is maximum rate of transport of substances.
11. Less common.

(Ref: Samson Wright's-13th/15; Guyton-12th; Harper's-29th)

Examples: A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using these specific carrier proteins. Eg,

1. Levodopa
2. Streptomycin
3. α-Methyl dopa
4. 5-Fluorouracil
5. Iron (Fe^{2+})
6. 5-Bromouracil.

Sites of active transport:

1. Neuronal membrane
2. Choroid plexus
3. Hepatocytes
4. Renal tubular cell

5. Biliary tract
6. Blood-brain barrier
7. Gastrointestinal tract.

(Ref: Rang & Dale's-8th; Tripathi-6th/15)

Q. Mention the criteria of facilitated diffusion. (DU-04S)

Q. Short note: Facilitated diffusion.

Ans.

Facilitated diffusion: Diffusion of drug molecules through a biological membrane along the concentration or electro-chemical gradient with the help of a carrier protein is called facilitated diffusion.

Criteria of facilitated diffusion:

1. Occurs along the concentration or electro-chemical gradient i.e. from higher to lower concentration (downhill transport process).
2. Transport protein or carrier protein is required.
3. It needs no energy. The driving force for facilitated transport is the concentration gradient.
4. It has got selectivity & specificity.
5. It may be inhibited.
6. It shows saturability, because the binding sites on the carrier are progressively become occupied by the drug.
7. Speed of action is medium.
8. It is independent of lipid : water partition co-efficient.

Examples: Absorption of the following occurs by facilitated diffusion-

1. Vitamin-B₁₂ absorption
2. Glucose (entry of glucose into muscle & adipose tissue by GLUT-4)
3. Tetracycline
4. Pyrimidine
5. Fat soluble vitamins, etc.

(Ref: Bennett & Brown-11th; Tripathi-6th/14,15)

Q. Short note: Endocytosis.

Ans.

Endocytosis: When the membrane engulfs the drug molecule by making a pseudopod, the process is called endocytosis.

Examples: Protein (PCT of kidney), aminoglycosides, insulin.

Types of endocytosis:

1. **Pinocytosis:** Engulfs water i.e. cell drinking.
2. **Phagocytosis:** Engulfs substances other than water i.e. cell eating.

Features of endocytosis:

1. It requires Ca²⁺
2. It requires contractile elements (microfilament).
3. It requires energy.

Pinocytosis: This is the process of transport across the cell in particulate form by formation of vesicles.

Q. Name the processes of glucose transport.

Ans.

Glucose transport:

- **In GIT & Kidney:** Na-dependent active transport
- **In RBC, muscle & adipose tissue:** Facilitated diffusion
- **In liver:** Simple diffusion.

Exocytosis → Ex: Nerve terminal & norepinephrine release

Q. Compare simple diffusion with active transport. (RU-17J, 16Ju, SU-09Ju)

Q. How does simple diffusion differ from active transport? (DU-05S)

Ans.

Comparison / Differences between simple diffusion & active transport:

Traits	Simple diffusion	Active transport
1. Movement occurs	Passage of substances towards electrical or chemical gradient	Against conc. or electrical gradient.
2. Energy	Not needed	Required.
3. Carrier protein	Not needed	Required.
4. Membrane	Not needed	Must be present.
5. Saturability	The process does not become saturated	Carrier mediated process, becomes saturated
6. Rate of transport	Slow	Fast

Q. How does simple diffusion differ from facilitated diffusion? (RU-04J)

Ans:

Differences between simple diffusion & facilitated diffusion:

Traits	Simple diffusion	Facilitated diffusion
1. Definition	Passage of substances towards electrical or chemical gradient without carrier and energy.	Passage of substances towards electrical or chemical gradients with the help of carrier protein.
2. Carrier	Not needed	Needed
3. Saturation of carrier	Absent	Saturation of carrier protein occurs
4. Diffusion capacity	Unlimited	Limited (due to saturation of carrier)
5. Substances that are transported	Lipid soluble	Lipid insoluble
6. Selectivity	Absent	Present
7. Lipid:water partition co-efficient	Depends	Not depend
8. Example	O ₂ , N ₂ , CO ₂ , alcohol, H ₂ O.	Glucose, amino acid, galactose.

(Ref: Guyton-11th/46, 49; Samson Wrights-13th /11)

Q. Lists differences between facilitated diffusion & active transport. (RU-08Ju)

Ans.

Differences between active transport & facilitated diffusion:

Traits	Active transport	Facilitated diffusion
1. Movement occurs	Against conc. or electrical gradient (uphill process)	Towards conc. or electrical gradient (downhill process)
2. Energy	Required	Not required
3. Presence of membrane	Must be present	May or may not be present
4. Direction of movement	Usually <u>unidirectional</u>	Can operate <u>bidirectionally</u>
5. Role of electrochemical gradient	Does not depend on them.	Depends on them.
6. Speed	Fast	Medium
7. Examples	Levodopa, Streptomycin, α -Methyl dopa, 5-Fluorouracil, Iron (Fe ²⁺), 5-Bromouracil.	Vitamin-B ₁₂ , Fat soluble vitamins, Glucose (entry of glucose into muscle & adipose tissue by GLUT-4), Tetracycline, Pyrimidine.

(Ref: Harper's-29th)

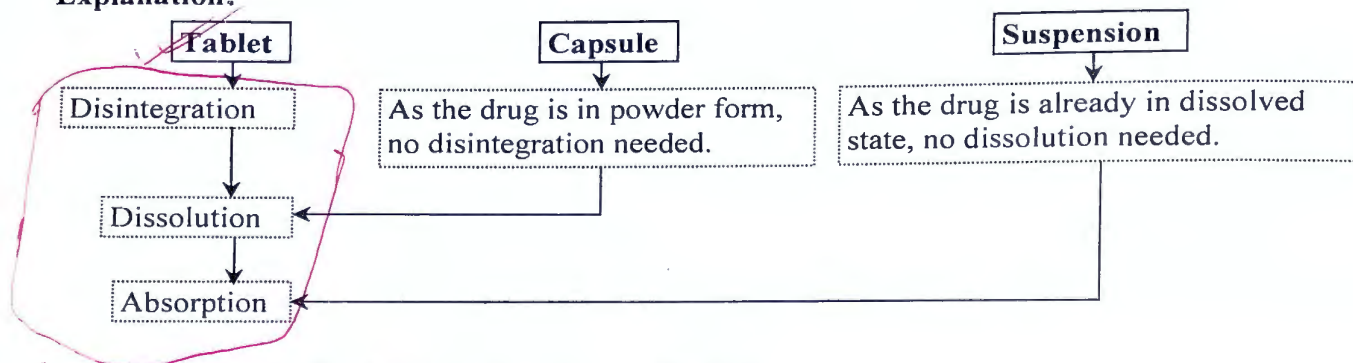
Factors influencing drug absorption

- Q. Which factors modify/influence the transport of drug across biomembrane? (DU-05S, SU-07J, CU-12Ju)
 Q. How drug factors modify absorption? (SU-16Ju)
 Q. Enumerate the factors influencing drug absorption from GI tract. (DU-11Ja, CU-14J,07J,04M)
 Q. Explain the relationship between nature of drug, pKa of drug & pH of the environment in absorption of drug from GIT. (DU-14Ju,10J, RU-12Ju)
 Q. Discuss in brief the role of disintegration & dissolution time in absorption of drug following oral ingestion. (DU-09J, RU-10J)
 Q. Describe factors that influence response magnitude after oral administration of drug. (CU-09J, SU-10J)
 Q. Explain how pH of a media & pK influence drug absorption. (DU-08Ju,07J, RU-06J, SU-14Ju,12Ju,11J)
 Q. Explain the role of gastric emptying and bowel transit time on drug absorption. (RU-15Ju)
 Q. Aspirin is a weak acid (pK 3.5) and morphine is a weak base (pK 8). How would these affect their absorption from stomach (pH 1.3) and intestine (pH 7.8) following oral administration? (SU-13Ju,10Ju)
 Ans.

Factors influencing drug absorption:

A. Factors related to the drug itself:

1. **Route of administration:** Absorption rate: IM > SC > Oral.
2. **Dosage formulation:** Absorption rate: Suspension > Capsule > Tablet.
Explanation:



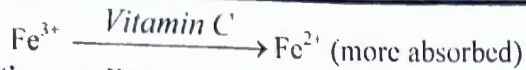
3. **Lipid solubility or lipid:water partition co-efficient:**
 - **Increased lipid solubility** (*high lipid:water partition co-efficient*) → Increased absorption ($\text{Absorption} \propto \text{Lipid solubility}$)
 - **More water solubility** → Less absorption ($\text{Absorption} \propto \frac{1}{\text{Water solubility}}$)
4. **Molecular weight & size of the drug:** Lipid soluble drugs of any size can be easily absorbed. So the size is not a matter for absorption of lipid-soluble drugs. Rather it is applied only for water soluble drugs.
 - ↓Molecular weight → ↓Size of the drug → ↑Rate of absorption (& vice versa)
 - MW > 100 Dalton → Can't absorb through the aqueous pores
 - MW 10-100 Dalton → more absorption
5. **Degree of ionization / pKa of drug:**
 - **Less pKa of drug** → **More ionization** → More water solubility → Drug molecules draw water molecules around them from the solution due to their electrostatic charges → Form hydrostatic shell which has a larger size than the actual drug size → Less penetration through the pores of cell membrane → Less absorption
 - **More pKa of drug** → **Less ionization** → Less water solubility → More absorption
 - **Unionized drug** → More lipid soluble → Maximum absorption.
 For example: Iron in Fe^{3+} form is less absorbed, but Fe^{2+} more absorbed.

$$K_a = \text{Dissociation const. of Acid} = 10^{-pK_a}$$

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$$\Rightarrow pK_a = -\log K_a$$

General Pharmacology



$pK_a = \text{negative base 10 logarithm of acid dis. constant}$

6. Concentration gradient:

- High dose $\rightarrow$ More concentration gradient across the membrane $\rightarrow$ More absorption
- Low dose $\rightarrow$ Less concentration gradient across the membrane $\rightarrow$ Less absorption

7. Physical states of the drugs:

- Gaseous drugs are more absorbed than liquid drugs.
- Liquid drugs are more absorbed than solid drugs.
- Absorption rate: Gaseous $>$ Liquid $>$ Solid drugs.
- Among liquid drugs, homogeneous solutions (crystalloids) are more absorbed than heterogeneous (colloidal) drugs.
 - Crystalloids $\rightarrow$ more absorption
 - Colloids $\rightarrow$ less absorption

$$K_a = \frac{1}{10^{pK_a}}$$

(conjugate base) $pK_a \downarrow = \uparrow \text{ionization}$

8. Use of binder:

- More binder $\rightarrow$ $\downarrow$ disintegration rate $\rightarrow$ delay absorption $\rightarrow$ therapeutic failure (Digoxin).
- Less binder $\rightarrow$ $\uparrow$ disintegration rate $\rightarrow$ rapid absorption $\rightarrow$ toxicity (Phenytoin).

B. Factors related to the absorptive organ /environment/ GIT:

1. Blood supply / Perfusion / Vascularity: $\text{Absorption} \propto \text{Vascularity}$

- IM route $\rightarrow$ Muscle $\rightarrow$ More Vascularity $\rightarrow$ More absorption
- Subcutaneous route $\rightarrow$ Less Vascularity $\rightarrow$ Less absorption
- Cold, shock $\rightarrow$ Less Vascularity $\rightarrow$ Less absorption
- Heat, fever $\rightarrow$ More Vascularity $\rightarrow$ More absorption
- Injection of drug $\rightarrow$ Local massage $\rightarrow$ Heat production $\rightarrow$ Vasodilation $\rightarrow$ More Vascularity $\rightarrow$ More absorption
- Intestine $\rightarrow$ More Vascularity $\rightarrow$ More absorption
- Stomach $\rightarrow$ Less Vascularity $\rightarrow$ Less absorption than intestine
- When a wrong drug is given by IM route, an ice is pressed over the site of injection immediately $\rightarrow$ Less Vascularity $\rightarrow$ Less absorption $\rightarrow$ Antidote is administered.

2. Surface area of absorption: $\text{More surface area} \rightarrow \text{More absorption}$

- Stomach: Less surface area $\rightarrow$ Less absorption.
 - Intestine: More surface area $\rightarrow$ More absorption.
- Surface area of small intestine is increased by $3 \times 10 \times 20 = 600$ times by the following structures-
- Valvulae conniventes (increase by 3 times)
 - Villi (increase by 10 times)
 - Microvilli (increase by 20 times)

In GIT, the decreasing order of absorption is as follows: **Jejunum $>$ duodenum $>$ stomach**. In case of **cancer of intestine**, a large segment is resected by surgery $\rightarrow$ less surface area $\rightarrow$ less absorption. So, parental route is chosen.

3. Presence of food in the intestine:

- Lipid soluble drugs (eg, spironolactone, griseofulvin, hydralazine) $\rightarrow$ More absorption in presence of food $\rightarrow$ Given after meal.
- Water soluble drugs (eg, ampicillin, tetracycline, levodopa, INH) $\rightarrow$ Less absorption in presence of food $\rightarrow$ Given in empty stomach.

4. Presence of another drug/ chemical substances in the intestine:

- Vitamin C increases iron absorption. $Fe^{3+} \xrightarrow{\text{Vitamin C}} Fe^{2+}$ (more absorbed).
- Divalent cations (Ca^{2+} , Mg^{2+} , Fe^{2+}) + Tetracyclines $\rightarrow$ Less absorption of tetracyclines.

- Adrenaline + Lidocaine → vasoconstriction
Less absorption of insulin
Tetracycline chelate with calcium, antacids, dairy products
pH of the absorptive media:

For example-

- Atropine / morphine (pK 8) is an alkaline drug/ weak base. In stomach (pH = 1.3), it remains ionized, so absorption is less. In duodenum (pH=8-9), it remains unionized and so absorption is more.

- $\uparrow$ Peristalsis $\rightarrow$ $\uparrow$ Disintegration & dissolution of tablet & increased blood flow to the intestine $\rightarrow$ More absorption
- In constipation $\rightarrow$ $\downarrow$ Peristalsis $\rightarrow$ Less absorption.
- But in diarrhea $\rightarrow$ $\uparrow\uparrow$ Peristalsis $\rightarrow$ $\downarrow$ Transit time of drug $\rightarrow$ Less absorption.

~~8.~~ **Gastrointestinal diseases:**

- Coeliac disease, Chron's disease → Change in pattern of absorption → More absorption.
- Congestive cardiac failure (CCF), chronic liver disease (CLD) → vascular congestion → gut edema → Less absorption. So, diuretics in treatment of CCF, CLD are better given by IV route.

10. **Inactivation:** Insulin, oxytocin are inactivated in gut if given orally → Less absorption.

Ans.

Absorption of a tablet after being swallowed: It involves following steps-

- **Disintegration:** First, the tablet is disintegrated / broken into smaller particles. This is called disintegration.
- **Dissolution:** Then the drug molecules dissolve with the intestinal fluid.
- **Absorption:** Then, the drug molecules are absorbed by simple diffusion, facilitated diffusion or active transport, etc.

Q. What are the methods of delaying drug absorption? (SU-16J)

Ans.

Methods for delaying drug absorption:

1. By altering the route:

- S/C insulin → prolonged action.

2. By altering the formulation

- Gaseous formulation → rapid absorption & action.
- Sustained release (SR) formation → delayed absorption
- Depot release preparation (subcutaneous pellets) → prolong absorption

3. By adding 2nd substrate with drug:

- **Vasoconstrictor + LA:** Adrenaline (vasoconstrictor) + local anesthetic → vasoconstriction → ↓blood flow → ↓absorption of LA → prolong action.
- **Insulin + protamine:** Insulin alone has the half life of 15-30 min. but Insulin + protamine → prolong action.
- **Penicillin + Benzathine:** Penicillin alone → short duration of action. But penicillin + Benzathine → prolong action (one month)

Q. What are the methods of accelerating drug absorption? (SU-16J)

Q. How can you increase drug absorption?

Ans.

Factors accelerating drug absorption

1. **Application of heat:** Heat → vasodilatation → ↑blood flow → ↑absorption
2. **Massage:** ↑Local blood flow → ↑absorption
3. **By addition of some adjuvant:** e.g. phylline → ↑absorption of mercurial diuretics.
4. **High dose**

Q. Name the factors affecting drug absorption in inhalation route?

Ans.

Factors affecting drug absorption in inhalation route: The lungs serve as a major site of administration for a number of agents given for both local and systemic effects. Such drugs can be inhaled as gases (e.g., volatile anesthetics) or as aerosols (suspended liquid droplets or solid particles).

1. **Size of drug particles in solid and liquid aerosols:** Drug particles larger than 10 micron are trapped in the respiratory tract whereas the size of less than 2 micron can enter the alveoli.
2. **Surface area of alveoli and pulmonary circulation.**
3. **Lipid solubility of the drug:** $\text{Lipid solubility} \propto \text{Absorption}$. Pulmonary absorption of volatile anesthetics across the alveolar-capillary barrier is very rapid because of the relatively high lipid-water partition coefficients and small molecular radii of such agents.
4. **Concentration of drug molecule in the inhaled air** (so, should be shaken well before use)
5. **Concentration gradient between two sides of respiratory membrane.**

Q. What are the factors affecting drug absorption in IM route?

Ans.

Factors affecting drug absorption in IM route:

1. **Blood flow to absorptive area:** More blood flow → More absorption
2. **Concentration gradient** between two sides of biological membrane.
3. **Lipid solubility of the drug** ($\text{Lipid solubility} \propto \text{Absorption}$).
4. **Time of contact**
5. **Tourniquet** → ↓blood supply → less absorption
6. **Application of heat massage** → vasodilation → ↑blood supply → more absorption
7. **Size of the pores** in the membrane proteins (small size → less absorption)
8. **Size of the drug molecule** (MW > 100 Dalton can't absorb through the aqueous pores).
9. **Use of local vasoconstrictor (adrenaline)** → Local vasoconstriction → Slow absorption → Prolong action.

Q. Name the factors affecting drug absorption through skin.

Ans.

Factors affecting drug absorption through skin:

1. **Skin condition**— injury and disease.
2. **Age**— infant skin is more permeable than adult skin.
3. **Region**— plantar < forearm < scalp < scrotum < posterior auricular skin.
4. **Hydration of the stratum corneum**— this is very important. Increased hydration increases permeability. Plastic-film occlusion (sometimes employed by dermatologists) increases hydration. Penetration of glucocorticoids is increased up to 100-fold, and systemic side effects are more common.
5. **Vehicle**— little is known about the importance of the various substances which over the years have been empirically included in skin creams and ointments. The physical chemistry of these mixtures may be very complex and change during an application.
6. **Physical properties of the drug**— penetration increases with increasing lipid solubility. Reduction of particle size enhances absorption, and solutions penetrate best of all.
7. **Surface area to which the drug is applied**— this is especially important when treating infants who have a relatively large surface area to volume ratio.

(Ref: A Textbook of Clinical Pharmacology and Therapeutics by Ritter & Lewis-5th/20)

Q. What is lipid-water partition coefficient?

Q. Short note : Lipid : water partition co-efficient.

Ans.

Lipid : water partition co-efficient.

Definition: It means the relative solubility of drug in lipid as compared to water and that can be measured as the ratio of concentration of the drug in lipid-water phase.

Lipid phase

Water phase

Explanation: Here, lipid represents cell membrane and water represents plasma.

- When the numerical value of a drug is higher in lipid portion than that of water, then it possesses higher lipid solubility, ie, high lipid : water partition co-efficient.
- When the numerical value of a drug is higher in water portion than that of lipid portion, then it possesses less lipid solubility, ie, low lipid : water partition co-efficient.

Example:

1. For urea:
 - Numerical value in lipid phase- 1
 - Numerical value in water phase- 6250
 - Lipid: water partition co-efficient = $1/6250 = 0.0016$
 - Its co-efficient is very low and it is less lipid soluble.
2. Phenobarbitone has a co-efficient of 5.9, so it has a very high lipid : water partition co-efficient. Therefore it is more lipid soluble.

Importance:

1. **High lipid : water partition co-efficient drug has high lipid solubility**, so-
 - a. They are easily absorbed.
 - b. Can penetrate cell membrane, so they have high volume of distribution.
 - c. Redistribution occurs during elimination in renal tubule.
2. **Low lipid : water partition co-efficient drug has low high lipid solubility**. So they have the effect opposite to the high lipid : water partition co-efficient drug.

Q. Short note: pH partition. (NTK)

Ans.

pH partition: It is a phenomenon in which a drug cannot cross biological membrane as a result of ionization due to pH variation of that particular drug with its surrounding environment. The result is that an acidic drug is concentrated in the compartment with high pH ('ion trapping'), and vice versa.

Example:

- A weakly acidic drug **aspirin** is more ionized in alkaline urine → less reabsorption from tubular fluid into plasma → more excretion of aspirin. Conversely, aspirin in acidic pH of stomach is less ionized → more absorption of aspirin into blood.
- A weak base (e.g. **pethidine**) is more ionized in acidic pH of stomach → less absorbed from stomach.

Significance: There are several important consequences of pH partition.

1. **Urinary acidification** accelerates excretion of weak bases and retards that of weak acids.
2. **Urinary alkalization** has the opposite effects: it reduces excretion of weak bases and increases excretion of weak acids, eg, **aspirin**.
3. **Increasing plasma pH** (e.g. by sodium bicarbonate) causes weakly acidic drugs to be extracted from the CNS into the plasma.
4. **Reducing plasma pH** (e.g. by carbonic anhydrase inhibitor such as acetazolamide) causes weakly acidic drugs to become concentrated in the CNS, increasing their neurotoxicity.

This has practical consequences in choosing a means to alkalinize urine in treating **aspirin overdose**: bicarbonate and acetazolamide each increase urine pH and hence increase aspirin elimination, but bicarbonate reduces whereas acetazolamide increases distribution of aspirin to the CNS.

(Ref: Rang & Dale's-8th/103)

Q. Short note: Ion trapping. (NTK)

Ans.

Ion trapping: It is a process by which an ionized drug becomes concentrated in any particular compartment (eg, plasma, urine, gastric juice) due to pH partition. An acidic drug is concentrated in the compartment with high pH ('ion trapping'), and vice versa.

Example: Aspirin is ionized in the alkaline urine and is concentrated there and is less reabsorbed.

Q. Enlist biological barriers. (CU-14J, SU-16J)**Q. Name two important physiological barriers. (CU-08J)****Q. Diagrammatically discuss the importance of the named physiological barriers. (CU-08J)**

Ans.

Type of barrier for drug:

1. **Single layered:** Lipid bilayer of cell membrane
2. **Multiple layered:**
 - Blood brain barrier (BBB)
 - Blood placental barrier (BPB)

Q. Write down about "blood-placental barrier". (CU-08J)

Ans.

Blood-placental barrier: The placental membrane which separates maternal and fetal blood is called the blood-placental barrier. It is initially composed of 4 layers -

1. The endothelial lining of fetal vessels.
2. The connective tissue in the villous core.
3. The Cytotrophoblastic layer &
4. The Syncytium

FCS

Passage of drugs through BPB:

1. Lipid soluble drugs can cross the blood placental barrier by simple diffusion.

2. Water soluble drugs (MW > 500) cannot cross the BPB.
3. Drugs that are rapidly metabolized by placental enzymes and are bound to placenta cannot cross.
4. Drugs with MW < 600 can cross the BPB.

Importance of BPB:

1. **Withdrawal syndrome:** If mother is addicted with morphine, it crosses BPB and the fetus may also be addicted which is elicited by withdrawal syndrome.
2. **Teratogenicity:** Drugs passing through the BPB can cause teratogenicity.

Q. Write down about "blood-brain barrier" (BBB). (CU-08J)

Q. Define blood-brain barrier with its location. (CU-15Ju)

Q. Explain with examples the importance of BBB in drug disposition. What constitutes its functional components? (CU-17M)

Ans.

Blood-brain barrier (BBB): This barrier exists between the plasma and the extracellular space of the brain. Only lipid soluble drugs readily penetrate the BBB. Ionized or polar drugs fail to enter the CNS.

Structures / functional components:

1. **Tight junction** between endothelial cells of brain capillary (mainly responsible for the BBB).
2. A continuous **basement membrane**
3. **Pia mater**
4. **Foot processes** of the astrocytes that adhere to the outer surface of the capillary wall.
5. **Efflux pump** present in BBB returns ion in circulation from CSF.

Criteria for passage through BBB:

1. **Highly lipid soluble drugs** easily cross the BBB & enter into the brain & exert their CNS effects. Eg. diazepam, morphine, thiopental Na.
2. The rate and speed at which drug can enter the BBB.
3. Minimum plasma protein binding. The barrier is almost impermeable to plasma proteins.
4. Low ionization at plasma pH.
5. Some **water-soluble drugs** can cross BBB via **selective transport system**, eg, **Levodopa**.
6. Gases and water pass readily through the barrier.
7. Glucose and electrolytes pass more slowly.

Drugs that cannot cross BBB

1. High molecular weight > 60,000.
2. Highly water soluble (e.g. Streptomycin, Neostigmine etc.)
3. Highly ionized drug.
4. High plasma protein binding.

Conditions where drug can cross BBB without having the ideal criteria: When meninges is inflamed, ie, in meningitis, antibiotics (eg. **benzylpenicillin**) can easily cross BBB.

Importance of BBB

1. It maintains internal environment of CNS.
2. In the fetus, BBB is not well-developed. It is absent in children up to 5 yrs. So chance of CNS toxicity is more in these patients.
3. BBB is absent in CTZ (**Chemoreceptor trigger zone**) in the **medulla oblongata** & **ant. hypothalamus**. So, even lipid-insoluble drugs are emetic.
4. To get desired therapeutic effect:
 - a. Diazepam for sedation.
 - b. Pethidine for analgesia
5. To avoid some adverse effects:
 - a. Propranolol can cross BBB, thus produces CNS adverse effects.

b. Atenolol (water soluble) cannot cross BBB, so devoid of CNS side effects.

(Ref: Bennett & Brown-11th; Tripathi-6th/19,20)

Q. Enumerate the difference between brain capillary and capillary in other locations of the body. (CU-15Ju)

Ans.

Difference between brain capillary and capillary in other locations of the body: Brain capillary is distinguished from other body capillary, as they have-

1. Tight junction between endothelial cells of brain capillary.
2. A continuous basement membrane.
3. Foot processes of the astrocytes that adhere to the outer surface of the capillary wall.

Bioavailability

Q. Define bioavailability. (DU-16J,15J,14Ju,13/12/10J,09Ju, CU-07J, RU-15Ju,13/12J,10Ju; SU-16Ju,07Ju)

Q. Discuss the factors influencing bioavailability of drugs. (DU-16J,15J,13J,12J,09Ju; CU-07J, RU-06M; SU-16Ju)

Q. How routes of administration affect bioavailability? (DU-03S, RU-04M, SU-02S)

Q. Short note: Bioavailability. (RU-16Ju, SU-04S)

Ans.

Bioavailability

Definition: Bioavailability is defined as the fraction of unchanged drug reaching the systemic circulation following administration by any route.

(Ref: Katzung-13th/47)

Definition: Bioavailability is the **rate** and **extent** to which an administered drug reaches the systemic circulation.

(Ref: Lippincott's-6th/8)

Example: If 100 mg of a drug is administered orally and 70 mg of this drug reaches the systemic circulation in a chemically unchanged form, then the bioavailability of that drug is 70%.

(Ref: Lippincott's-6th/8)

Factors modifying bioavailability:

A. Pharmaceutical factor:

1. Solubility of the drug:

- Increased lipid solubility → Increased absorption → ↑Bioavailability.
- More water solubility → Less absorption → ↓Bioavailability.

2. Physical state: Liquid > Solid

3. Size of drug: Crystalloid > Colloid.

4. Disintegration time: ↑Disintegration time → ↓Absorption → ↓Bioavailability.

5. Dissolution rate: ↑Dissolution rate → ↑Bioavailability.

6. Chemical instability: Some drugs, eg, penicillin G, are unstable in gastric pH. Others, eg, insulin are destroyed in the GI tract by degradative enzymes. So they have low bioavailability in those routes.

7. Nature of the drug formulation: For example, particle size, salt form, crystal polymorphism, enteric coatings and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

8. Ionization → ↓Absorption → ↓Bioavailability.

B. First-pass hepatic metabolism (FPM): ↑FPM → ↓Bioavailability. Many drugs, such as propranolol or lidocaine, undergo significant biotransformation during a single passage through the liver.

(Ref: Lippincott's-6th/8,9)

more than 90%. Nitroglycerin is destroyed during FPM

∴ Given by S. Inguinal / T. dermal

C. **Biological factor:**

1. Gastric transit time

2. Presence of other agents; eg, vit-C $\rightarrow$ $\uparrow$ Absorption of iron $\rightarrow$ $\uparrow$ Bioavailability.3. **Time of administration:**• Empty stomach $\rightarrow$ $\uparrow$ Bioavailability of antibiotics• Full stomach $\rightarrow$ $\uparrow$ Bioavailability of Fe.4. **pH of GIT:**• Acidic drug better absorbed in acidic stomach $\rightarrow$ $\uparrow$ absorption $\rightarrow$ $\uparrow$ bioavailability.• Circulation & Surface area. $\uparrow$ Circulation $\rightarrow$ $\uparrow$ bioavailability.5. **Route of administration:**

Route	Bioavailability (%)	Characteristics (Nice to know)
Intravenous (IV)	100 (by definition)	Most rapid onset
Intramuscular (IM)	75 to $\leq$ 100	Large volumes often feasible; may be painful
Subcutaneous (SC)	75 to $\leq$ 100	Smaller volumes than IM; may be painful
Oral (PO)	5 to $<$ 100	Most convenient; first-pass effect may be significant
Rectal (PR)	30 to $<$ 100	Less first-pass effect than oral
Inhalation	5 to $<$ 100	Often very rapid onset
Transdermal	80 to $\leq$ 100	Usually very slow absorption; used for lack of first-pass effect; prolonged duration of action

(Ref: Katzung-13th/47)

Q. Mention the clinical significance of bioavailability of drugs. (RU-15Ju,13J,12J,10Ju)

Ans.

Importance of bioavailability:

1. To calculate drug dosages for nonintravenous routes of administration.
2. To assess loading dose.
3. To compare different formulations produced by different companies.
4. To compare different formulations of same drug.
5. To assess drug serum concentration and individualization of doses.
 - Where intensity or effect is difficult to judge clinically (Phenytoin for epilepsy)
 - Low safety margin (lithium).

Q. How bioavailability studies are done? (CU-04M)

Q. How could you calculate bioavailability of a drug? (RU-06M)

Ans.

Determination of bioavailability: Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with plasma drug levels achieved by IV injection, in which all of the agent rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, one can measure the area under the curve (AUC). This curve reflects the extent of absorption of the drug. [Note: By definition, this is 100% for drugs delivered IV.] Bioavailability of a drug administered orally is the ratio of the area calculated for oral administration compared with the area calculated for IV injection.

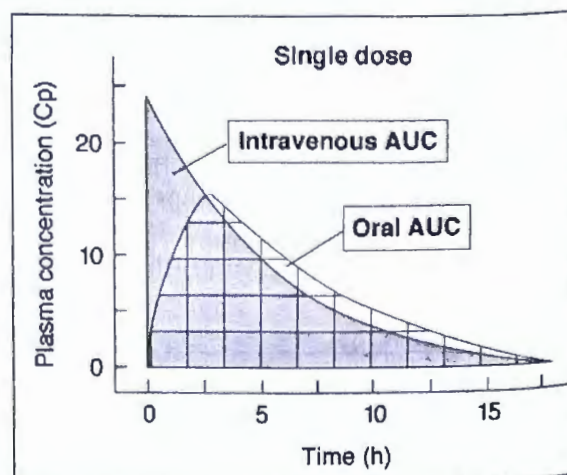
(Ref: Lippincott's-6th/8)

Figure: Determination of bioavailability of a drug.
AUC = Area under curve

$$\text{Bioavailability} = \frac{AUC_{\text{oral}}}{AUC_{\text{injected}}} \times 100$$

(Ref: Lippincott's-6th/8)

Q. Compare the bioavailability differences of 3 drugs A, B and C from the following curve and explain how they affect therapeutic action.

Ans.

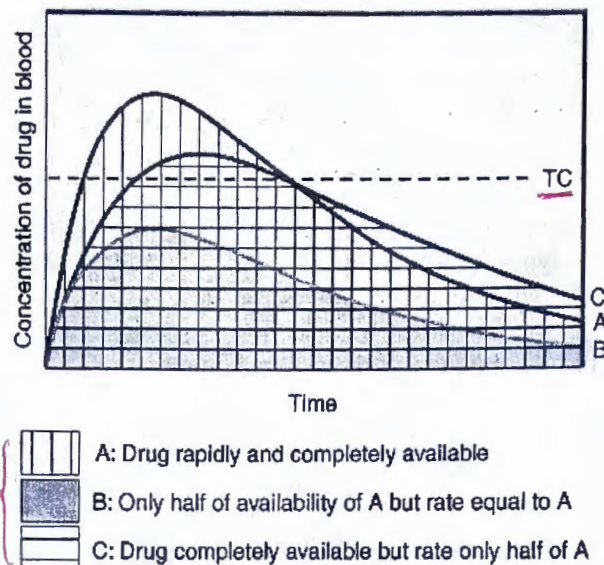


Fig. **Blood concentration-time curves**, illustrating how changes in the rate of absorption and extent of bioavailability can influence both the duration of action and the effectiveness of the same total dose of a drug administered in three different formulations. The dashed line indicates the target concentration (TC) of the drug in the blood.

(Ref: Katzung-13th/47)

Bioavailability is the rate and extent where drug is available at systemic circulation. We can find from the bioavailability curve the following 2 things-

1. Rate *of Absorption / of B.*
2. Extent *of B.*

Rate of bioavailability: It is the time to reach peak plasma concentration.

$$\text{Rate} \propto \frac{1}{\text{Time}}$$

In this curve: Rate of A > C > B

Extent of bioavailability: The extent of systemic availability is ordinarily calculated by relating the area under curve (AUC) after a single oral dose to that obtained after IV administration of the same amount.

In this curve: Extent of A > C > B

- B cannot reach the target concentration (TC). So it has no therapeutic effect.
- A & C reach the target concentration (TC) rapidly. So they have therapeutic effect.

Nice to know

- ✓ **Area under the curve (AUC):** The graphic area under a plot of drug concentration versus time after a single dose or during a single dosing interval
- ✓ **Minimum effective concentration (MEC):** The plasma drug concentration below which a patient's response is too small for clinical benefit.

(Ref: Katzung & Trevor's-11th edition)

Phases of bioavailability: Two phases-

1. **Rising phase:** due to bioavailability.
2. **Falling phase:** due to distribution / metabolism / excretion.

Rate of bioavailability: It is the time to reach peak plasma concentration.

Extent of bioavailability: Means the concentration of drug in the systemic circulation.

Q. Define bioequivalence. (CU-16Ju)

Q. Short note: Bioequivalence. (CU-14Ju)

Q. Enumerate the parameters for studying bioequivalence of two drugs. (CU-16Ju)

Ans.

Bioequivalence

Definition: Under suitable test conditions, when the rates & extents of bioavailability of two drugs of two pharmaceutically equivalent drug products are not significantly different, then they are considered to be bioequivalent to each other & this property is called bioequivalence.

Definition: Two drug formulations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.

(Ref: Lippincott's-6th/9)

Parameters for studying bioequivalence of two drugs

1. Rates of bioavailability
2. Extents of bioavailability

Q. Define therapeutic equivalence.

Ans.

Therapeutic equivalence: Two drug formulations are therapeutically equivalent if they are pharmaceutically equivalent (that is, they have the same dosage form, contain the same active ingredient, and use the same route of administration) with similar clinical and safety profiles.

(Ref: Lippincott's-6th/9)

(Note: Clinical effectiveness often depends on maximum serum drug concentrations and on the time after administration required to reach peak concentration. Therefore, two drugs that are bioequivalent may not be therapeutically equivalent.)

(Ref: Lippincott's-6th/9)

First pass Metabolism

Q. Define first-pass metabolism. (SU-16Ju)

Q. What do you mean by hepatic first pass metabolism? (DU-09J)

Q. Explain first-pass metabolism. (DU-17J)

Q. Explain with example presystemic elimination of drug. (DU-11Ju)

Q. Discuss the clinical significance of hepatic first pass metabolism? (RU-11Ju)

Q. Short note: First-pass metabolism. (DU-11Ja)

Q. Short note: First-pass effect. (RU-16Ja)

Ans.

First pass metabolism/ First-pass effect / Presystemic elimination: The elimination / metabolism of drug that occurs after administration but before it enters the systemic circulation (eg, during passage through the gut wall, portal circulation, or liver for an orally administered drug) is called first-pass effect / presystemic elimination / first-pass metabolism.

(Ref: Katzung & Trevor's-11th edition)

Sites of 1st pass metabolism:

1. Liver (main sites; hence called *first pass hepatic metabolism*)
2. Intestinal wall.
3. Stomach.
4. Lungs

(Ref: Misbahuddin-5th/135)**Clinical significance of hepatic first pass metabolism**

1. A significant amount of drug may be lost before entering into systemic circulation due to 1st pass metabolism.
2. Due to 1st pass metabolism, higher dose is required.
3. An alternative route should be chosen to avoid 1st pass metabolism.

Q. What are the factors for modifying 1st pass hepatic metabolism?

Ans.

Factors that modify 1st pass hepatic metabolism:

1. Routes of drug administration
2. Hepatic circulation
3. Hepatic biotransforming enzyme activity
4. Hepatic diseases

Q. Name four (4) drugs that undergo first pass effect. (DU-17J)

Ans. Write from below.

Some drugs that undergo 1st pass hepatic metabolism:

Low 1 st pass metabolism	Intermediate 1 st pass metabolism	High 1 st pass metabolism	
1. Tolbutamide 2. Phenobarbitone 3. Theophylline 4. Isosorbide mononitrate 5. Pindolol 6. Phenylbutazone	1. Aspirin 2. Quinidine 3. Desipramine 4. Nortryptiline 5. Chlorpromazine 6. Pentazocine 7. Metoprolol	Oral drugs	Non-oral
		1. Propranolol 2. Verapamil 3. Salbutamol 4. GTN 5. Morphine 6. Pethidine	1. Isoprenaline 2. Lidocaine 3. Hydrocortisone 4. Testosterone

(Ref: Tripathi-6th/28)**Q. What is extraction ratio?**

Ans.

Extraction ratio:

Definition: Extraction ratio is the percentage of the drug removed by an organ from the perfusing blood during its passage through that organ.

(Ref: Katzung & Trevor's-11th edition)

Importance: Drugs that have a high hepatic extraction ratio have a large first-pass effect; the bioavailability of these drugs after oral administration is low.

(Ref: Katzung & Trevor's-11th edition)

Q. List the routes that bypass 1st pass metabolism. (SU-06M)

Ans.

Routes that bypass 1st pass metabolism:

1. Intramuscular
2. Intravenous
3. Sublingual
4. Transdermal
5. Subcutaneous

6. Intradermal
7. **Rectal:** Drugs absorbed from lower rectum enter inferior vena cava, thus bypassing the liver. Drugs absorbed from upper rectum enter portal circulation and undergo first-pass hepatic metabolism. Thus, only about 50% of a rectal dose can be assumed to bypass the liver.
8. **Inhalation:** Although inhalation bypasses the hepatic first-pass effect, the lung may also serve as a site of first-pass loss by excretion and possibly metabolism.

(Ref: Katzung-13th/48)

Drug Distribution

The major compartments where drugs distribute are:

- plasma (5% of body weight)
- interstitial fluid (16%)
- intracellular fluid (35%)
- transcellular fluid (2%)
- fat (20%).

Volume Lippincott - 11, 12
Dis.

(Ref: Rang & Dale's-8th)

Q. Define drug distribution. (SU-06M, RU-06S)

Q. What are the factors modifying drug distribution? (RU-06S, SU-11J, 06M)

Q. Write down causes/factors of unequal distribution of drugs. (DU-07J, SU-08Ju)

Ans.

Drug distribution:

Definition: Drug distribution is the process by which a drug reversibly leaves the blood stream & enters into the interstitium (ECF) &/or the cells of the tissues.

(Ref: Lippincott's-6th/9)

Factors modifying drug distribution / causes of unequal distribution of drugs:

1. Physio-chemical properties of the drugs:

a. Solubility:

- Lipid soluble drugs → distribute mainly intracellularly.
- Water soluble drugs → distribute mainly extracellularly.

b. Ionization of drugs:

- Polar or ionized drugs → ↓lipid soluble → extracellular distribution.
- Non-polar or unionized drugs → ↑lipid soluble → intracellular distribution.
- Monovalent ionized drugs → intracellular distribution.

c. Size of drugs:

- Colloids → extracellular distribution.
- Crystalloids → intracellular distribution.

Capillary
Permeability,
Vd to tissue protein
Binding - Lip (10-12)

2. Regional blood flow: ↑Circulation to organ → ↑Drug availability to that organ. Due to variation in blood flow, distribution of drugs occurs in 3 phases-

Rapid distribution	Drugs distribute rapidly in highly perfused organs (eg, <u>brain, liver, kidney</u>) within few minutes.
Intermediate distribution	Drugs distribute within few minutes to few hours in moderately perfused organs (eg, <u>muscle</u>).
Slow distribution	Drugs distribute slowly in less perfused organs (eg, <u>fat</u>) in hours or more.

3. Plasma protein binding (PPB) of drugs:

- High PPB drugs mainly remain in the plasma compartment and have slow distribution.
- Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows their transfer out of the vascular compartment.
- Binding is relatively nonselective as to chemical structure and takes place at sites on the protein to which endogenous compounds, such as bilirubin, normally attach.
- Plasma albumin is the major drug-binding protein and may act as a drug reservoir; that is, as the concentration of the free drug decreases due to elimination by metabolism or excretion, the bound drug

dissociates from the protein. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

4. **Tissue binding of the drugs:** Certain drugs have special affinity for certain tissues and they exist in higher concentration in that tissue compared to plasma. Eg, digoxin in heart muscle, iodine in thyroid gland, tetracycline in bone and teeth. This phenomenon is called **selective distribution** of drug and the tissues are called **cellular reservoir of drug**.

Q. What do you mean by selective distribution of drug? (DU-01S, CU-01S, SU-06S)

Q. Explain- Distribution of drug in body is unequal. (DU-07Ju)

Ans.

Selective distribution of drug: It means special distribution of drug in the certain tissue of the body due to special affinity between particular drug & particular body constituents. The drugs exist in these tissues in highest concentration compared to plasma. This phenomenon is called cellular reservoir of drug and the tissues are called selective reservoir. It is due to presence of nucleoprotein in the tissue.

Examples:

Tissue /organ	Drugs
Thyroid	Iodine
Heart	Digoxin (bound to muscle protein), Quinidine
Liver	Chloroquine, Doxycycline, Digoxin, Fe
Brain	Chlorpromazine, INH
Retina (melanin containing tissue)	Chloroquine
Bone & Teeth (Ca^{2+} containing tissue)	Tetracycline, Bisphosphonates, Ca^{2+} , iron, lead
Iris	Atropine, Ephedrine
Fat	Morphine, Thiopental Na, OPC, Barbiturate
Hair & Nail	As, Heavy metal
Lungs	TCA, Amiodarone
Gastric parietal cell	Omeprazole

Q. What are the causes of unequal distribution of drug?

Ans.

Causes of unequal distribution of drug

1. **Plasma protein binding:** high PPB $\rightarrow$ $\downarrow$ distribution
2. **Tissue binding:** Cardiac glycoside binds with cardiac muscle due to presence of sugar part.
3. **Blood brain barrier:** $\uparrow$ Penetration $\rightarrow$ $\uparrow$ distribution.
4. **Sequestration in adipose tissue:** $\uparrow$ body fat $\rightarrow$ $\uparrow$ distribution of thiopental Na^+
5. **Disease state:** hypoproteinemia due to liver cirrhosis, nephrotic syndrome $\rightarrow$ $\downarrow$ albumin $\rightarrow$ $\downarrow$ PPB $\rightarrow$ $\uparrow$ distribution.

Nice to now

Clinical significance of tissue binding of a drug:

1. Large volume of distribution
2. Long duration action (Digoxin & Doxycycline has half-life of 40 hours & 20 hours respectively)
3. May exert local toxicity due to high concentration e.g. Digoxin toxicity on heart; Tetracycline toxicity on bones & teeth etc.

Criteria of free drug:

1. This is the active form of drug & responsible for its pharmacological action.
2. Produces equilibrium with the protein bound drug.
3. Short duration of action.
4. Is metabolized & excreted readily.
5. Is filtered through the glomerulus along with plasma.

Advantages of free of drug:

1. Can produce pharmacological effect.
2. Rapid action so can be used in emergency condition
3. Undergo metabolism & excretion so cannot accumulate in the body resulting less side effects.

Disadvantages of free form of drug:

- frequency of administration is more
- Biological half life is less i.e. action is of short duration, i.e. no sustained action.

Criteria of the bound drug:

1. This the inactive form of drug but ready for action after dissociation into free form.
2. Is not responsible for the pharmacological actions of that drug.
3. Produces equilibrium with the free drug.
4. Acts as a temporary reservoir of the drug.
5. Sustained & long duration of action.
6. Is not metabolized & excreted
7. As plasma protein is not filtered through the glomerular filtrate, protein bound drug is not filtered.

Advantages of binding form of drug:

1. Suitable for chronic case (Prophylactic use)
2. Frequency of administration is less.
3. Prolonged sustained action
4. Acts as temporary depot of drug.

Disadvantages:

1. No pharmacological action
2. Mild / slow active
3. Toxic drug produces prolonged toxicity.
4. Drug interaction may occur at distribution level.
5. Delayed action so cannot be used in emergency condition

Compare:

Free drug	PPB drug
1. Active	1. Inactive
2. Produces pharmacological effect	2. No effect.
3. Rapid action, so can be used in emergency condition	3. Delayed action so cannot be used in emergency condition
4. Short duration of action, due to metabolism & excretion	4. Sustained action
5. No drug interaction	5. Drug interaction may occur at distribution level
6. Short duration of action	6. Produces prolong toxic action
7. Undergoes biotransformation	7. No biotransformation
8. Excrete through kidney	8. No excretion

Q. What do you mean by redistribution of drug? Give example. (RU-15J,09Ju,08J)

Ans.

Redistribution of drug: After administration, drugs are quickly distributed to the organs that are highly perfused, eg, brain. After sometime, the **highly lipid-soluble** drugs are distributed into other tissues from the first organ of distribution. This distribution of drug from one organ to another is called redistribution of drugs.

Mechanism of redistribution: This occurs due to higher affinity to the second organ. Drugs are stored in that organ (cellular reserve) and are then released from there slowly. The greater the lipid solubility of the drug, the faster is its redistribution.

Examples of Drugs which are redistributed:

Drugs which are redistributed	Tissues where redistribution occurs
Iodine	• Thyroid
Chloroquine	• Retina
Ephedrine, Atropine	• Iris
Tetracycline, Iron.	• Bone & teeth

(Ref: Goodman & Gilman's-12th)

Nice to know:

Explanation of redistribution: Thiopental-Na is a highly lipid-soluble IV anesthetic. As the blood flow to the brain is very high, thiopental-Na reaches to its maximum concentration in the brain within minute in case of IV injection. But there is little binding of drugs with the brain constituents and as a result, the drug is redistributed from the brain to the adipose tissues. The concentration of the drug falls in the brain tissue within minutes and the action of the drug in the brain is terminated. Thiopental-Na produces unconsciousness within 10-30 seconds with a peak effect in 1 min & duration of anaesthesia is 5-8 minutes. But its half life is 12 hours due to its redistribution.

(Ref: Goodman & Gilman's-12th)

Plasma Protein Binding (PPB)

Plasma protein binding (PPB): Reversible binding of some plasma proteins with the drugs in the circulation is called plasma protein binding or PPB.

Plasma proteins that binds with different drugs:

1. **Albumin:**
 - a. Principal drug binder.
 - b. Usually binds with acidic drugs with high affinity; e.g. NSAIDs, Warfarin, Benzodiazepines etc.
2. **α 1-acid glycoprotein:** Usually binds with basic drugs; e.g. β -blockers, Prazosin, Verapamil etc.
3. **Globulin:**
 - o Thyroid binding globulin (TBG)
 - o Corticosteroid binding globulin (CBG)

Factors responsible for plasma protein binding:

1. Affinity of the drug for the plasma protein
2. Concentration of free drugs
3. Concentration of plasma proteins
4. Diseases causing hypoproteinaemia / hypoalbuminaemia (eg, chronic liver disease, CLD)

Important characteristics / criteria of PPB:

1. One drug can bind to many sites on the albumin molecule. Conversely more than one drug can bind with the same plasma protein.
2. If two drugs has same binding site on a protein & are administered at the same time, affinity to bind with the protein determines the binding. Drug with better affinity binds with the protein & the other remains as free drug.
3. As the binding sites may not overlap, two highly protein bound drugs (of same plasma protein) do not necessarily displace each other. Example: Both Probenecid & Indomethacin are highly bound to albumin; but don't displace each other.
4. Acidic drugs don't displace basic drugs & the vice versa.

5. There is equilibrium between free drugs & bound drugs. When free drug concentration decreases, protein bound drugs dissociate from binding site & the equilibrium maintains.
6. As plasma proteins are not filtered through healthy glomerulus & free drug is eliminated along with plasma, the net concentration difference between bound & free drug remain as it is.
7. Highly protein bound drugs are not removed by haemodialysis & need special techniques for the Rx of poisoning.

Q. What are the consequences of plasma protein binding of a drug? (DU-11Ju, SU-11J, RU-16Ju, 08J, 06S)

Q. What is the importance of plasma protein binding of a drug? (DU-14Ju, CU-17M, RU-14Ju, SU-17M, 11Ju)

Ans.

Significance of PPB:

1. High PPB restricts a drug into the vascular compartments. So, its volume of distribution is less.
2. High PPB makes a drug long acting, because PPB makes the drug unavailable for metabolism or excretion.
3. The drug bound with plasma protein does not exert its action but acts after dissociation into free drug. So, PPB acts as a temporary storage of drugs.
4. If the affinity to plasma protein is more & the binding site is same, higher affinity drug can displace the other. So, concentration of free drug of 2nd one is more & excretion is increased. As a result 2nd drug needs frequent dosing. Moreover chance of adverse drug reaction or toxicity is increased.
5. In chronic liver disease (CLD) or hypoproteinemia due to any cause, there is less PPB. So, frequent dosing needed & chance of toxicity is increased.

Q. What interaction may occur at the level of protein bound drugs? (SU-07J)

Q. Give examples of drug interactions at the level of distribution. (SU-07J)

Q. Give examples of 5 extensive protein binding drugs along with its significance. (RU-16Ju, 14Ju)

Q. Gives 3 examples of the effects of drug displacement by competition for plasma proteins binding sites. (CU-01M)

Ans.

Clinically important drug interactions at the level of plasma protein binding: A drug having more affinity to plasma protein can displace another drug having less affinity for the same binding site. So the displaced drug becomes free which is pharmacologically active and produces action.

Displacing drug: This drug has more affinity for plasma protein. So it remains protein-bound.	Displaced drug: This drug has less affinity for plasma protein. So it remains free in the plasma and its concentration in plasma increases.	Result/effect
▪ Sulfonamide ▪ Salicylates ▪ Vitamin K	<u>Bilirubin</u>	Kernicterus (newborn) <i>N. Janssen</i>
▪ Sulfonamide ▪ Salicylates	Methotrexate	Agranulocytosis
▪ Sulfonamide ▪ Salicylates ▪ Phenylbutazone	<u>Tolbutamide</u> (<u>Oral hypoglycemic agent</u>)	<u>Hypoglycemic shock</u>
▪ Salicylates	<u>Sulfonamide</u>	<u>Sulfonamide toxicity</u>
▪ Quinidine	<u>Digoxin</u>	<u>Digoxin toxicity</u>
▪ Valproate	Phenytoin	Phenytoin toxicity
▪ Indomethacin & <u>Phenytoin</u>	<u>Warfarin</u>	<u>Bleeding</u>

(Ref: Bennett & Brown-11th; Tripathi-6th/22)

Q. Explain “plasma protein binding influences both pharmacodynamics & pharmacokinetics”. (DU-08J)

Ans.

Effects of plasma protein binding on pharmacodynamics:

1. If a drug is displaced from plasma protein, it would increase the unbound drug concentration and increase the effect.
2. Highly plasma protein-bound drug is displaced slowly, and thus acts slowly.
3. If a drug is displaced more from plasma protein, it would cause more toxic effect.

Effects of plasma protein binding on pharmacokinetics:

1. When the amount of unbound drug in plasma increases, the rate of elimination will increase.
2. More plasma protein bound drug has increased duration of action.
3. It helps to interpret the drug concentration measurement.
4. When the plasma protein is lower than normal, then total drug concentration will be lower but unbound concentration will not be affected.
5. Competitive binding of a drug with plasma protein can increase the serum concentration of another drug.

(Ref: Katzung-13th)

Volume of Distribution (Vd)

Q. Define volume of distribution. (CU-01M)

Q. What are the factors affecting volume of distribution?

Q. Short note: Volume of distribution. (DU-11Ju)

Ans.

Volume of distribution (Vd):

Definition: Volume of distribution (V_d) is defined as the virtual volume of plasma that would contain the total body content of the drug at a concentration equal to that in the plasma.

(Ref: Rang & Dale's-8th)

$$\text{Volume of distribution } (V_d) = \frac{\text{Total amount of drug}}{\text{Plasma concentration of drug}}$$

Factors influencing volume of distribution:

1. Lipid-water partition coefficient of the drugs.
2. pKa value of the drug.
3. Degree of plasma protein binding (PPB)
4. Affinity for different tissues.
5. Fat & lean body mass ratio (it can also vary with age, sex, obesity etc.)
6. Pathological condition such as CCF, CLD, uremia etc.

(Ref: Tripathi-6th. 19)

Nice to know

Concept of volume of distribution: The calculated parameter for the V_d has no direct physical equivalent; therefore, it is usually denoted the apparent V_d . A drug that is completely retained in the plasma compartment will have a V_d equal to the plasma volume (about 4% of body weight). The V_d of drugs that are normally bound to plasma proteins such as albumin can be altered by liver disease (through reduced protein synthesis) and kidney disease (through urinary protein loss). On the other hand, if a drug is avidly bound in peripheral tissues, the drug's concentration in plasma may drop to very low values even though the total amount in the body is large. As a result, the V_d may greatly exceed the total physical volume of the body. For example, 50,000 liters is the average V_d for the drug quinacrine in persons whose average physical body volume is 70 liters.

(Ref: Katzung & Trevor's-11th edition)

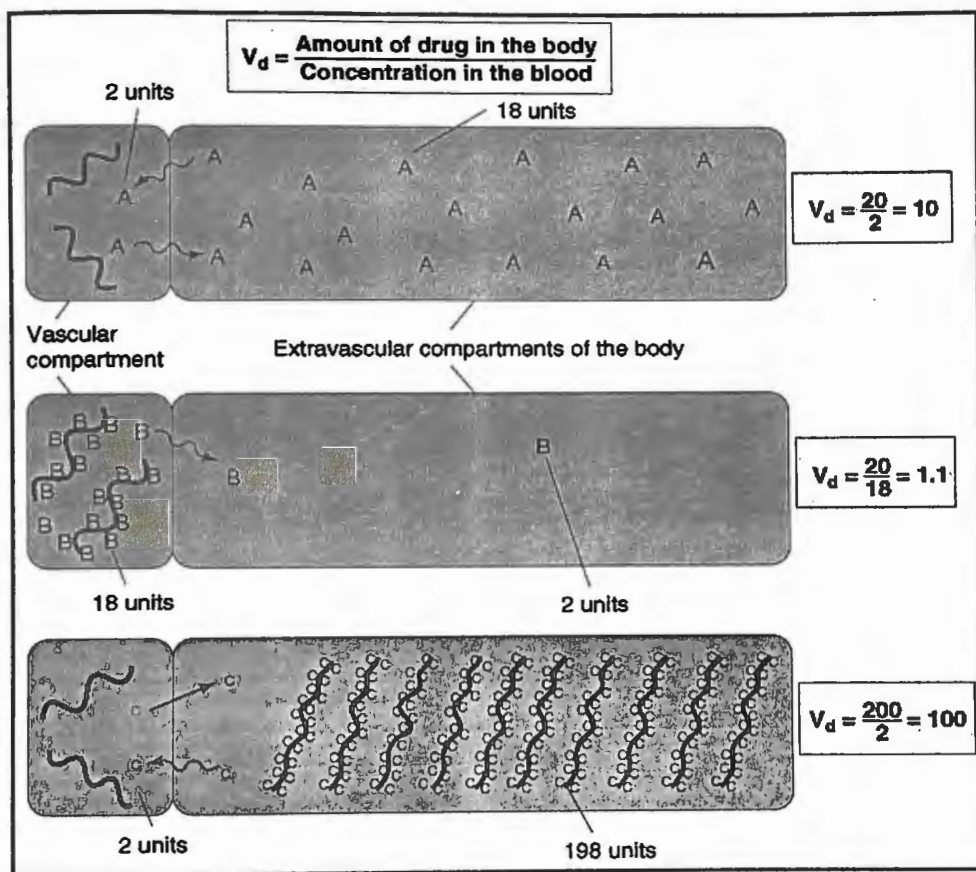


Fig. Effect of drug binding on volume of distribution. Drug A diffuses freely between the 2 compartments and does not bind to macromolecules (heavy wavy lines) in the vascular or the extravascular compartments of the hypothetical organism in the diagram. With 20 units of the drug in the body, the steady-state distribution leaves a blood concentration of 2 units. Drug B, on the other hand, binds avidly to proteins in the blood. At equilibrium, only 2 units of the total are present in the extravascular volume, leaving 18 units still in the blood. In each case, the total amount of drug in the body is the same (20 units), but the apparent volumes of distribution are very different. Drug C is avidly bound to molecules in peripheral tissues, so that a larger total dose (200 units) is required to achieve measurable plasma concentrations. At equilibrium, 198 units are found in the peripheral tissues and only 2 units in the plasma, so that the calculated volume of distribution is greater than the physical volume of the system.

(Ref: Katzung & Trevor's-11th edition)

Q. Explain the effect of a large V_d on the half-life of a drug.

Ans.

Effect of a large V_d on the half-life of a drug: A large V_d has an important influence on the half-life of a drug, because drug elimination depends on the amount of drug delivered to the liver or kidney (or other organs where metabolism occurs) per unit of time. Delivery of drug to the organs of elimination depends not only on blood flow, but also on the fraction of the drug in the plasma. If the V_d for a drug is large, most of the drug is in the extraplasmaic space and is unavailable to the excretory organs. Therefore, any factor that increases the volume of distribution can lead to an increase in the half-life and extend the duration of action of the drug.

(Ref: Lippincott's-6th/12)

Q. Name 2 drugs with large volume of distribution.

Q. Name 2 drugs with low volume of distribution.

Ans.

Drugs with high V_d	Drugs with low V_d
1. Fluoxetine (2500 litres)	1. Frusemide (7.7 L)
2. Imipramine (1600 L)	2. Aspirin (11 L)
3. Nortriptyline (1300 L)	3. Indomethacin
4. Digoxin	4. Salicylic acid
5. Chloroquine	5. Valproic acid
	6. Amoxicillin
	6. Ampicillin
	7. Gentamicin

Q. What information will you get if it is said that V_d of a drug is either low or high? (DU-98M)

Q. What do you mean by V_d of nortriptyline 1300 litres?

Q. Write the significance of high volume of distribution.

Q. Write the significances of low volume of distribution.

Ans.

Significance of high volume of distribution / significances of low volume of distribution

Significance of high V_d (eg, 1300L)	Significance of low V_d (eg, 5L)
1. The drug is almost confined to the tissue, ie, it has high tissue binding.	1. The drug is almost confined to the blood, ie, it has less tissue binding.
2. It has least plasma protein binding	2. It has high plasma protein binding
3. Its distribution is high	3. Its distribution is low
4. Prolonged half life	4. Short half life
5. Its action is wide	5. Its action is restricted
6. It is more lipid soluble	6. It is more water soluble
7. It can be given orally	7. It should be given by injection
8. It can cross BBB	8. It cannot cross BBB
9. It has CNS effect	9. It has no CNS effect
10. Action is rapid	10. Action is delayed
11. Adverse effects are more	11. Adverse effects are less.
12. In case of poisoning, the drug cannot be easily removed by hemodialysis.	12. In case of poisoning, the drug can be easily removed by hemodialysis.

Drug Metabolism (Biotransformation)

Q. What do you mean by drug metabolism? (DU-11Ja)

Q. Define biotransformation. (DU-17M; CU-16J,15J, RU-09/07/05J; SU-08Ju,07J,06S)

Ans.

Biotransformation: Molecular alteration of a drug in the body to make it inactive and suitable for excretion from the body is called biotransformation (drug metabolism). The process of metabolism transforms lipophilic drugs into more polar readily excretable products.

Nice to know

Why drug metabolism is necessary: Renal excretion plays a pivotal role in terminating the biologic activity of some drugs, particularly those that are polar and water-soluble. However, most drugs are relatively lipid soluble and are not excreted easily. Consequently, most drugs would have a prolonged duration of action if termination of their action depended solely on renal excretion.

An alternative process that can lead to the termination or alteration of biologic activity is metabolism. In general, lipid soluble xenobiotics are transformed to more polar and hence more readily excreted products. The role that metabolism plays in the inactivation of lipid-soluble drugs can be quite dramatic. For example, lipophilic barbiturates such as thiopental and pentobarbital would have extremely long half-lives if it were not for their metabolic conversion to more water-soluble compounds.

(Ref: Katzung-13th/15th)

Q. Name the organs /organelles /sites of biotransformation. (SU-07J,06M/J)

Ans.

Organs where biotransformation occurs:

Degree of biotransformation	Organs
Main organ	▪ Liver (about 99% of biotransformation occurs in the liver)
Intermediate degree	▪ Lungs ▪ Kidneys ▪ Intestinal mucosa ▪ Skin
Lower degree	▪ Blood ▪ Brain ▪ Gonad ▪ Eye ▪ Adrenal glands ▪ Placenta ▪ Spleen ▪ Leukocytes ▪ Spleen ▪ Cardiac muscles

Organelles where biotransformation occurs:

- Smooth endoplasmic reticulum (mainly)
- Mitochondria
- Cytoplasm.

(Ref: Misbahuddin-5th/127)

Q. What are the aims & objectives of biotransformation? (DU-06S, CU-15J,07Ju; SU-16J,14J,11Ju,08J,07J)

Q. Discuss the changes in biological activity of drugs caused by biotransformation. (DU-16Ju,11Ja)

- Q. Write down the consequences of biotransformation? (DU-17M,13Ju,06S, CU-07J,06S, RU-14J)
 Q. Enumerate the functions / importance of biotransformation of drugs. (SU-07J/Ju)
 Q. Explain the purposes of biotransformation? (RU-09J)
 Q. List the importance of drug biotransformation? (SU-12Ju)

Ans.

Aims / objectives / purposes / consequences / changes of drug biotransformation / metabolism:

A. Pharmacokinetic property/ consequence: Drug metabolism often converts lipophilic drugs into *more readily excreted* polar products.

B. Pharmacodynamic property / consequences: Alters biological activity of the drugs.

1. Active drug is converted into inactive metabolite:

- Morphine → Morphine-3-glucoronide

2. Active drug is converted into another active metabolite: (Prolongs the drug action)

- Codeine → Morphine
- Morphine → Morphine-6-glucoronide
- Paracetamol → N-Acetyl-p-benzoquinone imine
- Amitriptyline → Nortriptyline
- Chloroquine → Hydroxy-chloroquine
- Diazepam → Oxazepam
- Allopurinol → Alloxanthine
- Digitoxin → Digoxin
- Imipramine → Desipramine

3. Inactive drug (prodrug) is converted into active drug:

- Levodopa → Dopamine
- Talampicillin → Ampicillin

4. Toxic drug is converted into less toxic or non-toxic drug:

- Morphine → Morphine-3-glucoronide

5. Non-toxic drug is converted into toxic drug:

- Parathion → Parathionoxone
- Malathion → Malathionoxone

(Ref: Bennett & Brown-11th)

Q. Define prodrug? (DU-13Ju,12Ju,11Ju, CU-13Ju,05J, RU-13Ju, SU-17J,16Ju,15J,14J,09J)

Q. What are the purposes/objectives of using prodrug? (DU-17J, RU-13Ju, SU-14J,09J)

Q. Explain the clinical importance of prodrug. (DU-12Ju,04S, CU-05J, SU-17M,11Ju,04M)

Q. Write down the advantage and disadvantage of prodrug administration. (CU-13Ju,12Ju)

Q. What is the utility/significance/importance of prodrug? (DU-13Ju, CU-06J, SU-15J)

Q. Give four/two examples of prodrug. (DU-17J,13Ju, SU-16Ju)

Q. Short note: Prodrug. (CU-06J, RU-17J, SU-16J)

Ans.

Prodrug:

Definition: An inactive precursor chemical that is readily absorbed & distributed & then converted to the active drug by biological process inside the body is called a prodrug.

(Ref: Katzung-13th/7)

Definition: "There are some chemical substances which do not produce pharmacological effects until they are chemically altered within the body. Such chemical substances are called prodrug".

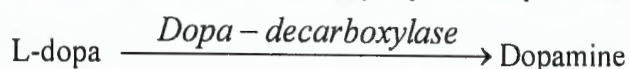
(Ref: Misbahuddin-5th/5)

Significance / purposes/ advantage/ clinical importance: Prodrugs are used for the following purposes-

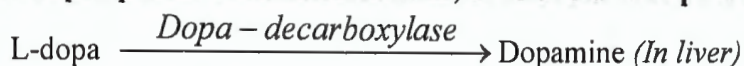
1. To increase absorption, eg, →

Prodrug	Active	Advantage
Talampicillin	Ampicillin	↑ absorption
Levodopa	Dopamine	Levodopa but not dopamine can cross the BBB.
Dipiverine HCl	Adrenaline	High lipid solubility of dipiverine gives the drug 147 times more penetrance than adrenaline, when applied over the eye for the treatment of glaucoma.

2. **To reduce unexpected tissue damage**, eg, the cytotoxic drug cyclophosphamide becomes active after it has been metabolized in the liver & can be taken orally without causing injury to the GIT.
3. **To modify route of administration**: Fosphenytoin is a more soluble prodrug of phenytoin and is rapidly converted to phenytoin in the blood. Phenytoin should never be given IM because it can cause tissue damage and necrosis. Fosphenytoin is the drug of choice and standard of care for IV and IM administration.
4. **To increase bioavailability of drug at receptor sites**: Carbidopa (prodrug) is used with levodopa to prevent its breakdown by inhibiting peripheral dopa decarboxylase.



5. **To prevent peripheral biotransformation, or to avoid first-pass metabolism** eg,



6. **To reduce offensive odor of the drugs**, eg, Chloramphenicol palmitate prodrug is used because of the bitter taste of chloramphenicol.
7. **To increase the specificity of drug action at desired site**: Zidovudine is used in the form of zidovudine triphosphate.

8. **To modify duration of action.**

Disadvantage of prodrug administration:

1. Requires activation before pharmaceutical action.

Q. Write down the prodrugs with their active metabolites. (SU-09J,05M, CU-01M)

Q. Write down three/four/five prodrugs with their active metabolites & uses. (SU-17J,14J,06S)

Ans.

Examples of prodrug:

Prodrug	Active drug
Levodopa	Dopamine
Talampicillin	Ampicillin
α-Methyldopa	α-Methyl Noradrenaline
Prednisone	Prednisolone
Sulfasalazine	5-Amino salicylic acid
Cyclophosphamide	Aldophosphamide, Phosphoramidate mustard
Acyclovir	Acyclovir triphosphate
Zidovudin	Zidovudin triphosphate
Proguanil	Cycloguanil
Cholecalciferol	1-α-Cholecalciferol
Sulindac	Sulindac sulfide

- Q. Name the different reactions involved in biotransformation of drug with examples. (DU-10J)
- Q. Discuss the phases of biotransformation. (CU-15J, 09J, 06S, SU-14J, 06J)
- Q. Explain phase-I biotransformation with example. (SU-10J)
- Q. Write down about phase-I & phase-II reactions of biotransformation. (CU-12Ju, RU-07/05J, SU-06S)
- Q. What is phase-II reaction? What are the reactions in phase-II reaction? (DU-17M, CU-16Ju; RU-07J; SU-12Ju, 11Ju, 10J, 08Ju, 07J, 06S)
- Q. Describe the synthetic phase of biotransformation with examples. (SU-17J)
- Q. Outline phase-II biotransformation. Mention its importance. (SU-17M, 15Ju, 14Ju, 13Ju, 12J)
- Q. Mention different conjugation reactions with examples. (DU-13Ju, RU-14J, 05J; SU-06J)
- Q. How does conjugation reaction take place? Mention their outcome. (RU-07J, SU-08J)
- Q. Short note: Phase-II biotransformation. (SU-15J)

ARS.

Reactions / processes of drug biotransformation

Phase I / Non-synthetic phase / Non-conjugation phase: Phase I reactions usually convert the parent drug to a more polar metabolite by introducing or unmasking a functional group ($-OH$, $-NH_2$, $-SH$). Often these metabolites are inactive, although in some instances activity is only modified or even enhanced. There will be no new product.

Criteria of phase I:

1. The phase is catabolic in nature.
2. The drug may lose its activity.
3. The drug may retain its activity.
4. The drug may gain its activity.
5. Lipid solubility of the drug is decreased.
6. Many phase-I products are not eliminated rapidly due to insufficient polarity & go to phase-II phase subsequently. If phase I metabolites are sufficiently polar, they may be readily excreted without going to phase-II reaction.

Reactions of phase I:

Types	Microsomal	Non-microsomal
1. Oxidation	Codeine $\rightarrow$ Morphine	Adrenaline/Noradrenaline $\rightarrow$ Vanillyl Mandelic Acid (VMA)
2. Reduction	Cortisone $\rightarrow$ Hydrocortisone	Acetic acid $\rightarrow$ Ethanal $\rightarrow$ Ethanol
3. Hydrolysis	Pethidine (Mepiridine) $\rightarrow$ Mepiridinic acid	Acetylcholine $\rightarrow$ Acetate + Choline

Phase II/ Synthetic / Conjugation reaction: Parent drugs or phase I metabolites conjugate with endogenous substrates such as glucuronic acid, sulfuric acid, acetic acid, amino acid etc. to produce a drug-conjugate complex which is polar and readily excretable through the kidney.

Criteria of phase II:

1. The phase is anabolic in nature.
2. Drug loses its activity.
3. Lipid solubility is totally destroyed.
4. Drugs become polar.
5. Drugs are readily excretable through the kidney or bile.
6. Phase II reaction requires high energy.

Reactions of phase II:

A. Microsomal

1. **Glucuronidation:** Glucuronic acid conjugation

morphine, Paracetamol, Steroid

B. Non-microsomal

1. **Sulfation:** Sulphate conjugation : OCP, Paracetamol, Steroid
2. **Amino acid or glycine conjugation** : Salicylate, Benzoic Acid
3. **Acetylation:** Acetyl Conjugation : Sulfonamides, Procainamide, INH
4. **Methylation:** Methyl Conjugation : N/A
5. **Mercapturic acid synthesis**

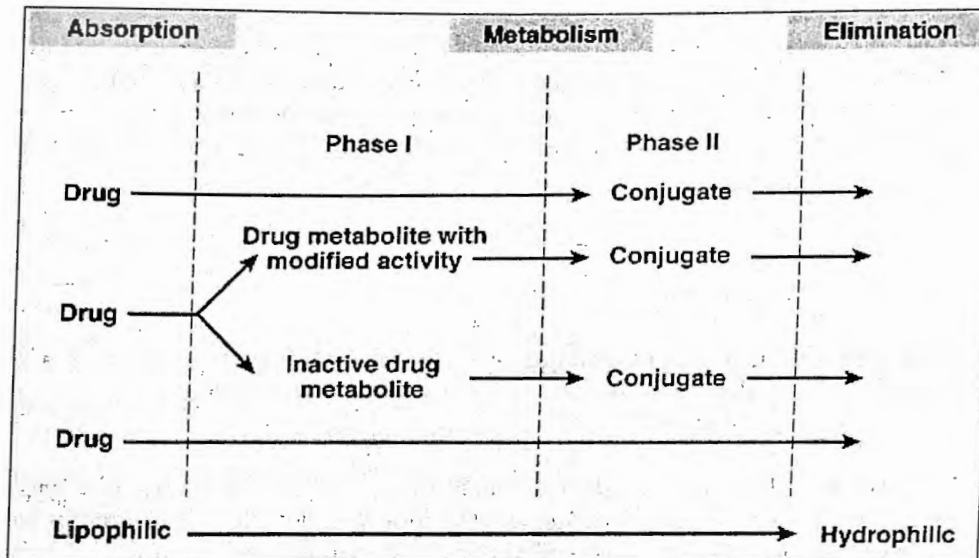
(Ref- Misbahuddin-5th/130-134)

Fig. Phase I and phase II reactions, and direct elimination, in drug biotransformation. Phase II reactions may also precede phase I reactions.

(Ref: Katzung-13th/57)

Q. List the enzymes involved in biotransformation. (SU-13J)

Q. What are the enzymes used /required in phase I reactions?

Ans.

Enzymes of biotransformation

A. Microsomal enzymes: These are located on the smooth endoplasmic reticulum, mainly in the liver. However, activity is also present in the kidneys, gastrointestinal tract, skin, brain, spleen etc.

1. Mixed function oxidase (MFO) / Monooxygenases:
 - Cytochrome P₄₅₀ (a haemoprotein)
 - NADPH-Cytochrome P₄₅₀ reductase (a flavoprotein)
2. Amine oxidase
3. Epoxide hydratase
4. Glucoronyl transferases
5. Hydroxylase
6. Dehydrogenase

B. Non-microsomal enzymes: They are present on the cytoplasm & mitochondria of hepatic cells. They are found mostly in the liver, plasma, kidney & other tissues. Less lipid soluble drugs are metabolized which cannot cross the microsomal membrane.

1. Amylase
2. Esterase
3. Amidase
4. Dehydrogenase- Alcohol and aldehyde dehydrogenases.
5. Hydrolase
6. Reductase

6. Sulfotransferase
7. Transferases- Acetyl transferase, Methyl transferase, Catechol-O-Methyl Transferase (COMT)
7. Glutathion-s-transferase
8. Monoamine oxidase (MAO)

(Ref- Misbahuddin-5th/128,129)

Q. Short note: Hepatic microsomal enzyme system. (CU-06J)

Ans.

Hepatic microsomal enzyme system: Many drug-metabolizing enzymes are located in the lipophilic endoplasmic reticulum membranes of the liver and other tissues. When these lamellar membranes are isolated by homogenization and fractionation of the cell, they re-form into vesicles called **microsomes**. Microsomes contain the important class of enzymes known as microsomal enzyme system.

Microsomal enzymes: Write from above.

(Ref: Katzung-13th/58)

Q. What do you mean by microsomal biotransformation? (SU-10J)

Ans.

Microsomal biotransformation: It is the fundamental process for chemical alteration of a drug to make it suitable for excretion from the body under the influence of microsomal biotransforming enzymes.

Nice to know

- *Most of the oxidation, reduction, hydrolysis & glucuronidation are catalyzed by microsomal enzymes. Microsomal enzymes are inducible by drugs. The non-microsomal enzymes are not inducible, but many of them show genetic polymorphism (acetyl transferase, Pseudocholinesterase).*
- *Microsomal & non-microsomal enzymes are deficit in the newborn, especially premature newborn. So, they are more susceptible to many drug toxicities (e.g. chloramphenicol, opioids). The deficit is mainly in Glucuronidation & it takes about 3 months to make up.*
- *Oxidation reaction (Phase I): Oxidations are the most important drug metabolizing reactions. This reaction involves addition of oxygen (or negatively charged radical) or removal of hydrogen (or positively charged radical). Various oxidation reactions are as follows:*
 1. Hydroxylation
 2. Dealkylation
 3. Deamination
 4. Desulfuration
- *Microsomal oxidations require —*
 1. P450
 2. P450 reductase
 3. NADPH
 4. Molecular O₂

Viva Q. Name some drugs that are metabolized by acetylation.

Ans.

Drug metabolized by acetylation:

1. Isoniazid
2. Sulfonamides
3. Acebutolol
4. Procainamide
5. Hydralazine
6. Phenelzine
7. Nitrazepam

(Ref: Goodman & Gilman's-12th)

Q. What is entero-hepatic recycling? What is its importance?

Q. Enumerate the drugs that undergo entero-hepatic recycling. (CU-13J)

Q. Outline the clinical significance of entero-hepatic recycling. (CU-13J, 10Ju)

Q. Outline therapeutic importance of biliary excretion. (SU-15Ju)

Q. Short note: Entero-hepatic circulation and its clinical implications. (RU-14Ju)

Ans.

Entero-hepatic recycling: Glucuronidation increases the molecular weight of the drugs which favours its excretion in bile. Excreted drugs through bile can be metabolized by normal flora of intestine. The drugs get free again & reabsorb again & undergo the same fate. This is called entero-hepatic recycling.

Mechanism: Glucuronidation of drug → Excretion of drug through bile → Detachment of the drug from Glucuronic acid by glucuronidase by normal floral bacteria → Reabsorption of the drug → Metabolism →→→ the cycle repeats.

Drugs that undergo entero-hepatic recycling

1. Oral contraceptive pills (OCP)
2. Tetracycline

Clinical significance of entero-hepatic recycling:

1. Increases the life time of the drug and thus small amount of drug can cause prolong action through this cycle, eg, OCP.
2. Recycling causes less frequent dosing eg, OCP, Phenolphthalein.
3. Excretion of some drugs through bile (eg, tetracycline) can be used to treat the infection of biliary tree or dysentery.
4. Sometimes it may cause drug toxicity.

Q. What factors modify hepatic biotransformation of drug? (CU-12J, 11J, 09J)

Q. Enumerate factors modifying drug biotransformation? (DU-06S; CU-16Ju/J; RU-04M; SU-07Ju)

Q. Explain how age modifies drug biotransformation? (SU-08Ju, RU-06M)

Q. How genetic factor modifies drug biotransformation? (RU-06M; SU-08Ju)

Ans

Factors modifying drug biotransformation:

1. **Age:**

- **In extreme of ages** (too young & too old), there is decreased enzyme activity.
- **In premature babies**, enzyme system (mainly enzymes for phase II reactions & specially glucuronidation) is poorly developed → less biotransformation → development of toxicity. For example, administration of chloramphenicol in the premature babies causes Gray baby syndrome.
- **In elderly**, enzymes of phase I reactions are less active, kidney & liver functions are impaired → less biotransformation & less drug elimination → development of toxicity. For example, conventional doses of streptomycin may cause adverse effects. Conventional doses of benzodiazepines may cause CNS depression.
- **In young adult**, enzyme system is well developed → proper biotransformation → tolerate conventional adult doses.

2. **Sex:** Testosterone is an enzyme inducer and estradiol is an enzyme inhibitor. So, males have greater ability to metabolize drugs than female.

3. **Race:** In 10% American black, administration of oxidative drugs (primaquine) causes hemolytic anemia.

4. **Nutritional status:** Mineral (eg, calcium, copper, selenium), vitamin (eg, vitamin C) and protein deficiency causes decreased activity of enzymes of biotransformation.

5. **Genetic factors:** Genetic deficiency of drug-metabolizing enzymes cause less biotransformation & produce toxicities. For example,

- **Succinylcholine** (a muscle relaxant used in anesthesia) causes muscle paralysis required during surgery. It is metabolized by the enzyme **pseudocholinesterase** and then, its action is terminated. If the enzyme pseudocholinesterase is genetically absent or deficient or abnormal, then there will be less biotransformation and prolonged action of the drug. This may lead to respiratory muscle paralysis & death.
- Some people genetically possess high level of **acetyl transferase** referred as rapid acetylator and vice versa as slow acetylator.
 - **Rapid acetylator:** Isoniazid drug → ↑Acetylation → ↑Biotransformation → Require large dose.
 - **Slow acetylator:** Isoniazid → ↓Acetylation of isoniazid → ↓Metabolism & ↑isoniazid bioavailability → ↑Pyridoxine excretion → causes **peripheral neuropathy** → so, low dose of isoniazid is given.

6. **Pathological condition:**

- | | |
|--|-----------------------|
| <ul style="list-style-type: none"> ▪ Liver disease ▪ Nephrotic syndrome ▪ Hypothyroidism ▪ Hypopituitarism | → ↓ Biotransformation |
|--|-----------------------|
- Hyperthyroidism → ↑drug biotransformation
 - Kidney disease → ↓insulin biotransformation
 - Pulmonary disease → ↓isoprenaline biotransformation

7. **Environmental factors:**

- **In urban people:** ↑Hydrocarbon production → induces microsomal enzymes → ↑drug biotransformation.
- **People living in high altitude:** → ↓microsomal enzymes → ↓drug biotransformation.
- **Smoking** → benzo(α)pyrene of cigarette induces microsomal enzymes → ↑drug biotransformation, eg, theophylline, imipramine.
- **Alcoholism:**
 - Acute alcohol intake → ↓drug biotransformation.
 - Chronic alcohol intake → ↑drug biotransformation.

8. **Rate of absorption:** Increased rate of absorption permits higher concentration of a drug at the active centers of enzymes involved in its metabolism.

9. **Transfer across cell membranes:** Most of the drug metabolizing enzymes are located intracellularly. So more lipid soluble drugs enter the cell faster than water soluble drugs and are metabolized earlier.

10. **Protein binding:** Extracellular and intracellular protein binding reduces drug metabolism.

11. **Excretion:** The more rapid the excretion of a foreign compound or its product, the less is the opportunity for interaction of the compound or product with critical target molecules in the organism.

12. **Circadian rhythms:** This variation is thought to be largely due to the result of a variation of levels of the enzymes of the P450 monooxygenase with the variation in the endocrine functions in different times of day and night.

13. **Enzyme induction:** Causes increased metabolism of drug.

14. **Enzyme inhibition:** Causes decreased metabolism of drug.

Q. Define enzyme induction. (DU-12Ju,10J; CU-07Ju; RU-10Ju,06J,01M)

Q. Short note: Enzyme induction. (CU-04M, RU-15Ju, SU-17J)

Q. Explain enzyme induction with examples. (DU-16Ju, CU-07J)

Ans.

Enzyme induction:

Definition: Enzyme induction is the process of increasing synthesis and activity of hepatic microsomal enzymes by repeated administration of inducing drug/agent. Enzyme induction results in increased metabolism and usually in a decrease in the pharmacologic action of the inducer and also of co-administered drugs.

Mechanism of induction: Enzyme inducers interact with DNA & increase the synthesis of microsomal enzymes, especially cytochrome P450 & Glucuronyl transferase. As a result, rate of drug metabolism of inducing drug &/ or the co-administered drugs is increased.

Properties of induction:

1. Highly lipid-soluble drugs that have long half life usually induce enzymes.
2. Enzyme induction increases the rate of metabolism by 2-4 folds.
3. Enzyme induction is a chronic process (where enzyme inhibition is an acute process & may occur within hours).
4. Single dose cannot induce drug metabolism. It takes 4 -14 days to reach the peak & is maintained till the inducing drug is being given.
5. The enzyme returns to their original value over 1-3 weeks.

Q. State with examples the clinical significances of enzyme induction. (RU-09J)

Q. Mention the clinical significance of enzyme induction. (DU-12Ju,10J,07M; CU-07J,05S; RU-10Ju,06J; SU-13J)

Q. Enumerate the importance of stimulation of hepatic drug metabolizing enzyme. (CU-17M)

Ans.

Significance of enzyme induction:

1. Therapeutic failure of the primary drug:

- Failure of contraception: If an OCP user female is treated with Rifampicin (an anti-TB drug), increased metabolism of OCP will occur due to enzyme inducing activity of rifampicin. So, there will be contraception failure.
- Intermittent use of an inducer may interfere the drug concentration of other regular medications; e.g. oral hypoglycemic drugs, anti-hypertensive drugs, anti-epileptic drugs etc.
- Treatment: Dose adjustment of regular therapy.

2. Development of tolerance: Repeated administration of a drug may induce its own metabolism, a process called autoinduction. This autoinduction causes development of tolerance. Drugs which develop tolerance by enzyme induction are rifampicin, carbamazepine, phenobarbitone, etc.

Mechanism: Phenobarbitone → Auto induction → Phenobarbitone increases its own biotransforming enzyme → ↑Metabolism of Phenobarbitone → Phenobarbitone tolerance (Pharmacokinetic tolerance)

3. Development of drug toxicity: Induction may cause increased metabolism of a drug to a toxic metabolite; e.g. Rifampicin → Enzyme induction → ↑Metabolism of paracetamol to a more toxic intermediate NABQI which binds with cell protein → Hepatotoxicity.

4. Disease may result by induction: e.g. Antiepileptic drugs increase the breakdown of dietary and endogenous vitamin-D, producing an inactive metabolite. So, a vitamin D deficiency state results which can cause osteomalacia.

Metabolism of some endogenous substances are also increased; e.g. steroids, bilirubin.

Enzyme induction causes individual variation of drug response.

(Ref: Bennett & Brown-11th; Tripathi-6th/ 27,28)

Q. Name some enzyme inducers. (DU-12Ju, RU-06J)

Q. Name four enzyme inducing drugs with clinical significance. (DU-07M; RU-13Ju)

Q. List four enzyme that stimulate hepatic microsomal enzyme. (RU-11Ju)

Ans.

Enzyme inducing drugs:

1. Rifampicin
2. Barbiturates (eg, phenobarbitone)
3. Phenytoin
4. Phenylbutazone
5. Carbamazepine
6. Griseofulvin
7. Testosterone
8. Hydrocarbon

Inducer	Drug whose metabolism is induced	Effect
Rifampicin	Oral contraceptives	Failure of contraception
Phenobarbitone	Oral contraceptives	Failure of contraception
Phenytoin	Oral contraceptives	Failure of contraception
Rifampicin	Warfarin	Decreased anticoagulation
Phenobarbitone	Warfarin	Decreased anticoagulation
Phenytoin	Warfarin	Decreased anticoagulation
Phenylbutazone	Warfarin	Decreased anticoagulation
Phenobarbitone	Chloramphenicol (in premature baby)	No Gray baby syndrome

(Ref: Katzung-13th/70)

Q. What is enzyme inhibition? (RU-06J)

Ans.

Enzyme inhibition: Enzyme inhibition means inhibition of drug biotransforming enzyme, particularly cytochrome P450 microsomal enzymes.

Enzyme inhibition is an acute process. It occurs faster (within minutes) compared with enzyme induction. Single dose can inhibit the enzyme.

Important examples of enzyme inhibition

Inhibitor	Drug whose metabolism is inhibited	Effect
Cimetidine	Warfarin	Hemorrhage
Chloramphenicol	Warfarin	Hemorrhage
Metronidazole	Tolbutamide	Hypoglycemic shock
Allopurinol	Azothioprin	Bone marrow suppression

Q. Name some enzyme inhibitors. (DU-12Ju, RU-04J)

Q. Name hepatic enzyme inhibitors. (SU-04M)

Q. List four/five drugs that inhibit hepatic microsomal enzyme. (DU-07M, RU-11Ju)

Ans.

Enzyme inhibitors:

Inhibitor	Drug Whose Metabolism Is Inhibited
Allopurinol, chloramphenicol, isoniazid	Antipyrine, dicumarol, probenecid, tolbutamide
Cimetidine	Chlordiazepoxide, diazepam, warfarin, others
Dicumarol	Phenytoin
Disulfiram	Antipyrine, ethanol, phenytoin, warfarin
Ketoconazole	Cyclosporine, astemizole, terfenadine
Nortriptyline	Antipyrine
Oral contraceptives	Antipyrine
Phenylbutazone	Phenytoin, tolbutamide
Secobarbital	Secobarbital

(Ref: Katzung-13th/70)

- Q. State with examples the clinical significances of enzyme inhibition. (RU-09J)
 Q. Mention the clinical significance of enzyme inhibition. (DU-07M)
 Q. Mention the clinical significance of microsomal enzyme inhibition. (SU-17M)

Ans.

Significance of enzyme inhibition:

1. Enzyme inhibitors reduces metabolism of primary drug and thus effectiveness of primary drug is increased.
2. Decrease cost of therapy by decreasing the dose of the principle drug with the help of enzyme inhibitor.
 Example: Cyclosporine (immune-suppressive drug) used in graft operation in 2-3 divided doses for 2¹/₂ - 3 months. But with Ketoconazole (enzyme inhibitor) 1 dose of cyclosporine daily for 2¹/₂ - 3 months decreases 50% of cost.
3. There is increased chance of toxic effects of primary drug.

(Ref: Katzung-13th/59)

Drug Excretion

Q. Define drug excretion. (RU-07J, 05M, 04M)

Ans.

Drug excretion: It is the process by which a drug or its metabolites are eliminated from the body.

Q. Enumerate the processes of drug excretion with examples. (SU-14J, 10/09J, CU-11J, 06J)

Q. Lists the routes of drug elimination. (DU-06M; CU-09J, RU-09Ju, 07J, SU-04S)

Q. Mention minor routes of drug elimination with examples. (SU-15Ju)

Ans.

Routes of drug excretion:

Major routes	1. Kidney (MW < 300) ▪ All drugs except plasma protein bound drugs, eg, frusemide, pethidine. 2. Hepato-biliary process (MW > 300) ▪ Antimicrobials ▪ Benzodiazepines ▪ Tetracycline ▪ Chloramphenicol ▪ Cardiac glycosides ▪ Rifampicin ▪ Chlorpromazine 3. Gastro-intestinal ▪ Antacid ▪ BaSO₄ ▪ Aminoglycoside 4. Lungs ▪ Inhalation anesthetic (eg, halothane, N₂O, ether) ▪ Alcohol
Minor routes	1. Skin (sweat): Vitamin C, iron, griseofulvin 2. Saliva: Morphine, caffeine 3. Breast milk: Morphine, phenobarbitone, benzodiazepines, penicillin. 4. Vagina: Metronidazole → Used in trichomonas vaginitis 5. Tear: Rifampicin 6. Hair/nails: Mercury, arsenic, lead.

Q. Enumerate general principles of drug excretion through kidney. (DU-06M, CU-02M)

Q. Shortly explain the renal mechanism of drug excretion. (CU-09J, SU-14J, 10/09J, DU-06M; RU-07J)

Q. How does kidney handle the drug metabolites? (RU-07J)

Ans.

General principles of drug excretion through kidney: Renal excretion involves following 3 basic mechanisms-

1. Glomerular filtration (passive process)
2. Tubular secretion (active process)
3. Tubular reabsorption (active + passive process)

$$\text{Net renal excretion} = (\text{Glomerular filtration} + \text{Tubular secretion}) - \text{Tubular reabsorption}$$

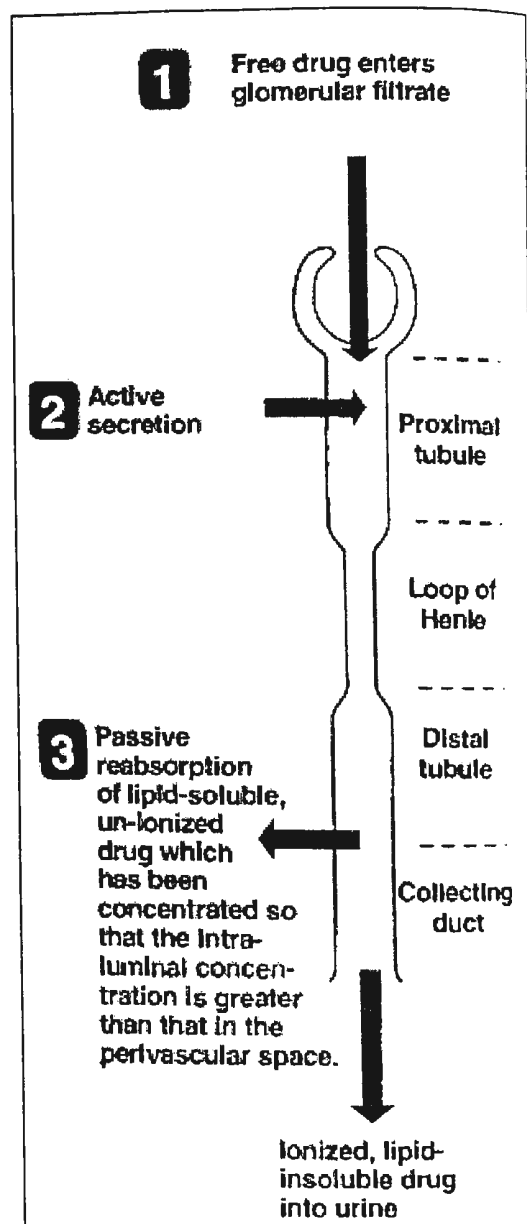
A. Glomerular filtration (GF): GF depends on-

1. **Molecular weight of the drug:** Drugs with MW <10,000 Dalton are easily filtered. Drugs with MW >50,000 Dalton are not filtered except heparin, dextran, protein hormone.
2. **Plasma protein binding (PPB):** Only free drugs are filtered through the glomerular membrane. Plasma albumin (MW 68000) is almost completely impermeable, but most drugs-with the exception of macromolecules such as **heparin**- cross the barrier freely. If a drug binds appreciably to plasma albumin, its concentration in the filtrate will be less than the total plasma concentration. If, like **warfarin**, a drug is approximately 98% bound to albumin, the concentration in the filtrate is only 2% of that in plasma, and clearance by filtration is correspondingly reduced.
3. **Concentration of drug in plasma**
4. **Renal blood flow:** In shock → ↓renal blood flow → ↓drug excretion.
5. **GFR:** Congestive cardiac failure, renal failure → ↓GFR → ↓drug excretion.
6. **Polarity of drug:**
 - Charged drug → slowly filtered.
 - Neutral drug → rapidly filtered.

B. Active tubular secretion: Tubular secretion is an **active process**. The cells of the proximal convoluted tubule actively transport drugs from the plasma into the lumen of the tubule. There are at least two types of transport systems-

1. **Acidic/anionic transport protein:** Transport acidic drugs (eg, metabolites of glycine, sulfate or glucuronic acid conjugates). Unchanged drugs such as penicillin can also be secreted.
2. **Basic/cationic transport protein:** Transport basic drugs (eg, morphine, amiloride, histamine, ethambutol, hexamethonium, catecholamines etc.).

Fig. Urinary elimination of drugs and metabolites by glomerular filtration and/or tubular secretion and reabsorption.



C. Tubular reabsorption: The reabsorption of drug from the lumen of the distal convoluted tubules into the plasma occurs either by simple diffusion or by **active transport**. Most drugs are reabsorbed by simple diffusion. Passive tubular reabsorption delays drug excretion. Extent of reabsorption depends on-

1. **Lipid solubility:** Lipid soluble drugs are more reabsorbed. Water soluble drugs are more excreted.

2. **Degree of ionization/ pH of drugs:**

- Acidic drug in acidic urine → Less ionization → More lipid soluble → More reabsorbed.
- Alkaline drug in alkaline urine → Less ionization → More lipid soluble → More reabsorbed.
- Acidic drug in alkaline urine → More ionization → Less lipid soluble → More excreted.
- Alkaline drug in acidic urine → More ionization → Less lipid soluble → More excreted.

(Ref: Misbahuddin-5th/139,140)

Q. Enumerate the factors that can influence drug elimination/excretion. (CU-13Ju, SU-15Ju)

Q. Mention the factors modifying renal excretion of drug. (DU-07M, CU-15Ju, 11J, 09Ju, 07J, RU-05M)

Q. Enumerate factors that can modify glomerular filtration and tubular secretion. (CU-06S)

Q. Explain how urinary pH influences / modify drug excretion? (DU-06M; CU-14Ju, SU-12Ju, 06S; RU-17J, 14Ju, 13Ju)

Q. Explain the role of pH of media in drug excretion with example. (SU-13J)

Ans.

Factors modifying renal excretion of drug:

A. **Factors related to drug:**

1. **Molecular weight of the drug:** Drugs with MW <10,000 Dalton are easily filtered. Drugs with MW >50,000 Dalton are not filtered except heparin, dextran, protein hormone.

2. **Plasma protein binding (PPB):** Only free drugs are filtered through the glomerular membrane. If a drug (i.e. warfarin) is approximately 98% bound to plasma albumin, the concentration in the filtrate is only 2% of that in plasma and clearance by filtration simultaneously reduced.

3. **Concentration of drug in plasma**

4. **Drug interaction at the level of tubular secretion:** The tubular secretion of drug (being an active process) can be suppressed by a competing substance; e.g.

Probenecid + penicillin: Probenecid competes with penicillin for secretion into renal tubule and thus suppresses the secretion of penicillin. As a result, the excretion of penicillin is decreased and the action of penicillin is prolonged.

5. **Polarity of drug:**

- Charged drug → slowly filtered.
- Neutral drug → rapidly filtered.

6. **Lipid solubility:** More lipid soluble drugs are more reabsorbed. More water soluble drugs are more excreted.

7. **Degree of ionization/ pH of drugs:**

- Acidic drug in acidic urine → Less ionization → More lipid soluble → More reabsorbed.
- Alkaline drug in alkaline urine → Less ionization → More lipid soluble → More reabsorbed.
- Acidic drug in alkaline urine → More ionization → Less lipid soluble → More excreted.
- Alkaline drug in acidic urine → More ionization → Less lipid soluble → More excreted.

B. **Factors related to kidney:**

1. **Renal blood flow:** In shock → ↓renal blood flow → ↓drug excretion.

2. **GFR:** Congestive cardiac failure, renal failure → ↓GFR → ↓drug excretion.

(Ref: Tripathi-6th 30, 31)

Q. How renal excretion of a drug can be increased? (SU-05J, 04S)

Q. How excretion of an acidic drug can be enhanced? (CU-06J)

Q. How urinary excretion of a phenobarbitone can be increased? (SU-00S)

Q. Explain the Manipulation of urine pH in drug overdose. (DU-16Ju)

Ans.

Renal excretion of a drug can be increased by:

1. By changing the pH of the urine:
 - Acidic drug (eg, phenobarbitone) can be excreted more by making the urine alkaline (as with NaHCO_3).
 - Alkaline drug (eg, morphine, pethidine) can be excreted more by making the urine acidic (as with NH_4Cl).
2. Diuretics: Diuretics increase excretion of drugs.
3. Intake of plenty of water causes excretion of drugs by diuresis.
4. IV infusion of normal saline, plasma or blood cause excretion of drugs by diuresis.

Q. What factors modify the drug excretion through lungs? (CU-08Ju)

Ans.

Factors modifying drug excretion through lungs:

1. **Lipid solubility of the drug in blood:** "The Blood : Gas partition coefficient" is a useful indicator of solubility & defines the relative affinity of an anesthetic for the blood compared with that of inspired gas. Inhaled anesthetic that are relatively insoluble in blood (i.e. low blood: gas partition coefficient) are eliminated at faster rate than the more soluble anesthetics.
2. **Lipid solubility of drug in tissues:** Anesthetics with higher lipid solubility continue to enter adipose tissue for hours & also leave it slowly.
3. **Pulmonary ventilation:** An increase in pulmonary ventilation is accompanied by only a slight increase in arterial tension of an anesthetic with low blood solubility or low coefficient but a significantly increase tension of agents with moderate to high blood solubility.
4. **Pulmonary blood flow:** $\uparrow$ Pulmonary blood flow $\rightarrow$ $\uparrow$ Pulmonary excretion.
5. **Alveolar exchange:** $\uparrow$ Alveolar exchange $\rightarrow$ $\uparrow$ Pulmonary excretion.

Q. Explain with examples how the action of a drug can be prolonged. (DU-16J; CU-14J, SU-14Ju,08Ju; RU-05M)**Q. How can you delay the excretion of drugs? (CU-04S, RU-03S)**

Ans.

Prolongation of drug action:**1. By prolonging absorption from site of administration:**▪ **In oral route:**

- Sustained release tablets
- Controlled release tablet / capsules
- Spansule capsules
- Coating of drug particles with resins, plastic materials

▪ **Parenteral route:**

- The SC & IM injection of drug in insoluble form prolong the drug action; e.g. benzathine penicillin, lente insulin.
- As oily solution of SC & IM injection; e.g. Depot progestins.

▪ **Transdermal drug delivery system:**

- The impregnated drug in adhesive patches, strips or as ointment applied on skin is becoming popular; e.g. GTN.

Spansule: Capsules containing medicines, coated with materials having slow dissolving rates so that the medicine is delivered at a time after the capsule is taken. Origin: span + (cap)sule

2. **By increasing plasma protein binding:** Drug congeners have been prepared which are highly bound to plasma protein & are slowly released in the free active form; e.g. sulfadoxine.
3. **By reducing rate of distribution:** Adrenaline is added with local anesthetics. Adrenaline causes vasoconstriction which reduces the spread of local anesthetic agent to the surrounding tissues & the blood. So the local anesthetic agent acts locally for a prolonged period.

4. **By reducing rate of metabolism:**

- **Small chemical modification:** Addition of an ethinyl group to estradiol, eg, OCP.
- **Inhibition of specific enzymes:** Allopurinol inhibits the degradation of 6-mercaptopurine.
- **Inhibition of microsomal enzymes by drugs, eg,** cimetidine, metronidazole, disulfiram, isoniazid etc.

5. **By reducing renal excretion:** The tubular secretion of drug (being an active process) can be suppressed by a competing substance, resulting in prolongation of drug action.

For example: after simultaneous administration of **probenecid & penicillin**, both drugs compete for the same active site of the carrier protein for secretion into the renal tubules. But probenecid has more affinity for the carrier protein. So, probenecid is secreted into the renal tubule, whereas penicillin remains in the plasma. Thus the action of penicillin is prolonged.

6. **Others:**

- Increase the dose
- Increase frequency
- By decreasing gut motility.

(Ref: Tripathi-6th/35,36)

Advantages of prolongation of drug action:

1. **Frequency of administration** is reduced & it is more convenient & cost effective.
2. **Improved patient compliance:** A single morning dose is more likely to be forgotten than a 6 / 8 hourly regimen; a monthly or quarterly administered contraceptive over one that has to be taken daily.
3. **Large fluctuation in plasma concentration are avoided-** side effects related to high peak plasma level just after a dose (e.g. nifedipine) would be minimized; better round-the-clock control of blood sugar etc.
4. Drug effect could be maintained overnight without disturbing sleep; e.g. anti-asthmatic, anticonvulsants.

(Ref: Tripathi-5th/35)

Q. Name some drugs excreted in milk. What is its clinical importance? (RU-02J)

Ans.

Drugs excreted through breast milk:

1. Barbiturates, eg, phenobarbitone
2. Benzodiazepines
3. Amphetamine
4. Anticancer drugs
5. Ampicillin
6. Aspirin
7. Folic acid
8. Tetracycline

Clinical importance of breast milk elimination of drugs: Drug enters into the infant body & can produce its adverse effect. For example-

1. If a lactating mother takes CNS depressant drugs, it will pass to baby via milk and will cause CNS depression to the baby.
2. If a lactating mother takes tetracycline, it will pass to baby via milk, deposit to bone & teeth and will cause growth retardation.

(Ref: Tripathi-6th/912)

Nice to know

Drugs that are contraindicated during breastfeeding	Fecal elimination of drugs
1. Barbiturates 2. Benzodiazepines 3. Amphetamine 4. Anticancer drugs 5. Azathioprine 6. Amiloride 7. Amiodarone 8. Androgens 9. Chloramphenicol	1. Oral contraceptive pills (OCPs) 2. Erythromycin 3. Ampicillin 4. Rifampicin 5. Tetracycline 6. Phenolphthalein 7. Heavy metal 8. Anthracene purgatives
Drugs that need special precautions during breastfeeding	Drugs eliminated through saliva & sweats
1. Anti-convulsants 2. Anti-depressants 3. Anti-psychotics 4. Carbamazepine 5. Carbimazole 6. Bromocriptine 7. Buspirone 8. ACE inhibitors 9. Amoxicillin 10. Ampicillin 11. Allopurinol	1. Rifampicin 2. Metronidazole 3. Lithium 4. Heavy metals 5. Potassium iodide.
	Drugs eliminated through lungs
	1. General anesthetics 2. Paraldehyde 3. Alcohol

(Ref: Tripathi-6th/93&912)**Viva Q.** Why should we be cautious about use of diazepam in a lactating mother?

Ans. Caution of diazepam administration in a lactating mother: About 90% drugs (although at a trace amount) can reach the child through breast milk. Diazepam → Reaches to child through breast milk → Skeletal muscle relaxation → Child will be unable to suck milk → Child remains sleeping.

Clinical Pharmacokinetics

Q. Categorize order kinetics in relation to plasma half life. (SU-14Ju)**Ans.**

The rate at which absorption, distribution, metabolism and excretion takes place follow two orders-

- First-order (exponential) kinetics
- Zero-order (saturation) kinetics

(Ref: Bennett & Brown-11th edition)**Q.** What do you mean by first-order kinetics? Give examples. (CU-07J,06M, SU-06M)**Q.** Short note: First order kinetics. (DU-13J)**Q.** Short note: First-order elimination. (DU-10J)**Ans.****First order kinetics**

Definition: In the majority of instances the rates at which absorption, distribution, metabolism and excretion of a drug occur are directly proportional to its concentration in the body. This is called first-order kinetics. In first-order kinetics, a **constant fraction (percentage)** of a drug is metabolized and eliminated per unit time.

(Ref: Bennett & Brown-11th edition+ Lippincott's-6th/13)

Explanation: The metabolic transformation of drugs is catalyzed by enzymes, and most of the reactions obey Michaelis-Menten kinetics:

$$V = \text{Rate of drug metabolism} = \frac{V_{\max} [C]}{K_m + [C]}$$

In most clinical situations, the concentration of the drug, $[C]$, is much less than the **Michaelis constant, K_m** , and the Michaelis-Menten equation reduces to,

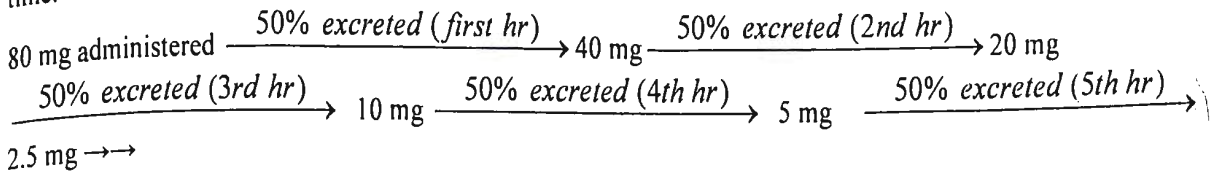
$$V = \text{Rate of drug metabolism} = \frac{V_{\max} [C]}{K_m}$$

$$V \propto [C]$$

Therefore, rate of drug metabolism is directly proportional to the drug concentration.

(Ref: Lippincott's-6th/13)

Example: A drug X follows first order kinetics and is excreted 50% of its initial plasma concentration per unit time.



Criteria:

1. In doses used clinically, most drugs are subject to first-order processes of absorption, distribution, metabolism and elimination.
2. Rate of metabolism is proportional to the plasma drug concentration.
3. Rate of elimination is proportional to the plasma drug concentration.
4. Half life of the drugs is constant.
5. Enzyme in liver is in excess, so metabolism of a drug can increase whenever its plasma concentration increases.
6. In this mechanism, there is less chance of toxicity, because increase in dose of drug increases its metabolism and elimination.

Drugs that follow 1st order kinetics: 98 — 99% drugs follow first order kinetics.

1. Low dose Aspirin (75 mg)
2. Phenobarbitone
3. Paracetamol
4. Carbamazepine
5. Low dose phenytoin (25 mg)

Q. What do you mean by zero order kinetics? Give examples. (SU-06M)

Q. Short note: Zero-order kinetics. (DU-13J)

Q. Short note: Zero-order elimination. (DU-10J)

Ans.

Zero order kinetics / non-linear /saturation kinetics:

Definition: When the rates of metabolism and excretion of a drug **do not vary with the drug concentration** in the body and a **fixed amount** of drug is metabolized or excreted per unit time, it is called zero-order kinetics.

(Ref: Bennett & Brown-11th edition+ Lippincott's-6th/14)

Explanation: Enzyme-mediated metabolic reactions most commonly show zero-order kinetics, because the amount of enzyme present is finite. As the amount of drug in the body rises, the enzymes become saturated and the rate of metabolic reactions or processes reaches the maximum amount at which it stays constant. Passive diffusion does not become saturated.

(Ref: Bennett & Brown-11th edition)

With a few drugs, such as **aspirin, ethanol, and phenytoin**, the doses are very large. Therefore $[C]$ is much greater than K_m , and the velocity equation becomes-

$$V = \text{Rate of drug metabolism} = \frac{V_{\max} [C]}{K_m + [C]}$$

$$V = \text{Rate of drug metabolism} = \frac{V_{\max} [C]}{[C]} \quad (\text{When } [C] \text{ is much greater than } K_m)$$

$$V = V_{\max}$$

The enzyme is saturated by a high free-drug concentration, and the rate of metabolism remains constant over time.
(Ref: Lippincott's-6th/14)

Example: A drug Y is always excreted 10 mg per unit time regardless its initial plasma concentration.

80 mg administered $\xrightarrow{10 \text{ mg excreted (1st hr)}}$ 70 mg $\xrightarrow{10 \text{ mg excreted (2nd hr)}}$ 60 mg
 $\xrightarrow{10 \text{ mg excreted (3rd hr)}}$ 50 mg $\xrightarrow{10 \text{ mg excreted (4th hr)}}$ 40 mg
 $\xrightarrow{10 \text{ mg excreted (5th hr)}}$ 30 mg $\rightarrow \rightarrow$

Criteria:

1. The **rate of drug metabolism** remains **constant** over time.
2. The **rate of drug excretion** also remains **constant** and a fixed amount of drug is excreted per unit time.
3. Plasma **half life varies** with the concentration of the drug. The higher the concentration, the longer the half life.
4. **Increase in the dose** of the drug does not increase metabolism and elimination. This may markedly prolong the apparent serum half-life and **increase toxicity**.
5. Zero-order kinetics is also known as rate-limited or dose-dependent or *saturation kinetics*.
6. Zero-order *absorption* processes apply to iron, to depot i.m. formulations and to drug implants, e.g. antipsychotics and sex hormones.

Drugs that follow zero order kinetics:

1. High dose aspirin (Anti inflammatory effect)
2. High dose phenytoin
3. Ethanol
4. Tolbutamide
5. Theophylline
6. Warfarin

Q. Write down differences between first order & zero order kinetics. (DU-16J,14Ju,10J, RU-10Ju)

Q. Compare & contrast: 1st order kinetics & zero order kinetics. (CU-07J,06M, RU-13Ju)

Q. Compare first order kinetics of elimination with zero order kinetics of elimination. (CU-15Ju)

Ans.

Comparison between 1st order & zero order kinetics:

First order kinetics	Zero order kinetics
1. Rate of metabolism is proportional to the plasma drug concentration.	1. Rate of metabolism remains constant over time.
2. Rate of elimination is proportional to the plasma drug concentration. A constant fraction (percentage) of a drug is eliminated per unit time.	2. Rate of elimination remains constant and a fixed amount of drug is excreted per unit time.
3. It occurs when concentration of drug is low.	3. It occurs when concentration of drug is very high and metabolism is saturated.
4. Half life of the drugs is constant.	4. Plasma half life varies with the concentration of the drug. The higher the concentration, the longer the half life.

5. There is less chance of toxicity, because increase in dose of drug increases its elimination.	5. Increase in the dose of the drug may markedly prolong the apparent serum half-life and increase toxicity
6. Example: Most drugs follow 1 st order kinetics. Eg, Low dose Aspirin, Phenobarbitone, Carbamazepine etc.	6. Example: Few drugs follow zero order kinetics. High dose Aspirin, Phenytoin, Tolbutamide, Theophylline, Warfarin etc.

Q. Why plasma half life varies when drug elimination follows zero-order kinetics? (CU-14Ju)

Ans.

Plasma half life varies in zero-order kinetics: In zero-order kinetics, the rates of metabolism and excretion of a drug do not vary with the drug concentration in the body and a fixed amount of drug is metabolized or excreted per unit time. Increase in the dose of the drug does not increase metabolism and elimination. As a result, plasma half life varies with the concentration of the drug. The higher the concentration, the longer the half life.

Q. Short note: Clearance / Cl.

Ans.

Clearance (Cl)

Definition: Clearance is defined as the virtual volume of blood from which drug can be completely removed per unit of time (eg, 100 mL/minute).

(Ref: Modern Pharmacology With Clinical Applications by Charles & Robert-6th/51)

Definition: The ratio of the rate of elimination of a drug to the concentration of the drug in the plasma or blood is called the clearance.

(Ref: Katzung-13th/42)

$$\text{Clearance (Cl)} = \frac{\text{Rate of elimination of drug}}{\text{Plasma drug concentration (C)}}$$

$$\text{mL/min} = \frac{9 \text{ L/min}}{9 \text{ mL}}$$

$$\text{Rate of elimination} = \text{Cl} \times \text{C} = \text{Rate of administration}$$

Criteria:

1. Conceptually, clearance is a measure of the capacity of the body to remove a drug.
2. Drugs with "high" clearance are rapidly removed from the body, and drugs with "low" clearance are removed slowly.
3. For a drug eliminated with first-order kinetics, clearance is a constant.
4. For drugs eliminated with zero-order kinetics, clearance is *not* constant.
5. Clearance depends on the drug and the condition of the organs of elimination (eg, kidney) in the patient.
6. The units of clearance are volume/time.

(Ref: Katzung-13th/42-46; BRS Pharmacology-6th/11)

Half life ($t_{1/2}$)

Q. Define plasma half life. (DU-10Ju,06J, CU-07J,06M; SU-15J,13J,09Ju; RU-17J,12Ju)

Q. Define & classify half life. (DU-07Ju; RU-06M; SU-06J)

Q. What do you mean by plasma half life of a drug? (RU-08J)

Q. How could you calculate plasma half life? (RU-08J)

Q. Short note: Plasma half life ($t_{1/2}$) of a drug. (DU-15J,13Ju,09Ju; CU-06S/J)

Q. Short note: Half life ($t_{1/2}$) of a drug. (RU-15J, SU-17J)

Ans.

Half life

Definition: Half-life ($t_{1/2}$) is the time required to change the amount of drug in the body by one-half during elimination (or during a constant infusion).

Half-life is useful because it indicates the time required to attain 50% of steady state—or to decay 50% from steady-state conditions—after a change in the rate of drug administration.

(Ref: Katzung-13th/46)

$$\text{Half-life } (t_{1/2}) = \frac{0.7 \times V_d}{Cl}$$

Here, V_d = Volume of distribution and Cl = Clearance, $0.7 = \ln 2 = \text{constant}$.

(Ref: Katzung-13th/46)

Types of half-life:

1. **Plasma half-life:** The time by which plasma concentration of a drug becomes 50% of steady state after the administration of that drug is called plasma half-life.
2. **Elimination half-life:** The time by which 50% of the drug is eliminated from steady-state conditions is called elimination half-life.
3. **Biological half-life:** The time by which 50% of the effect of the drug is gained is called the biological half-life.

Nice to know

Concept of half-life: The half-life determines the rate at which blood concentration rises during a constant infusion and falls after administration is stopped. After start of a constant infusion, the plasma concentration rises smoothly with time and always reaches 50% of steady state after 1 half-life, 75% after 2 half-lives, 87.5% after 3 half-lives, and so on. The decline in concentration after stopping drug administration follows the same type of curve: 50% is left after 1 half-life, 25% after 2 half-lives, and so on. The asymptotic approach to steady state on both increasing and decreasing limbs of the curve is characteristic of drugs that have first-order kinetics.

As for example, during constant infusion, with the passage of each half life period of time, the plasma concentration rises by half the difference between the current concentration and the ultimate steady state (100%) concentration. Thus,

- In $1 \times t_{1/2}$: The plasma conc. will reach $(100/2) = 50\%$
- In $2 \times t_{1/2}$: The plasma conc. will reach $\{50 + (100-50)/2\} = 75\%$
- In $3 \times t_{1/2}$: The plasma conc. will reach $\{75 + (100-75)/2\} = 87.5\%$
- In $4 \times t_{1/2}$: The plasma conc. will reach $\{87.5 + (100-87.5)/2\} = 93.75\%$
- In $5 \times t_{1/2}$: The plasma conc. will reach $\{93.75 + (100-93.75)/2\} = 96.875\%$ of the ultimate steady state.

(Ref: Bennett & Brown-11th)

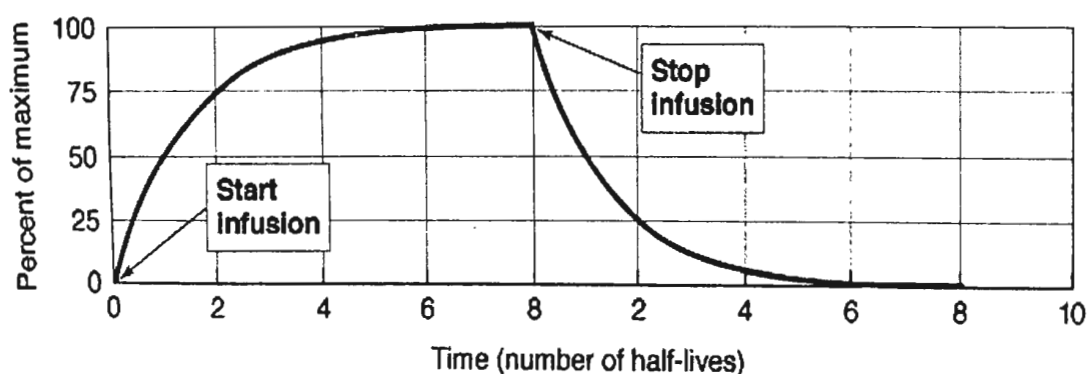


Fig. Plasma concentration (plotted as percent of maximum) of a drug given by constant intravenous infusion for 8 half-lives and then stopped.

Q. Short note: Steady state. (NTK)

Q. Explain the Relation of plasma half-life with steady state concentration. (DU-16Ju)

Ans.

Steady state: When a drug dose is given repeatedly over a period, a state is eventually reached, at which point the amount of drug absorbed is in equilibrium with that eliminated from the body. This state is called steady state.

Steady state is usually achieved within 4 to 5 half-life for most of the drugs governed by first-order kinetics. For example, a drug with half-life of 4 hours will be expected to get a steady state after more than 24 hours of infusion.

(Ref: Misbahuddin-5th/102)

Importance of steady state: To know when steady state has been reached, for maintaining the same dosing schedule, will then ensure a constant amount of drug in the body and the patient will experience neither acute toxicity nor decline of effect.

(Ref: Bennett & Brown-11th)

Q. What factors modifying plasma half life? (DU-07J, CU-06M/S/J.05M)

Ans.

Factors modifying plasma half life:

1. **Routes of drug administration:** Decreasing order of $t_{1/2}$ is: Subcutaneous > IM > Oral > IV.
2. **Drug absorption:** $\uparrow$ Drug absorption $\rightarrow$ $\downarrow$ Plasma half life
3. **Drug distribution:**
 - **PPB:** $\uparrow$ PPB $\rightarrow$ $\uparrow t_{1/2}$
 - **Tissue binding:** $\uparrow$ Tissue binding $\rightarrow$ $\uparrow t_{1/2}$
 - **Vd:** $\uparrow$ Vd $\rightarrow$ $\uparrow t_{1/2}$
4. **Biotransformation:**
 - $\uparrow$ Biotransformation $\rightarrow$ $\downarrow t_{1/2}$ and vice versa.
 - Liver diseases $\rightarrow$ $\downarrow$ Biotransformation $\rightarrow$ $\downarrow$ Excretion $\rightarrow$ $\uparrow t_{1/2}$
5. **Drug excretion:**
 - $\uparrow$ Excretion $\rightarrow$ $\downarrow t_{1/2}$ and vice versa
 - Kidney diseases $\rightarrow$ $\downarrow$ Excretion $\rightarrow$ $\uparrow t_{1/2}$
6. **Genetic Factor:** Isoniazid-
 - Slow acetylator- $t_{1/2}$ 3 hr
 - First acetylator- $t_{1/2}$ 1 hr

Q. Name 4 drugs with long half life. (RU-06M)

Q. Give some examples of long & short plasma half life. (RU-05S)

Ans.

Drugs having long half life	Half life	Drugs having short half life	Half life
Chloroquine	214 h	Aspirin	0.25 h
Digitoxin	160 h	Cephalothin	0.57 h
Digoxin	50h	Cephalexin	0.9 h
Phenobarbitone	98 h	Ampicillin	1.3 h
Diazepam	43 h	Amoxicillin	1.7 h
Fluoxetine	53 h	Lidocaine	1.8 h
Warfarin	37 h	Midazolam	1.9h

(Ref: Katzung-13th/43-44)

Q. Mention the clinical situation in which half life is increased.

Ans.

Clinical situation in which half life is increased:

1. **Diminished renal blood flow** due to cardiogenic shock, hemorrhage, heart failure $\rightarrow$ $\downarrow$ Excretion of drug $\rightarrow$ $\uparrow t_{1/2}$.
2. **Liver diseases** $\rightarrow$ $\downarrow$ Biotransformation $\rightarrow$ $\downarrow$ Excretion $\rightarrow$ $\uparrow t_{1/2}$
3. **Kidney diseases** $\rightarrow$ $\downarrow$ Excretion $\rightarrow$ $\uparrow t_{1/2}$

4. **Addition of 2nd drug** that inhibits metabolism of the first drug → ↓ Excretion of first drug → ↑ $t_{1/2}$
5. **Addition of 2nd drug** that displaces the first drug from albumin → ↑ volume of distribution → ↑ $t_{1/2}$
eg. Phenylbutazone + OHA
Phenylbutazone displaces OHA from binding site, thus increases the half of OHA.

- Q. Explain the clinical significance of measurement of plasma drug concentration. (DU-09J)
 Q. Mention the clinical significance / utilities of half life. (DU-10Ju,07Ju; RU-17J,16J, SU-13J)
 Q. What are the significances/importance of plasma half life? (RU-12Ju,06M, SU-13Ju)
 Q. Outline the clinical importance of knowing plasma half life of a drug. (CU-05M; SU-12Ju,08/07Ju)
 Ans.

Significances / Clinical importance of half life of a drug

1. Half life gives a gross idea about the pharmacokinetic & pharmacodynamic properties of the drug.
2. To predict the duration of action
3. To formulate a dosage schedule (amount of drug & frequency of interval)
 - **Long $t_{1/2}$:** Should be given once/twice daily to prevent accumulation.
 - **Short $t_{1/2}$:** Should be given repeatedly.
4. To handle a case of overdose.
5. To determine the time to achieve steady state plasma concentration.
6. Gives idea about near total elimination time of a drug.
7. It also gives general knowledge-
 - Whether the drug is metabolized or eliminated unchanged.
 - Whether the drug itself is active or converted into active metabolite or both, eg, diazepam.
 - Whether the drug has irreversible action or not, eg, reserpine.
 - Presence of disease in the organ of metabolism or excretion.

Q. What information we get from plasma half life? (SU-09Ju,06M)

Q. Compare pharmacokinetic & pharmacodynamic parameters of 2 drugs having plasma half lives of 3 hours & 12 hours respectively. (DU-04M)

Ans.

Significance of long and short half life:

Information	Significance of long half life ($t_{1/2}$ = 12 hrs)	Significance of short half life ($t_{1/2}$ = 2 hrs)
1. Time required to fall plasma drug concentration by 50% of the steady state	12 hrs	2 hrs
2. Absorption	Slow	Rapid
3. Plasma protein binding	More	Less
4. Metabolism	Slow	Rapid
5. Excretion	Slow	Rapid
6. Action	Slow & Sustained	Rapid
7. Suitable in	Chronic case	Emergency case
8. Patient compliance	Good	Not so good
9. Frequency of administration	Less	More

Q. State the Therapeutic advantages and disadvantages of drugs with long and short half lives.

Ans.

	Therapeutic advantages	Therapeutic disadvantages
Long half-life	• Long duration of action. • Less dose frequency. • Better patient compliance. • Can be used in prophylaxis, eg, Salmeterol ($t_{1/2}$ 12 hours) → used to prevent night asthma. • Tolerance does not develop.	• Cannot be given in emergency by oral route. • More cumulative effect, eg, diazepam causes next-day hangover. • More drug interaction as it is highly protein bound. • Chance of toxicity is more as it is less rapidly metabolized or eliminated.
Short half-life	• Can be given in emergency to treat acute attack, eg, GTN in acute angina. • Rapidly excreted, so less chance of toxicity. • No cumulative effect. • No drug interaction.	• Short duration of action, so cannot be used as prophylactic measure. • More dose frequency. • Less patient compliance. • Development of tolerance is more if frequently used.

Q. Explain solubility status is determinant of every aspect of pharmacokinetic properties of drug. (SU-17M, 13Ju, 12Ju)

Ans.

Solubility status of drug influences every aspect of pharmacokinetic properties of drug. Eg,

1. **Absorption:**

- Increased lipid solubility → Increased absorption ($Absorption \propto Lipid\ solubility$)
- More water solubility → Less absorption

2. **Distribution:**

- Lipid soluble drugs → distribute mainly intracellularly.
- Water soluble drugs → distribute mainly extracellularly.

3. **Biotransformation:** Most of the drug metabolizing enzymes are located intracellularly. So more lipid soluble drugs enter the cell faster than water soluble drugs and are metabolized earlier.

4. **Excretion:**

- More lipid soluble drugs are more reabsorbed.
- More water soluble drugs are more excreted.

V_d, loading dose & maintenance dose- Described above.

$$t_{1/2} = \ln 2 \frac{V_d}{Cl}$$

$$V_d = \frac{M}{C}$$

$$Cl = \frac{\text{Rate of ex.}}{C}$$

Pharmacodynamics

Q. Define pharmacodynamics. (DU-06S; RU-07Ju)

Ans.

Pharmacodynamics: This is the branch of pharmacology which deals with the biochemical and physiological effect of drugs and their mechanism of action.

(Ref: Goodman & Gilman's-12th)

Pharmacodynamics: Pharmacodynamic is the study of biological effects produced by the drug". Simply pharmacodynamics means "what the drug does to the body."

(Ref: Misbahuddin-5th/03)

Mechanism of drug action

Q. Enumerate the process by which drugs act. (RU-16Ju, 14Ju)

Ans.

Processes by which drugs act: Drugs may act by 2 ways-

1. **Specific mechanism:** Drugs go to the specific site, bind with receptor & form a drug-receptor complex which causes the desired drug actions. Most of the drugs act by this mechanism.

- Receptor mechanism
- Enzyme mechanism
- Ion channel mechanism
- Carrier mechanism

2. **Non-specific mechanism:** In non-specific mechanism, the drugs don't bind to specific receptor. Drugs act in 3 ways-

- By altering physio-chemical properties of cells
- By direct chemical interaction
- By physical means.

Non-specific mechanism

Q. Briefly discuss the non-specific mechanism of drug action.

Ans.

Non-specific mechanism of drug action:

1. **By altering physiochemical properties of cells:**

- a. By stopping the streaming (rolling) movement of cell cytoplasm. Eg, anesthetic drugs enter into the reticular system of brain → cytoplasmic streaming stop → anesthesia of the pt.
- b. By stabilization of cell membrane, so no ion exchange.
- c. By lowering surface tension.
- d. By inhibiting energy production / utilization of cell.

2. **By direct chemical interaction:**

- a. **Neutralization**, eg,
 - Antacids directly interact with the gastric HCl and neutralize the acid.
 - Protamine sulphate (+ve charged) directly interact with heparin (-ve charged) and neutralize the action of heparin.
- b. **Chelation:** Antacids chelate tetracycline.
- c. **Anti-coagulation:** Anti-coagulants (Oxalate, EDTA, citrate) trap Ca^{2+} of blood → No coagulation of blood.

3. By physical means:a. By osmosis:

- **Purgatives:** Milk of magnesia (MgSO_4) is a purgative.
 $\text{MgSO}_4 \rightarrow \text{Mg}^{2+} + \text{SO}_4^-$ (osmotically active) $\rightarrow$ These ions attract water from food and intestinal wall and form water jacket $\rightarrow$ Larger molecule $\rightarrow$ Stretch the intestine $\rightarrow$ $\uparrow$ Peristalsis $\rightarrow$ Defecation.
- **Osmotic diuretics:** Mannitol is filtered by glomerulus $\rightarrow$ not absorbed $\rightarrow$ Retain large amount of water in the renal tubules as it is osmotically active $\rightarrow$ Excreted with large amount of water $\rightarrow$ Diuresis.

b. **By adsorption:** Activated charcoal adsorbs alkaloid poisons.c. **By emollient & demulcent action:** Mg trisilicate in PUD. (Peptic Ulcer Disease)d. **By mass of drug:** Bulk laxative.e. **Radioactivity:** ^{131}I .

Specific mechanism

Receptor mechanism of drug action

Q. Mention the target proteins with which drugs bind to produce action. (DU-10/09Ju, CU-13Ju; RU-13J,10Ju,08J)

Q. What are the molecular targets of drug action? (DU-13Ju, CU-07J,06M)

Q. Enlist the targets of drug action in human body. (CU-17M,14Ju)

Ans.

Target proteins for drug binding / Molecular targets of drug action:

1. Receptors
2. Ion channels
3. Enzymes
4. Carrier proteins
5. Structural proteins (such as tubulin)
6. Plasma protein

(Ref: Rang & Dale's-8th)

Q. Define & classify receptors. (DU-15J,12Ju,11J,08J; RU-13Ju,09J; SU-17J,10J, CU-16J,11J,08J)

Q. Classify receptors according to location. (DU-15J,12J)

Q. Define & classify receptors on the basis of mechanism of action. (SU-15Ju)

Q. Classify drug receptors according to signaling mechanism. (DU-17M)

Q. Illustrate different types of receptors on the basis of mechanism of action. (SU-12Ju)

Q. Categorize drug receptors. (CU-15J,11J,09Ju,07J; SU-13J)

Q. What are the main types of receptor super family? (CU-04M)

Q. Classify receptor according to receptor-effector linkage with examples. (RU-15Ju,13Ju,09J)

Ans.

Receptor: Receptor is the component of the cell to which a ligand specifically binds & may produce response(s).

Definition: Receptors are specialized target macromolecules to which drugs bind and initiate events leading to alterations in biochemical and/or biophysical activity of a cell, and consequently, the function of an organ.

(Ref: Lippincott's-6th)

Drug (D) + Receptor (R) $\rightarrow$ D-R complex $\rightarrow$ Response

onset: Fast, Slow, Silent

Classification of receptors:

A. According to location: Receptors are of 3 types—

Location

1. Membrane / cell surface receptors	• α and β -adrenoceptors, Cholinergic receptors, Insulin receptor
2. Cytoplasmic receptors	• Steroid hormone receptors
3. Nuclear receptors	• Thyroid hormone receptors

B. According to activity:1. Primary or specific receptor:

- **Physiological / pharmacological / active receptor:** Drugs selectively combine with this receptor and produce action. They are only 1-2%. Eg, cholinergic receptors, α and β -adrenoceptors, histamine receptor.
- **Spare receptor/reserve receptor:** Anatomically & functionally these receptors are same as physiological / pharmacological receptors. But they do not act normally. They come into action only when pharmacological receptors are exhausted or blocked. *eg. 99% of spare receptors*

2. Secondary / non-specific / silent / dead receptor: Drugs binds with these receptors without producing any response. Eg, plasma proteins are this kind of receptors.

- Any drugs can combine with these receptors. So these receptors are called non-specific.
- The drug-receptor complex is pharmacologically inactive / inert & does not produce any action. So the receptors are called silent or dead.
- The receptors act only as store house of drugs and prolong their pharmacological effects.

C. According to receptor mechanism of drug action/ receptor-effector linkage:1. Classical / physiological receptors: The receptors for which ligands are physiologically or endogenously present in our body are called classical receptors.

- Type I / ligand-gated ion channels (fast receptors):** Nicotinic receptor, GABA_A receptor.
- Type II / G-protein-coupled receptors (slow receptors):** Muscarinic receptor, adrenoceptors.
- Type III / receptor kinases:** Insulin, growth factors, cytokine receptors.
- Type IV / nuclear receptors:** Steroid receptors.

(Ref: Rang & Dale's-8th)

2. Non-classical receptors: Receptors having no physiological / endogenous ligand are called non-classical receptor.

a. Enzyme as receptor	• Dihydrofolate reductase: Receptor for methotrexate. • Acetyl-transferase: Receptor for acetylcholine.
b. Transport protein as receptor	• Na⁺-K⁺ ATPase: Receptor for digoxin • H⁺-K⁺-ATPase: Receptor for omeprazole.
c. Voltage gated ion channel	• Na⁺ channel • Ca²⁺ channel • K⁺ channel
d. Structural protein as receptor	• Microtubules • Tubulin: Receptor for colchicines.
e. Nucleic acid as receptor	• Nucleic acid: Receptor for thyroid hormones

Q. Diagrammatically discuss the ligand-gated ion channel with example. (CU-06M)

Ans.

Ligand-gated ion channels (ionotropic receptors): These are membrane proteins which are responsible for regulation of the flow of ions across cell membranes. They have a ligand-binding site (receptor), usually in the extracellular domain. The activity of these channels is regulated by the binding of a ligand to the channel. Response to these receptors is very rapid, having durations of a few milliseconds. Typically, these are the receptors on which fast neurotransmitters act.

Examples:

- **Nicotinic acetylcholine receptor:** Stimulation of this receptor results in **sodium** influx, generation of an action potential, and activation of contraction in skeletal muscle.
- **GABA_A receptor:** Benzodiazepines enhance the stimulation of the GABA receptor by GABA, resulting in increased **chloride** influx and hyperpolarization of the respective cell.

• Glutamate receptors of the NMDA, AMPA.

(Ref: Rang & Dale's-8th+ Lippincott's-6th)

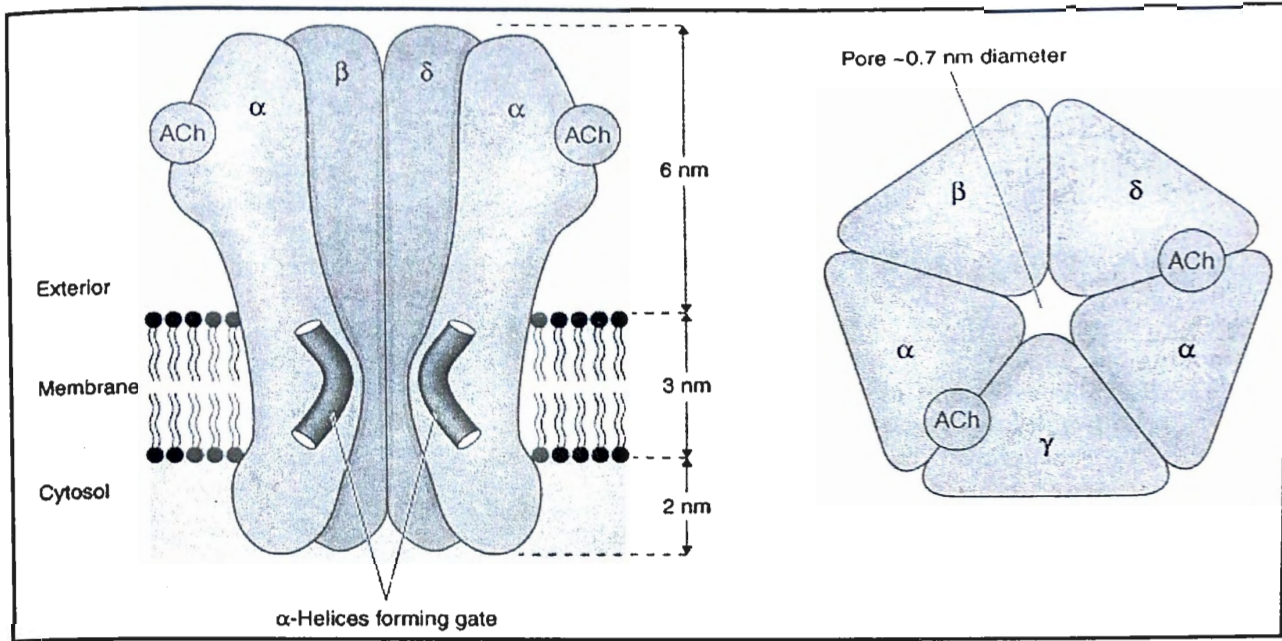


Figure. Structure of the **nicotinic acetylcholine receptor** (a typical **ligand-gated ion channel**) in side view (left) and plan view (right). The five receptor subunits (α 2, β , γ , δ) form a central transmembrane pore. There are two acetylcholine binding sites in the extracellular portion of the receptor.

Nice to know

Characteristics of Classical / physiological receptors:

Traits	Type I: ligand-gated ion channels	Type II: G-protein-coupled receptors	Type III: receptor kinases	Type IV: nuclear receptors
Location	Membrane	Membrane	Membrane	Intracellular
Effector	Ion channel	Channel or enzyme	Protein kinases	Gene transcription
Coupling	Direct	G-protein	Direct	Via DNA
Responding time	Within milliseconds	Within second	Within hours	Within hours
Structure	Oligomeric	Monomeric, dimeric, assembly of subunits forming transmembrane helix	Single transmembrane helix	Monomeric
Examples	Nicotinic receptor GABA receptor Glutamate receptor 5HT ₃ receptor	Muscarinic receptor Adrenoceptors Dopaminergic receptor Opioid receptor Neuropeptide receptor 5HT ₃ receptor	Insulin, growth factors, cytokine receptors	Steroid receptors Vitamin D Retinoic acid Thyroid hormone

(Ref: Rang & Dale's-8th)

Q. Enlist G-protein coupled receptors. (CU-17J)

Ans.

G-protein coupled receptors

1. Muscarinic receptor
2. Adrenoceptors
3. Dopaminergic receptor
4. Opioid receptor

5. Neuropeptide receptor
6. 5HT₃ receptor

Q. Categorize G-protein coupled receptor. (CU-12J)

Ans.

Classification of G-protein coupled receptor: On the basis of GTP:

1. **G_s:** Stimulatory G protein.
2. **G_i:** Inhibitory G protein.
3. **G_q:** Stimulatory but not direct stimulatory as G_s.

Q. Give examples of some drugs which mediate drug effect by opening and closing ion channel. (RU-11Ju)

Ans.

Drugs which mediate drug effect by opening and closing ion channel

1. **Blocking Na⁺ channel:**
 - a. **Local anesthetic:** Lidocaine.
 - b. **Anti-epileptic drugs:** Phenytoin, carbamazepine, etc.
 - c. **Anti-arrhythmic drugs:** Quinidine, procainamide, etc.
2. **Blocking K⁺ channel:**
 - a. Anti-arrhythmic drugs, eg, Amiodarone, sotalol.
3. **Blocking Ca²⁺ channel:**
 - a. Antihypertensive drugs: Captopril, verapamil, etc.
4. **Opening Cl⁻ channel:**
 - a. Sedative & hypnotic drugs, eg, benzodiazepine & barbiturates.

Q. Short note: Spare receptor.

Ans.

Spare Receptors:

Definition: Spare receptors are receptors that exist in excess of those required to produce a full effect.

Synonym: Surplus receptor, reserve receptor.

Salient features of spare receptors:

1. Anatomically & functionally these receptors are same as physiological / pharmacological receptors.
2. They do not act normally.
3. They come into action only when pharmacological receptors are exhausted or blocked.
4. **Functions:**
 - a. Spare receptors increases sensitivity to the drug.
 - b. Spare receptors amplify the signal duration and intensity.

(Ref: Katzung & Trevor's-11th edition)

Examples of spare receptors:

- Spare receptors are exhibited by receptors that respond to hormones, neurotransmitters, and peptides.
- 99 % of the insulin receptors are "spare." This constitutes an immense functional reserve that ensures adequate amounts of glucose enter the cell.
- In human heart 5-10% of the total **β-adrenoceptors** are spare. As a result, little functional reserve exists in the failing heart; most receptors must be occupied to obtain maximum contractility.

(Ref: Lippincott's-6th/29)

Q. Write down about receptor regulation. (CU-08J, SU-12J)

Ans.

Receptor regulations: Receptor number is regulated by two ways-

1. Receptor down regulation
2. Receptor up regulation

- A. **Down regulation / adaptation / refractoriness / desensitization:** Prolonged high concentration of agonist causes a reduction in the number of receptors available for activation. This is called receptor down regulation. The vanishing receptors are taken into the cell by endocytosis.

(Ref: Bennett & Brown 11th)

Example: Repeated use of β -agonist bronchodilator for the treatment of asthma results in down-regulation or desensitization of β -adrenoceptors.

Mechanism of down regulation:

1. Decreased synthesis & increased destruction of receptors
2. Internalization of the receptor.

(Ref: Bennett & Brown-11th; Rang & Dale's-8th)

- B. **Receptor up regulation:** Changes in receptor occupancy & affinity & prolong exposure of receptor with the antagonist leads to an increase in the sensitivity & number of receptor. This is called receptor up regulation.

Examples: The occasional exacerbation of ischemic heart diseases (IHD) on sudden withdrawal of a β -blocker is due to up regulation.

Prolong blocking of β -receptor by the β -blocker drug



Receptor up regulation & sensitization.



On withdrawal, an "above-normal" number of receptors suddenly become accessible to the normal neurotransmitters (noradrenaline & adrenaline).



Exacerbation of IHD (so β -blocker drugs should not be suddenly stopped, their dose should be gradually tapered and then stopped if needed).

Mechanism of up regulation:

1. Increased formation of receptor & decreased degradation of receptors.
2. Accentuation of signal amplification by the transducer
3. Increase sensitization of receptor to agonist e.g. development of withdrawal syndrome,

(Ref: Bennett & Brown-11th; Tripathi-6th/50,52)

Q. Describe briefly the consequences of drug-receptor interaction? (DU-10Ju, SU-17J)

Q. Discuss the receptor-effector linkage following drug receptor interaction. (RU-07J; SU-14J,08J)

Q. What are consequences of drug receptor interaction? (DU-13Ju,12Ju,09Ju; CU-06J; RU-08J, SU-17M,13Ju,11Ju,06J)

Q. What are the molecular consequences/mechanism of drug receptor interaction? (CU-13J; RU-08J)

Ans.

Consequences of / molecular consequences of drug receptor interaction:

1. **Post-receptor events of ion channel coupled receptor:**

- Opening of ion channel
- Closing of ion channel

2. **Post-receptor events of G-protein coupled receptors:**

- Formation of 2nd messengers
- Inhibition of 2nd messengers
- Ca²⁺ release
- May open / close receptor-operated ion channel

3. **Post-receptor events of tyrosine kinase receptors:** Phosphorylation of proteins

4. **Post-receptor events of DNA coupled receptors:** Gene transcription.

(Ref: Rang & Dale's-8th)

Nice to know

- ✓ **Ligand:** They are the chemical substances which can combine with receptors. Endogenous ligands are neurotransmitters, hormone, autacoids (cytokines). Exogenous ligands are drug molecules.
- ✓ **First messenger:** The extracellular ligands are called first messengers. Hormones, neurotransmitters, drug molecules all are examples of first messengers. *Drugs*

(Ref: Ganong's-24th)

Q. What are the 2nd messengers? (DU-07J, SU-06S)

Q. Enlist the second messengers with their functions. (CU-16Ju)

Q. Short note: 2nd messengers. (DU-17J)

Ans.

✓ **2nd messengers:** The intracellular mediators which are produced as a result of binding of the first messengers (eg, drug, hormones, neurotransmitter) with the receptors are called second messengers. Second messengers are responsible for the ultimate physiological / pharmacological effects of the first messengers.

2 nd messengers	Functions
1. Cyclic adenosine monophosphate (cAMP)	• cAMP activates various protein kinases that control cell function in many different ways by causing phosphorylation of various enzymes, carriers and other proteins.
2. Inositol triphosphate (IP3)	• IP ₃ increases free cytosolic Ca ²⁺ by releasing Ca ²⁺ from intracellular compartments.
3. Diacyl glycerol (DAG)	• DAG activates protein kinase C, which controls many cellular functions by phosphorylating a variety of proteins.
4. Ca ²⁺ ion	• Increased free Ca ²⁺ initiates many events, including contraction, secretion, enzyme activation and membrane hyperpolarisation.
5. Cyclic guanosine monophosphate (cGMP)	• cGMP is active only a few cell types including intestinal mucosa and vascular smooth muscle. • cGMP acts by stimulating a cGMP-dependent protein kinase. • Increased cGMP concentration causes relaxation of vascular smooth muscle by a kinase-mediated mechanism.

(Ref: Katzung-13th/30-34)Nice to know**Functions of cAMP:** Acting as an intracellular second messenger, cAMP mediates-

1. Mobilization of stored energy (the breakdown of carbohydrates in liver or triglycerides in fat cells stimulated by β -adrenomimetic catecholamines).
2. Conservation of water by the kidney (mediated by vasopressin)
3. Ca²⁺ homeostasis (regulated by parathyroid hormone).
4. Increased rate and contractile force of heart muscle (β -adrenomimetic catecholamines).
5. Production of adrenal and sex steroids (in response to ACTH, FSH).
6. Relaxation of smooth muscle.
7. Many other endocrine and neural processes.

(Ref: Katzung-13th/31-33)

Examples of ligands acting through Second messenger system:

1. **cAMP 2nd messenger system:** ACTH, FSH, LH, TSH, ADH (V_2 receptor, epithelial cells), Parathormone (PTH), Catecholamines (β -receptors), Glucagon, Calcitonin, CRH, HCG, Angiotensin II (epithelial cells). Secretin act by the cAMP 2nd messenger system.
2. **Cell membrane-phospholipid 2nd messenger system:** The following hormones act by membrane-phospholipid 2nd messenger system: Catecholamines (α -receptor), GnRH, GHRH, TRH, Oxytocin, ADH (V_1 receptor, vascular smooth muscle), Angiotensin II (vascular smooth muscle) act by membrane-phospholipid 2nd messenger system.

3. **Ca^{2+} -Calmodulin system:** Local hormones act by this way. For example, calmodulin activates myosin kinase, which acts directly on the myosin to cause smooth muscle contraction.

(Ref: Guyton-13th, Harpers-30th)

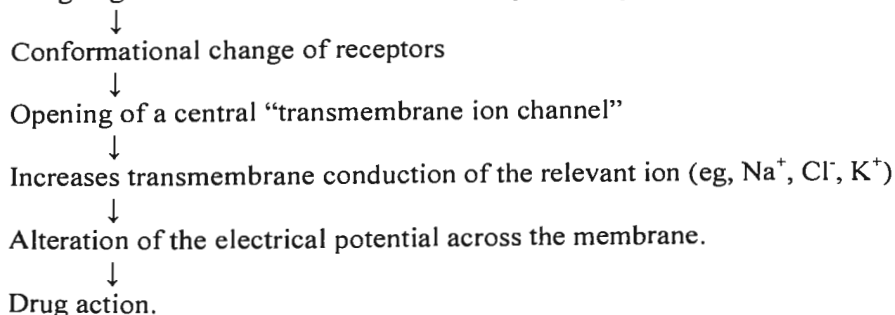
- Q. Write down about mechanism of drug action. (DU-06S; RU-04S, SU-16Ju)
 Q. Shortly discuss with diagram & examples the receptor mediated drug action. (SU-09J)
 Q. Briefly describe the receptor mediated drug action. (DU-15J, SU-16J/Ju)
 Q. Discuss briefly the receptor mechanism of drug action with examples. (DU-14Ju, 12J, 08J; SU-12J)
 Q. Describe the signal transduction mechanism that follows drug receptor interaction. (CU-16J)
 Q. Mention the ways with examples by which drug can produce its action. (DU-06S)
 Q. Discuss the receptor-effector coupling through ligand-gated ion channel coupled receptor. (CU-11Ju, 10Ju)
 Q. Discuss with example the modulation of ion channel through ligand-gated ion channel coupled receptor. (CU-14Ju)
 Q. Explain with examples- the ion channel mechanism of drug action. (RU-17J)
 Q. Mention 2nd messenger action of drugs with examples. (DU-12Ju, SU-13J, 12Ju)
 Q. Write down the mechanism of G-protein coupled receptor. (DU-16Ju, 07J, CU-11Ju, 10Ju, SU-14Ju)
 Q. Outline receptor-effector coupling through G-protein coupled receptor. (SU-15Ju)
 Q. Explain the signal transduction induced by G-protein coupled receptor. (CU-13Ju)
 Q. Mention the role of G-protein in the signal transduction mechanism. (CU-17J, 15J)
 Q. Explain how G protein influences second messenger system. (DU-17M)
 Q. Describe signal transduction mechanism due to β -receptor stimulation. (CU-16Ju)

Ans.

Receptor mediated mechanism of drug action/ Drug-receptor interaction:

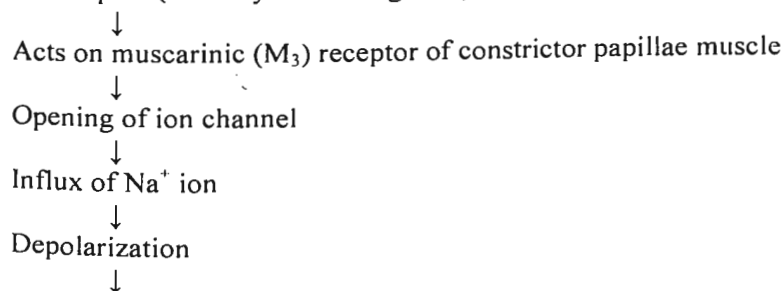
- A. **Mechanism of drug action via ligand-gated ion channel coupled receptors (ICCR):** Many of the most useful drugs in clinical medicine act by mimicking or blocking the actions of endogenous ligands that regulate the flow of ions through plasma membrane channels. The natural ligands include acetylcholine, serotonin, GABA, and glutamate.

Drugs/ligands binds with ion channel coupled receptors (ICCR)



Example: Muscle relaxant, cholinomimetic drugs act by this way.

Pilocarpine (an acetylcholine agonist)



Action potential
 ↓
 Contraction of constrictor papillae muscle
 ↓
 Miosis (constriction of pupil)

(α, β, δ ... binding)

B. Mechanism of drug action via G-protein coupled receptor (GPCR) / second messenger action:

Extracellular ligands bind with G-protein coupled receptors (R, eg, β -adrenoceptors, glucagon receptors)

↓
 Activation of G protein

↓
 G protein regulates the activity of effector enzyme or ion channel (E)

- Increase in the intracellular concentrations of **second messengers** such as cAMP, calcium ion, phosphoinositides. *phospholipase C*
- Opening of ion channels

↓
 Pharmacologic action

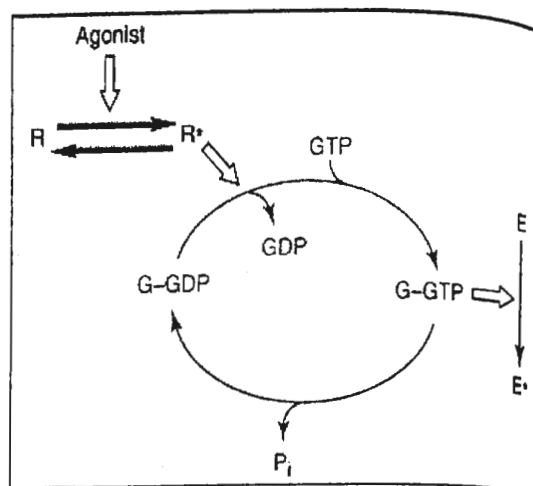


Fig. Mechanism of drug action via G-protein coupled receptor.

For example: Mechanism of drug action by cAMP 2nd messenger pathway:

Drug-Receptor complex

↓
 Activation of G protein

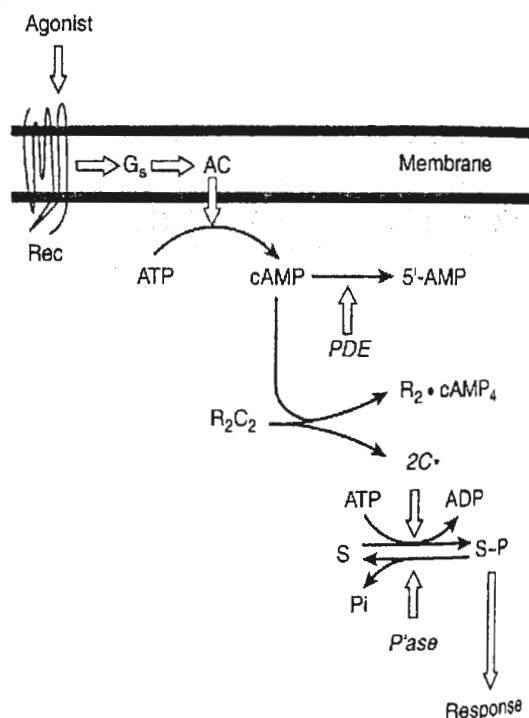
↓
 G protein stimulates adenylyl cyclase

↓
 ATP → ↑ cAMP

↓
 cAMP-dependent protein kinases

↓
 Phosphorylation of protein

↓
 Drug effect



(Ref: Katzung-13th/31-33)

Fig. The cAMP second messenger pathway. hormone receptors (Rec), a stimulatory G protein (G_s), adenylyl cyclase (AC), phosphodiesterases (PDE), regulatory (R) and catalytic (C) subunits, protein substrates (S) of the kinases, and phosphatases (P'ase).

- C. **Mechanism of drug action by tyrosine kinase coupled receptor:** Insulin, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), atrial natriuretic peptide (ANP), transforming growth factor- β (TGF- β), and many other trophic hormones act by this receptor. GTN, nitroprusside act by this receptor.

Binding of drug or hormone with the extracellular domain of the receptor

↓
The resulting change in receptor conformation causes two monomers of the receptor molecules to bind to one another non-covalently in the plane of cell membrane

↓
The cytoplasmic tyrosine kinase domain becomes enzymatically active.

↓
The tyrosine kinase then phosphorylate one another as well as additional downstream signaling proteins

↓
Drug response.

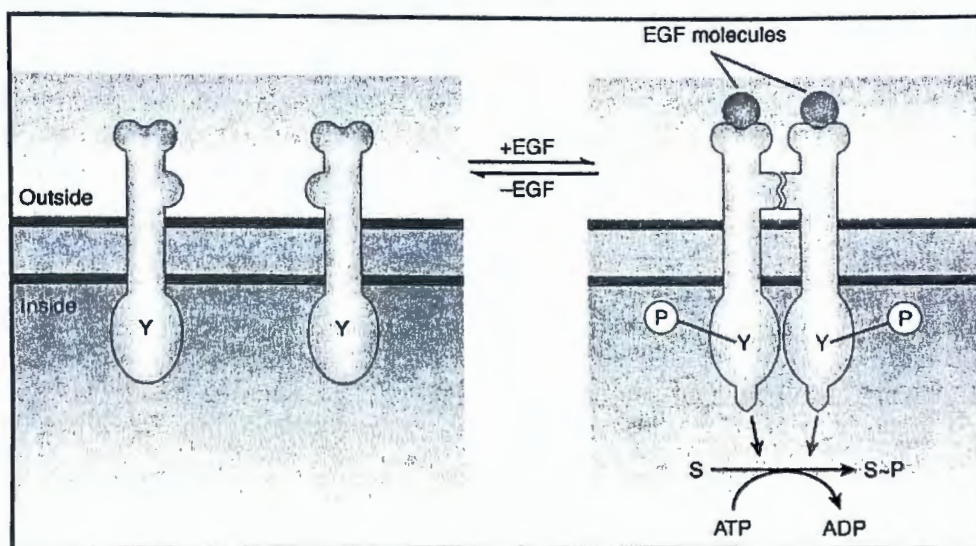


Fig. Mechanism of activation of the epidermal growth factor (EGF) receptor, a representative receptor tyrosine kinase.

(Ref: Katzung-13th/28-29)

- D. **Mechanism of drug action by DNA coupled receptor:** Lipid-soluble ligands such as steroids (corticosteroids, mineralocorticoids, sex steroids, vitamin D), and thyroid hormone act by DNA coupled receptor.

A lipid-soluble drug (steroid, thyroid hormone) crosses the plasma membrane

↓
Steroid binds with receptors in the cytoplasm and the drug-receptor complex goes to the nucleus.
Thyroid hormone binds with receptors in the nucleus.

↓
Drug-receptor complex in the nucleus

↓
Drug-receptor complex binds with DNA & stimulates transcription of specific gene

↓
mRNA

↓
Protein

↓
Drug response

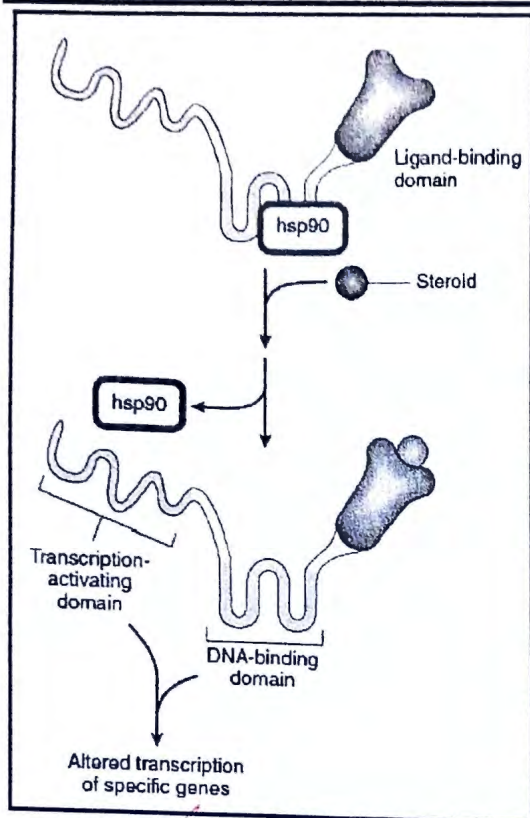


Fig. A Mechanism of glucocorticoid action. The glucocorticoid receptor polypeptide has three distinct domains. A heat-shock protein, hsp90, binds to the receptor in the absence of hormone and prevents folding into the active conformation of the receptor. Binding of a hormone ligand (steroid) causes dissociation of the hsp90 stabilizer and permits conversion to the active configuration.

(Ref: Katzung-13th/27)

Q. Describe signal transduction mechanism due to α -receptor stimulation. (CU-17M)

Ans.

Signal transduction mechanism due to α -receptor stimulation

After stimulation of α -receptor, signal is transduced through cell membrane-phospholipid 2nd messenger system by the following way-

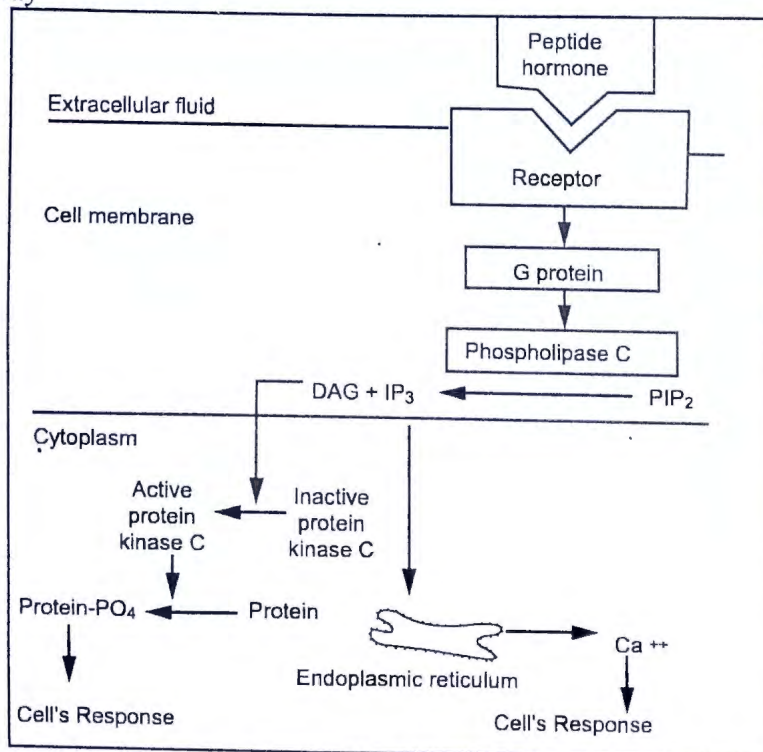


Fig : Membrane phospholipid system

Nice to know

G protein: G protein is a membrane protein consisting of 3 subunits (α , β , γ) that binds with GDP and is always coupled with receptor. α GTP has the GTPase activity.

Activation-inactivation of G proteins: The agonist activates the receptor ($R \rightarrow R^*$), which promotes release of GDP from the G protein (G), allowing entry of GTP into the nucleotide binding site. In its GTP-bound state (G-GTP), the G protein regulates activity of an effector enzyme or ion channel (E). The signal is terminated by hydrolysis of GTP, followed by return of the system to the basal unstimulated state.

(Ref: Katzung-12th/25)

Mechanism of drug action by non-classical receptors

Q. Explain drug-enzyme interactions; (RU-14Ju)

Q. Give the examples of drug-enzyme interactions. (RU-16Ju)

Q. How does the therapeutic benefit can be obtained by modulations of enzyme activity by drugs? (CU-16Ju)

Ans.

Drug-enzyme interactions: Enzyme acts as a non-classical receptor. Drugs bind with enzyme and produce action.

Enzyme stimulation: eg, Nitrovasodilator $\rightarrow$ NO $\rightarrow$ Stimulates guanylyl cyclase $\rightarrow$ $\uparrow$ cGMP $\rightarrow$ Drug action.

False substrate mechanism: Drug is converted into other substrate that is less active than true substrate. Example—

α -Methyl Dopa (False substrate)

$\downarrow$ Dopa decarboxylase

α -Methyl Dopamine (Here, true substrate is Dopa)

Enzyme inhibition: Enzyme inhibition is a common mode of drug action. This is of two types—

1. **Nonspecific inhibition:** Heavy metals, strong acids & alkali, alcohol etc. non-specifically inhibits enzymes.

2. **Specific inhibition:**

(a) **Competitive inhibition:**

Drug	Enzyme which is inhibited	Competes with
Physostigmine & Neostigmine	Cholinesterase enzyme	Acetylcholine
Captopril	Angiotensin converting enzyme	Angiotensin-I
Sulfonamide	Folate synthetase enzyme	PABA
Allopurinol	Xanthine oxidase enzyme	Hypoxanthine
Carbidopa & methyl Dopa	Dopa decarboxylase enzyme	Levodopa

(b) **Non-competitive inhibition:**

Drug	Enzyme which is inhibited
Acetazolamide	Carbonic anhydrase
Aspirin	Cyclooxygenase
Omeprazole	$H^+ - K^+ - ATPase$
Digoxin	$Na^+ - K^+ - ATPase$
Theophylline	Phosphodiesterase
Disulfiram	Aldehyde dehydrogenase

Quantitative aspects of drug action

Dose-response relationship

Q. Define dose-response relationship. What are the types of it?

Q. Enumerate the dose-response relationship. (CU-04S)

Q. Short note: Dose-response relationship. (DU-17J, CU-05M, 04M)

Ans.

Dose-response relationship:

Definition: The graphical representation of concentration of drug (at the site of action) & response is called dose-response relationship.

Type of dose-response relationship:

1. **Graded dose-response relationship:** Represents response variability according to dose.
2. **Quantal dose-response relationship/ percent-dose relationship/all or none relationship:** Represents individual variation of response at a fixed dose.

Q. Define graded dose-response relationship. (DU-08J)

Q. Discuss about graded dose-response relationship. Q. What information can we get from it? (DU-15Ju)

Q. What information can we get from a log dose response curve? (DU-08J)

Q. Short note: Graded dose-response relationship. (CU-05M)

Ans.

Graded Dose Response Relationship:

Definition: When the response to a drug is measured against increasing concentrations of a drug, the graph of the response versus the drug concentration or dose is called a *graded dose-response curve*.

(Ref: Katzung & Trevor's-11th edition)

As the concentration of a drug increases, the response also increases. The response is a graded effect, meaning that the response is continuous and gradual.

(Ref: Lippincott's-6th/30)

Types of graded dose response curve: Two types-

1. **Arithmetic form:** Shape is hyperbola. Here response is plotted against arithmetic concentration of drug.
2. **Log scale form:** Shape is sigmoid. Here response is plotted against semilogarithmic concentration of drug.

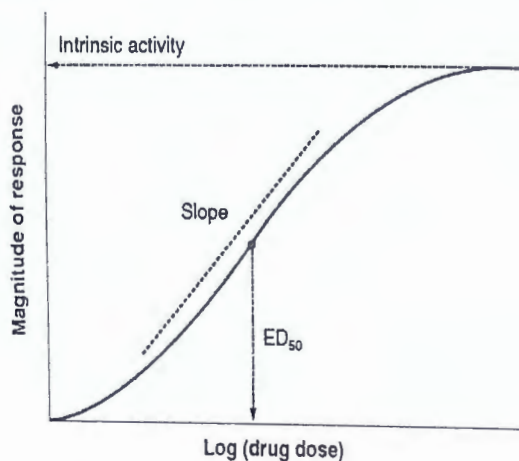


Fig. Graded dose-response graphs.

Information we get from log dose response curve:

1. Efficacy (E_{max})
2. Potency (EC_{50}): The *smaller* the EC_{50} (or ED_{50}), the *greater* the potency of the drug.
3. Affinity

4. Selectivity of a drug.
5. Sensitivity of a drug.
6. Safety margin of a drug
7. Potential variability of responsiveness among individual
8. Types of drug antagonism.

Importance:

1. For calculation of ED_{50} and LD_{50} .
2. A wide range of drug doses can be easily displayed on a graph.
3. Comparison between agonists and study of antagonists become easier.
4. To compare efficacy and affinity of drug.

Advantages of log scale form:

1. Easy to calculate the response
2. Large numbers of figures can be accumulated.
3. Maximum portion of the curve remains in the linear way. So we can compare the efficacy and potency of one drug with the other.
4. Short paper is needed.
5. We can perform a valid comparison as middle portion of the curve is straight line.

Q. Write down about quantal dose-response relationship.

Ans.

Quantal dose-response relationship:

Definition: The quantal dose-response curve is graphical presentation of the dosage of a drug to the frequency with which a designated response will occur within a population. The response may be an "all-or-none" phenomenon; e.g., individuals either do or do not fall asleep after receiving a sedative.

(Ref: BRS Pharmacology-6th/6)

Definition: A graph of the fraction of a population that shows a specified response at progressively increasing doses is called quantal dose-response relationship.

(Ref: Katzung & Trevor's-11th edition)

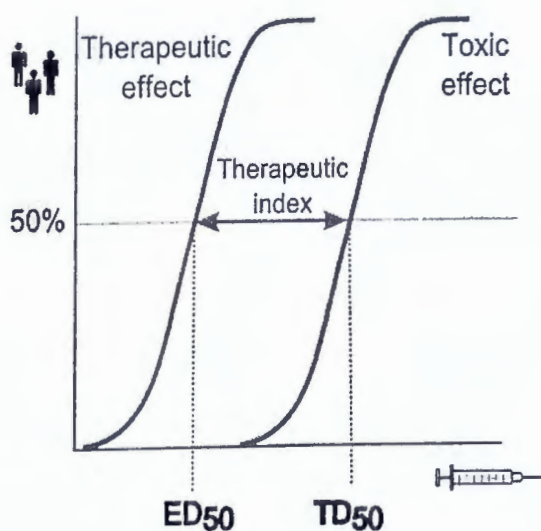


Figure: Quantal dose response curve showing TI, ED_{50} , TD_{50} . Dose of drug in plasma is plotted in the horizontal axis while the percentage of individuals (animals or humans) that responds or shows a toxic effect is represented in the vertical axis.

Shape of the curve: Sigmoid shaped

Examples of quantal responses: Quantal responses obey all-or-none law. There is either maximum response or no response at all. Examples of such responses are-

1. Prevention of convulsions
2. Prevention of arrhythmia
3. Prevention of death
4. Relief of headache etc.

(Ref: Katzung-13th/36)

Information from quantal dose response curve:

1. Therapeutic index (TI)
2. Median effective dose (ED_{50})
3. Median toxic dose (TD_{50})
4. Median lethal dose (LD_{50}) (in animals).
5. Variation in sensitivity to the drug in a given population.
6. Potency

(Ref: Katzung & Trevor's-11th edition)

Disadvantages of quantal-dose response curve:

1. Very long paper is needed.
2. Two drugs cannot be compared.

Nice to know

- **ED 100 (Effective dose 100):** It is the amount of a drug that is going to produce desired effect among cent percent of respondent in experimental population.
- **TD100 (Toxic dose 100):** It is the amount of a drug that is going to produce toxic effect among the whole respondent in experimental population.
- **Risk-benefit ratio:** This term is very frequently used & conveys a judgment on the estimated harm (adverse effects, cost, & inconvenience) versus expected advantages (relief of symptoms, cure & reduction of complication or mortality, improvement in quality of life). A drug should be prescribed only when the benefits outweigh the risks.

(Ref: Tripathi-6th/55)

Q. Differentiate between graded dose response curves and quantal dose response curve.

Ans.

Between graded dose response curves and quantal dose response curve

Graded dose response curves	Quantal dose response curves
1. It displays the response to a drug measured against increasing concentrations of a drug.	1. It is a graph of the fraction of a population that shows a specified response at progressively increasing doses.
2. Responses are graded when they increment gradually (eg, heart rate change) as the dose of drug increases.	2. They are quantal and follow all-or-none law .
3. Plots the increment in physiologic or biochemical response as dose or concentration is increased.	3. Plots the increment in the percent of the population under study that responds as the dose is increased
4. Efficacy of drug can be measured.	4. Efficacy of drug cannot be measured.
5. Therapeutic index (TI) cannot be measured.	5. Therapeutic index (TI) can be measured.
6. Data is obtained from small number of individuals.	6. Data is obtained from many individuals.

Agonists: Efficacy, Potency

Q. Define affinity, potency and efficacy with example. (RU-15J)

Q. Define intrinsic activity and potency. (CU-13Ju)

Q. Short note: Potency and efficacy. (DU-15Ju, 13J, 12J, 10Ju)

Ans.

Affinity: Tendency of a drug to bind with its receptor is called affinity.

Potency:

Definition: Potency is a measure of the amount of drug necessary to produce an effect of a given magnitude. For a number of reasons, the concentration producing an effect that is 50% of the maximum is used to determine potency.

Explanation: Potency is commonly designated as the EC_{50} . (EC_{50} is the drug dose that shows fifty percent of maximal response.) The term potency is used as a comparative term for distinguishing which agonist has a higher affinity for a given receptor. The drug which can produce an effect at lower drug concentrations is "more potent".

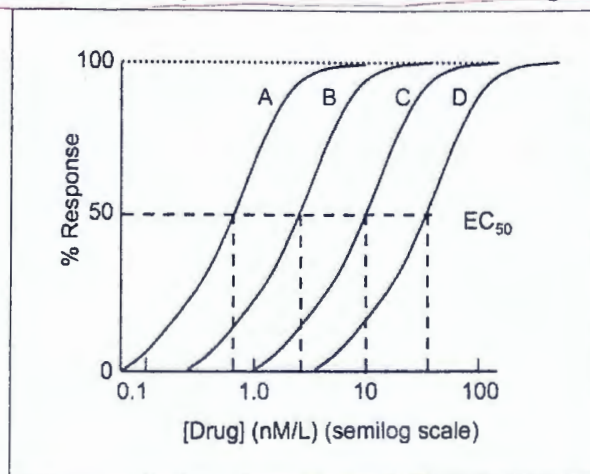


Figure. Dose-response curves for a series of agonists (A, B, C and D) that have the same efficacy, but differ in terms of their potency. The most potent drug (Drug A) has the lowest EC_{50} value, and Drug D is the least potent.

Efficacy / Intrinsic activity (IA):

Definition: Efficacy (intrinsic activity) is an inherent property of an agonist to illicit a physiologic response when it interacts with a receptor.

Efficacy—often called maximal efficacy—is the greatest effect (E_{max}) an agonist can produce if the dose is taken to very high levels.

Important features of efficacy:

1. By definition, it is a property of the drug, not the receptor or tissue.
2. Efficacy is dependent on the number of drug-receptor complexes formed.
3. It can be measured with a graded dose-response curve but not with a quantal dose-response curve.
4. Efficacy is more important than potency. A drug with greater efficacy is more therapeutically beneficial than one that is more potent.

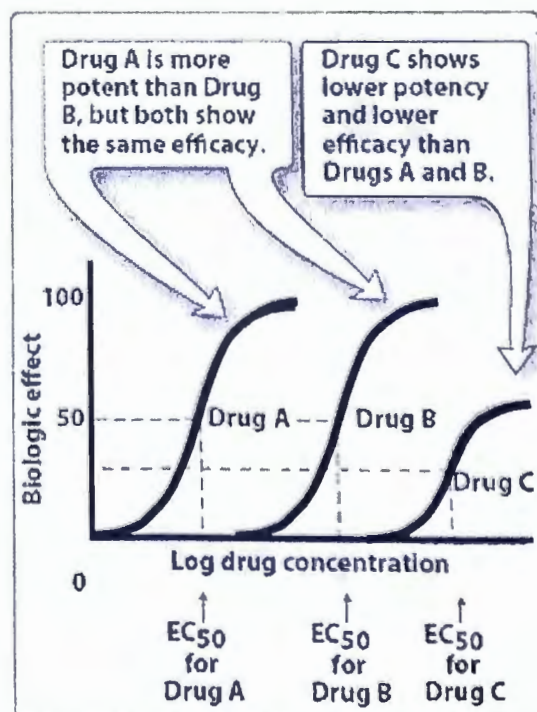


Figure. Typical dose-response curve for drugs showing differences in potency and efficacy.

Q. What are the differences between potency and efficacy of a drug? (DU-13J,11Ju)

Q. Compare potency with efficacy with example. (RU-12Ju)

Ans.

Differences between potency and efficacy of a drug

Traits	Potency	Efficacy
1. Definition	Potency is a measure of the amount of drug necessary to produce an effect of a given magnitude. Potency $\equiv$ Affinity	Efficacy is an inherent property of an agonist to illicit a physiologic response when it interacts with a receptor. Efficacy $\equiv$ Intrinsic activity
2. Measurement	The dose producing 50% of the maximum response is used to determine potency.	Efficacy is the greatest effect (E_{max}) an agonist can produce if the dose is taken to very high levels.
3. Determination	Determined from either graded or quantal dose-response curves.	Determined from graded dose-response curve.
4. Significance	A drug with greater potency is not more therapeutically beneficial than one that is more efficacious.	A drug with greater efficacy is more therapeutically beneficial than one that is more potent.
5. Depends on	- Affinity of receptor for binding with drug. - Efficacy of drug receptor interaction.	Mode of interaction with receptor.
6. Importance	- It determines the dose of the chosen drug. - Important in drugs of low therapeutic index.	- Determines the clinical effectiveness of drug. - Efficacy helps to choose a drug among a particular group.

Q. Define agonist with example. (RU-17J,16J,15J,14J,11J,08Ju,05M; SU-06M)

Q. Short note: Agonist. (DU-15Ju,12J,10Ju)

Ans.

Agonist:

Definition: If a drug binds to a receptor and produces a biologic response that mimics the response to the endogenous ligand, it is known as an agonist.

(Ref: Lippincott's-6th/33)

Definition: Drugs having strong **affinity** to a receptor as well as good **efficacy** are called agonist.

(Ref: Lippincott's-6th/33)

Agonist + Receptor $\xrightarrow{\text{Affinity}}$ Agonist-Receptor complex $\xrightarrow{\text{Efficacy}}$ Tissue response

Example:

1. Phenylephrine is an agonist at α_1 -adrenoceptors.
2. Salbutamol is an agonist to β -adrenoceptor.
3. Pilocarpine is an agonist to muscarinic receptor.

Antagonists

Q. Define antagonist with example. (RU-17J,16J,15J,14J,11J,10J,08Ju, SU-06M)

Q. Short note: Antagonist. (DU-15Ju,10Ju)

Ans.

Antagonist:

Definition: Antagonists bind to the receptor but do not initiate a response; that is, they block the action of an agonist or endogenous substance that works through the receptor.

(Ref: BRS pharmacology-6th/5)

Definition: Drug having **affinity** to a receptor but **no efficacy** (no intrinsic activity) is called antagonist.

Antagonist + Receptor $\xrightarrow{\text{Affinity}}$ Antagonist-Receptor complex $\xrightarrow{\text{No efficacy}}$ No tissue response

Example:

- Muscarinic receptor antagonists: Atropine, Tropicamide.
- H₂-receptor antagonists: Ranitidine, Cimetidine.

Types of antagonists:

1. **Pharmacologic Antagonists:** When one drug antagonizes the action of another drug by acting on the *same* receptor, it is called pharmacological antagonism.

- a. **Competitive antagonist:** Competitive antagonists combine with the same site on the receptor but their binding does not activate the receptor. Competitive antagonists may be **reversible** or **irreversible**. Reversible, competitive antagonists are not covalently bound, shift the dose-response curve for the agonist to the right, and increase the ED₅₀.

(Ref: BRS Pharmacology-6th/5)

For example, the antihypertensive drug **prazosin** competes with **norepinephrine**, at α_1 receptor, causing vasodilation and reducing blood pressure. The agonist, if given in a high enough concentration, can displace the antagonist and fully activate the receptors.

- b. **Noncompetitive antagonist:** Noncompetitive antagonists bind to the receptor at a site other than the agonist-binding site and either prevent the agonist from binding correctly or prevent it from activating the receptor. Receptors unoccupied by antagonist retain the same affinity for agonist, and the ED₅₀ is unchanged.

(Ref: BRS Pharmacology-6th/5)

For example, drugs such as **verapamil** and **nifedipine** prevent the influx of Ca²⁺ through the cell membrane and thus block non-specifically the contraction of smooth muscle produced by other drugs.

(Ref: Lippincott's-6th/33+ Katzung & Trevor's-11th edition)

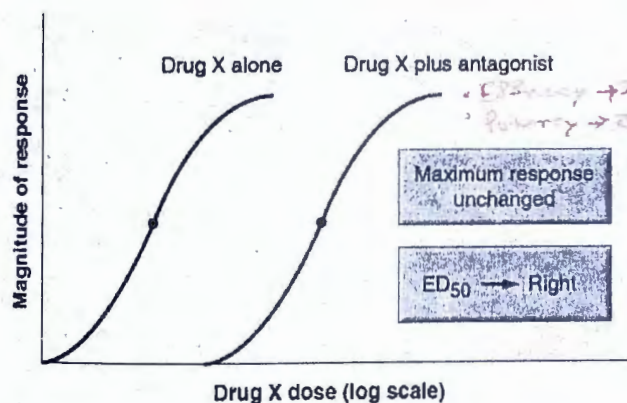


Fig. Graded dose-response curves illustrating the effects of competitive antagonists.

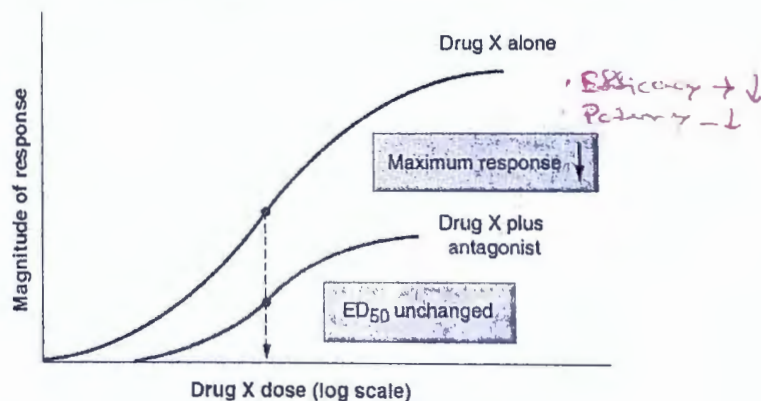


Fig. Graded dose-response curves illustrating the effects of noncompetitive antagonists.

2. **Physiologic Antagonists:** A physiologic antagonist binds to a *different* receptor molecule, producing an effect opposite to that produced by the drug it antagonizes.

Examples:

- Histamine binds with histamine receptors and cause bronchoconstriction. But epinephrine binds with β_2 receptors and cause bronchodilation.
- Acetylcholine causes bronchoconstriction by acting on M₂ receptor. Adrenaline causes bronchodilation by acting on β_2 receptor.

3. **Chemical Antagonists:** When one drug antagonizes the effect of another drug by simple chemical reaction, it is called chemical antagonist. Here no receptors are involved.

Examples:

- Heparin (acidic) + Protamine sulphate (basic) → Chemical neutralization of heparin
- Gastric acid (HCl) + antacid → Chemical neutralization of HCl → No HCl-induced-peptic ulcer.
- Dimercaprol + Lead → Chelation.

(Ref: Tripathi-6th/56)

Q. Define partial agonist. (RU-16J,08Ju,05M; SU-06M)

Q. Short note: Partial agonist. (DU-12J)

Ans.

Partial agonist:

Definition: The drug that combines with its specific receptor and evokes weak responses and also prevents a full agonist from acting on that receptor, is termed partial agonist.

(Ref: Bennett & Brown-11th)

Criteria:

1. Partial agonists cannot produce a maximal response. Such drugs have an intrinsic activity of < 1 . (Full agonists occupy receptors to cause maximal activation; intrinsic activity = 1.)
2. Partial agonists are partial antagonist also i.e. they have both antagonist and agonist action. Individually it acts as a weak agonist but in presence of a potent agonist it will act as an antagonist.

(Ref: Bennett & Brown-11th; BRS Pharmacology-6th/5)

Example: Nalorphine, Clonidine, Pindolol, Acebutolol etc.

- Nalorphine when administered alone produces relief of pain by blocking morphine receptor. If Nalorphine is given to a Morphine treated patient, it opposes the effect of morphine. So, Nalorphine is a partial agonist.
- Pindolol (β -blocker) has a partial agonistic activity. The partial agonistic activity of Pindolol is called "Intrinsic Sympathomimetic Activity (ISA)".

(Ref: Bennett & Brown-11th)

Q. Explain- Partial agonists are partial antagonist also.

Ans.

Partial agonists are partial antagonist also i.e. they have both antagonist and agonist action. Individually it acts as a weak agonist but in presence of a potent agonist it will act as an antagonist

(Ref: Bennett & Brown-11th)

Consider what would happen to the $E_{\max}$ of an agonist in the presence of increasing concentrations of a partial agonist. As the number of receptors occupied by the partial agonist increases, the $E_{\max}$ would decrease until it reached the $E_{\max}$ of the partial agonist. This potential of partial agonists to act both agonistically and antagonistically may be therapeutically exploited.

(Ref: Lippincott's-6th/33)

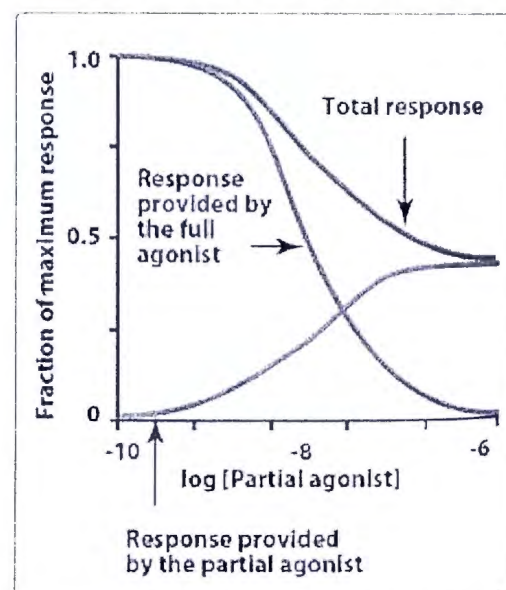


Figure. Effects of partial agonists.

Q. Define inverse agonist with example. (RU-16J, 14J, 08Ju, 05M; SU-16Ju)

Ans.

Inverse agonist:

Definition: If a drug activates a receptor to produce effects that are specifically opposite to those of the agonist, then the drug is called inverse agonist.

Example:

- **Benzodiazepines** are **agonists** on the benzodiazepine receptor in the CNS and produces sedation, anxiolysis, muscle relaxation and controls convulsions.
- **β -carbolines** which also bind to this receptor cause stimulation, anxiety, increased muscle tone and convulsions; they are **inverse agonists**.
- Both types of drug act by modulating the effects of the neurotransmitter GABA.

(Ref: Bennett & Brown-11th)

Nice to know

Inverse agonists have an intrinsic activity less than zero, reverse the activity of receptors, and exert the opposite pharmacological effect of agonists.

(Ref: Lippincott's-6th/34)

Q. Write down the differences between antagonist and partial agonist. (DU-16J)

Ans.

Differences between antagonist and partial agonist

Traits	Antagonist	Partial agonist
1. Definition	They have affinity to a receptor but no efficacy .	They combine with specific receptor and evoke weak responses and also prevent a full agonist from acting on that receptor.
2. Intrinsic activity	Zero	Greater than zero but less than one.
3. Nature	They never act as agonist.	They have both antagonist and agonist action.
4. Examples	Muscarinic receptor antagonists: Atropine, Tropicamide.	Nalorphine, Clonidine, Pindolol, Acebutolol etc.

Q. Define therapeutic index. (DU-10Ju, RU-13J; SU-09Ju, 06J)

Q. What information we get from TI? (SU-09Ju, 06J)

Q. What are the clinical significances of TI? (DU-10Ju, RU-13Ju, 11Ju, 10J; SU-05S)

Q. Short note: Therapeutic Index (TI). (DU-14J, 09Ju; CU-06M; SU-06M, RU-03M)

Ans.

Therapeutic index (TI):

Definition: Therapeutic Index (TI) is usually defined as the ratio of the median toxic dose (TD_{50}) to the median effective dose (ED_{50}).

(Ref: Katzung-13th/37)

Definition: Therapeutic Index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD_{50}) to the dose that produces a clinically desired or effective response (ED_{50}) in half the population

(Ref: Lippincott's-6th/35)

Determination of TI: In humans, the therapeutic index of a drug is determined using drug trials and accumulated clinical experience. These usually reveal a range of effective doses and a different range of toxic doses. Obviously, a full range of toxic doses cannot be ethically studied in humans. The TD_{50} and ED_{50} are determined from **quantal dose-response curves**.

$$\text{Therapeutic Index (TI)} = \frac{TD_{50}}{ED_{50}}$$

(Ref: Lippincott's-6th 35)

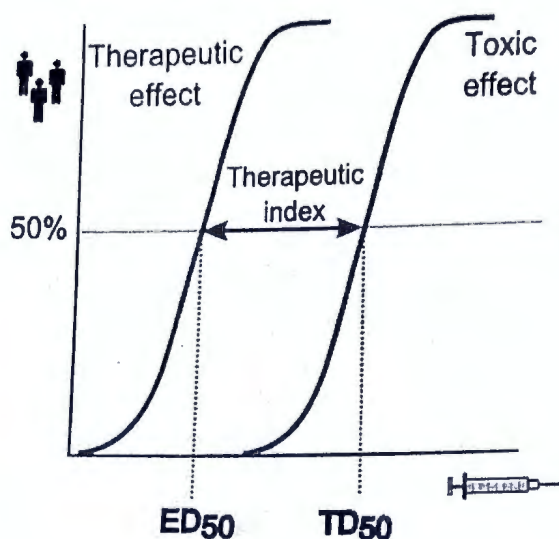


Figure: Quantal dose response curve showing Therapeutic Index, ED_{50} , TD_{50}

Information we get from TI / Importance of TI:

1. The therapeutic index represents an estimate of the safety of a drug, because a very safe drug might be expected to have a very large toxic dose and a much smaller effective dose. Therefore, the higher the TI, the safer the drug is & vice versa.
2. If TI of a drug is low, it should be used with caution.
3. For safer therapeutic application of a drug, its TI must be > 1 .
4. If $TI = 1$, the drug acts as a poison. Eg, the TI of the poison $K_6(CN)_6$ is 1.
5. A drug may have different TI depending upon its clinical use; e.g. aspirin.
 - in headache: TI is high.
 - in rheumatoid arthritis: TI is low.
6. For application of new drug, TI has greater significance.

Limitation of therapeutic index

1. It is based on animal toxicity data, which may not reflect forms of toxicity that are important clinically.
2. It takes no account of idiosyncratic toxic reactions.

Q. Name 2 drugs having low therapeutic index. (DU-06J, RU-11Ju)

Ans.

Drugs having low therapeutic index

1. Barbiturate
 - a. Thiopental Na
 - b. Phenobarbitone
2. Narcotic analgesic (morphine, pethidine)
3. Cardiac glycosides (eg, digoxin)
4. Aminoglycoside antibiotics
5. Anticoagulants (eg, warfarin)
6. Anticonvulsants
7. Antihypertensive drugs
8. Lithium.
9. Anticancer drugs
10. Oral contraceptives
11. Steroids
12. Quinidine
13. Drugs acting on the CNS.

Q. Name 2 drugs having high therapeutic index. (RU-11Ju)

Ans.

Drugs having high therapeutic index

1. Antibiotics
 - a. Penicillins (24 lac may be given without producing toxicity)
 - b. Sulfonamide
2. Benzodiazepines
 - a. Diazepam (200 mg can be given at a time if respiration is maintained)
 - b. Clonazepam
3. NSAIDs (eg, paracetamol)
4. Diuretics (thiazide)
5. Phenytoin

Q. Define Therapeutic window. Mention their clinical importance. (DU-12Ju)

Q. Short note: Therapeutic window.

Ans.

Therapeutic window (TW):

Definition: The range between the minimum toxic dose and the minimum therapeutic dose is called the therapeutic window.

(Ref: Katzung-13th/37)

In other words, therapeutic window of a drug is the range of drug dosages which can treat disease effectively while staying within the safety range.

For example, if the average minimum therapeutic plasma concentration of theophylline is 8 mg/L and toxic effects are observed at 18 mg/L, the therapeutic window is 8–18 mg/L.

(Ref: Katzung & Trevor's-11th edition)

Clinical importance

1. TW is a more clinically useful index of safety.
2. TW is of greater practical value in choosing the dose for a patient.
3. It can help to avoid most of the potential side effects.
4. It is more reliable than the therapeutic index, since it considers the biological variation among individuals to a larger extent.

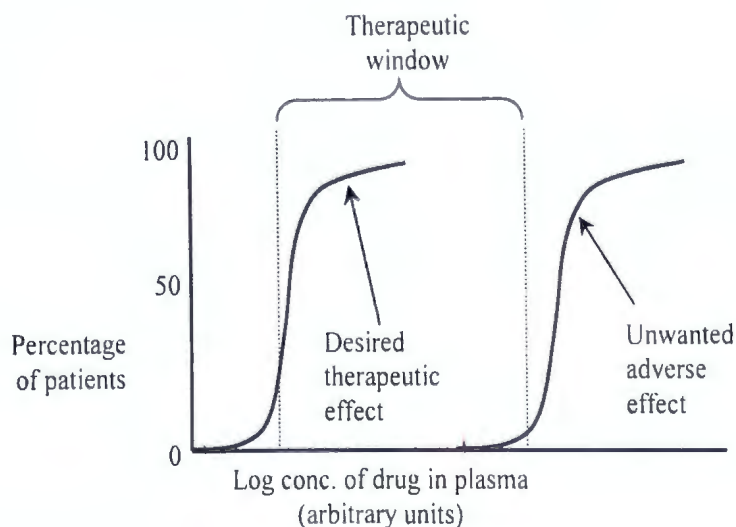


Fig. Therapeutic window.

Individual variations in drug responses

Q. Describe factors of individual variations of drug response. (CU-13Ju,12J,05J, SU-14Ju)

Ans.

Individual variations of drug response: Drug response varies among individuals due to the following factors.

1. Personal factors:
 - Age
 - Sex
 - Body weight and surface area
 - Nutrition
 - Alcohol
 - Cigarette smoking
2. Pathological conditions
3. Immunological factor
4. Genetic factor
5. Environmental factor
6. Psychological factor

Describe these factors from below.

Q. What are the factors modifying drug action? (DU-11Ju, CU-08, RU-03S, SU-14Ju)

Q. Explain with examples how age, pathological conditions & genetic factors modify drug action. (DU-11Ju,10J, RU-12J)

Q. Explain with examples how age, and environmental factors modify drug action. (DU-13J)

Q. Explain with examples how route of administration modify drug action. (RU-14J,11Ju)

Q. Describe the factors that influence response development after receptor activation. (CU-08Ju)

Q. Discuss the genetic factors that modify drug action. (CU-05S; RU-16Ju,13Ju,12J)

Q. How age, sex, body weight, nutritional status & pathological factors modify drug action? (RU-12J,06S)

Ans.

Factors modifying drug action:

A. Factors related to the patient:

1. Personal factors:
 - Age
 - Sex
 - Body weight and surface area
 - Nutrition
 - Alcohol
 - Cigarette smoking
2. Pathological conditions
3. Immunological factor
4. Genetic factor
5. Environmental factor
6. Psychological factor

B. Factors related to the drug:

1. Route of administration
2. Dose of drug
3. Time of administration
4. Drug combination
5. Drug interaction
6. Cumulation
7. **Tolerance:** Addiction

8. **Intolerance:** Hypersensitivity
9. Rate & extent of absorption
10. Distribution into body fluid
11. Plasma protein binding
12. Rate of metabolism & elimination

A. Factors related to the patient:

1. **Age:** Extreme of ages (too young or too old) alters drug action. Generally, drug doses should be reduced in both these cases.

a. Newborn & children:

- **Absorption of drug from the GIT is slower in neonates.** Transdermal absorption is faster because their skin is thin & more permeable. Hexachlorophane should not be applied over the skin of children.
- **Newborn has poor renal function.** So half life of the drugs excreted by glomerular filtration (Gentamicin) & tubular secretion (Penicillin) is prolonged by 3-5 times.
- **Hepatic drug metabolizing system is inadequate** in newborn. If chloramphenicol is given in diseases like enteric fever → It is not metabolized due to absence or deficiency of glucoronyl transferase in the liver → Moreover, maximum lipid-soluble drug cannot be excreted through the kidney → So accumulate in the body → Cross BBB → Goes to cardio-respiratory center → Normal lung & heart function is impaired → Gray baby syndrome.
- **Blood brain barrier is more permeable** → drugs attain higher concentration in the CNS. So, infants are more sensitive to CNS depressant drugs.
- **More plasma protein binding** → Enteric fever in infant → Administer sulphonamide → It has more affinity for plasma protein than bilirubin → So, bilirubin is displaced → Cross the BBB → Deposit in basal ganglia & auditory nucleus → Kernicterus.
- **Tetracycline** → Administered to baby below 5 yrs → Retarded bone & teeth growth.
- **Glucocorticoids/steroids** → Early fusion of epiphysis & diaphysis → short stature.

b. Elderly:

- **Renal function progressively declines** → ↓Drug excretion → ↑Drug half-life → ↑Drug action (there may be toxicity) → Drug dose should be reduced.
- Reduction in the hepatic microsomal enzyme & liver blood flow → ↓**Drug metabolism** → ↑Systemic bioavailability → ↑Drug action (there may be toxicity) → Drug dose should be reduced.
- **Slower absorption** due to reduced motility & less blood flow to intestine.
- **Lesser plasma protein binding** due to lower albumin.
- **Increased or decreased volume of distribution** of lipophilic & hydrophilic drugs respectively.

2. **Sex: Male** → Testosterone increases enzyme activity → ↑Metabolism → Short duration of action → Needs larger doses than females. Female metabolizes drugs less rapidly due to estradiol. Estradiol → Inhibits enzyme that metabolize drugs → Longer duration of drug action. So, they require smaller dose.

In case of **female**, following factors modify drug action-

a. Menstruation:

- Dysmenorrhea → Aspirin → Antiplatelet action → Inhibits platelet aggregation → ↑Blood loss.
- Constipation/pelvic congestion → Purgatives → ↑Motility of colon → It affects the uterus → ↑Blood loss during menstruation.

b. Pregnancy

- **First trimester:** Use of drugs may produce teratogenic effects.

Teratogenic effects:

- Aspirin → Cleft lip, palate
- Steroids → Talipes deformity.
- Thalidomide (hypnotic) → Phocomelia (Total absence of limbs).

Abortion: Aspirin & H₁ blocker → Implantation is interfered.

- **Second trimester:** Relatively safer. Order of safety: 2nd > 3rd > 1st trimester

1st - abortion
2nd - Teratogenicity
3rd - Foetal hypoxia / Foetal death

- **Third trimester:** Drug affects both mother & fetus equally.
 - Aspirin → ↓Synthesis of prostaglandin → delayed labor pain → Overmaturity of fetus → Bad for both mother & fetus.
 - Aspirin interferes with the patency of ductus arteriosus of fetus leading to CVS disorder.
 - Mother consumes tetracycline → It crosses blood-placental barrier (BPB) → Deposits in bones & teeth of fetus → Growth retardation.
 - Mother consumes steroid → BPB → Premature closure of metaphysis → Short stature.
 - Mother is hyperthyroidism → Antithyroid drugs are taken → Hypothyroidism of future baby.
- So, **risk-benefit ratio** should be considered before giving drugs.

- c. **Lactation:** A nursing mother should take the drug cautiously as drugs may go to the neonates through breast-feeding and cause side effects.
- Mother consumes tetracycline → Goes to neonates through breast-milk → Growth retardation.
 - Insomnia of mother → Consumes sleeping pill → Goes to neonates through breast-milk → CNS depression of neonates.
3. **Body weight and surface area:** It influences the concentration of the drug molecule attained at the site of action. So, dosage of drug should be modified according to body weight and surface area of the patient.
4. **Nutrition:**
- Malnutrition impairs the biotransformation of drugs.
 - Some vegetables such as cabbage, cauliflowers stimulate the intestinal biotransformation of some drugs.
5. **Alcohol:**
- Acute intake of alcohol inhibits the biotransformation of drug.
 - Chronic intake of alcohol increases the biotransformation of drug.
6. **Cigarette smoking:** Cigarette smoke is a rich source of benzopyrene, which is a potent enzyme inducer. Biotransformation of some drugs such as theophylline, caffeine and imipramine are several times higher in cigarette smokers.
7. **Genetic factor:** All key determinants of drug response; e.g. transporters, metabolizing enzymes, ion channels, receptors with their couplers & effectors are controlled genetically. Few examples are —
- The population of rapid acetylators metabolizes isoniazid to acetyl-isoniazid which is excreted in the urine. Slow acetylators metabolize isoniazid in a slower rate and are subjected to isoniazid toxicity such as peripheral neuropathy.
 - Glucose-6-phosphate dehydrogenase deficiency is responsible for haemolysis when these patients are exposed to certain drugs like primaquine, dapsone, quinolone, etc.
 - Acute intermittent porphyria precipitated by barbiturates is due to genetic defect in repression of porphyrin synthesis.
 - Resistance to warfarin is due to an abnormal epoxide reductase which has low affinity for the warfarin.
 - Pseudocholinesterase deficiency: Suxamethonium → ↓Metabolism → Suxamethonium apnea after surgery.
 - Down's syndrome: Atropine → Hypersensitivity.
 - Glucuronyl transferase deficiency: Salicylate → ↓metabolism → ↑Salicylate concentration → Salicylism.
8. **Pathological conditions:**
- **Meningitis:** Some antimicrobials (eg, benzylpenicillin, ampicillin, tetracyclines, streptomycin, gentamicin and cephalosporin) penetrate well the meninges when it is inflamed (meningitis).
 - **Gastrointestinal disease:**
 - In Coeliac disease, absorption of amoxicillin is decreased but that of cephalosporins & cotrimoxazole is increased.
 - Gastric stasis occurring during migraine attack retards the absorption of ingested drugs.
 - Achlorhydria decreases aspirin absorption by favouring its ionization.

- **Chronic liver diseases (CLD):**
 - Bioavailability of drugs having high 1st pass metabolism is increased due to loss of hepatocellular function & portocaval shunting.
 - Serum albumin is reduced; so protein binding of acidic drugs (diclofenac, warfarin etc.) is reduced & more drugs is present in free form for more pronounced drug action. So dose should be reduced.
 - Prodrug needing hepatic metabolism for activation, eg, prednisolone should be avoided.
 - The sensitivity of brain to depressant action to morphine & barbiturate is markedly increased in cirrhosis; so normal dose can produce coma.
 - Oral anticoagulants can markedly increase prothrombin time because clotting factors are already low.
- **Renal diseases:**
 - Clearance of drugs that are excreted unchanged in urine is reduced in renal diseases.
 - The permeability of blood brain barrier is increased in renal failure; Opiates, barbiturates, phenothiazines, benzodiazepines etc. produce more CNS depression.
- **Thyroid diseases:**
 - The hypothyroid patients are more sensitive to digoxin, morphine & CNS depressants.
 - Hyperthyroid patients are relatively resistant to inotropic action but more prone to arrhythmic action of digoxin.

9. Immunological factors:

- **Type I reaction:** Penicillin may cause anaphylactic shock.
- **Type II reaction:** Drug induced hemolytic anemia.
- **Type III reaction:** Glomerulonephritis may be induced by penicillamine.
- **Type IV reaction:** Contact dermatitis.

10. Environmental factor:

- Exposure to insecticides, carcinogens, tobacco smokes are known to induce drug metabolism.
- People living in urban/town area are exposed to hydrocarbon → Hydrocarbons induce hepatic microsomal enzyme → Rapid metabolism of drugs → ↓Drug action.
- Persons working in insecticidal factory → Insecticides induce hepatic microsomal enzyme → Rapid metabolism of drugs → ↓Drug action.
- People living in high altitude or hilly area → Inhibits hepatic microsomal enzyme → ↓Metabolism of drugs → ↑Drug action.
- People working with radiation, asbestos, benzene → Susceptible to cancer.

11. **Psychological factor:** Efficiency of a drug can be affected by patient's belief, attitudes & expectations. This is particularly applicable to centrally acting drugs; e.g. a nervous & anxious patient may require more general anesthetic drugs.

B. Factors related to the drug:

1. **Route of administration:** Route of administration governs the speed & intensity of drug response-
 - ***Onset of action:***
 - Oral route → Slow onset.
 - I/V, I/M, sublingual, inhalation → Rapid onset of action.
 - ***A drug may have entirely different uses through different routes; e.g.***
 - **Streptomycin:** When used in I/M route → Anti-tubercular effect.
When used orally → No action in lung → Acts as gut sterilizer.
 - **MgSO₄:** When taken orally → Acts as purgatives.
When given I/V → Acts as anticonvulsants in eclampsia.
When given as paste over sprained joint → Decreases swelling.

2. Time of administration:▪ **In relation to meal:**

- Antacid/aspirin → Effective after meal.
- Antihelminthic → After meal
- Foul-smelling & irritating drug (metronidazole) → After meal.

▪ **In relation to daytime:**

- Sedatives at night → More effective.
- Statins at night → More effective.

3. Dose of drug: Some drugs in different doses produce different effects, eg, as for phenobarbitone,

- 75 mg/kg is lethal dose.
- 1/2 of the lethal dose is anesthetic dose.
- 1/3 of anesthetic dose is hypnotic dose.
- 1/4 of anesthetic dose is sedative dose.

4. Cumulation: Any drug will accumulate in the body if rate of administration is more than the rate of elimination. However slowly eliminated drugs are particularly liable to cause cumulative toxicity; e.g. prolonged use of chloroquine causes retinal damage. Drugs having high $t_{1/2}$ shows cumulation. Eg, digitalis, Phenobarbitone, sulfonamide.

Advantage of cumulation: It is generally undesirable but desirable in the treatment of CCF, epilepsy.

5. Tolerance: It refers to the requirement of higher dose of a drug to produce a response. Tolerance is a widely occurring adaptive biological phenomenon.

(Ref: Tripathi-6th/61-67 + Misbahuddin-5th/42-45+Others)

Q. How dose of drug affects drug action?

Ans.

Effect on the dose of drug on drug action**1. Chlorpromazine**

- Low dose → Antiemetic.
- High dose → Antipsychotic.

2. Phenobarbitone:

- 75 mg/kg is lethal dose.
- 1/2 of the lethal dose is anesthetic dose.
- 1/3 of anesthetic dose is hypnotic dose.
- 1/4 of anesthetic dose is sedative dose.

3. Salicylate:

- Low dose (2 gm) → Increased accumulation of uric acid → Gout.
- High low dose (> 4 gm) → Increased excretion of uric acid → Relief of gout.

4. Paracetamol:

- Recommended dose → Antipyretic.
- High dose (10 tabs) → Hepatotoxicity.

5. Benzyl penicillin:

- Large dose → Prolong duration of action.

6. Any CNS depressant drug: Gradual increase of dose will give rise of the following effects-

- Sedation
- Hypnosis
- Narcosis

- Anesthesia
- Coma
- Death

7. Adrenaline

- In minimum effective dose → ↓BP.
- In therapeutic dose → ↑BP.

Q. How does route of administration affect drug action?

Ans.

Effect of Route of administration on drug action: Route of administration governs the speed & intensity of drug response-

1. Onset of action:

- Oral route → Slow onset.
- I/V, I/M, sublingual, inhalation → Rapid onset of action.

2. Duration of action: Oral route → Prolong duration of action.

3. On biotransformation: Oral route → First pass metabolism → Decreased action.

4. A drug may have entirely different uses through different routes; e.g. Streptomycin:

- When used in I/M route → Anti-tubercular effect.
- When used orally → No action in lung → Acts as gut sterilizer.

MgSO₄:

- When taken orally → Acts as purgatives.
- When given I/V → Acts as anticonvulsants in eclampsia.
- When given as paste over sprained joint → Decreases swelling.

Nice to know

Principles of drug action:

1. **Stimulation:** Adrenaline stimulates heart.
2. **Depression:** Barbiturates depresses CNS.
3. **Replacement:** Insulin in diabetes mellitus.
4. **Cytotoxic action:** Methotrexate as anticancer drug.
5. **Irritant drug:** Castor oil (laxative).

(Ref: Tripathi-6th/37)

Drug Interaction

Q. Define drug interaction.

Q. Name different types of drug interaction with example. (DU-06M)

Q. Name the different sites of drug interaction. (SU-04S)

Ans.

Drug interaction:

Definition: Drug interaction is a phenomenon which occurs when the effects of one drug are modified by the prior or concurrent administration of another drug. Drug interaction may result beneficial or harmful effects.

Sites of drug interaction: Interactions can occur—

1. Outside the body
2. At the absorption level
3. At the distribution level
4. At the biotransformation level
5. At the excretion level
6. At the receptor level

Types of drug interaction:

■ According to site of interaction:

A. Pharmaceutical interaction:

1. Outside the body

B. Pharmacokinetic interaction: Drug interaction at —

1. At the absorption level
2. At the distribution level
3. At the biotransformation level
4. At the excretion level

C. Pharmacodynamic interaction:

1. At the receptor level

■ According to effect:

1. Positive interaction / synergism:
 - a. Summation / addition
 - b. Potentiation / Super-addition
2. Negative interaction / antagonism.

A. Drug interaction outside the body: Loss of potency can occur from drug combination outside the body, eg,

1. Thiopentone + Suxamethonium → Precipitation
2. Diazepam + Infusion fluid → Precipitation
3. Phenytoin + Infusion fluid → Precipitation
4. Heparin + Hydrocortisone → Inactivation of heparin
5. Kenamycin + Hydrocortisone → Inactivation of kenamycin
6. Carbenicillin + Gentamycin → Inactivation of gentamycin

B. Drug interaction at absorption level:

1. Tetracycline + Antacid $\xrightarrow{\text{Complex formation}}$ Decreased absorption of tetracycline
2. Tetracycline + Mg(OH)_2 $\xrightarrow{\text{Complex formation}}$ Decreased absorption of tetracycline
3. Tetracycline + Ca $\xrightarrow{\text{Complex formation}}$ Decreased absorption of tetracycline

4. Tetracycline + Al $\xrightarrow{\text{Complex formation}}$ Decreased absorption of tetracycline
5. Tetracycline + NaHCO_3 $\xrightarrow{\text{Complex formation}}$ Decreased absorption of tetracycline
6. Tetracycline + Iron $\xrightarrow{\text{Complex formation}}$ Decreased absorption of tetracycline
7. Iron + Vit C $\rightarrow$ Increased absorption of iron.

C. Drug interaction at distribution level: A drug having more affinity to plasma protein can displace another drug having less affinity for the same binding site. So the displaced drug becomes free which is pharmacologically active and produces action.

1. **Displacement from plasma protein binding site:**

Displacing drug	Displaced drug	Result/effect
• Sulfonamide	Bilirubin	Kernicterus
• Sulfonamide	Methotrexate	Agranulocytosis
• Salicylates	Methotrexate	Agranulocytosis
• Salicylates	Tolbutamide	Hypoglycemia
• Salicylates	Sulfonamide	Sulfonamide toxicity
• Quinidine	Digoxin	Digoxin toxicity
• Indomethacin & Phenytoin	Warfarin	Bleeding
• Vitamin K	Bilirubin	Kernicterus
• Clofibrate	Warfarin	Enhanced anticoagulation
• Phenylbutazone	Warfarin	Bleeding
• Na-Valproate	Phenytoin	Phenytoin toxicity

(Ref: Bennett & Brown-11th; Tripathi-6th/22)

2. **Displacement from tissue binding site:**

- Quinidine + Digoxin $\rightarrow$ Quinidine displaces digoxin

3. **Direct interaction:**

- Protamine- SO_4 + Heparin $\rightarrow$ Neutralization $\rightarrow$ $\downarrow$ Heparin action / toxicity
- Fe + Desferrioxamine $\rightarrow$ Neutralization $\rightarrow$ $\downarrow$ Fe action / toxicity

D. Drug interaction at biotransformation level:

1. **Enzyme induction:** Enzyme induction by one drug increases biotransformation of another drug and is a cause of therapeutic failure.

Inducer	Drug whose metabolism is induced	Effect
Rifampicin	Oral contraceptives	Failure of contraception
Phenobarbitone	Oral contraceptives	Failure of contraception
Phenytoin	Oral contraceptives	Failure of contraception
Rifampicin	Warfarin	Decreased anticoagulation
Phenobarbitone	Warfarin	Decreased anticoagulation
Phenytoin	Warfarin	Decreased anticoagulation
Phenylbutazone	Warfarin	Decreased anticoagulation
Phenobarbitone	Chloramphenicol (in premature baby)	No Gray baby syndrome

2. **Enzyme inhibition:** Enzyme inhibition by one drug limits biotransformation of other drugs and is a cause of intense drug action with a long duration.

Inhibitor	Drug whose metabolism is inhibited	Effect
Cimetidine	Warfarin	Hemorrhage
Chloramphenicol	Warfarin	Hemorrhage
Metronidazole	Tolbutamide	Hypoglycemic shock
Allopurinol	Azathioprine	Bone marrow suppression

E. Drug interaction at excretion level: When two drugs compete with each other for the same binding site of a carrier protein for excretion, one influences the excretion of the other. Eg,

1. **Penicillin + Probenecid:** Penicillin has a shorter half-life. Probenecid & Penicillin both use organic acid transporter for tubular secretion & probenecid has the better affinity. So, simultaneous administration of probenecid and penicillin causes decreased secretion of penicillin and this increases duration of action of penicillin.
 Penicillin + Probenecid → Probenecid inhibits active secretion of penicillin → decreased excretion of penicillin → increased duration of action of penicillin.
2. **Quinidine + Digoxin** → Quinidine inhibits active secretion of digoxin → decreased excretion of digoxin → increased duration of action of digoxin.

F. Drug interaction at receptor level / Pharmacodynamic interaction:

1. Positive interaction / synergism:
 - Summation / addition
 - Potentiation / Super-addition
2. Negative interaction / antagonism.

Q. Explain the consequence- Ferrous sulphate and antacid given together. (DU-13Ju)

Ans.

Iron + Antacid

Result: Decreased bioavailability of Iron only.

Explanation: Interaction takes place at the level of absorption. Aluminium (Al^{3+}) of Antacid forms insoluble complex with Iron. Thus absorption of Iron from GIT is impaired reducing its bioavailability.

Nice to know

Objectives of drug interaction:

1. To obtain a desired therapeutic effect.
2. To broaden the spectrum of activity in case of antibiotic therapy.
3. To treat more than one diseases simultaneously.
4. To prevent development of drug resistance.
5. To minimize adverse drug reaction
6. To delay the emergence of malignant cells in cancer chemotherapy.

Q. Classify drug interaction at receptor level / Pharmacodynamic interaction.

Ans.

Drug interaction at receptor level / Pharmacodynamic interaction

1. Positive interaction / synergism:
 - Summation / Addition
 - Potentiation / Super-addition
2. Negative interaction / Antagonism.

1. **Synergism:** When the net effect of two drugs used together is equal to or greater than the arithmetic sum of the effect of individual drug, it is called drug synergism.

a. **Summation / addition:** When the net effect of two drugs used together is equal to the arithmetic sum of the effect of individual drug, it is called summation. Here,

$$2 + 2 = 4$$

$$(\text{Effect of drug A} + \text{Effect of drug B}) = \text{Effect of drug (A+B)}$$

Example:

- Aspirin + Paracetamol → For Analgesia
- Amlodipine + Atenolol → For hypertension
- Glibenclamide + Metformin → For diabetes mellitus
- Antacids = $Mg(OH)_2 + Al(SiO_3)_3$ → For peptic ulcer

- b. **Potentiation:** When the net effect of two drugs used together is greater than the arithmetic sum of the effect of individual drug, it is called drug synergism. Here,

$$2 + 2 > 4$$

(Effect of drug A + Effect of drug B) > Effects of drug (A+B)

Example:

- Acetylcholine + Physostigmine
- Levodopa + Carbidopa
- Sulfamethoxazole + Trimethoprim = Co-trimoxazole
- Enalapril + Hydrochlorothiazide

(Ref: Tripathi-6th/56)

Benefits of synergism:

1. To increase the efficacy of drugs.
2. To reduce the toxic effects of drugs.
3. To reduce the dose of drugs.

2. **Drug antagonism:** See below

Q. Define drug antagonism. (DU-17M,16Ju, CU-15Ju,04J, SU-07Ju,06S)

Q. Name different types of drug antagonism with one example of each of them. (DU-17M,08Ju; SU-07J)

Q. What do you mean by physiological antagonism? (CU-11Ju, RU-08Ju)

Q. Discuss Physiological and Pharmacological antagonism. (DU-17J)

Q. Write short note on: Competitive antagonism. (DU-07M)

Q. Enumerate & discuss the criteria of competitive and noncompetitive pharmacological antagonism with example. (CU-15Ju,07Ju/J; SU-07J)

Q. Short note: Drug antagonism. (DU-14J)

Q. Short note: Physiological and Pharmacological antagonism. (DU-12J,10J)

Q. Short note: Physiological antagonism. (RU-16Ju,15J)

Ans.

Drug antagonism:

Definition: When the effect of one drug is reduced or abolished by the presence of another drug, the phenomenon is called drug antagonism.

Classification of drug antagonism:

A. **Receptor mediated antagonism:**

1. Physiological / Functional antagonism
2. Pharmacological antagonism

B. **Non-receptor mediated antagonism:**

1. Physical antagonism
2. Chemical antagonism.

Non-receptor mediated antagonism

Physical antagonism: When one drug antagonizes the effect of another drug by physical processes such as adsorption, it is called physical antagonism. Here no receptors are involved. e.g. Charcoal adsorbs alkaloids & can prevent their absorption- used in alkaloid poisoning.

(Ref: Tripathi-6th/56)

Chemical antagonism: When one drug antagonizes the effect of another drug by simple chemical reaction, it is called chemical antagonism. Here no receptors are involved. Example:

- Heparin (acidic) + Protamine sulphate (basic) → Chemical neutralization of heparin
- Gastric acid (HCl) + antacid → Chemical neutralization of gastric acid → No HCl-induced-peptic ulcer.

(Ref: Tripathi-6th/56)

Receptor mediated antagonism

Physiological / Functional antagonism: When one drug antagonizes the action of another drug by acting on two different types of receptors of the same physiological systems, it is called physiological antagonism.

Example:

- Acetylcholine causes bronchoconstriction by acting on M_2 receptor.
- Adrenaline causes bronchodilation by acting on β_2 receptor.

Properties of physiological antagonism:

1. Non-competitive antagonism: No competition of drug to reach the site of receptor.
2. Drugs act on different types of receptor.
3. It is dose independent.
4. The dose-response curve does not maintain parallel pathway.

Pharmacological antagonism: When one drug antagonizes the action of another drug by acting on the **same receptor**, it is called pharmacological antagonism. It is of 2 types-

1. Competitive / surmountable / reversible antagonism
2. Non-competitive / non-surmountable / irreversible antagonism

A. **Competitive antagonism:** If both the antagonist and the agonist bind to the **same site on the receptor** and are able to displace each other from the receptor site, it is called competitive drug antagonism.

Types:

1. **Reversible competitive antagonism:** Antagonists bind reversibly to the receptor. The agonist is able to displace the antagonist molecules from the receptors. It is the **commonest** and **most important** type of antagonism.
2. **Irreversible, or non-equilibrium, competitive antagonism:** It occurs when drugs form covalent bonds with the receptor. These are mainly used as experimental tools for investigating receptor function, and few are used clinically. Clinically used irreversible enzyme inhibitors include-
 - Aspirin
 - Omeprazole
 - Monoamine oxidase inhibitors.

Criteria of competitive antagonism:

1. There is often some similarity between the chemical structures of the agonist and antagonist molecules. The two drugs **compete with each other** for the same site on the receptor.
2. The antagonism is said to be **surmountable**, i.e., the effect of an antagonist can be overcome by increasing the dose of agonist.
3. In the presence of a reversible competitive antagonist, the **log dose-response curve** for an agonist is **shifted to the right**, but **maximal effect is unchanged**.
4. $ED_{50} \rightarrow$ Increased.

(Ref: Rang & Dale's-6th/16-18+ Katzung & Trevor's-11th edition)

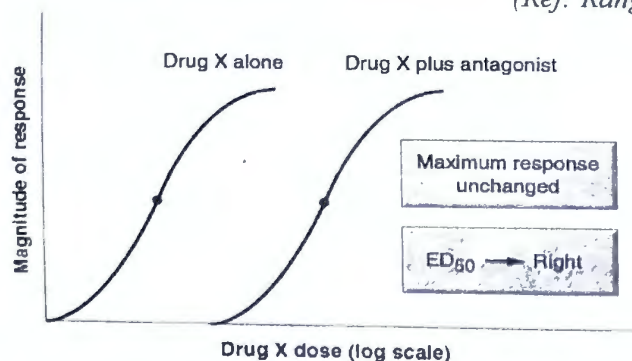


Fig. Graded dose-response curves illustrating the effects of **competitive antagonists**.

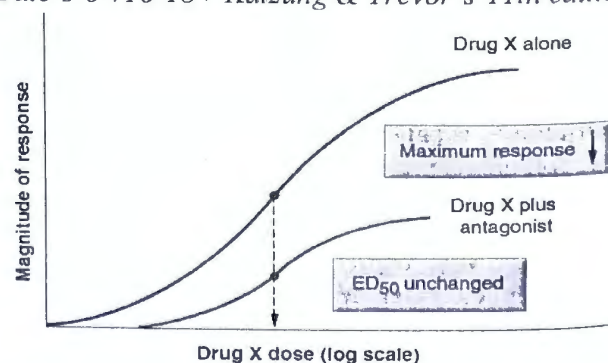


Fig. Graded dose-response curves illustrating the effects of **noncompetitive antagonists**.

B. Non-competitive antagonism:

Definition: Noncompetitive antagonists bind to the receptor at a site other than the agonist-binding site (allosteric site) and either prevent the agonist from binding correctly or prevent it from activating the receptor.

(Ref: BRS Pharmacology-6th/5)

For example, drugs such as **verapamil** and **nifedipine** prevent the influx of Ca^{2+} through the cell membrane and thus block non-specifically the contraction of smooth muscle produced by other drugs.

Types:

1. **Reversible:** Binds reversibly at an allosteric site of the receptor.
2. **Irreversible:** Binds irreversibly at an allosteric site of the receptor..

(Ref: Katzung & Trevor's-11th edition)

Properties:

1. No competition between antagonist and the agonist to bind with the receptor.
2. The antagonism is **not surmountable**, ie, the effect of an antagonist cannot be overcome by increasing the dose of agonist.
3. An irreversible antagonist causes a **downward shift of the maximum**, with **no shift of the curve** on the dose axis unless spare receptors are present.
4. Receptors unoccupied by antagonist retain the same affinity for agonist, and the **ED50** is **unchanged**.

Q. What is the clinical importance of drug antagonism? (RU-11J)

Ans.

Clinical importance of drug antagonism

1. **For specific antidote purpose:** In case of acute poisoning: e.g.
 - Naloxone in Morphine poisoning.
 - Pralidoxime in OPC poisoning.
2. **To prevent adverse drug reactions:** Isoniazid used in TB patient may cause peripheral neuropathy. Pyridoxine is used along with isoniazid to prevent peripheral neuropathy.
3. **For treatment purpose:** Antacids are used in peptic ulcer.

Q. Write the differences between pharmacological & physiological antagonism. (DU-10J, SU-17M)

Q. Compare & contrast pharmacological & physiological antagonism. (RU-13Ju, SU-15J)

Q. Write down the differences between competitive & physiological antagonism. (DU-16J)

Ans.

Differences between pharmacological & physiological antagonism:

Pharmacological antagonism	Physiological antagonism
1. Competitive / non-competitive	1. Always non-competitive
2. May be reversible or irreversible	2. Reversible
3. Acts by pharmacokinetic or pharmacodynamic mechanisms	3. Acts by pharmacodynamic mechanisms
4. May antagonize in the same physiological system or not.	4. Always antagonize in the same physiological system.
5. Dose dependent or not	5. Always dose dependent
6. Example: • Adrenaline + Propranolol → Antagonism • Adrenaline + Phenoxybenzamine → Antagonism	6. Examples: • Acetylcholine + Adrenaline → Antagonism • Insulin + Glucagon → Antagonism

Drug combination

Q. What is drug combination? What are the indications of use of drug combination?

Ans.

Drug combination: Drug combination means the simultaneous administration of two or more drugs either separately or in a single pharmaceutical formulation.

Indications of use of drug combination:

1. To obtain synergistic effect (e.g. co-trimoxazole).
2. To minimize adverse effects.
3. To broaden the spectrum of antimicrobial activity.
4. To prevent emergence of drug resistance.
5. To increase plasma concentration of one drug by another.
6. To treat severe infection.

Q. Short note: Fixed dose drug combination.

Ans.

Fixed dose drug combination: If the amount of drugs in a single pharmaceutical formulation is fixed, it is called fixed drug dose combination.

Example:

1. **Co-trimoxazole** = Trimethoprim (80 mg) + Sulfamethoxazole (400 mg)
2. **Fansider** = Sulfadoxine (500 mg) + Pyrimethamine (25 mg)
3. **Sinemet** = Levodopa (250 mg) + Carbidopa (25 mg)
4. **Rimstar 4-FDC**: Isoniazid 75mg + Rifampicin 150mg + Pyrazinamide 400mg + Ethambutol 275mg
5. **Rimstar 2-FDC**: Isoniazid 75mg + Rifampicin 150mg

Advantages of fixed drug dose combination:

1. Convenient to use.
2. Enhanced effect- Provides synergistic drug action (e.g. cotrimoxazole).
3. Minimization of unwanted effect.
4. Good patient compliance.
5. Prevention of emergence of drug resistance in antimicrobial therapy.

(Ref: Bennett, Brown-11th)

Therapeutic drug monitoring (TDM)

Therapeutic drug monitoring (TDM): Monitoring of drug therapy by measuring plasma concentration of a drug is known as therapeutic drug monitoring (TDM).

Indications of TDM:

1. Drugs with narrow therapeutic index (TI): Digoxin, phenytoin, aminoglycosides, etc.
2. Drugs showing wider inter-individual variations, eg, TCA.
3. To ascertain patient compliance.
4. In renal failure patients.
5. To check the bioavailability.
6. In patients who do not respond to therapy without any known cause.

TDM is not required in the following situations:

1. When clinical and biochemical parameters are available.
 - a. BP measurement for antihypertensive drugs.
 - b. Blood sugar estimation for anti-diabetic drugs.
 - c. PT, APTT, INR for anticoagulants.
2. Drugs producing tolerance.
3. Drugs whose effect persists longer than the drug itself, omeprazole.
4. If estimation is very expensive.

Drug safety and vigilance

Adverse drug Reactions

Q. What is adverse drug reaction (ADRs)? (DU-16J,13J,07Ju, CU-05J,04S, RU-07Ju, SU-09Ju)

Q. Outline adverse drug reaction. (SU-17M)

Q. Short note: Adverse drug reaction. (DU-15J, SU-15J)

Ans.

Adverse drug reaction (ADR): Adverse drug reaction is defined as harmful or seriously unpleasant effects occurring at doses intended for therapeutic (including prophylactic or diagnostic) effect and which call for reduction of dose or withdrawal of the drug and/or forecast hazard from future administration.

(Ref: Bennett & Brown-11th)

Q. Classify adverse effects & provide one example from each category. (DU-07Ju; CU-17J,15J,14J,10J, RU-12J)

Q. Describe different types of ADRs with example. (DU-16J,13J,07J, CU-08Ju,06J,05S; RU-12J,07Ju,06M, SU-11J,06S)

Q. Mention the dose unrelated ADRs with examples. (DU-08Ju)

Q. Describe Type-B adverse drug reactions. (SU-09Ju, CU-04S)

Ans.

Types of adverse drug reactions:

1. **Type-A / augmented (dose dependent) adverse drug reaction:** (*A for augmented*)

- Excessive therapeutic effects
- Pharmacological side effects
- Toxic side effects
- Secondary effects

2. **Type-B / Bizarre (dose independent) adverse drug reactions:** (*B for bizarre*)

- Immunological process (hypersensitivity reactions)
- Idiosyncrasy (unwanted effects due to inherited abnormalities)

3. **Type C (chronic):** Chronic reactions due to long term exposure; e.g.

- Isoniazid (INH) induced neuropathy
- Analgesic nephropathy
- Levodopa induced dyskinesia.

4. **Type D (delayed effect):**

- Carcinogenesis (delayed effects following prolong exposure)
- Teratogenesis (short term exposure at a critical time)

5. **Type E / withdrawal reactions (ending of use):** Here discontinuation of chronic therapy is too abrupt; e.g.

- Sudden / abrupt withdrawal of corticosteroids therapy causes iatrogenic Cushing's syndrome.
- Withdrawal syndrome after opioid analgesic.

(Ref: Bennett & Brown-11th)

Q. What are the factors that modify development of adverse drug reactions? (CU-09J)

Ans.

Factors influencing adverse drug reactions:

A. Non-drug factors:

▪ **Intrinsic to the patient:**

1. Age
2. Sex

3. Genetics
4. Habit
5. Personality
6. Tendency to allergy
7. Disease condition
8. Pregnancy

▪ **Extrinsic to the patient:**

1. The prescriber
2. The environment

B. Drug factors:

1. Use of the drug
2. Formulation of drug
3. Route of administration
4. Protein binding
5. Route and kinetics of metabolism
6. Excretion
7. Interactions between drugs

Q. Mention how to report adverse drug reactions. (CU-08J,06M)

Ans.

Reporting adverse drug reactions (ADRs): Health professionals play an important role in monitoring the safety of medicines by reporting any suspected adverse drug reactions (ADRs) to the therapeutic goods administration.

What to report: All suspected adverse reactions to any medicine, including prescription medicines, vaccines, over-the-counter medicines and complementary medicines.

1. Suspected ADRs to new medicines
2. Suspected drug interactions
3. Unexpected ADRs (i.e. reactions that are not described in the Product Information)
4. Serious ADRs, such as those suspected of causing:
 - a. Absence from productive activity
 - b. Admission to hospital
 - c. Prolongation of hospitalization
 - d. Increased investigation or treatment costs
 - e. Danger to life
 - f. Birth defects
 - g. Death

What should be included in the report: Each ADR report must include:

1. Patient identifier (e.g. initials)
2. Contact details for the reporter
3. A description of the reaction
4. Medicines suspected of causing the reaction

Q. Write down the cause of therapeutic failure. (CU-08J,06M)

Ans.

Causes of therapeutic failure:

1. Inappropriate drug
2. Inappropriate dosage regimen
3. Inappropriate route of administration
4. Inappropriate duration of treatment
5. Drug resistance
6. Inappropriate pt. compliance

Q. What are the differences between side effects & toxic effects?

Q. Mention the possible ways to prevent type A ADRs. (CU-05J)

Ans.

Differences between side effects & toxic effects:

Traits	Side effects	Toxic effects
1. Definition	It is the unwanted effect that develops within the therapeutic dose.	It is the severe form of side effect that develops on supra -therapeutic dose.
2. Forms of unwanted effect	Side effect may be the extension of main therapeutic action; e.g. dry mouth, blurred vision occurs in atropine therapy.	Toxic effect may occur with no relation to the main therapeutic effect of the drug; e.g. hepatotoxicity with rifampicin.
3. Predictability	Side effects can be predictable before Rx is begun. No / minimum monitoring is required for confirming side effects.	Prediction of toxic effects is confirmed after monitoring of the Rx; e.g. monitoring of blood picture after Rx with anti psychotics.
4. Ways of avoidance	Side effects can be avoided by reducing dose with compromising beneficial effects up to a certain limit / rearranging dosage schedule / modifying patients life styles; e.g. starting of captopril therapy from night reduces the 1 st dose hypotension.	With certain drugs toxic effects are unavoidable (bone marrow suppression in cytotoxic drugs). With certain drugs toxic effects are preventable (INH induced peripheral neuropathy is preventable with concomitant administration of pyridoxine).
5. Relation with therapeutic index	Side effects occur with drugs irrespective of therapeutic index.	Drugs having high TI rarely produce toxic effects when used in therapeutic doses.

Q. Write down about type-A reaction? (DU-07J, CU-06M/J)

Ans.

Type-A / augmented adverse drug reaction

Definition: Type A (Augmented) reactions will occur in everyone if enough of the drug is given because they are due to excess of normal, predictable, dose-related, pharmacodynamic effects. They are common and skilled management reduces their incidence.

Examples:

- Postural hypotension with antihypertensive
- Hypoglycemia with insulin
- Hypokalemia with diuretics

Type A reactions also include those that are not directly related to the desired pharmacological action of the drug (e.g. dry mouth that is associated with tricyclic antidepressants).

Criteria of Type-A ADRs:

1. Augmented drug effect
2. Dose dependent
3. Predictable
4. Morbidity more, mortality less.
5. More common, mostly preventable & reversible.

Processes:

1. **Excessive therapeutic effects:**
 - Insulin / OHA → produces hypoglycemia.
2. **Pharmacological side effects:** Adverse effect within normal therapeutic dose is called side effect. Eg,
 - Morphine (analgesic) → produces constipation.
3. **Toxic side effects:** Adverse effect due to over or excess of therapeutic dose is called toxic effect. Eg,
 - Drugs with high TI → less toxic effect.
 - Drugs with low TI → more toxic effect.

4. **Secondary effects:** Secondary effects are the indirect consequences of a primary drug action. Examples are:

- Vitamin deficiency or opportunistic infection which may occur in patients whose normal bowel flora has been altered by antibiotics;
- Diuretic-induced hypokalemia causing digoxin intolerance.

(Ref: Bennett & Brown-11th)

Immunosuppressant / Corticosteroid → infection susceptibility ↑

Nice to know

Intolerance: Intolerance means a low threshold to the normal pharmacodynamic action of a drug. Individuals vary greatly in their susceptibility to drugs, those at one extreme of the normal distribution curve being intolerant of the drugs, those at the other, tolerant.

(Ref: Bennett & Brown-11th)

Q. Describe type-B adverse drug reaction. (SU-09Ju)

Q. Write down the characteristics of type-B ADRs. (DU-07J, CU-04S)

Ans.

Type-B adverse drug reaction

Definition: Type B adverse drug reactions are unpredictable, uncommon, usually not related to the pharmacological actions of the drug.

Examples:

Mechanisms	Examples
1. Intolerance	Tinnitus with use of aspirin
2. Hypersensitivity	Immunological reaction e.g. anaphylaxis with penicillin injection.
3. Pseudoallergic	Non-immunological reaction e.g. radio-contrast dye reaction.
4. Idiosyncratic reaction.	Development of anemia with the use of anti-oxidant drugs in the presence of glucose-6 phosphate dehydrogenase deficiency.

Characteristics of type-B adverse drug reactions:

1. Type B (Bizarre) reactions will occur only in some people.
1. Bizarre in nature
2. Dose independent
3. These effects are unpredictable for the individual.
4. Morbidity less than type-A but mortality more.
5. Less common, generally more serious & require withdrawal of the drug & some specific measures.
6. Suitable tests to characterize the individual's phenotype is performed; e.g. skin test (intradermal, patch) or intranasal tests may forewarn incase of type-I hypersensitivity.

Q. Compare between Type A and Type B adverse drug reactions. (CU-17J,15J)

Ans.

Comparison between Type A and Type B reactions:

Type A	Type B
1. Predictable	1. Unpredictable
2. Usually dose dependent	2. Rarely dose dependent
3. High morbidity	3. Low morbidity
4. Low mortality	4. High mortality
5. Responds to dose reduction	5. Responds to drug withdrawal
6. Occurs in everyone if enough of the drug is given.	6. Occurs only in some people.
7. It is either is side effect or toxic effect, eg, hypoglycemia.	7. Mainly in the form of hypersensitivity and idiosyncrasy.

Drug hypersensitivity

Q. Discuss drug hypersensitivity. (CU-11Ju)

Q. Short note: Hypersensitivity. (RU-14Ju, SU-17J)

Ans.

Drug hypersensitivity: Allergic reaction to drugs is an abnormal immune response resulting from interaction of drug or metabolite or a non-drug element in the formulation with the patient and disease and subsequent re-exposure.

(Ref: Bennett & Brown-11th)

Features of drug allergy: The distinctive features of allergic reactions are:

1. Lack of correlation with known pharmacological properties of the drug
2. Lack of linear relation with drug dose (very small doses may cause very severe effects)
3. Rashes, angioedema, serum sickness syndrome, anaphylaxis or asthma; characteristics of classic protein allergy.
4. Requirement of an induction period on primary exposure, but not on re-exposure
5. Disappearance on cessation of administration and reappearance on re-exposure.
6. Occurrence in a minority of patients receiving the drug.
7. Temporary nature in some cases
8. Possible response to desensitization.

(Ref: Bennett & Brown-11th)

Classification of hypersensitivity: Coombs and Gel Classification-

1. Type I hypersensitivity or anaphylactic reaction
2. Type II or cytotoxic hypersensitivity
3. Type III or immune complex mediated hypersensitivity
4. Type IV or delayed or cell-mediated hypersensitivity
5. Type V or stimulatory type hypersensitivity.

Nice to know

Information on drug allergy:

1. There may be lack of history of previous exposure, and 'first dose reactions' are among the most dramatic. Exposure is not necessarily medical, e.g. penicillins may occur in dairy products following treatment of mastitis in cows, and penicillin antibodies are commonly present in those who deny ever having received the drug.
2. Immune responses to drugs may be harmful (allergy) or harmless.
3. The fact that antibodies are produced does not mean a patient will necessarily respond to re-exposure with clinical manifestations; most of the UK population has antibodies to penicillins but, fortunately, comparatively few react clinically to penicillin administration.
4. Whilst macromolecules (proteins, peptides, dextran polysaccharides) can act as complete antigens, most drugs are simple chemicals (mol. wt less than 1000) and act as incomplete antigens or haptens, which become complete antigens in combination with a body protein.
5. The chief target organs of drug allergy are the skin, respiratory tract, GIT, blood and blood vessels.

(Ref: Bennett & Brown-11th)

Type I hypersensitivity / Immediate hypersensitivity

Allergy: It means altered reactivity of tissue or body to subsequent exposure to the same antigen. Now-a-days allergy is considered as synonym of type-I hypersensitivity.

Allergens: They are immunogens that can produce type-I hypersensitivity.

Anaphylaxis: Anaphylaxis may be defined as a rapidly developing hypersensitivity response triggered by combination of antigen with IgE present on the mast cell or basophil in an individual who is pre-sensitized to that antigen and leading to anaphylactic shock.

Q. How does Penicillin produce anaphylaxis? (CU-16J)

Ans.

Mechanism of anaphylaxis / type-I hypersensitivity by drugs (eg, penicillin):

First exposure of a person to a drug to which he is allergic:

A drug (eg, penicillin) enters into the body for the first time



Taken up by macrophage



Macrophage processes & presents antigen to helper T-cell.



Helper T-cell stimulates B-cell



B cell transforms into plasma cells which produce IgE



IgE binds with receptors on the surface of mast cells and basophil (**Sensitization**)

Re-exposure (second & subsequent exposures) of the sensitized person to the same drug:

The drug molecule binds with IgE on the mast cell & basophil



Degranulation of mast cells and basophils



Release of mediators (eg, histamine, serotonin etc.)



- Increase vasodilatation
- Increase vascular permeability
- Increase glandular secretions (as in asthma, allergic rhinitis)
- Contraction of smooth muscle
- Anaphylactic shock



Anaphylaxis

Nice to know

Example of type I hypersensitivity:

Local anaphylaxis	▪ Skin allergy- Urticaria ▪ Allergic rhinitis ▪ Allergic conjunctivitis ▪ Atopic bronchial asthma ▪ Allergic gastroenteritis (food allergy)
Systemic anaphylaxis	▪ Penicillin hypersensitivity ▪ ATS hypersensitivity ▪ Bite of honey bees

Drugs causing type-I hypersensitivity:

▪ Penicillins ▪ Cephalosporins ▪ Sulfonamide ▪ Tetracyclines ▪ Quinolones ▪ Anti-TB drugs ▪ Phenothiazines	▪ Salicylates ▪ Carbamazepine ▪ Allopurinol ▪ ACE inhibitors ▪ Methyl Dopa ▪ Hydralazine ▪ Local anesthetics
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(Ref: Tripathi, 6th/83)

Type-II Hypersensitivity (Antibody-dependent cytotoxic type)

Definition: Type II hypersensitivity is mediated by antibody (IgG and IgM) toward antigen present on the cell surface resulting in cellular damage or cellular dysfunction.

Mechanism: The drug or metabolite combines with a protein in the body so that the body no longer recognizes the protein as self, treats it as a foreign protein and forms antibodies (IgG, IgM) that combine with the antigen and activate complement which damages cells.

(Ref: Bennett & Brown-11th)

Example:

Clinical condition	Offending drug
Hemolytic anemia	Penicillin Methyldopa Quinidine Sulfonamide
Thrombocytopenia	Phenylbutazone Quinine Rifampicin Sulfonamide TC
Agranulocytosis	Chloramphenicol Sulfonamide
Aplastic anemia	Chloramphenicol Sulfonamide
SLE	NH Hydralazine Sulfonamide

Type III hypersensitivity (immune complex-mediated type)

Definition: It is mediated by immune complex (antigen-antibody complex) and the tissue damage is mainly due to activation of complements and platelets.

Mechanism: Antigen and antibody form large complexes and activate complement. Small blood vessels are damaged or blocked. Leucocytes attracted to the site of reaction engulf the immune complexes and release pharmacologically active substances (including lysosomal enzymes), starting an inflammatory process.

Example of type III hypersensitivity:

1. SLE
2. Rheumatoid arthritis
3. Acute glomerulonephritis (AGN)
4. Arthus reaction, eg, Farmer's lung
5. Serum sickness:
 - a. Delayed complication of ATS & ADS.
 - b. Fever due to sulfonamide
 - c. Lymphadenopathy due to anticonvulsant
 - d. Urticaria due to penicillin

(Ref: Bennett & Brown-11th)

Type IV reactions (lymphocyte-mediated type): Antigen-specific receptors develop on T-lymphocytes. Subsequent administration leads to a local or tissue allergic reaction.

Example: Contact dermatitis- due to repeated exposure to inorganic substances.

(Ref: Bennett & Brown-11th)

Q. How can you prevent allergic drug reactions?

Ans.

Prevention of allergic drug reactions: Prevention is important since these reactions are unpleasant and may be fatal.

1. Taking a drug history.
2. Patients should always be told when they are thought to be allergic to a drug.
3. When looking for an alternative drug to avoid an adverse reaction it is important not to select one from the same chemical group.
4. Use of nonproprietary (generic) names as a matter of course.

(Ref: Bennett & Brown-11th)

Nice to know**Principal clinical manifestations of drug allergy**

1. Urticarial rashes and angioedema (types I, III). Commonest type of drug allergy.
2. Nonurticarial rashes (types I, II, IV).
3. **Diseases of the lymphoid system:** Infectious mononucleosis, lymphoma, leukaemia.
4. Anaphylactic shock (Type I)
5. **Pulmonary reactions:** asthma (type I). Aspirin and other NSAID may cause an asthmatic attack.
6. **Other types of pulmonary reaction (type III)** include syndromes resembling acute and chronic lung infections, pneumonitis, fibrosis and eosinophilia.
7. Serum sickness syndrome (type III).
5. **Blood disorders**
 - a. Thrombocytopenia (type II, but also pseudo-allergic)
 - b. Granulocytopenia (type II, but also pseudo-allergic)
 - c. Aplastic anaemia (type II, but not always allergic)
 - d. Haemolysis of all kinds.
8. Fever.
9. Collagen diseases (type II)
10. Hepatitis and cholestatic jaundice
11. Nephropathy of various kinds (types II, III)

(Ref: Bennett & Brown-11th)

Q. Short note: Pseudoallergic reactions.

Ans.

Pseudoallergic reactions

Definition: These are effects that mimic allergic reactions but have no immunological basis and are largely genetically determined.

Mechanism: They are due to release of endogenous, biologically active substances, e.g. histamine and leukotrienes, by the drug. A variety of mechanisms is probably involved, direct and indirect, including complement activation leading to formation of polypeptides that affect mast cells.

Example:

1. Pseudoallergic effects mimicking type I reactions are called **anaphylactoid** and they occur with-
 - Aspirin and other NSAIDs
 - corticotrophin (direct histamine release)
 - IV anesthetics
 - IV morphine, tubocurarine, dextran, radiographic contrast media
 - Inhaled (cromoglicate).

Severe cases are treated as for true allergic anaphylactic shock from which, at the time, they are not distinguishable.

2. Type II reactions are mimicked by the haemolysis induced by drugs (some antimalarials, sulphonamides and oxidizing agents) and food (broad beans) in subjects with inherited abnormalities of erythrocyte enzymes or hemoglobin.
3. Type III reactions are mimicked by-
 - Nitrofurantoin (pneumonitis)
 - Penicillamine (nephropathy)
 - Lupus erythematosus due to drugs (procainamide, isoniazid, phenytoin) may be pseudoallergic.

(Ref: Bennett & Brown-11th)

Idiosyncrasy

Q. Define idiosyncrasy. (CU-11Ju)

Q. Give three examples of idiosyncratic drug reactions. (CU-15Ju)

Q. Short note: Idiosyncrasy. (DU-12Ju, 11J; RU-17J, 14Ju, 13J)

Ans.

Idiosyncrasy

Greek

- Idios means- one's own, peculiar, distinct
- Synkrisis means- mixing together

Definition: This is an inherent qualitative abnormal reaction to a drug usually due to genetic abnormality.

(Ref: Bennett & Brown-11th)

Definition: Idiosyncratic drug reactions are type B adverse drug reactions that occur rarely and unpredictably amongst the population usually due to genetic abnormality.

Criteria

1. Reaction may occur at a **low dose**.
2. Most commonly, this is caused by an **enzymopathy**, congenital or acquired.
3. They do not occur in most patients but when they do occur they can be life-threatening.
4. **Genetic factors** may be responsible.

Examples:

1. **Chloroquine** and **primaquine** administration in an individual with **glucose-6-PO₄ dehydrogenase deficiency** causes hemolytic anemia.
2. **Suxamethonium** causes prolonged paralysis in patients with pseudocholinesterase deficiency.
3. **Troglitazone**-induced liver failure often leading to death or liver transplant.
4. **Clozapine**-induced agranulocytosis.
5. **Sulfonamide**-induced toxic epidermal necrolysis.

Q. Differentiate between hypersensitivity and idiosyncrasy. (CU-04J, SU-00S)

Ans.

Differences between hypersensitivity and idiosyncrasy:

Traits	Hypersensitivity	Idiosyncrasy
1. Definition	It is defined as inappropriate or excessive immune response to an antigenic stimulus in a pre-sensitized host leading to tissue damage.	This is an inherent qualitative abnormal reaction to a drug usually due to genetic abnormality.
2. Subtypes	4 subtypes	No subtypes
3. Time of occurrence	From the second exposure	From the first exposure
4. Examples	Penicillin hypersensitivity	Primaquine induced hemolytic anemia to an individual with glucose-6-PO ₄ dehydrogenase deficiency.

Q. What are the reasons for taking a drug history from a patient? (CU-13Ju)

Ans.

Reasons for taking a drug history from a patient

1. To find out any drug allergy
2. To find out any drug causing the current illness.
3. To avoid harmful drug interaction.

Tolerance

Q. Define & classify tolerance. (DU-12Ju,98J, RU-12Ju,08Ju; SU-13Ju)

Q. Write down the mechanism of tolerance.

Q. Short note: Tolerance. (DU-12Ju, CU-05S, RU-01J)

Ans.

Tolerance: Gradual decrease of response to a drug due to repeated administration of that drug is called tolerance. When tolerance develops, increased dose is required to get original response.

Types:

A. **Innate tolerance** (natural / pre-existing sensitivity/ insensitivity)

B. **Acquired tolerance:**

1. Pharmacokinetic (metabolic / dispositional)
2. Pharmacodynamic (functional)
3. Acute tolerance
4. Reverse tolerance
5. Cross tolerance

- **Innate tolerance:** Refers to genetically determined sensitivity or lack of sensitivity to a drug that is observed when the drug is administered for the first time eg, Penicillin allergy (anaphylactic shock).
- **Pharmacokinetic tolerance:** It refers to changes in the distribution or metabolism of a drug after repeated administration resulting in reduced conc. in the blood & subsequently at the site of action. Pharmacokinetic tolerance is achieved by-
 1. Drug absorption may be decreased, eg, alcohol.
 2. Drug metabolism may be increased.
 3. Drug distribution may be altered. It may bind with plasma protein more potently & cannot come to the field of action.
 4. The drug excretion may be increased.
E.g. Phenobarbitone (sleeping pill) → Induces microsomal enzymes in liver → ↑metabolism of drug → ↓action.

- **Pharmacodynamic tolerance:** It refers to adaptive changes that have taken place within system affected by the drug so that response to a given conc. of drug is reduced.

Mechanism:

1. **Down regulation of receptors:** In some cases prolonged exposure to agonists results in gradual reduction in the number of receptors.
 2. The sensitivity of the receptor may be decreased.
 3. There may be lack of drug-receptor dissociation, as in case of morphine, pethidine, heroine. So, subsequent dose must be higher than the previous dose to relieve pain.
- **Acute-tolerance:** It refers to rapid tolerance development with repeated use on a single occasion such as binge. e.g. Cocaine used with repeated doses over 1 to several hours.

- **Reverse tolerance** It refers to an increased response with repetition of the same dose of a drug. E.g., Repeated daily administration of a dose of cocaine to a constant rate produce increased motor activity & the effect increases over several days though the dose remains constant.
- **Cross tolerance:** It refers to the fact that repeated use of a drug of a given category produce tolerance not only to the drug being used but also other drugs of same structural & mechanical category. e.g. User to heroine are also tolerant to other opioids.

Q. Define tachyphylaxis. Give example. (RU-12Ju)

Q. Short note: Tachyphylaxis. (DU-12Ju)

Ans.

Tachyphylaxis: *Tachy = Rapid, Phylaxis = Prophylaxis/prevent = Tolerance.*

Definition: Rapid development of tolerance is tachyphylaxis. Tachyphylaxis can occur both after an initial dose of a drug or after a series of small doses.

Mechanism of tachyphylaxis:

1. Decrease in the number of neurotransmitter responsible for creating the drug's effect.
2. Decrease in the number of receptors available for the drug to bind to.

Drugs showing tachyphylaxis

1. Nitroglycerine demonstrates tachyphylaxis, requiring drug-free intervals
2. Repeated doses of ephedrine may display tachyphylaxis.
3. Hydralazine displays tachyphylaxis if given as a monotherapy for antihypertensive treatment.
4. Metoclopramide
5. Dobutamine
6. Desmopressin

Q. Write down the difference between tolerance and tachyphylaxis. (DU-16Ju,14Ju)

Ans.

Difference between tolerance and tachyphylaxis

Tolerance	Tachyphylaxis
1. It is a chronic phenomenon.	1. It is an acute phenomenon.
2. It occurs in intact human or animal.	2. Usually occurs in isolated tissue, rarely in animal.
3. Increased dose can produce initial dose.	3. Increased dose cannot produce initial dose.
4. Occurs either in the form of dispositional or true tolerance.	4. Occurs due to decrease in the number of neurotransmitter or receptors.

Drug Dependence, Addiction, and Habituation

Q. Narrate drug abuse with example. (RU-11J,06M)

Ans.

Drug abuse:

Definition: Drug abuse refers to use of a drug by self-medication in a manner & amount that deviates from the approved medical & social patterns in a given culture at a given time.

(Ref: Tripathi-6th/84)

Definition Drug abuse implies excessive (in terms of social norms) non medical or social drug use.

(Ref: Bennett & Brown-11th)

Non medical drug use: All drug use that has no generally accepted medical grounds, may be a term preferred to abuse. Non medical use means the continuous or occasional use of drugs by individuals, whether of their own 'free' choice or under feeling of compulsion, to achieve their own wellbeing, or that they conceive as their own wellbeing.

Drugs used for non medical purpose are often divided into two groups.

1. **Hard:** Produces serious dependence; e.g. heroin, cocaine.
2. **Soft:** Produces less dependence; e.g. alcohol, benzodiazepines, amphetamines, cannabis, hallucinogens, tobacco, caffeine.

(Ref: Bennett & Brown-11th)

Q. What do you mean by dependence?

Q. Name important drugs producing dependence. (RU-06S)

Q. Short note: Dependence. (DU-07J)

Ans.

Drug dependence:

Definition: Drug dependence is a state arising from repeated, periodic or continuous administration of a drug that results in harm to the individual & sometimes to society. The subject feels a desire, need or compulsion to continue using the drug & feels ill if abruptly deprived of it (abstinence or withdrawal syndrome).

(Ref: Bennett & Brown-10th/144)

Drug dependence includes both the terms 'addiction' and 'habituation'.

Types of drug dependence:

1. **Psychological dependence:** It is manifested by compulsive drug-seeking behaviour in which the individual uses the drug repetitively for personal satisfaction, often in the face of known risks to health. There is no withdrawal symptom.
2. **Physiologic / Physical dependence:** Physical dependence means that adaptive changes have taken place in body tissues so that when the drug is abruptly withdrawn these adaptive changes are left unopposed, resulting generally in a rebound overactivity. *receptor up regulation*

Mechanism of physical dependence: Prolonged use of exogenous opioid (morphine or pethidine) suppresses production of endogenous opioids (endorphins, dynorphins) by a feedback mechanism. When administration of exogenous opioid is suddenly stopped there is an immediate deficiency of endogenous opioid, which thus causes the withdrawal syndrome.

3. **Tolerance.**

(Ref: Bennett & Brown-11th & Katzung-12th/565)

Drugs producing dependence

1. Morphine
2. Heroine
3. Pethidine
4. Barbiturates
5. Amphetamine
6. Alcohols
7. Cocaine
8. LSD
9. Marijuana
10. Diazepam
11. Tobacco
12. Cannabis

(Ref: Bennett & Brown-10th/148)

Q. What is drug addiction?

Q. Short note: Drug addiction. (DU-02M)

Q. Name some drugs causing addiction. (RU-03M)

Ans.

Drug addiction: Addiction is a state of chronic intoxication due to repeated consumption of a drug and is characterized by physiological & psychological dependence and a tendency to increase the dose.

Criteria: Addiction is characterized by-

1. Overpowering desire to procure a drug
2. Tendency to increase the dose
3. Physiological & psychological dependence
4. Detrimental effects to the individual and to the society
5. Withdrawal syndrome or abstinence syndrome, if the drug is not given to the individual.

Drugs causing addiction

1. Morphine
2. Heroin
3. Pethidine
4. Barbiturates
5. Amphetamine
6. Alcohols
7. Cocaine
8. LSD
9. Marijuana

Q. What is drug habituation?

Ans.

Drug habituation: Drug habituation means desire to take a drug, but there is no compulsion. For example, smoking, coffee or tea drinking, etc.

Criteria: It is characterized by-

1. Urge to procure the drug but there is no compulsion.
2. There may be tendency to increase the dose but with increasing no bad effect.
3. Dependence is psychological but not physical.
4. Detrimental effects to the individual but not to the society
5. No withdrawal syndrome, if the drug is not given to the individual.

Q. What are the differences between drug addiction and drug habituation? (DU-07J)

Ans.

Differences between drug addiction and drug habituation:

Traits	Drug addiction	Drug habituation
1. Compulsion to take the drug	Present.	Absent
2. Tendency to increase the dose	Present.	Absent
3. Dependence	Psychological & physical	Some degree of psychological but not physical.
4. Withdrawal symptoms	Characteristic symptoms.	None or mild.
5. Harm	Both to the individual and society	If any, primarily to individual.

Teratogenicity

Q. What is meant by drug teratogenesis? (RU-12Ju, CU-05J)

Q. Briefly discuss teratogenesis. (CU-12Ju)

Q. Why drug should be avoided throughout the gestational age? (RU-07J)

Ans.

Teratogenesis: Greek Teratos means monster.

Definition: Teratogenesis refers to capacity of a drug to cause fetal abnormality when administered to pregnant mother & the drugs which can cause teratogenicity are called teratogenic drug.

Teratogenic condition:

1. The most vulnerable period for major anatomical abnormality is the **period of organogenesis (first trimester)** which occurs during 2-8 weeks of intrauterine life.
2. After the organs are formed, abnormalities are less anatomically dramatic.
3. The activity of a teratogen is most devastating soon after implantation, at doses that may not harm the mother.
4. The drug must cross the blood placental barrier to be teratogenic.
5. Some drugs are teratogenic before metabolism while others are after metabolism.

Mechanism of teratogenesis: Drugs may act on the embryo and fetus:

1. **Directly** (thalidomide, cytotoxic drugs, antithyroid drugs, aromatic retinoids, e.g. isotretinoin): any drug affecting cell division, enzymes, protein synthesis or DNA synthesis is a potential teratogen, e.g. many antimicrobials.
2. **Indirectly:**
 - a. On the uterus (vasoconstrictors reduce blood supply and cause fetal anoxia, misoprostol causes uterine contraction leading to abortion)
 - b. On the mother's hormone balance.

(Ref: Bennett & Brown-10th/125)

Nice to know**Stages of pregnancy and relative risk of teratogenesis:**

1. **Fertilization & implantation:** From conception to 17 days period is called so during which the adverse effect of teratogenic drugs are failure of continuation of pregnancy & often remain unnoticed.
2. **Organogenesis:** 18-55 days of gestation period is called so & is the most vulnerable period during which teratogenic drugs can cause failure of organogenesis & strict avoidance of teratogenic drugs should be needed.
3. **Growth & development:** Growth & development occurs in 55 days onwards and teratogenic drugs mainly cause functional abnormality of different organs.

(Ref: Tripathi-6th/84)

Q. Briefly discuss drug induced fetal damage. (CU-12Ju)

Q. Name 5 drugs that produce teratogenicity. (DU-07M)

Q. Give few examples of Teratogenesis. (CU-05J, RU-12Ju)

Q. Name 5 drugs that can affect the fetus & labour adversely. (RU-07J)

Q. Mention the drugs that are avoided in 1st trimester of pregnancy. (CU-14J)

Ans.

Drugs causing teratogenicity:

Drugs	Teratogenic effect
1. Thalidomide	Phocomelia
2. Methotrexate	Cleft palate, hydrocephalus, fetal death
3. Tetracyclines	Discolored & deformed teeth, Retarded bone growth
4. Warfarin	Depressed nose, eye & hand defect, growth retardation
5. Phenytoin	Cleft lip, cleft palate, microcephaly, hypoplastic phalanges
6. Carbamazepine	Neural tube defects
7. Valproic acid	Spina bifida & other neural tube defect
8. ACE inhibitors	Growth retardation, hypoplastic organs
9. Anti-thyroid drugs	Fetal goiter & hypothyroidism
10. Aspirin / Indomethacin	Premature closure of ductus arteriosus
11. Androgens	Virilization; Limb, esophageal & cardiac defect
12. Progestins	Virilization of female fetus
13. Isotretinoin	Craniofacial, cardiac & CNS defect.
14. Alcohol	
15. Lithium	
16. Sodium valproate	

(Ref: Tripathi-6th/85)

Nice to know

During the first week after fertilization, exposure to following drugs can cause abortion.

1. Antimetabolite
2. Misoprostol
3. Ergot alkaloids
4. Diethylstilbestrol

(Ref: Bennett & Brown-10th/125)

Q. Mention the drugs that are avoided prior to delivery. (CU-14J)

Ans.

Drugs that are avoided prior to delivery: Drugs given to the mother just prior to labour can cause postnatal effects.

1. **CNS depressants** may persist in and affect the baby for days after birth.
2. **Vasoconstrictors** can cause fetal distress by reducing uterine blood supply.
3. **β -blockers** may impair fetal response to hypoxia.
4. **Sulphonamides** displace bilirubin from plasma protein (risk of kernicterus).
5. **Inhibitors of prostaglandin synthesis (aspirin, indometacin)** may delay onset of labour and, in the fetus, cause closure of the ductus arteriosus, patency of which is dependent on prostaglandins.
6. **Opioid analgesics:** Can cause respiratory depression in the newborn.
7. **Sedatives and general anesthetics:** They may cause fetal distress by reducing uterine blood flow and prolong labour by depressing uterine muscle.

(Ref: Bennett & Brown-10th/125)

Q. Write the principles of prescription during pregnancy.

Ans.

Principles of prescribing drugs during pregnancy:

1. As far as possible, we should avoid medication in the initial 10 weeks of gestation.
2. Where possible, we should use non-drug therapy.
3. We should prescribe only when definitely needed. We should consider the **risk-benefit ratio** before giving any drug to pregnant women.
4. Drugs having the best safety recorded over time, are should be chosen.
5. We should avoid newer drugs, unless safety is clearly established.
6. Over the counter drugs can't be assumed to be safe.
7. We should use lowest effective dose.
8. If possible, we should prescribe intermittently.
9. If intermittent therapy is not possible, we should use the drugs for the shortest period as far as possible.
10. Always should be under observation of a specialist.

Q. Discuss US FDA classification of drug prescribing in pregnancy. (CU-14Ju)

Ans.

Risk category of drugs during pregnancy: The US FDA-assigned pregnancy categories as used in the Drug Formulary are as follows:

Category	Description	Examples
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).	▪ Inj. MgSO₄ ▪ Thyroxin
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.	▪ Penicillin V ▪ Amoxicillin ▪ Erythromycin ▪ Paracetamol ▪ Lignocaine

C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.	▪ Morphine ▪ Codeine ▪ Atropine ▪ Corticosteroids ▪ Adrenaline ▪ Thiopental Na ▪ Bupivacaine
D	There is positive evidence of human fetal risk, but the potential benefits from use of the drug may be acceptable despite the risk.	▪ Aspirin ▪ Phenytoin ▪ Carbamazepine ▪ Valproate ▪ Lorazepam
X	Studies in animals or human have demonstrated fetal abnormalities & potential risk clearly outweighs possible benefits.	▪ Estrogens ▪ Isotretinoin ▪ Ergometrine

(Ref: Tripathi-6th/85; Concerned websites,**Q. Enlist pregnancy category B proton pump inhibitors. (CU-14Ju)**

Ans.

Pregnancy category B proton pump inhibitors

1. Pantoprazole
2. Esomeprazole
3. Rabeprazole

Omeprazole → Pregnancy category C.

Nice to know**Anti-microbial drugs in pregnancy:**

Contraindicated	Unsafe
1. Fluoroquinolones 2. Tetracyclines: Tetracycline, Doxycycline. 3. Chloramphenicol 4. Aminoglycosides: Streptomycin, Kanamycin, Tobramycin 5. Anti-malarial: Sulfadoxine, Primaquine 6. Anti-amoebic: Tinidazole 7. Anthelmintic: Albendazole, Mebendazole, Diethylcarbamazine 8. Antifungal: Amphotericin B, Ketoconazole, Itraconazole, Griseofulvin 9. Anti-viral (other than HIV): Ganciclovir, Amantadine, α-Interferon, Vidarabine, Foscarnet.	1. Cotrimoxazole 2. Macrolides: Clarithromycin, Azithromycin 3. Clindamycin 4. Gentamicin 5. Vancomycin 6. Anti-tubercular drugs: Pyrazinamide, Ethambutol 7. Anti-malarial: Mefloquine, Pyrimethamine, Artemether, Artesunate 8. Anti-amoebic: Metronidazole 9. Anthelmintic: Pyrantel pamoate, Ivermectin, Praziquantel 10. Anti-fungal: Fluconazole, Terbinafine 11. Anti-viral (other than HIV): Acyclovir

(Ref: Tripathi, 6th edition)

Safe antimicrobials in pregnancy:

▪ Antibacterial	Penicillin G, Ampicillin, Amoxicillin, Clavulanic acid, Cloxacillin, Piperacillin, Cephalosporins, Erythromycin
▪ Antitubercular	INH, Rifampicin
▪ Antiamoebic	Diloxanide furoate
▪ Antimalarial	Quinine
▪ Anthelmintic	Piperazine, Niclosamide
▪ Antifungal	(Topical) Clotrimazole, Nystatin, Tolnaftate
▪ Antiviral	Zidovudine, Lamivudine, Nelfinavir

(Ref: Tripathi, 6th edition)

Drugs contraindicated / unsafe in pregnancy:

Group	Contraindicated	Unsafe
Antihypertensive	ACE inhibitors, ARB	Thiazides, Frusemide, Propranolol, Na-Nitroprusside
Antidiabetic	Sulfonylureas, Metformin, Acarbose	Pioglitazone, Rosiglitazone, Repaglinide, Nateglinide
Analgesics	Morphine	Pethidine, Tramadol, Codeine, NSAIDs
Antiemetics	Domperidone	Ondansetron
Anti-PUD drugs	Lansoprazole	Omeprazole, Pantoprazole, Cimetidine
Laxatives	----	Senna, Bisacodyl, Saline purgatives
Antidiarrheal	----	Loperamide, Diphenoxylate
Antipsychotics	Fluphenazine	Chlorpromazine, Clozapine, Olanzapine, Risperidone, Navaproate.
Antidepressants	Trimipramine, Dothiepine	Citalopram, Paroxetine, Trazodone
Anticoagulants	Warfarin, Phenindione	Acenocoumarin
Antiasthmatic	Ketotifen	Theophylline, Montelukast, Zafirlukast, Systemic corticosteroids
Antithyroid	Radioactive I ₂	Carbimazole, Iodine.

(Ref: Tripathi, 6th edition)

Drugs safe in pregnancy:

System	Safe drugs
Antihypertensive	α -Methyl dopa, Hydralazine, Atenolol, Metoprolol, Pindolol, Nifedipine, Prazosin, Clonidine
Hematinics	Oral Fe salts, Fe Dextran, Folic acid, Vit-B ₁₂
Antidiabetic	Insulin (preferably human insulin)
Corticosteroids	Inhaled & topical corticosteroids, Low dose oral prednisolone
Thyroid hormone	Thyroxine
Antithyroid	Propylthiouracil
Antipsychotics	Haloperidol, Trifluoperazine
Antidepressants	Amitriptyline, Imipramine, Clomipramine, Fluoxetine
Anticoagulants	Heparin (unfractionated), Low-molecular-weight heparin
Antiasthmatic	Salbutamol, Salmeterol, Ipratropium bromide, Beclomethasone, Budesonide, Na-cromoglycate
Antiemetics	Promethazine, Cyclizine, Dicyclomine, Prochlorperazine, Metoclopramide, Doxylamine
Drugs for PUD	Ranitidine, Famotidine
Laxatives	Dietary fibers, Lactulose, Ispaghula husk
Antidiarrheal	ORS
Analgesics	Paracetamol, Low dose ibuprofen

(Ref: Tripathi, 6th edition)

Q. Short note: Orphan Drugs.

Ans.

Orphan Drugs

Definition: An orphan drug is a pharmaceutical agent that has been developed specifically to treat a **rare** medical condition, the condition itself being referred to as an **orphan disease**.

Orphan diseases: A rare disease, also referred to as an "orphan disease", is any disease that affects a small percentage of the population. Most rare diseases are genetic, and thus are present throughout the person's entire life. Examples are-

1. Cystic fibrosis
2. Homozygous familial hypercholesterolemia
3. Wilson's disease

(Ref: Katzung-13th/18)

MCQ

Q. Drug action can be prolonged by- (DU-17M,17J)

- a) vasoconstriction
 - b) vasodilatation
 - c) delaying excretion
 - d) altering drug formulation
 - e) promoting drug metabolism
- a.-T, b.-F, c.-T, d.-T, e.-F*

Q. Pharmacodynamics deals with- (DU-17M,17J)

- a. mechanism of drug action
 - b. biotransformation
 - c. absorption
 - d. elimination
 - e. dose-response
- a.-T, b.-F, c.-F, d.-F, e.-T*

Q. Drugs used orally are- (DU-17M,14J)

- a. paracetamol
 - b. insulin
 - c. heparin
 - d. nitroglycerine
 - e. ampicillin
- a.-T, b.-F, c.-F, d.-T, e.-T*

Q. Drug passage through cell membrane is influenced by- (DU-17M)

- a) lipid solubility of the drug
 - b) source of the drug
 - c) molecular weight
 - d) mechanism of drug action
 - e) dose of the drug
- a.-T, b.-F, c.-T, d.-F, e.-F*

Q. Drug obtained from plant source are- (DU-17M,17J)

- a) atropine
 - b) insulin
 - c) paracetamol
 - d) digitalis
 - e) morphine
- a.-T, b.-F, c.-F, d.-T, e.-T*

Q. Drugs act by binding with- (DU-17J,11J)

- a) enzyme
- b) hormone
- c) receptor
- d) plasma protein

c) ion channel

a.-F, b.-F, c.-T, d.-F, e.-T

Q. Well established 2nd messengers are- (DU-17J)

- a. DAG
 - b. Phospholipase C
 - c. cAMP
 - d. adenylyl cyclase
 - e. IP₃
- a.-T, b.-F, c.-T, d.-F, e.-T*

Q. 1st pass metabolism can be avoided by administering the drugs- (DU-17J)

- a) orally
 - b) sublingually
 - c) subcutaneously
 - d) intragastric
 - e) per-rectally
- a.-F, b.-T, c.-T, d.-F, e.-F*

Q. Phase II biotransformation reactions are- (DU-17J)

- a. oxidation
 - b. acetylation
 - c. reduction
 - d. glucuronidation
 - e. methylation
- a.-F, b.-T, c.-F, d.-T, e.-T*

Q. Drugs having low TI are- (DU-17J)

- a. 5 fluorouracil
 - b. paracetamol
 - c. digoxin
 - d. ranitidine
 - e. amoxicillin
- a.-T, b.-F, c.-T, d.-F, e.-F*

Q. Passage of drug through cell membrane is influenced by- (DU-16J)

- a) lipid solubility
 - b) sources of drug
 - c) molecular weight
 - d) mode of action
 - e) dose of the drug
- a. T, b. F, c. T, d. F, e. T*

Q. Following are the characteristics of a drug- (DU-16J)

- a) either weak acid base
b) interact with living organism
c) produce energy
d) can cross biological barrier
e) produce only beneficial effects
a. T, b. T, c. F, d. T, e. F
- Q. Following are the 2nd messengers-** (DU-16J,12Ju)
a) DAG
b) phospholipase C
c) cAMP
d) adenylyl cyclase
e) IP₃
a. T, b. F, c. T, d. F, e. T
- Q. Safe drug during pregnancy-** (DU-16J)
a) ciprofloxacin
b) tetracycline
c) insulin
d) α -methyldopa
e) captopril
a. F, b. F, c. T, d. T, e. F
- Q. Following are the characteristics of simple diffusion-** (DU-16J)
a) directly proportional to lipid solubility
b) needs carrier
c) need energy
d) drug goes down the concentrative gradient
e) exhibit saturability
a. T, b. F, c. F, d. T, e. F
- Q. Pharmacodynamics deals with-** (DU-15Ju)
a. receptor
b. dose-response
c. absorption
d. tolerance
e. elimination
a. T, b. T, c. F, d. T, e. F
- Q. Bioavailability of drug depends on-** (DU-15Ju)
a. rate of absorption of a drug
b. first pass metabolism of drug
c. distribution of a drug
d. excretion of drug
e. route of drug administration
a. T, b. T, c. F, d. F, e. T
- Q. More than 90% plasma protein bound drugs are-** (DU-15Ju)
a. warfarin
b. phenytoin
c. diazepam
d. digoxin
e. ampicillin
a. F, b. F, c. F, d. F, e. T
- Q. Receptor mainly present at-** (DU-14Ju)
a. cell membrane
b. mitochondria
c. cytoplasm
d. nucleus
e. endoplasmic reticulum
a. T, b. F, c. T, d. T, e. F
- Q. Alkaloids are-** (DU-14Ju)
a. morphine
b. adrenaline
c. reserpine
d. neostigmine
e. atropine
a. T, b. F, c. T, d. F, e. T
- Q. The following drugs are highly plasma protein bound-** (DU-14Ju)
a. aspirin
b. imipramine
c. ranitidine
d. nifedipine
e. propranolol
a. T, b. T, c. F, d. F, e. T
- Q. The following drugs act by inhibiting enzymes-** (DU-14Ju)
a. neostigmine
b. morphine
c. aspirin
d. ramipril
e. propranolol
a. T, b. F, c. T, d. T, e. F
- Q. Phase II metabolizing reactions are-** (DU-14Ju)
a. acetylation
b. hydrolysis
c. glucoronidation
d. oxidation
e. reduction
a. T, b. F, c. T, d. F, e. F

Q. Following statements about drug pharmacodynamics are: (CU-14Ju)

- a. Expose processes by which effective concentration of a drug at the site of action is determined.
 - b. G-protein coupled receptors signaling include formation of cGMP.
 - c. Nitric acid may act as drug receptor.
 - d. cAMP mediates excitation-contraction coupling in smooth muscle.
 - e. Effect of Protamine sulfate exemplifies non-receptor mechanism.
- a. ?T, b. T, c. F, d. F, e. T*

Q. Following is/are not a primary/fundamental, but a derived pharmacokinetic parameter: (CU-14Ju)

- a. Absorption.
 - b. Bioavailability.
 - c. Volume of distribution
 - d. Clearance.
 - e. Plasma half life.
- a. F, b. T, c. T, d. T, e. T*

Q. The factors influencing drug absorption are- (DU-14J)

- a. lipid solubility
 - b. pH of the drug
 - c. Presence of other substance
 - d. dose response relationship
 - e. plasma half life
- a. T, b. T, c. T, d. F, e. F*

Q. The following drugs cause hepatic enzyme induction- (DU-14J)

- a. rifampicin
 - b. carbamazepine
 - c. ciprofloxacin
 - d. phenobarbitone
 - e. metronidazole
- a. T, b. T, c. F, d. T, e. F*

Q. Following are the characteristics of a drug- (DU-13Ju)

- a. either weak acid or base.
 - b. interact with living organism.
 - c. produce energy.
 - d. can cross biological effect.
 - e. produce only beneficial effect.
- a. T, b. T, c. F, d. T, e. F*

Q. The following drugs are metabolized by acetylation- (DU-13Ju)

- a. morphine.
 - b. sulfonamide.
 - c. diazepam.
 - d. acetaminophen.
 - e. isoniazide.
- a. F, b. T, c. F, d. F, e. T*

Q. A highly ionized drug- (DU-13Ju)

- a. is excreted mainly by the kidney.
 - b. do not cross the placental barrier easily.
 - c. is well absorbed from the intestine.
 - d. Is highly plasma protein bound.
 - e. Can accumulate in the cellular lipid.
- a. T, b. T, c. F, d. F, e. F*

Q. Clearance of drug depends on- (DU-13Ju)

- a. bioavailability.
 - b. plasma half life.
 - c. volume of distribution.
 - d. diffusion co-efficient.
 - e. rate of absorption.
- a. F, b. T, c. T, d. T, e. F*

Q. Microsomal enzyme inhibitors are- (DU-13J)

- a. spironolactone.
 - b. phenytoin.
 - c. ketoconazole.
 - d. erythromycin.
 - e. rifampicin.
- a. F, b. F, c. T, d. T, e. F*

Q. Following drugs are absorbed through active transport from GIT - (DU-13J)

- a. paracetamol.
 - b. diazepam
 - c. levodopa.
 - d. Vit-B12.
 - e. iron.
- a. F, b. F, c. T, d. F, e. T*

Q. Drugs act by binding with- (DU-13J)

- a. enzyme.
 - b. receptor.
 - c. plasma protein.
 - d. hormone.
 - e. ion channel.
- a. T, b. T, c. F, d. F, e. T*

Q. Drug absorption following oral administration- (SU-13J)

- a) Most commonly by simple diffusion
 - b) Occurs throughout intestine
 - c) Delayed by antimuscarinic agents
 - d) Non-polar drugs are readily absorbed
 - e) Peptides are readily absorbed.
- a. T, b. T, c. F, d. T, e. F*

Q. Drug distribution is influenced by- (SU-13J)

- a) Enzyme induction
 - b) Plasma protein binding
 - c) Hepatic microsomal enzyme deficiency
 - d) Regional blood flow
 - e) Solubility of drug
- a. F, b. T, c. F, d. T, e. T*

Q. Following are the characteristics of drugs- (DU-12Ju)

- a. Most of the drugs are either weak acid or weak base. (T)
- b. Interact with living organism. (T)
- c. Produce energy. (F)
- d. Can cross biological barrier. (T)
- e. Produce only beneficial effects. (F)

Q. Bioavailability of a drug can be influenced by- (DU-12Ju)

- a. Routes of administration of drug. (T)
- b. Half life of a drug. (T)
- c. Pharmaceutical factor. (T)
- d. First pass effect. (T)
- e. Gender of the patient. (F)

Q. Following are pro-drugs- (DU-12Ju)

- a. Levodopa (T)
- b. Atropine (F)
- c. Enalapril (F)
- d. Propranolol (F)
- e. Omeprazole (T)

Q. Dose-response curve gives information about drug- (DU-12Ju)

- a. Efficacy (T)
- b. Potency (T)
- c. Therapeutic index (T)
- d. Bioavailability (T)
- e. Half life (F)

Q. Benefit by the use of drugs are- (DU-12J)

- a. Prophylaxis of disease. (T)

- b. Development of new drug. (F)
- c. Control of disease. (T)
- d. Epidemiological survey of disease. (F)
- e. Treatment of disease. (T)

Q. Drug action can be prolonged by- (DU-12J)

- a. Vasoconstriction (T)
- b. Vasodilation (F)
- c. Delaying excretion. (T)
- d. Altering drug formulation. (T)
- e. Promoting drug metabolism. (F)

Q. Following drugs act principally by inhibiting enzymes- (DU-12J)

- a. Enalapril (T)
- b. Physostigmine (T)
- c. Salbutamol (F)
- d. Morphine (F)
- e. Diclofenac (T)

Q. Drugs having low TI are- (DU-12J)

- a. Methotrexate. (T)
- b. Paracetamol (F)
- c. Digoxin (T)
- d. Aminophylline (T)
- e. Penicillin (F)

Q. High plasma protein binding (DU-11Ju)

- a. Increases the volume of distribution of drug. (F)
- b. Facilitates glomerular filtration of drug (F)
- c. Can cause more drug interaction. (T)
- d. Generally increases the duration of action of the drug. (T)
- e. Has clinical significance if a drug has low therapeutic index. (T)

Q. The following drugs act principally by inhibiting enzymes: (DU-11Ju)

- a. Enalapril (T)
- b. Carbidopa (T)
- c. Aspirin (T)
- d. Atropine (F)
- e. Adrenaline (F)

Q. The following drugs easily penetrate the BBB: (DU-11Ju)

- a. Physostigmine (T)
- b. Atenolol (F)
- c. Propranolol (T)
- d. Atracurium
- e. Heparin (F)

Q. Bioavailability could be influenced by:

(DU-11Ju)

- a. Route of administration (T)
- b. Half life of the drug (T)
- c. Pharmaceutical factor (T)
- d. Gender of the patient (F)
- e. First pass metabolism (T)

Q. Drug receptors- (DU-11Ju)

- a. Are specialized target molecules. (T)
- b. Are present only on the cell membrane (F)
- c. Have the ability to recognize ligands. (T)
- d. Do not have the ability to cause conformational change (F)
- e. Are mostly regulatory molecules. (T)

Q. Drugs having long plasma half life exhibit- (DU-11Ju)

- a. Slow and sustained effect. (T)
- b. Undergoes rapid metabolism. (F)
- c. Having more binding with tissues. (F)
- d. Suitable for acute emergency. (F)
- e. Less frequently administered. (T)

Q. Criteria of active transport of drug- (DU-11J)

- a. Lipid solubility (F)
- b. Water solubility (T)
- c. Energy mediated (T)
- d. Carrier needed (T)
- e. Exhibits selectibility & saturability (T)

Q. Drug metabolizing enzyme inhibitors are- (DU-11J)

- a. Metronidazole (T)
- b. Phenytoin (F)
- c. Griseofulvin (F)
- d. Rifampicin (F)
- e. Erythromycin (T)

Q. Regarding bioavailability curve- (DU-10Ju)

- a. It is a drug plasma concentration-time curve. (T)
- b. It is a drug effect- time curve (F)
- c. It is a drug dose-response curve (F)
- d. Extent is measured by AUC (F)
- e. Rate is measured by AUC (F)

Q. Most drugs- (DU-10Ju)

- a. are either weakly acidic or weakly basic in nature (T)
- b. are lipid soluble when in non-ionized form (T)
- c. are evenly distributed throughout the body fluid (F)
- d. binds with plasma globulin in the circulation (T)
- e. explore or modify the physiological system (T)

Q. Vd of a drug less than 15 L interprets that the drug is- (DU-10Ju)

- a. distributed in plasma (T)
- b. distributed in ICF (T)
- c. distributed in ECF (T)
- d. accumulated in the tissues (T)
- e. highly lipid soluble (T)

Q. Receptors mainly present at- (DU-10Ju)

- a. Cell membrane (T)
- b. Mitochondria (F)
- c. Cytoplasm (T)
- d. Nucleus (T)
- e. Endoplasmic reticulum (F)

Q. Following drugs are absorbed through active transport from GIT- (DU-10J)

- a. paracetamol (?)
- b. diazepam (?)
- c. levodopa (T)
- d. vit-B12 (F)
- e. iron (T)

Q. High plasma protein bound drugs show- (DU-10J)

- a. rapid onset of action (F)
- b. prolonged duration of action (T)
- c. short plasma half- life (F)
- d. slow excretion (T)
- e. rapid metabolism (F)

Q. Renal drug excretion will be more if- (DU-10J)

- a. the drug remains in ionized state in tubules (T)
- b. the drug remains in un-ionized state in tubules (F)
- c. passive tubular reabsorption is more (F)
- d. active tubular secretion is more (T)
- e. the drug is less protein bound (T)

Chapter 2

Autonomic Pharmacology

Introduction to ANS

Autonomic pharmacology: Study of drugs which modify the action of ANS is called autonomic pharmacology.

Divisions of nervous system:

A. **Central nervous system (CNS):** Brain & spinal cord.

B. **Peripheral nervous system (PNS):**

1. Somatic nervous system: Cranial & spinal nerves. - *Voluntary*
2. Autonomic nervous system / ANS: - *Involuntary*

a. **Anatomically:**

- Cranio-sacral outflow
- Thoraco-lumbar outflow

b. **Physiologically:**

- Sympathetic
- Parasympathetic
- Enteric

c. **Pharmacologically:**

- Adrenergic (neurotransmitter is nor-adrenaline)
- Cholinergic (neurotransmitter is acetylcholine)

ANS: The part of the nervous system which is not in our own control is called autonomic nervous system. The ANS innervates involuntary structures such as heart, lungs, intestine, glands, smooth muscle and cardiac muscle.

Differences between somatic & autonomic nervous system:

Somatic nervous system	Autonomic nervous system
1. It is voluntary	1. It is involuntary
2. It supplies skeletal muscles.	2. It supplies smooth muscles, heart muscles, glands and other visceral organs.
3. Somatic nerves are myelinated.	3. Post-ganglionic autonomic nerves are generally myelinated.
4. Somatic nerves usually don't form plexus.	4. Many autonomic nerves form extensive plexus.
5. Synapses are located entirely within the cerebro-spinal axis.	5. Synapses occur in ganglia that are entirely outside the cerebro-spinal axis. Ganglia are located between pre-ganglionic and post-ganglionic neurons.
6. When nerves are interrupted, the skeletal muscles are paralyzed and atrophied.	6. When nerves are interrupted, the smooth muscles and glands generally show some level of spontaneous activity.

Q. Name the cholinergic neurons. (SU-06M)

Q. Name the sites where acetylcholine is released.

Ans.

Cholinergic neurons: All the neurons that secrete acetylcholine are called cholinergic neurons.

Cholinergic neurons / Sites of acetylcholine secretion:

1. All the preganglionic neurons of the autonomic nervous system.
2. The postganglionic neurons of the parasympathetic nervous system.
3. The postganglionic neurons of the sympathetic nervous system supplying the sweat glands & blood vessels in skeletal muscles.
4. The motor neurons that innervate skeletal muscles.
5. Also from neurons in the brain, cortex, & basal ganglia.

Q. Indicate the sites where adrenaline is released. (SU-05J)

Ans.

Adrenergic neurons: All the neurons that secrete nor-adrenaline/norepinephrine are called adrenergic neurons.

Sites where adrenaline is released:

1. The postganglionic neurons of the sympathetic nervous system except those supplying the sweat glands & blood vessels in skeletal muscles.
2. Adrenal medulla.

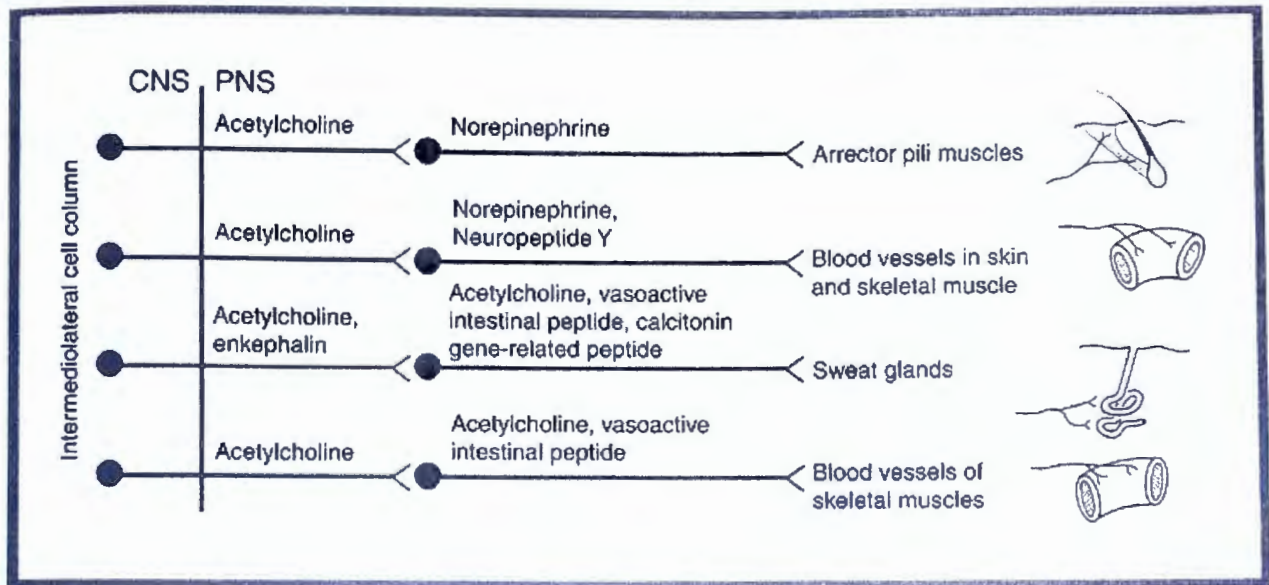


Figure: Chemical coding of sympathetic preganglionic and postganglionic neurons. (Ref: Ganong-23rd)

Nice to know

Burns hypothesis: The hypothesis states that "all the pre-ganglionic sympathetic nerves first release acetylcholine which further initiate release of noradrenaline from the post ganglionic sympathetic fibers.

Adrenoceptors: The receptors on which epinephrine (adrenaline) and norepinephrine (noradrenaline) act are called adrenoceptors. Adrenoceptors are of 2 types-

1. α -adrenoceptors (α_1 , α_2)
2. β -adrenoceptors (β_1 , β_2 , β_3)

Cholinoceptors: The receptors on which acetylcholine act are called cholinoceptors. Cholinoceptors are of 2 types-

1. Muscarinic receptors (M_1 , M_2 , M_3 , M_4 , M_5)
2. Nicotinic receptors (N_M , N_N)

Differences between sympathetic & parasympathetic systems

Structural:

	Sympathetic system	Parasympathetic system
Outflow	Thoracolumbar (T1 – L2)	Craniosacral (cranial nerves: III, VII, IX & X and S2, S3, & S4 spinal segments)
Preganglionic fibers	Myelinated, <i>short</i>	Myelinated, <i>long</i>
Postganglionic fibers	Long, nonmyelinated	Short, nonmyelinated
Ganglia	Paravertebral (sympathetic trunk) and prevertebral (eg, celiac) <i>close to spinal cord</i>	Small ganglia close to viscera (eg, ciliary) or ganglion cells in plexuses (eg, cardiac, pulmonary)
Neurotransmitter at the preganglionic endings	Acetylcholine	Acetylcholine

Preganglionic fibre branches Extensive

Minimal

Neurotransmitter at the postganglionic endings	Norepinephrine at most endings and acetylcholine at sweat glands & blood vessels supplying skeletal muscles.	Acetylcholine
--	--	---------------

(Ref: Snell Neuroanatomy-7th)

Functional:

	Sympathetic action	Parasympathetic action
Action	Prepares body for emergency	Conserves & restores energy
Range of activity	Widespread	Localized
Eye		
• Pupil	Dilatation (mydriasis)	Constriction (miosis)
• Ciliary muscle	Relaxation for far vision	Contraction for near vision
Heart		
• Heart rate	Increased	Decreased
• Force of contraction of heart muscle	Increased	Decreased
Lung		
• Bronchial muscle	Relaxation	Contraction
• Bronchial secretion	Decreased	Increased
GIT		
• Peristalsis	Decreased	Increased
• Sphincter	Contraction (usually)	Relaxation (usually)
• Secretion	Decreased	Increased
Liver	Glycogenolysis	---
Kidney	Decreased output & renin secretion	None
Urinary bladder		
• Detrusor muscle	Relaxation (usually)	Contraction
• Trigone & sphincter	Contraction	Relaxation
Penis	Ejaculation	Erection
Uterus	Contraction (pregnant) Relaxation (pregnant & nonpregnant)	Variable
Blood vessels	Most often constricted	Most often little or no effect
Arteriole		
• Abdominal viscera	Constriction	None
• Skeletal muscle	Constriction (α_1 receptor) Dilation (β_2 receptor) Dilation (cholinergic)	None
• Skin	Constriction	None

(Ref: Ganong-24th; Guyton-12th; Snell-Neuro-7th)

Neurotransmitters (NT)

Q. Define neurotransmitter. (DU-11Ja,10Ja; RU-04M,03Ja; SU-06S)

Q. Classify neurotransmitter. (SU-07Ja,06S)

Q. Enumerate some important neurotransmitters. (DU-10Ja)

Q. Name the central neurotransmitters. (RU-09Ja,07Ju/Ja)

Q. Short note: Neurotransmitter. (RU-16J)

Ans.

Neurotransmitter

Definition: These are chemical agents that are released from the nerve endings and transmit nerve impulses through the synapse from nerve to nerve or nerve to effector organ (muscle or gland).

(Ref: Guyton-12th)

Definition: Neurotransmitters are the specific chemical signals that are released from nerve terminal & maintain communication between nerve cells or between nerve cells & effector organs.

(Ref: Lippincott's pharmacology-6th)

Classification of neurotransmitter

A. According to type of action:

Excitatory	Inhibitory	Both Excitatory & Inhibitory
1. Epinephrine	1. GABA	1. Acetylcholine
2. Glutamate	2. Dopamine	2. Nor epinephrine
	3. Serotonin	3. Histamine
	4. Glycine	4. Prostaglandin
	5. Alanine	5. 5-HT (Hydroxytryptamine)
	6. Taurine	Dopamine

(Ref: Guyton-12th)

B. According to site of action:

1. **Peripheral neurotransmitter:** Acetylcholine (Ach), epinephrine, nor-epinephrine, histamine.
2. **Central neurotransmitter:** Dopamine, GABA, glycine, glutamate, aspartate, serotonin, NA, Ach.

Q. Define neurotransmission. Name the processes involved in neurotransmission. (RU-04M)

Q. What do you mean by neurohormonal transmission? Name the steps involved in neurohormonal transmission. (RU-08Ju)

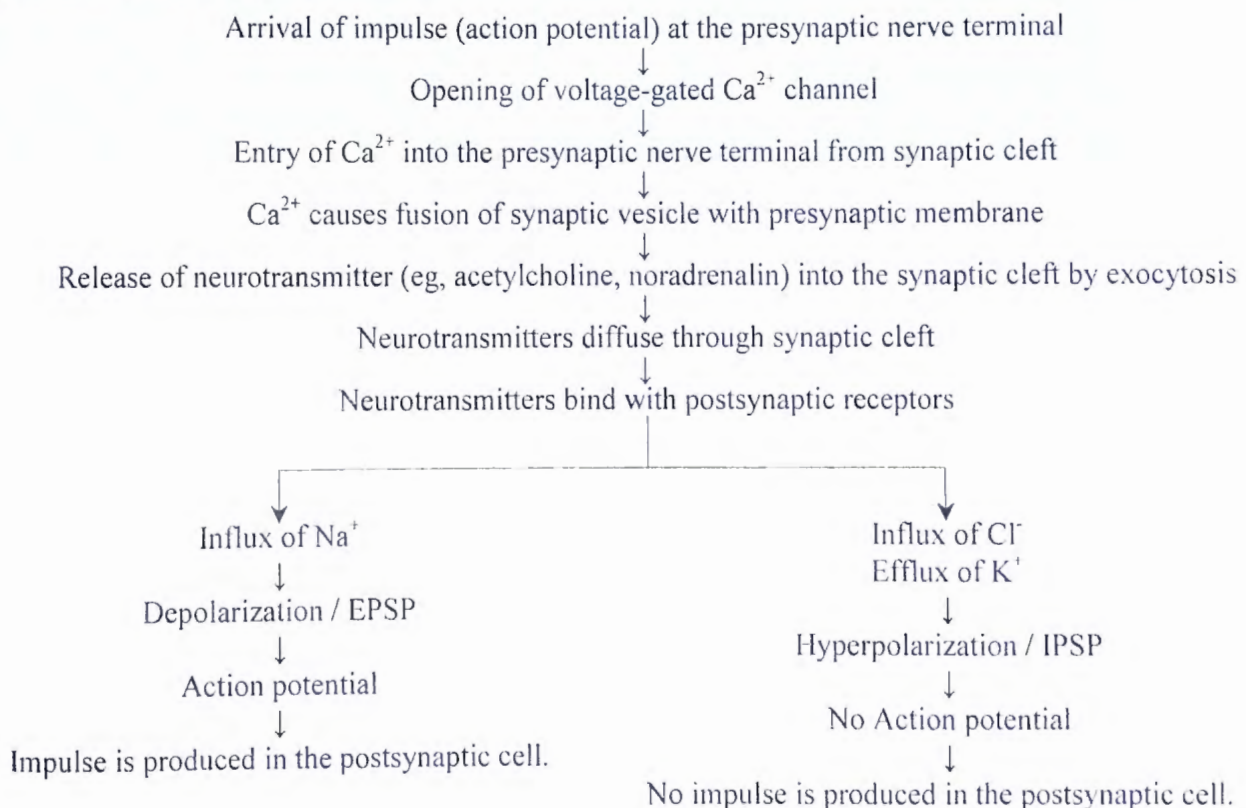
Q. Outline the steps of cholinergic neurotransmission. (SU-11J,09Ju,08J,RU-12J)

Q. Outline noradrenergic neurotransmission. (SU-13Ju)

Ans.

Neurotransmission / neurohumoral transmission: Transmission of nerve impulse across the synapses & neuro-effector junctions by releasing humoral (chemical) messengers is called neurohumoral transmission.

Steps of neurohumoral transmission:



After transmission of the nerve impulse, some transmitters are destroyed by enzymes, some may diffuse out, and some may be re-uptaken by the nerve ending.

(Ref: Ganong-24th; Guyton-12th; Tripathi-6th/89)

Q. Describe briefly the criteria of ideal neurotransmitter. (DU-11Ja, 10Ja)

Q. What are the criteria of a neurotransmitter substance? (SU-07J)

Ans.

Criteria of a neurotransmitter (NT) substance:

1. It should be present in the pre-synaptic neuron (usually along with its synthesizing enzyme)
2. It should be released in response to nerve stimulation.
3. Its application should produce responses identical to those produced by nerve stimulation.
4. Its effects should be antagonized or potentiated by other substances which similarly alter effect of nerve stimulation.

(Ref: Katzung-13th; Tripathi-6th/90)

Viva Q. Why adrenaline is released from nerve ending?

Ans.

Adrenaline is synthesized in the adrenal medulla. It is not synthesized in the nerve ending, still it is released from the nerve ending. From adrenal medulla it is released into the bloodstream, from blood it reaches the synaptic cleft and from there it enters into the nerve terminal by reuptake-II.

Q. What is the role of pre-synaptic autoreceptor? (SU-03J)

Q. Discuss the role of pre-synaptic autoreceptors in the regulation of neurotransmission. (SU-06M)

Ans.

Pre-synaptic autoreceptor: Presynaptic receptors that respond to the transmitter substances released by the nerve ending are called autoreceptors. Autoreceptors are usually **inhibitory**, but many cholinergic fibers, especially somatic motor fibers, have excitatory nicotinic autoreceptors.

Example:

1. α_2 autoreceptors inhibit further release of norepinephrine (NE) from sympathetic neurons.
2. M_2 & M_4 autoreceptors inhibit further ACh release from parasympathetic neurons.

(Ref: Katzung-13th/99)

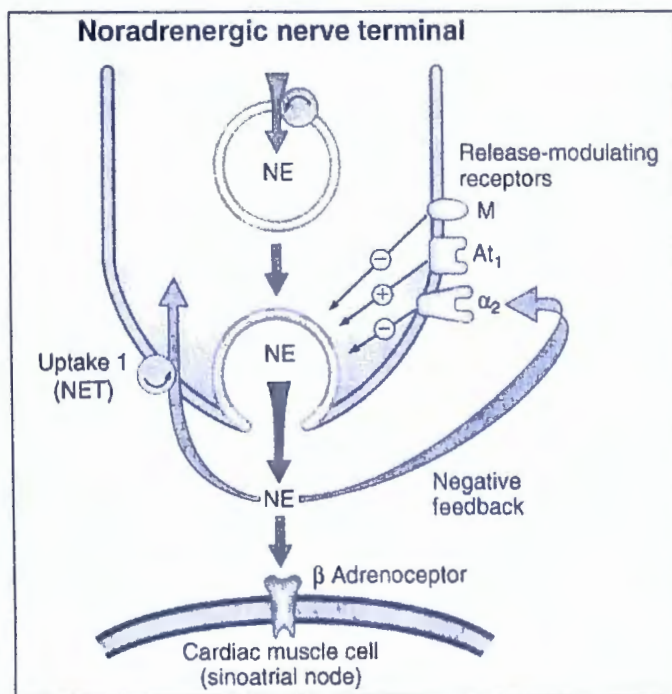
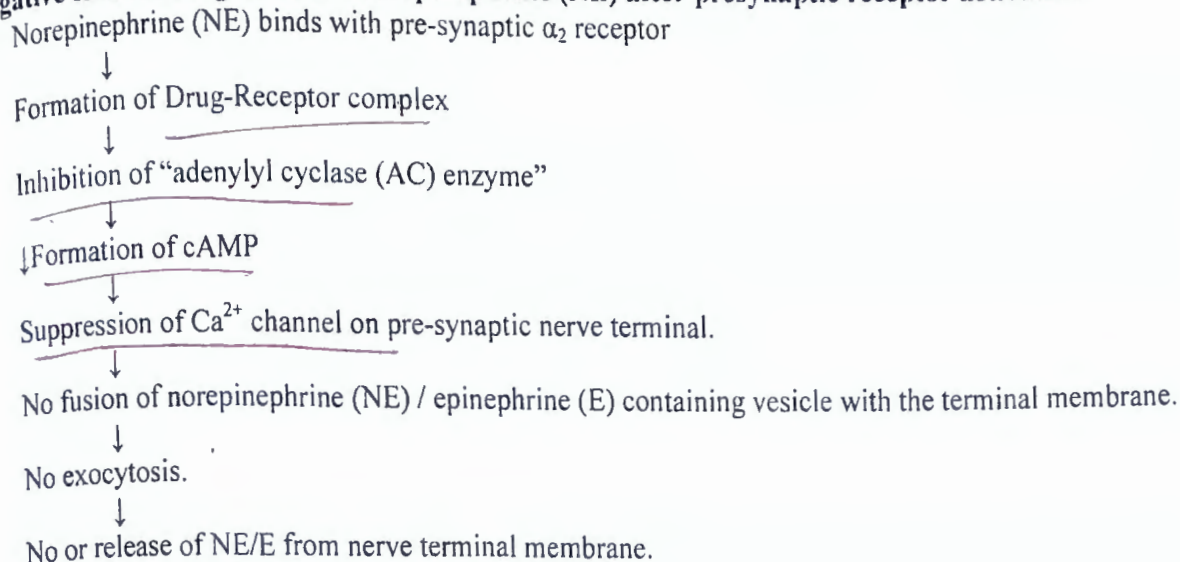


Fig. Regulation of the release of norepinephrine (NE) from a sympathetic nerve ending by norepinephrine itself, acting on presynaptic α_2 autoreceptors, and by acetylcholine and angiotensin II. AT_1 , angiotensin II receptor; M , muscarinic receptor; NET, norepinephrine transporter.

Negative feedback regulation of norepinephrine (NE) after presynaptic receptor activation:

This auto-inhibitory effect of NE after α_2 -receptor activation is called "negative feedback regulation".

Nice to know

■ **Presynaptic regulation:** It is mediated by autoreceptors and heteroreceptors. It occurs by homotropic and heterotropic interaction.

■ **Heteroreceptor:** Heteroreceptors are pre-synaptic receptors, which respond to neurotransmitters or neuro-hormones released from adjacent neurons or cells.

Example: Noradrenaline (NA) can influence the release of ACh from parasympathetic neurons by acting on α_2 receptors. Similarly, ACh can influence the release of NA from sympathetic neurons by acting on M_2 & M_4 receptors. For example, some vagal fibers in the myocardium synapse on sympathetic noradrenergic nerve terminals and inhibit norepinephrine release.

■ **Heterotropic interaction:** When one neurotransmitter (NT) affects the release of another NT, it is called heterotropic interaction. Eg, NA inhibits ACh release & ACh also inhibits NA release in the pre-synaptic neurons in heart.

■ **Homotropic interaction:** When one NT affects the release of the same NT, it is called homotropic interaction. Eg, NA inhibits the release of other NA by acting on α_2 receptors.

(Ref: Katzung-13th/99-100; Goodman & Gilman's-12th; Rang Dale-8th)

Cholinergic pharmacology

Q. Enlist the cholinesterases. (DU-08J)

Ans.

Cholinesterases

1. True acetylcholinesterases:

- Only metabolizes the Ach.
- Found in the synaptic cleft of cholinergic nerve endings, RBC, placenta.

2. False/pseudo acetylcholinesterase / butyryl-cholinesterase:

- Metabolize mainly other drugs-
 - ➔ Succinylcholine, suxamethonium
 - ➔ Procaine
- It may metabolize Ach.
- Found in lungs, glial cells, gut mucosa, plasma, liver and many other tissues.

Q. Outline the steps of biosynthesis and fate of acetylcholine. (RU-16Ju, 13J, 11Ju, SU-17M)

Q. How acetylcholine (ACh) is synthesized and metabolized? (SU-09/08Ju)

Q. Draw & label a diagram to show the synthesis, release and termination of action of acetylcholine. (CU-03J; RU-04M; SU-08J)

Q. Describe the fate of transmitter involved in cholinergic neurotransmission. (SU-13J, 11J)

Q. Illustrate cholinergic neurotransmission mentioning neurotransmitter synthesis, fate and receptors. (SU-12Ju, 08J/Ju)

Ans.

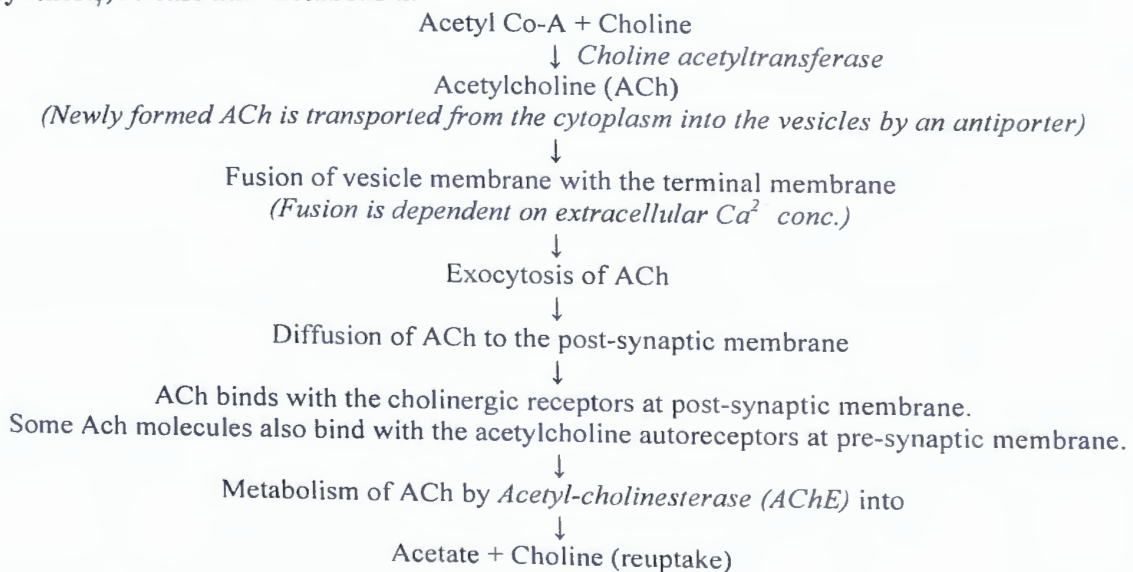
Synthesis, release and metabolism / fate of acetylcholine (ACh)

Site of Ach synthesis: Cytoplasm of nerve terminal.

Required substances:

1. Acetyl Co-A (*Synthesized in the mitochondria*)
2. Choline (*transported from extracellular fluid in to the nerve terminal by a Na-dependent membrane carrier*).
3. Choline-acetyltransferase

Steps of synthesis, release and metabolism:



Lippincott - 94-95
51-53

Rate limiting step: Choline uptake in the pre-synaptic nerve terminal is the rate limiting step.

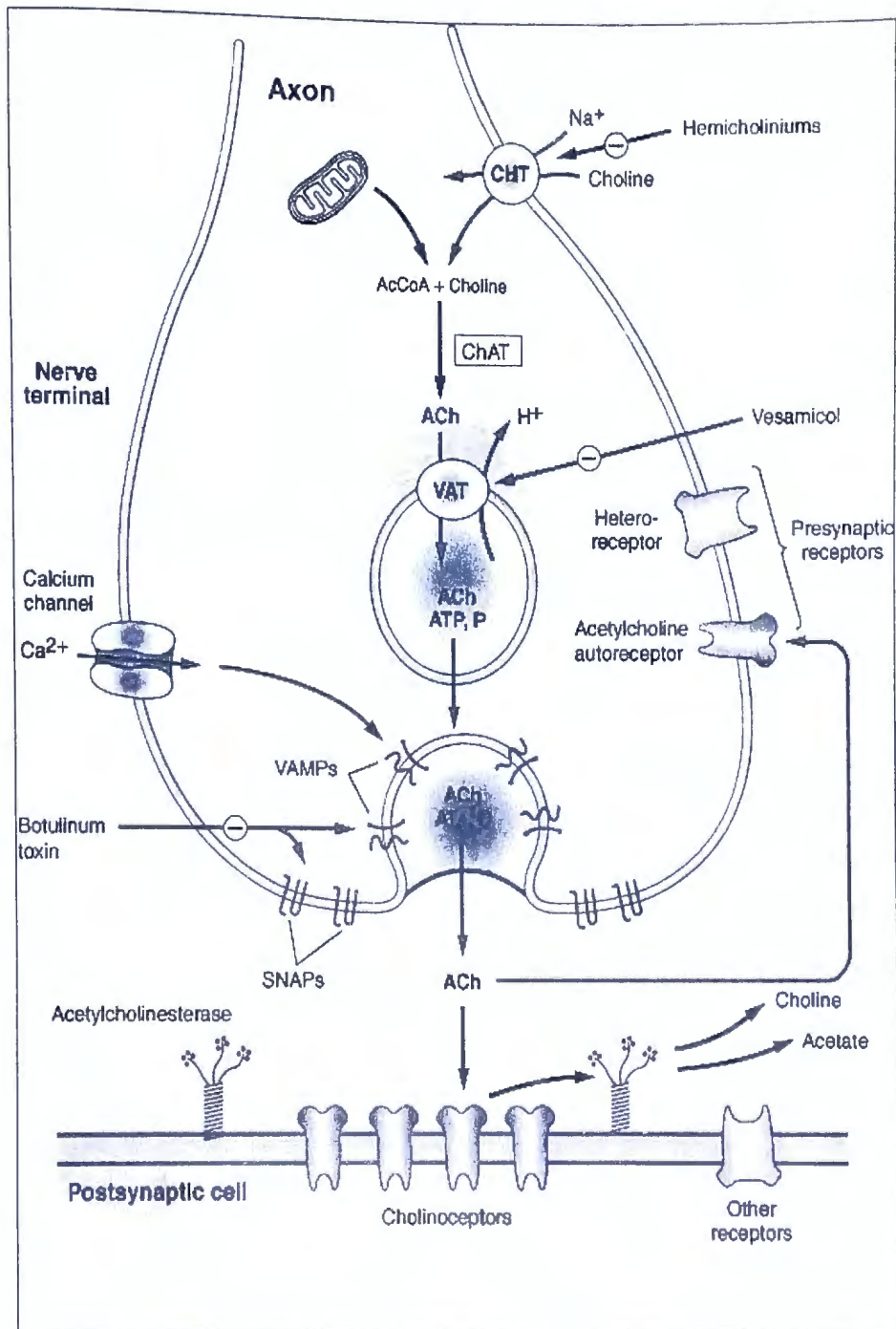


Figure: Schematic illustration of a generalized cholinergic junction (Ref: Katzung-13th/91)

- Q. List the cholinergic receptors & their important locations. (CU-09Ju,06M; RU-04M; SU-12Ju,07Ju)
- Q. Show the distribution of various cholinergic receptors sites. (DU-14J, SU-13Ju)
- Q. Briefly outline the effects of activation of cholinergic receptors. (DU-07J, CU-07J,06M)
- Q. Name the nicotinic receptors and their sites. (SU-16J/Ju)
- Q. Name cholinergic receptors. (CU-09Ju)
- Q. Name the cholinergic receptors & outline relevant mechanisms that can influence cardiac function. (CU-09Ju)

Ans.

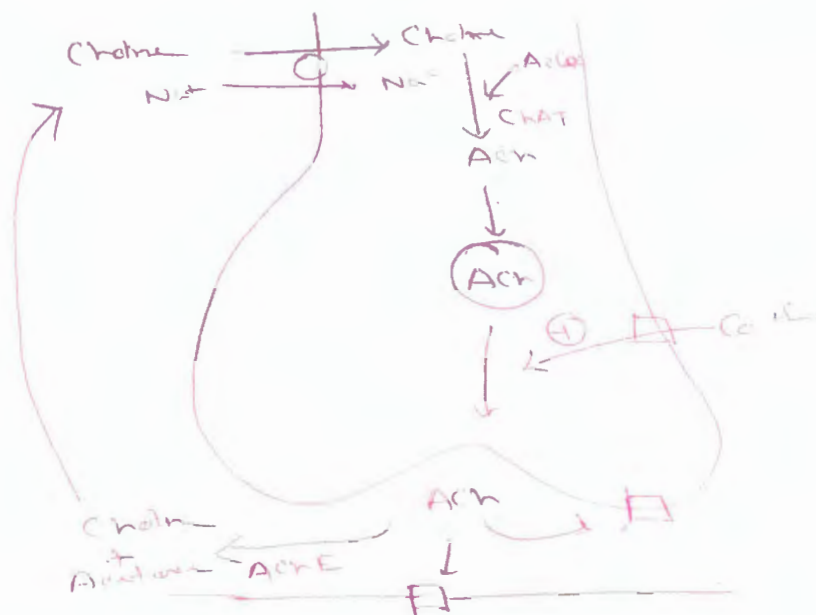
Cholinomimetic / cholinergic receptors / Cholinoceptors: There are two types of receptor.

1. **Muscarinic receptors:** These receptors respond to muscarine (an alkaloid) as well as to acetylcholine. Subtypes are M_1 , M_2 , M_3 , M_4 , M_5

2. **Nicotinic receptor:** These receptors are located on ion channels and respond to acetylcholine and nicotine, another acetylcholine mimic (but not to muscarine) by opening the channel. Subtypes are N_M & N_N

Receptor Name	Typical Locations	Result of Ligand Binding	Effect
Muscarinic M_1 (Neural)	- CNS neurons - Sympathetic postganglionic neurons - Some presynaptic sites - Gastric parietal cell	- Formation of IP3 and DAG - Increased intracellular calcium	CNS excitation Gastric secretion
Muscarinic M_2 (Cardiac)	- Myocardium - Smooth muscle - Some presynaptic sites	- Opening of K^+ channels - Inhibition of adenylyl cyclase	Cardiac inhibition Neural inhibition Central effect: Tremor, hypothermia
Muscarinic M_3 (Glandular)	- Exocrine glands - Vessels (smooth muscle and endothelium)	- Formation of IP3 and DAG - Increased intracellular calcium	Increased gastric, salivary secretion GIT muscle contraction Ocular accommodation Vasodilatation
Muscarinic M_4	CNS neurons, possibly vagal nerve endings	Like M_2	Neural inhibition
Muscarinic M_5	- Vascular endothelium, especially cerebral vessels - CNS neurons	Like M_1	Neural excitation
Nicotinic N_N	- Postganglionic neurons - Some presynaptic cholinergic terminals	- Opening of Na^+, K^+ channels - Depolarization	Excitation
Nicotinic N_M	Skeletal muscle neuromuscular end plates	- Opening of Na^+, K^+ channels - Depolarization	Skeletal muscle contraction

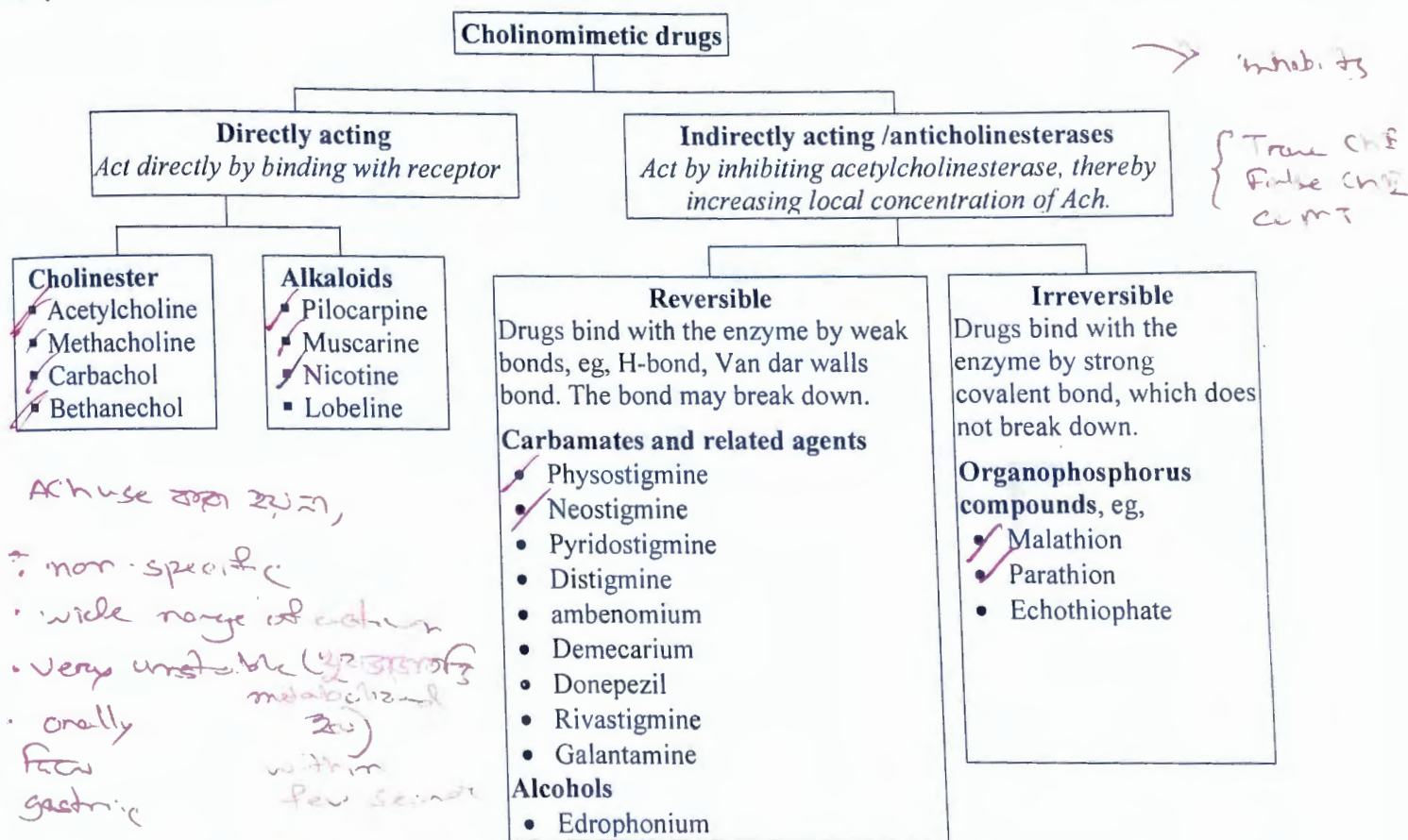
(Ref: Katzung-13th/97; Rang Dale-8th)



Cholinomimetic drugs

- Q. What are the cholinergic drugs? (DU-07J,04J;CU-04J;RU-01M;SU-05J,04M/J)
 Q. Enlist the cholinomimetics. (CU-17J)
 Q. Enlist anticholinesterases / cholinesterase inhibitors. (DU-11J,10J,08J,06S; CU-17M,08J; RU-07Ju,05S,02J;SU-11J,07J,06S/J)
 Q. List different cholinergic receptor agonists. (CU-12Ju,09J, RU-15J)
 Q. Enlist 4 cholinergic drugs. (DU-15Ju)
 Q. Enlist the indirectly-acting cholinomimetics. (DU-15J)
 Q. Enlist the indirectly-acting cholinergic agonists with their role/effects. (SU-15Ju,15J)
 Ans.

Cholinomimetic / cholinergic drugs: These are the drugs which increase cholinergic activity by directly stimulating cholinergic receptors or by indirectly increasing acetylcholine concentration by inhibiting acetylcholinesterase enzyme.



(Ref: Katzung-13th/107-120; Lippincott's-6th; Goodman & Gilman's-12th)

Important definitions

- Parasympathomimetic:** A drug whose effects resemble those of stimulating the parasympathetic nerves.
- Choline ester:** A cholinomimetic drug consisting of choline (an alcohol) esterified with an acidic substance, (eg, acetic or carbamic acid); usually poorly lipid-soluble.
- Cholinomimetic alkaloid:** A drug with weakly basic properties (usually of plant origin) whose effects resemble those of acetylcholine; usually lipid-soluble.
- Direct-acting cholinomimetic:** A drug that binds and activates cholinergic receptors; the effects mimic those of acetylcholine.

- **Indirect-acting cholinomimetic:** A drug that amplifies the effects of endogenous acetylcholine by inhibiting acetylcholinesterase.
- **Muscarinic agonist:** A cholinomimetic drug that binds muscarinic receptors and has primarily muscarine-like actions.
- **Nicotinic agonist:** A cholinomimetic drug that binds nicotinic receptors and has primarily nicotine-like actions
- **Organophosphate:** An ester of phosphoric acid and an alcohol that inhibits cholinesterase
- **Organophosphate aging:** A process whereby the organophosphate, after binding to cholinesterase, is chemically modified and becomes more firmly bound to the enzyme
- **Cholinergic crisis:** The clinical condition of excessive activation of cholinergic receptors; it may include skeletal muscle weakness as well as parasympathetic signs
- **Myasthenic crisis:** In patients with myasthenia, an acute worsening of symptoms; usually relieved by increasing cholinomimetic treatment

Q. Mention the muscarinic effects of acetylcholine.

Q. Mention the nicotinic effects of acetylcholine.

Q. Enumerate the pharmacological actions of different cholinergic receptor agonists. (CU-09J)

Q. Enumerate the pharmacological actions of neostigmine. (CU-12Ju, SU-16Ju)

Q. What are the therapeutic effects of anticholinesterase drugs? (RU-07Ju)

Q. Write down the effects of cholinesterases on CVS.

Ans.

Pharmacological effects of acetylcholine

Muscarinic effects of acetylcholine:

Effector organs	Effect	Receptors
1. Eye	▪ Constriction of pupil (miosis) ▪ Contraction of ciliary muscle for near vision	M ₃ receptors
2. Heart	▪ ↓Heart rate (negative chronotropy) ⇒ <i>Brady Cardia</i> ▪ ↓Force of contraction (negative inotropy) ▪ ↓Conduction velocity (negative dromotropy) Result: ↓Cardiac output → ↓blood pressure	M ₂ receptors
3. Blood vessels		
▪ Arteries	▪ Dilation (via EDRF). Constriction (high-dose direct effect)	
▪ Veins	▪ Dilation (via EDRF). Constriction (high-dose direct effect)	
4. Lungs	▪ Bronchoconstriction: Contraction of bronchial muscle ▪ Increased bronchial secretion Clinical significance: Aggravation of bronchial asthma.	M ₃ receptors
5. GIT	▪ Contraction of GIT smooth muscle ▪ Relaxation of sphincter ▪ Increased secretion of HCl & digestive enzymes	M ₃ receptors
6. Genitor-urinary system	▪ Contraction of detrusor muscle of urinary bladder ▪ Relaxation of trigone ▪ Relaxation of sphincter Result: Promote voiding of urine	M ₃ receptors
7. Glands	▪ Increases secretion of all exocrine glands.	M ₃ receptors
8. Uterus, pregnant	▪ Contraction	M ₃ receptors

(Ref: Katzung-13th/110)

Nicotinic effects of acetylcholine:

Receptor	Effect
1. CNS	In high concentrations, ✱ Tremor ✱ Emesis • Stimulation of the respiratory center. • Convulsions • Coma
2. PNS (Peripheral nervous system): N_N receptor activation at post-ganglionic neuron in autonomic ganglia	▪ Initial response → Simultaneous discharge of both parasympathetic and sympathetic systems. ▪ In CVS → Effects of nicotine are chiefly sympathomimetics: Hypertension. ▪ Sympathetic tachycardia may alternate with a bradycardia mediated by vagal discharge. ▪ In GIT and urinary tracts → Effects are largely parasympathomimetic: nausea, vomiting, diarrhea, and voiding of urine. ▪ Acetylcholine stimulates adrenal medulla → release of adrenaline → sympathetic effects.
3. N_M receptor activation at NMJ	▪ Fasciculation to strong contraction of skeletal muscle. ▪ If depolarizing nicotinic agents are not rapidly hydrolyzed- 1. Depolarization blockade 2. Flaccid paralysis of skeletal muscle.

(Ref: Katzung-13th/112)

Q. Why neostigmine is called indirectly-acting drug? (SU-17J)

Ans.

Neostigmine amplifies the effects of endogenous acetylcholine by inhibiting acetylcholinesterase without directly acting on acetylcholine receptors. This is why **neostigmine is called indirectly-acting drug**.

Q. "Acetylcholine has got no clinical utility"- explain.

Q. Why acetylcholine cannot be used therapeutically?

Ans.

"Acetylcholine has got no clinical utility"- because

1. The duration of action of acetylcholine is very short. This is because; Ach is rapidly inactivated by acetylcholinesterase enzyme. *orally → inactivated by gastric juice*
2. Ach has diverse action throughout the body. So, there will be more adverse effects. *(NM-specific)*

(Ref: Lippincott's-6th)

Q. How can you experimentally prove that ACh has both muscarinic & nicotinic effect? (SU-13Ju,11J)

Ans.

ACh has both muscarinic & nicotinic effects: We can prove it by experimental pharmacology by observing the effect of ACh on BP before & after atropine administration to a phenobarbital anaesthetized cat.

Procedures:

1. At first, the base line BP was measured. It is normal.
2. After the administration of ACh, there was fall of BP. This was due to decrease in heart rate & peripheral resistance. This indicates the action of ACh over M_2 receptors on heart & M_3 receptors in the peripheral blood vessels.
3. Again ACh was administered & same effect was observed.
4. Then Atropine was administered. Atropine blocks the muscarinic receptors & BP gets normal again & this procedure was done once again.
5. After Atropine administration, again ACh was administered & a dramatic rise of BP was observed. This time Ach cannot act on the muscarinic receptors because they are blocked by the atropine. This time ACh acts on N_N receptor of autonomic ganglia and cause release of adrenaline resulting in rise of BP.

6. After administration of the nicotinic receptor blocker, the BP again goes back to normal. This proves the previous rise of BP by ACh is due to its nicotinic effect.

So, at last we can surely say that, ACh has both muscarinic and nicotinic effect.

Q. Describe the clinical uses of cholinergic drugs with examples. (DU-07Ja/05S, SU-04S)

Q. Mention the indications of cholinesters

Q. Mention the indications of Bethanechol (DU-04J)

Q. Discuss the important uses of indirectly acting cholinomimetics in different clinical conditions. (CU-08J)

Q. Write down the important clinical indications of anticholinesterases. (DU-10J)

Q. Mention the clinical uses of each anticholinesterase. (DU-08J,06S; CU-15J,08J)

Q. Mention the clinical uses of physostigmine (DU-06S, SU-08J, RU-13J)

Q. Mention the clinical uses of neostigmine. (DU-15J, SU-04M)

Q. Mention the clinical uses of OPC. (CU-04J, SU-02M)

Ans.

Indications of cholinergic drugs / Bethanechol / physostigmine / neostigmine:

Drug	Clinical use
Bethanechol	• Postoperative ileus (atony or paralysis of the stomach or bowel following surgical manipulation). • Congenital megacolon. • To stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention secondary to spinal cord injury or disease (neurogenic bladder). • To increase the tone of the lower esophageal sphincter in patients with reflux esophagitis. • Preferable to carbachol because it is more muscarinic.
Carbachol	• Glaucoma (Because of its high potency, receptor nonselectivity, and relatively long duration of action, carbachol is rarely used therapeutically except in the eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure.) (Ref: Lippincott's-6th)
Pilocarpine	• Glaucoma (both closed-angle and open-angle glaucoma.) • Sjögren's syndrome (increases salivation).
Physostigmine	• Glaucoma • Overdoses of anticholinergic drugs, such as atropine, phenothiazines, and tricyclic antidepressants. • Atony of bladder and bowel. (Ref: Lippincott's-6th)
Neostigmine	• Myasthenia gravis • Paralytic ileus or atony of urinary bladder, e.g. after surgery. • Reversal of neuromuscular block by nondepolarizing drugs. CE-03 A-muscarinic neu-sec
Edrophonium	• Diagnosis of myasthenia gravis. • To differentiate a myasthenia gravis to cholinergic crisis. • Reversal of neuromuscular block by nondepolarizing drugs.
Pyridostigmine	• Myasthenia gravis.
Ambenonium	• Myasthenia gravis
Demecarium	• Chronic open-angle glaucoma • Closed-angle glaucoma after iridectomy. • Diagnosis and treatment of accommodative esotropia.
Rivastigmine, galantamine, donepezil, tacrine (obsolete)	• Alzheimer's disease

Echothiophate	• Chronic treatment of open-angle glaucoma. <i>(The effects may last for up to one week after a single administration.)</i>
Parathion	• Insecticide only
Malathion	• Insecticide • Scabicide (topical)

(Ref: Katzung-13th/114-119; Katzung & Trevor's-11th edition, Lippincott's-6th)

Q. Discuss the role of neostigmine at the end of abdominal surgery. (CU-14Ju)

Ans.

Role of neostigmine at the end of abdominal surgery

1. It is used to stimulate the bladder & bowel in paralytic ileus or atony of urinary bladder, e.g. after surgery.
2. It is used to reverse the action of non-depolarizing neuromuscular blocking agents in surgery.

Q. Write the adverse effects of cholinomimetic drugs.

Q. Mention the adverse effects of anticholinesterase drugs. (CU-15J)

Ans.

Adverse effects cholinomimetic drugs / anticholinesterase drugs:

1. **CVS:** Bradycardia, hypotension.
2. **Respiratory:** Bronchoconstriction, aggravation of bronchial asthma.
3. **GIT:** Diarrhoea, vomiting, hyperacidity.
4. **Urinary:** Urinary urgency.
5. **Exocrine:** Severe salivation & sweating.
6. **CNS:** Tremor, hypothermia, respiratory centre stimulation.

Q. Write the contraindications of cholinergic drugs?

Ans.

Contraindications of cholinomimetic drugs:

1. Bronchial asthma
2. Peptic ulcers disease (PUD)
3. Myocardial infarction
4. Hyperthyroidism
5. Obstructive urinary retention
6. Mechanical obstruction of the GIT

Q. What is cyclospasm?

Q. Briefly explain- Cycloplegia. (CU-99S, SU.99S)

Ans.

Cyclospasm: Marked contraction of ciliary muscle is called cyclospasm.

Cause: Cholinesterase inhibitor intoxication.

Cycloplegia: Paralysis of the ciliary muscle is called cycloplegia.

Cause: Anti-cholinergic side effect of anti-psychotic or anti-depressants.

Direct-acting cholinomimetic

Bethanechol

General properties

1. It is **not hydrolyzed by acetylcholinesterase** (due to the addition of carbonic acid), although it is inactivated through hydrolysis by other esterases.
2. It has **strong muscarinic** activity.
3. It **lacks nicotinic** actions (due to the addition of the methyl group)

- Its major actions are on the smooth muscle of the bladder and GIT.
- Duration of action:** 1 hour.

Actions:

- Increased intestinal motility and tone.
- It stimulates the detrusor muscles of the bladder whereas the trigone and sphincter are relaxed, causing expulsion of urine.

Therapeutic applications: See the table.

Adverse effects: Bethanechol causes the effects of generalized cholinergic stimulation. These include sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.

(Ref: Lippincott's-6th)

Pilocarpine

General properties

- The alkaloid pilocarpine is a tertiary amine and is stable to hydrolysis by acetylcholinesterase.
- Less potent
- Penetrate the CNS at therapeutic doses.
- Exhibits muscarinic activity
- Used primarily in ophthalmology.

Eye drop

(Ref: Lippincott's-)

Q. Write the mode of action of pilocarpine. (CU-09J,07Ju)

Q. How does pilocarpine reduce IOP in glaucoma? (RU-16Ju)

Q. Outline receptor mediated action of pilocarpine. (SU-07Ju)

Ans.

Mode of action of pilocarpine

<u>Miosis</u>	<u>Reduction of IOP</u>
Pilocarpine ↓ Acts on M₃ receptor of constrictor pupillae muscle ↓ Contraction of constrictor pupillae muscle ↓ Miosis (constriction of pupil)	Pilocarpine ↓ Acts on M₃ receptor of ciliary muscle ↓ Contraction of ciliary muscle ↓ ↑Tension of trabecular meshwork around the canal of Schlemm ↓ Opening of pore ↓ ↑Drainage of aqueous humour ↓ ↓Intraocular pressure (IOP)

Q. Discuss the pharmacological effects of pilocarpine. (SU-16Ju)

Q. Write down the role of Pilocarpine on eye. (CU-17J)

Ans.

Pharmacological effect of pilocarpine: Pilocarpine is a directly acting cholinomimetic drug. It exhibits **muscarinic** activity. It has **no nicotinic** effect.

- On systemic administration it has prominent GIT & genito-urinary effects but less effect on CVS.
- Applied topically to the cornea, pilocarpine produces-
 - Rapid miosis
 - Contraction of the ciliary muscle and ↓Intraocular pressure (IOP).
 - Spasm of accommodation.
 - Vision is fixed at some particular distance, making it impossible to focus.

3. Stimulates secretions of sweat, tears, and saliva.

4. Promotes salivation in patients with-

- Xerostomia *resulting from irradiation of the head and neck.*
- Sjögren's syndrome *(characterized by dry mouth and lack of tears)*

(Ref: Goodman & Gilman's-12th; Lippincott's-6th)

Q. What are the indications of Pilocarpine?

Ans.

Indications of pilocarpine:

1. Emergency treatment of both closed-angle and open-angle glaucoma.
2. Xerostomia (dry mouth) due to-
 - Sjögren's syndrome
 - Irradiation of the head and neck.

Q. What is the role & uses of pilocarpine in ophthalmology?

Q. Write down the role of Pilocarpine on eye. (CU-17J)

Ans.

Uses of pilocarpine / miotics: Pilocarpine is used in-

1. Emergency treatment of both closed-angle and open-angle glaucoma.
2. Accommodative convergent squint.
3. Accommodation weakness
4. Cataract surgery
5. To counteract the effects of mydriatics.

(Ref: Basak ophthalmology-4th/102)

Q. Explain the pharmacological basis of using pilocarpine in glaucoma. (RU-15Ju)

Q. What is the role of pilocarpine in glaucoma?

Ans.

Role of Pilocarpine in glaucoma or in reducing IOP: Pilocarpine is the drug of choice in the emergency lowering of intraocular pressure of both closed-angle and open-angle glaucoma. Pilocarpine is extremely effective in opening the trabecular meshwork around Schlemm's canal, causing an immediate drop in intraocular pressure as a result of the increased drainage of aqueous humor. This action lasts up to 8 hours and can be repeated.

(Ref: Lippincott's-6th)

Q. Describe the mechanism of reduction of IOP by pilocarpine and timolol. (SU-15J)

Q. Compare and contrast the role of pilocarpine and timolol in the treatment of glaucoma. (RU-07J)

Ans.

Mechanism of reduction of IOP by pilocarpine and timolol:

Pilocarpine	Timolol
Pilocarpine ↓ Contraction of ciliary muscle via M₃ receptor ↓ ↑Tension of trabecular meshwork around the canal of Schlemm ↓ Opening of pore ↓ ↑Drainage of aqueous humour ↓ ↓Intraocular pressure (IOP) ↓ Relief from glaucoma	Timolol ↓ Blocks β-receptor on secretory epithelium of ciliary body ↓ Decrease aqueous secretion from ciliary body ↓ ↓Intraocular pressure (IOP) ↓ Relief from glaucoma

Q. What are the adverse effects of pilocarpine? (RU-06M; SU-03S)

Q. What are the adverse effects of bethanechol? (DU-04J)

Ans.

Adverse effects of pilocarpine / bethanechol / cholinergic drugs: Pilocarpine is usually used as topical eye drop. So there is less chance of systemic adverse effects. In case of sufficient absorption from eye into the systemic circulation, the following adverse effects may occur.

1. Bronchoconstriction
2. Bradycardia
3. Hypotension
4. Miosis
5. Diarrhoea
6. Urinary urgency (↑frequency).
7. Profuse sweating & salivation.
8. Enter into the brain & causes CNS disturbances.

(Ref: Lippincott's-6th & Goodman & Gilman's-12th)

Indirect-acting cholinomimetic

Q. Enumerate important anticholinesterases. (DU-12Ju,10J)

Q. Enumerate the anticholinesterases used in therapy with their clinical applications. (RU-14J)

Q. Lists the clinically important anticholinesterase drugs. (DU-14J,04M; CU-05S, RU-07Ju,05S)

Ans.

Clinically used / important Anticholinesterases:

1. Physostigmine
2. Neostigmine
3. Edrophonium
4. Pyridostigmine
5. Ambenonium
6. Donepezil

(Ref: Lippincott's-6th)

Viva Q. Name the cholinomimetic drug that has both direct & indirect action.

Ans.

Neostigmine

- ⇒ **Direct action:** Acts on N_M receptor, ie, nicotinic action is direct.
- ⇒ **Indirect action:** Inhibits cholinesterase.

Q. Discuss the mode of action of anticholinesterases. (DU-10J,06S)

Q. Explain the mechanism of action of physostigmine. (DU-07/06J, RU-15J, SU-02M)

Ans.

Mode of action of anticholinesterases (eg, physostigmine)

Acetylcholinesterase (AChE) is the enzyme that specifically cleaves acetylcholine to acetate and choline and, thus, terminates its action. All of the anticholinesterases (cholinesterase inhibitors) increase the concentration of endogenous acetylcholine at cholinergic receptors by inhibiting acetylcholinesterase.



- **Reversible** anticholinesterase drugs (eg, physostigmine) bind with active site of the AChE by electrostatic and hydrogen bonds.
- **Irreversible** anticholinesterase drugs (eg, OPC) bind with active site of the AChE by a covalent bond.

↓
AChE becomes inactive. In case of the irreversible anticholinesterase drugs, AChE is permanently inactivated.

↓
No hydrolysis of acetylcholine (ACh).

↓
The lifetime of ACh is prolonged, so, there is accumulation (increased concentration) of ACh in the synaptic cleft.

↓
Prolonged & increased cholinergic action.

Q. Explain the clinical uses of physostigmine. (RU-15J)

Ans.

Clinical uses of physostigmine

1. Glaucoma (along with pilocarpine)
2. Atropine poisoning (as an antidote)

Myasthenia gravis

Definition: It is an autoimmune disease characterized by formation of autoantibodies to nicotinic acetylcholine receptors (N_M receptor) in the neuromuscular junction (NMJ). These antibodies block neuromuscular transmission and cause complement-mediated destruction of the acetylcholine receptors.

Clinical features:

1. **Cardinal symptom** → Abnormal fatigable weakness of the muscles. Worsening of symptoms towards the end of the day or following exercise is characteristic.
2. **First symptoms** → Intermittent ptosis or diplopia.
3. Difficulty in speaking & swallowing.
4. Weakness in the extremities
5. Weakness in the muscles of respiration.

Diagnosis:

1. **Tensilon test:** The IV injection of the short-acting anticholinesterase, **edrophonium bromide**, is a valuable diagnostic aid; 2 mg is injected initially, with a further 8 mg given half a minute later if there are no undesirable side-effects. Improvement in muscle power occurs within 30 seconds and usually persists for 2-3 minutes. The improvement in muscle power confirms that it is myasthenia gravis.
2. **Anti-acetylcholine receptor antibody:** Positive in over 80% of cases.

Treatment:

1. **Cholinesterase inhibitors:** Neostigmine, Pyridostigmine, Ambenonium
2. Plasma exchange
3. Intravenous immunoglobulin
4. Immunosuppressive drugs: e.g. Corticosteroid, azathioprine.

(Ref: Katzung-13th/117; Davidson's medicine-22nd)

Q. Describe the role of Neostigmine in myasthenia gravis. (CU-16Ju)

Ans.

Role of neostigmine in the Rx of myasthenia gravis: Neostigmine has a prominent nicotinic effect than muscarinic effect.

Neostigmine → Inhibits cholinesterase enzyme → No hydrolysis of ACh → Increased concentration of ACh in the NMJ → Opposite effect of Myasthenia gravis.

Q. Why neostigmine is preferred to Physostigmine in reversing non-depolarizing muscle relaxant action? (SU-14Ju)

Q. Why neostigmine is given instead of physostigmine?

Ans.

Neostigmine is preferred to Physostigmine in reversing non-depolarizing muscle relaxant action:

1. Unlike physostigmine, neostigmine has a quaternary nitrogen; hence, it is more polar and does not enter the CNS. So, there is less CNS adverse effects. Physostigmine can enter and stimulate the cholinergic sites in the CNS.
2. Neostigmine's effect on skeletal muscle is greater than that of physostigmine, and it can stimulate contractility before it paralyzes.
3. Neostigmine has both direct and indirect effect.
4. Nicotinic effect of neostigmine is prominent. Physostigmine has a wide range of effects as a result of its action, and the muscarinic effect is prominent.

(Ref: Lippincott's-6th)

Q. Compare physostigmine & neostigmine as cholinesterase enzyme inhibitor. (CU-16Ju; SU-06S)

Q. Compare & contrast between physostigmine & neostigmine. (SU-09Ju)

Ans.

Comparison between physostigmine & neostigmine:

Traits	Physostigmine	Neostigmine
1. Source	Plant (alkaloid)	Synthetic
2. Chemistry	Tertiary amine	Quaternary amine
3. Lipid solubility	More	Less.
4. Blood brain barrier	Can cross	Cannot cross.
5. CNS effects	More	Less
6. Action	More muscarinic	More nicotinic (Remember: Neostigmine Nicotinic)
7. Clinical uses	▪ Glaucoma (along with pilocarpine) ▪ Atropine poisoning (as an antidote)	▪ Myasthenia gravis ▪ D-Tubocurarine poisoning (as an antidote) ▪ To stimulate bladder and bowel, eg, after surgery.

(Ref: Katzung-13th/114 & Lippincott's-6th)

Q. How does neostigmine reverse the action of gallamine? (DU-04J)

Ans.

Reversal of action of gallamine by neostigmine: Gallamine is a competitive neuromuscular blocker & causes flaccid type of muscle paralysis. It is used in abdominal & pelvic surgery.

Neostigmine → Inhibits cholinesterase enzyme → No hydrolysis of ACh → Increased concentration of ACh in the NMJ → Competitive antagonism between ACh & gallamine → ACh displaces the gallamine from the nicotinic receptor → ACh binds with nicotinic receptor and causes contraction of skeletal muscle → Reversal of muscle relaxation.

Organophosphorus compounds (OPC)

Q. Write short notes on OPC. (RU-08Ju)

Q. Name the drugs used in OPC poisoning. (CU-07J)

Ans.

Organophosphorus compounds (OPC): Diazinon, parathion, malathion etc.

Criteria of OPC:

1. Binds with cholinesterase enzyme irreversibly by strong covalent bond.
2. Highly lipid soluble
3. Absorbed from skin, lungs, GIT → CNS.
4. Echothiophate is used in glaucoma (more polar, so doesn't go to CNS).

5. Use- Insecticide (malathion), suicidal & homicidal.

Nice to knowMechanism of OPC poisoning:

OPCs irreversibly bind with active site of the acetylcholinesterase enzyme by a covalent bond



The enzyme becomes permanently inactive and cannot act on its substrate, acetylcholine (ACh).



No hydrolysis of acetylcholine (ACh)



The lifetime of ACh is prolonged, so, there is accumulation (increased concentration) of ACh in the synaptic cleft



Prolonged & increased cholinergic action.



Toxic effects are produced by excess ACh.

Signs
Pin point pupil
Salivation
Rest. of urine
(Ref: Katzung-13th/128, 1009-1010)

Route
Inh.
Inj.
Intr. skin

SLUDGE ⇒ Salivation, Lacrimation, Urination, Defecation, Gastric irritation, Emesis

Q. What are the sign & symptoms (S/S) of OPC poisoning? (DU-08Ju, CU-05S/J, RU-17J, SU-09J,07/06J)

Q. Describe briefly the drug management of OPC poisoning. (DU-11J, SU-11J)

Q. Describe the management of OPC poisoning. (DU-15Ju,14J,12Ju,08Ju; CU-05S/J; RU-17J,14Ju,13Ju,07Ju; SU-13J,09J/Ju,07J)

Ans.

OPC poisoning

Clinical features (sign & symptoms) / (S/S): Due to increased concentration of ACh in the body-

1. **Eye:** Miosis (pin-point pupil).
2. **CVS:** Bradycardia, hypotension.
3. **Respiratory:** Bronchoconstriction, bronchorrhea, cough, wheeze, dyspnea.
4. **GIT:** Diarrhoea, vomiting, abdominal cramp, involuntary defecation, hyperacidity (heart burn).
5. **Urinary:** Urinary incontinence, urgency, frequency.
6. **Exocrine:** Severe salivation & sweating.
7. **CNS:** Tremor, restlessness, convulsion, hypothermia, respiratory centre stimulation.
8. **NMJ:** Flaccid paralysis of skeletal muscles leads to weakness.

Cause of death in OPC poisoning: Respiratory failure due to respiratory muscle paralysis, bronchoconstriction, bronchorrhea.

(Ref: Katzung-13th/128, 1009-1010)

Management of OPC poisoning:A. Non-pharmacological approach:

1. Immediate ABC resuscitation, if needed.
2. A short & complete history to confirm poisoning.
3. **Examination & monitoring of vital signs:** BP, pulse, respiratory rate, temperature, urine output, pupil,
4. Contaminated clothing should be removed & stored for medico-legal purpose.
5. Contaminated skin should be washed by normal saline.
6. **Gastric suction:** By 2% KMnO₄

ABCD & Decontamination

Respiratory mask

Up to atropinization (full dilatation of pupil)

B. Pharmacological / Drug management:

1. **Atropine:** 1.8 to 3 mg atropine IV stat and then double the dose every 5 minutes up to atropinization. Then maintain the 20-30% of atropinization dose hourly up to 3 days.
2. **Specific antidote: Pralidoxime (I/V).** The dose for an adult is 2 g IV over 4 mins, repeated 4-6-hourly.
3. **Diazepam:** If convulsion present

6-8 hr

Fluid → Dextrose saline

(Ref: Katzung-13th/128, 1009-1010 + Davidson's-22nd)

(Dehydrated)

C. **Follow up:** After discharging from the hospital, the patient should be advised to take rest for at least 6 weeks for re-synthesis of the cholinesterase enzyme.

Q. What is "atropinization"? (CU-07Ju,06S)

Ans.

Atropinization: The signs produced by atropine given in OPC poisoning, are called atropinization. In OPC poisoning, IV atropine should be continued until atropinization is reached. After atropinization, the dose of atropine should be reduced gradually, otherwise atropine toxicity may develop.

Signs of atropinization:

1. Mydriasis
2. Tachycardia
3. Dry mouth
4. Dry skin
5. Raised temperature
6. Disappearance of crepitation in lungs.
7. Loss of light reflex
8. Patient becomes restless.

Q. Describe the role of atropine in OPC poisoning. (DU-17M/J, CU-16J, SU-17J) 1.8-3 mg

Q. Explain the pharmacological basis of using atropine in OPC poisoning. (CU-07Ju/J,06S)

Ans.

Rationale of using atropine in OPC poisoning:

- Atropine reverses the action of acetylcholine by blocking muscarinic receptors. Early use of sufficient doses of atropine is potentially life-saving in patients with severe OPC poisoning. Atropine reverses ACh-induced bronchospasm, bronchorrhea, bradycardia and hypotension.
- When the diagnosis is uncertain, a marked increase in heart rate associated with skin flushing after a 1 mg intravenous dose makes OPC poisoning unlikely.
- In OPC poisoning, atropine should be administered until secretions are controlled, the skin is dry and there is a sinus tachycardia.
- Large doses may be needed but excessive doses may cause anticholinergic effects.

Q. What is the role of oxime compound in OPC poisoning? (CU-07Ju/J, RU-07Ju,06S)

Q. Explain the role of pralidoxime in OPC poisoning. (DU-17J)

Ans.

Role of oxime compound (eg, pralidoxime) in OPC poisoning: In OPC poisoning, an oxime such as pralidoxime or obidoxime, if available, should be administered, as this may reverse or prevent muscle weakness, convulsions or coma, especially if administered rapidly after exposure. The dose for an adult is 2 g IV over 4 mins, repeated 4-6-hourly. Oximes work by reactivating AChE that has not undergone 'ageing'. Oximes may provoke hypotension, especially if administered rapidly.

(Ref: Katzung-13th/128-129, Lippincott's-6th)

Q. Justify early administration of oxime in OPC poisoning. (CU-04M)

Q. Describe the mechanism of action of pralidoxime in OPC poisoning.

Q. Short note: Pralidoxime. (RU-15Ju)

Ans.

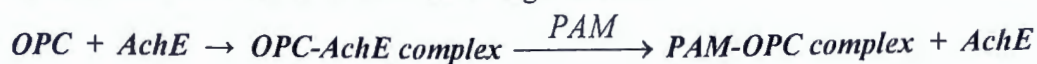
Mechanism of reactivation of acetylcholinesterase by pralidoxime: Oxime compounds can reactivate inhibited acetylcholinesterase (AChE) from the OPC-AChE complex. This is why oxime compounds are called **cholinesterase regenerator**. These oxime agents include pralidoxime (PAM), diacetylmonoxime and others.

OPCs irreversibly bind with active site of the AChE by a covalent bond and form OPC-AChE complex.

↓

Pralidoxime binds with OPC and frees AChE. This can take place if the OPC-AChE complex has not "aged".

↓
 ↑Concentration of active AChE
 ↓
 ↑Hydrolysis of ACh by AChE and relief from cholinergic effects.



Because of the positive charge of PAM, it does not enter the CNS and is ineffective in reversing the CNS effects of OPC poisoning.

(Ref: Katzung-13th/128-129, Lippincott's-6th)

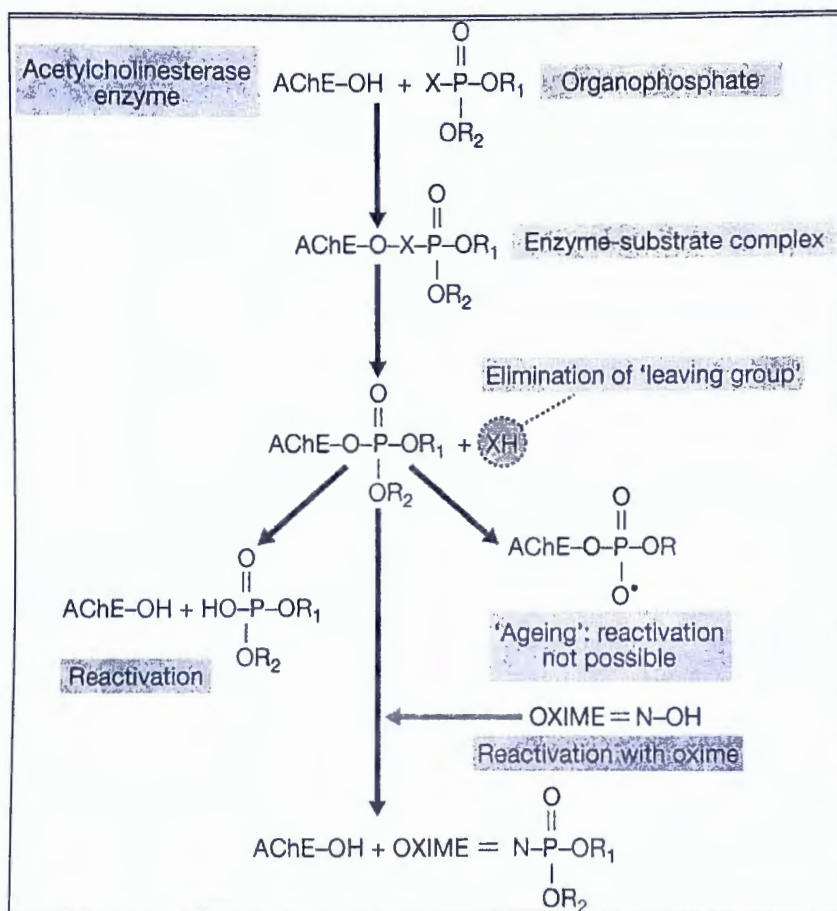


Figure. Mechanism of toxicity of OPC and treatment with oxime.

(Ref: Davidson's-22nd)

Q/ What is aging process? What is its significance?

Ans.

Aging process: After binding of OPC with the acetylcholinesterase enzyme (AChE), there is loss of an alkyl group from the complex. This causes permanent inactivation of the AChE. This loss of alkyl group from the OPC-AChE complex and permanent inactivation of the AChE enzyme is called **aging**. For the treatment of OPC poisoning by pralidoxime, pralidoxime must be administered before the aging process.

this is why it is irreversible

(Ref: Lippincott's-6th)

(6-8 hrs)

Anti-cholinergic drugs

Q. Classify anti-cholinergic drugs. (SU-06S/J)

Q. Classify cholinceptor-blocking drugs. (SU-04J)

Q. Mention important atropine substitutes with their role/effects. (SU-15Ju,15J,12Ju)

Q. List the atropine substitutes. (CU-16J,06M, SU-06J)

Q. Enumerate the drugs that antagonize the muscarinic cholinergic receptors. (SU-08Ju)

Ans.

Anti-cholinergic drugs: Two types-

1. **Anti-muscarinic drugs:** Block muscarinic receptors

- a. **Natural:** Atropine, scopolamine, homatropine.
- b. **Synthetic: Atropine substitutes-**

Quaternary amines	
☒	Anisotropine
☐	Clidinium
☒	Glycopyrrolate
☒	Isopropamide
☐	Mepenzolate
☐	Methantheline
☐	Methscopolamine
☐	Oxyphenonium
☐	Propantheline
☐	Tridihexethyl
☒	Tropium
Tertiary amines	
☐	Darifenacin
☒	Dicyclomine
☒	Oxybutynin
☐	Oxyphenacyclimine
☐	Propiverine
☒	Scopolamine
☐	Solifenacin
☐	Tolterodine

2. **Anti-nicotinic drugs:** Block nicotinic receptors

- a. Ganglion blocker
- b. NMJ blocker.

(Ref: Katzung-13th/128)

Anti-muscarinic drugs

Q. Explain organ smooth muscle effects of anti-muscarinic agents. (SU-17M)

Q. Describe the dose related effects of atropine. (CU-17M)

Q. Explain the role of atropine on CVS. (SU-07J)

Q. Discuss the effects of atropine on urinary system. (SU-07J)

Q. Describe the effects of atropine on GIT. (DU-15J,13J,12J,10Ju, RU-03J, SU-07J,06M)

Q. Explain the pharmacological properties of ipratropium bromide, tropicamide & procyclidine. (SU-08J)

- Q. Explain the pharmacological effects of atropine on eye. (DU-13J,12J,10Ju,07J; CU-06M/J; RU-11J,06J, SU-13Ju,09/07J,06M)
- Q. Write down the effects of atropine on eye. (DU-17J,15J,14J, RU-14J)
- Q. Explain the action of tropicamide on eye. (SU-14J)
- Q. Explain how does atropine cause mydriasis? (DU-09Ju)
- Q. Explain the mydriatic effect of atropine. (DU-14Ju)
- Q. Explain how does atropine increase IOP?

Ans.

Pharmacological effects of atropine:

System / organ	Effect of atropine
CVS	- Low dose atropine → Block pre-junctional M_1 autoreceptors on vagal post-ganglionic fibers → ↓ACh release in SA node → Bradycardia. - Moderate-high dose atropine → Block M_2 receptor on the SA node → ACh cannot act on M_2 receptor → No inhibitory effect of ACh (i.e. no bradycardia) → Tachycardia. - On endothelium → Oppose vasodilation caused by cholinergic stimulation. - Net CVS effects of atropine in patients with normal hemodynamics are not dramatic: tachycardia may occur, but there is little effect on blood pressure.
Eye	- Atropine blocks M_3 receptor → Relaxation of constrictor pupillae muscle → Dilation of pupil (mydriasis). - Atropine blocks M_3 receptor → Relaxation of ciliary muscle → Cycloplegia → Obstruction of the "canal of Schlemm" & loss of light & accommodation reflex & photophobia → ↓Drainage of aqueous humor → ↑Intra-ocular pressure. Reduction of lacrimal secretion. Patients occasionally complain of dry or "sandy" eyes. ↑Intraocular pressure (acute glaucoma may be precipitated).
Lungs	- Bronchodilatation ↓Bronchial secretion
GIT	- Constipation due to- - Relaxation of GIT smooth muscle → ↓Motility - Constriction of sphincter. - HCl secretion is less affected.
Urinary bladder	- Urinary retention due to- - Relaxation of detrusor muscle - Contraction of trigone - Constriction of sphincter
Exocrine gland	↓Lacrimation → Dry or sandy eyes ↓Sweating → ↑Body temperature (Atropine fever) ↓Salivation → Dry mouth ↓Gastric HCl secretion ⇒ <i>little effect</i> ↓Bronchial secretion (so, used in pre-anesthetic medication)
CNS	In usual dose - Mild restlessness - Drowsiness In toxic dose - Excitement - Agitation - Hallucination - Disorientation - Finally coma, if untreated

(Ref: Katzung-13th/122-125; Lippincott's-6th)

Q. What is atropine fever?

Ans.

Atropine fever: Atropine suppresses thermoregulatory sweating which results in increased body temperature called **atropine fever**. Sympathetic cholinergic fibers innervate eccrine sweat glands, and their muscarinic receptors are readily accessible to antimuscarinic drugs. In adults, body temperature is elevated by this effect only if large doses are administered, but in infants and children even ordinary doses may cause "atropine fever."

(Ref: Katzung-13th/126)

Q. What are the indications of atropine? (DU-06S; CU-03S/J; RU-04S; SU-07Ju,05J)

Q. Mention six important uses of atropine. (RU-16J)

Q. Write down the ophthalmic use of atropine. (RU-10J)

Ans.

Indication of atropine:

1. **Antidote for cholinergic agonists:** Atropine is used for the treatment of OPC poisoning and some types of mushroom poisoning (*certain mushrooms contain cholinergic substances that block cholinesterases*).
2. **Antisecretory:** Atropine is used as pre-anesthetic medication to block secretions in the upper and lower respiratory tracts prior to surgery.
3. **Antispasmodic agent:** To relax GI tract & gall bladder.
4. **Ophthalmic:** As mydriatics. It is less used for long duration of action.
5. Parkinson's disease
6. Cholinergic crisis.

⊗ To prevent bradycardia

(Ref: Lippincott's-6th)

Q. Justify the use of atropine in peri-operative period. (CU-04M)

Q. Explain pharmacological basis of using atropine in pre-anesthetic medication. (SU-14Ju)

Q. Atropine is used in pre-anesthetic medication. Why?

Ans.

Use of atropine in peri-operative period/ as pre-anesthetic medication:

1. To reduce bronchial secretion
2. To reduce HCl secretion.
3. To reduce salivation
4. To reduce reflex bradycardia & hypotension.

Q. What is the role of atropine in uveitis?

Ans.

Role of atropine in uveitis:

1. Gives rest of the eyeball by ocular muscle relaxation
2. Prevent synechia (synechia: adhesion of iris with lens)
3. ↑Blood flow & causes improvement of inflammatory process.
4. Long duration cycloplegia.

Q. Why natural atropine is not preferred in all cases? (DU-05M, SU-07Ju)

Q. What are the advantages of atropine-like synthetic drugs over atropine? (DU-11J)

Ans.

Natural atropine is not preferred in all cases, because-

1. Prolonged duration of action of atropine- 7 to 10 days.
2. Wide range of action of atropine causes more adverse effects.

Advantages of atropine-like synthetic drugs over atropine

1. Short duration of action.
2. More specific action and so less adverse effects.

- Q. Mention the adverse effect of atropine or other anti-muscarinic drugs. (CU-14J,06M)
 Q. Name the possible adverse effects of atropine substitutes used as mydriatics. (DU-09Ju; CU-06M)
 Q. Mention the adverse effect of anti-cholinergic drugs. (CU-15J)

Ans.

Adverse effects of atropine & other anti-muscarinic drugs:

1. **Eye:** Blurred vision, raised IOP & aggravation of glaucoma, mydriasis, loss of accommodation reflex (loss of near vision), dry eye etc.
2. **CVS:** Tachycardia.
3. **GIT:** Constipation
4. **Urinary:** Urinary retention
5. **Exocrine:** ↓Salivation (dry mouth), ↓sweating (hot dry skin), hyperthermia (atropine fever) etc.
6. **CNS:** Restlessness, agitation, excitement, hallucination, drowsiness, convulsion etc.

(Ref: Katzung-13th/129)

Q. What are the contraindications of atropine? (RU-06J)

Ans.

Contraindications of atropine & other anti-muscarinic drugs:

1. Old MI
2. Glaucoma (*because, atropine increases IOP & aggravates glaucoma*).
3. BPH & Old aged male (*because, atropine causes retention of urine in elderly men having benign prostatic hyperplasia, BPH*).
4. Patients with psychosis & Schizophrenia.

(Ref: Katzung-13th/129)

Q. List the antimuscarinic drugs used as mydriatics. Discuss their ophthalmological indications. (DU-17M,15J,13J,12J)

Q. Enlist the drugs used as mydriatics with their duration of action. (DU-09Ju)

Q. List the diseases of eye where homatropine is used for diagnostic and treatment purposes. (DU-01J)

Q. Enlist the currently used mydriatic agents. (DU-17J)

Q. Write down the role of Cyclopentolate on eye. (CU-17J)

Ans.

Drugs used as mydriatics:

Drugs	Duration of action
1. Atropine	5-6 days
2. Scopolamine	3 — 7 days
3. Homatropine	12-24 hours
4. Cyclopentolate	3-6 hours
5. Tropicamide	15-60 min

ASACT

Clinical uses / Indications of mydriatics in ophthalmology: Mydriatics cause mydriasis and mydriasis is required for-

A. Diagnostic purposes:

1. Accurate measurement of **refractive error** in non-cooperative patients (young children).
2. Ophthalmologic **examination of retina** to detect retinal problems like **retinal hemorrhage**, diabetic or hypertensive **retinopathies**, **papilledema** etc.

B. Treatment purposes:

1. To prevent synechia (adhesion between iris and lens) formation in **uveitis** and **iritis** (homatropine).

(Ref: Katzung-13th/127)

Viva Q: Which one of the above listed drug will you use for mydriasis and why?

Ans. **Tropicamide**. Because it has shortest duration of action, so less blurring of vision.

Nice to know:

Role of atropine in MI: Sinus bradycardia is the most common arrhythmia, seen during recent inferior or posterior MI. In case of recent MI, excessive vagal tone causes sinus or nodal bradycardia. Atropine may prevent further clinical deterioration in case of high vagal tone or AV block. That's why, it may be considered in the initial Rx of recent MI. In old MI, heart rate is already high. Atropine increases heart rate more which may aggravate MI. This is why, atropine is contraindicated in old MI.

(Ref: Goodman & Gilman's-12th)

Q. Explain the pharmacological rationale of using atropine substitutes as mydriatics. (CU-06M)

Ans.

Atropine produces mydriasis but it is not used as a mydriatic, because-

1. Mydriasis with atropine last for several days which causes blurring of vision.
2. Atropine aggravates glaucoma
3. Cycloplegia is marked in comparison to homatropine.
4. Mydriasis is not reversed by pilocarpine.

On the other hand, atropine substitutes can be used as a mydriatic, because-

1. They are shorter acting than atropine.
2. They produce less cycloplegia.
3. Mydriasis is reversed by pilocarpine.
4. Produce less visual disturbance.

Q. Compare & contrast: Atropine, Homatropine & Tropicamide. (DU-07J; CU-04M, RU-11J)

Q. Compare the effects of Atropine & Homatropine on eye. (CU-04M)

Ans.

Comparison among Atropine, Homatropine & Tropicamide:

Points	Atropine	Homatropine	Tropicamide
1. Source	Natural alkaloid	Synthetic	Synthetic (tertiary amine)
2. Onset of action	Slow	Rapid	Rapid
3. Duration of mydriasis	5-6 days	12-24 hours	15-60 min
4. Duration of cycloplegia	5-6 days	12-24 hours	15-60 min
5. Uses	• OPC poisoning • Post MI bradycardia	Ophthalmic use	Ophthalmic use

(Ref: Katzung-13th/127)

Q. Why tropicamide is superior to atropine as mydriatics. (DU-07J)

Q. What is the advantage of tropicamide over atropine as mydriatics? (DU-04S; SU-05J)

Q. What is the advantage of eucatropine over atropine as mydriatics?

Ans.

Advantages of tropicamide/ eucatropine over atropine as mydriatics:

1. Onset: Rapid
2. Tropicamide has a less duration of mydriasis & cycloplegia

Drug	Duration of mydriasis & cycloplegia
Atropine	5-6 days
Tropicamide	15-60 min

3. Tropicamide is less potent than atropine.
4. Tropicamide has less side effects and specific action
5. Chance of poisoning is less.

So, tropicamide/ eucatropine is clinically used as mydriatics in ophthalmologic examination.

(Ref: Katzung-13th/127)

Q. What are the adverse effects of atropine as local mydriatics? (CU-06M)

Ans.

Adverse effects of atropine as local mydriatics:

1. Prolong duration of action (7-10 days). So, prolong mydriasis → prolong blurring of vision.
2. Increases intraocular pressure. So, it can induce acute glaucoma in persons with a narrow anterior chamber angle.
3. Difficulty in near vision, due to loss of accommodation reflex
4. Dry or sandy eyes
5. Photophobia

(Ref: Katzung-13th/129)

Q. Explain why atropine is contraindicated in patients suffering from glaucoma. (DU-16Ju)

Ans.

Atropine blocks M₃ receptor → Relaxation of ciliary muscle → **Cycloplegia** → Obstruction of the "canal of Schlemm" → ↓ Drainage of aqueous humor → ↑ **Intra-ocular pressure (IOP)**.

Thus, atropine Increases intraocular pressure. So, it can induce acute glaucoma in persons with a narrow anterior chamber angle.

Q. Why phenylephrine is preferred as mydriatics than anti-muscarinic drugs for fundoscopic examination?

Ans.

Phenylephrine is preferred as mydriatics than anti-muscarinic drugs: Parasympathoplegic drugs should never be used for mydriasis unless cycloplegia or prolong action is required. α-agonists (e.g. phenylephrine) produce a short acting mydriasis that is usually sufficient for fundoscopic examination.

(Ref: Katzung-13th/127)

Atropine poisoning

- Datura

Q. Write the management of atropine poisoning? (RU-04J)

Q. Mention the specific antidote of atropine poisoning.

Ans.

Clinical features (S/S) of atropine poisoning:

1. **Eye:** Blurred vision, raised IOP & aggravation of glaucoma, mydriasis, loss of accommodation reflex, dry eye etc.
2. **CVS:** Tachycardia.
3. **GIT:** Constipation
4. **Urinary:** Urinary retention
5. **Exocrine:** ↓ Salivation (dry mouth), ↓ sweating (hot dry skin), hyperthermia (atropine fever) etc.
6. **CNS:** Restlessness, agitation, excitement, hallucination, drowsiness, convulsion etc.

Classic signs & symptoms of atropine poisoning-

1. Red as a beet (*Skin flushed*)
2. Hot as a hare (*Hyperthermia*)
3. Dry as a bone (*Dry mucous membrane, no sweating*)
4. Blind as a bat (*Cycloplegia, blurred vision*)
5. Mad as a hatter (*Confusion, delirium*)

(Ref: Katzung-13th/1008)

Management of atropine poisoning:

A. General / non-pharmacological approach:

1. Initial ABCD management
2. A short & complete history

3. **Vital sign monitoring:** Pulse, BP, Temperature, and Pupil etc.
4. **Catheterization:** To prevent excessive urine retention
5. **Gastric suction:** By 2% KMnO₄

B. Specific / pharmacological approach:

1. **Physostigmine:** Adult dose is 0.5-1mg IV slowly.
2. **Diazepam:** To control convulsion, restlessness, talkativeness and for sedation.
3. **Anti-pyretic:** Paracetamol (to control hyperthermia)

(Ref: Katzung-13th/1008)

- Q. List the atropine like drugs according to clinical uses. (DU-11J, SU-07Ju)
- Q. List the synthetic atropine substitutes indicating their important therapeutic uses. (RU-12J, 10J, SU-13Ju, 12Ju, 10Ju)
- Q. Classify antimuscarinic drugs according to their clinical uses. (DU-14Ju, 05M, CU-07J, 05S, 1, SU-17J, 14J, 13J, 12J, 11Ju, 09/07J, 07Ju)
- Q. Mention the uses of anticholinergic drugs. (CU-15J)
- Q. What are the antimuscarinic drugs used in eye condition / mydriasis. (DU-09Ju, CU-06M, RU-04M)
- Q. Name the atropine like antispasmodics with their clinical uses. (RU-14Ju, 13Ju)
- Q. Name the spasmolytics. (SU-06J)
- Q. Name the antimuscarinic drugs used in ocular & GIT condition. (RU-03S)

Ans.

Classification of anti-muscarinic drugs according to their clinical uses:

Clinical uses		Antimuscarinic drugs/ atropine substitutes
1. Mydriatics (Used topically on eye)		▪ Tropicamide ▪ Homatropine ▪ Scopolamine ▪ Cyclopentolate ▪ Atropine
2. CVS disorder ➔ Post-MI bradycardia ➔ Complete heart block		▪ Atropine (used in IV route)
3. Respiratory: Asthma, COPD - <i>Bronchodilator</i>		▪ Ipratropium bromide (used by inhalation)
4. Pre-anesthetic medication		▪ Atropine (used in IV route)
5. Anti-parkinsonism <i>Used in drug induced parkinsonism, EPS</i>		▪ Benhexol ▪ Benztropine ▪ Procyclidine. ▪ Biperidine ▪ Orphenadrine. ▪ Trihexyphenidyl
6. GIT - Peptic ulcer disease - Traveler's diarrhea - To facilitate endoscopic examination		▪ Pirenzepine & Telenzepine ▪ Atropine diphenoxylate ▪ Hyoscine butyl bromide.
7. Anti-spasmodic or spasmolytic, eg, in ➔ GI tract colic ➔ Renal colic, <i>dysmenorrhea</i> ➔ Biliary colic		▪ Hyoscine butyl bromide. ▪ Propantheline ▪ Dicyclomine
8. Motion sickness		▪ Scopolamine ▪ Hyoscine

9. Urinary disease	▪ To relieve bladder spasm after urologic surgery, eg, prostatectomy ▪ To reduce involuntary voiding in children with neurologic disease	▪ Oxybutynin ▪ <i>Trosipium</i>
	▪ Urinary incontinence in adult	▪ Tolterodin

(Ref: Katzung-13th/126-127)

Anti-nicotinic drugs

Q. Name nicotinic receptor antagonists. (RU-04J, SU-06M)

Q. Name some anti-nicotinic drugs. (CU-14Ju)

Ans.

Anti-nicotinic drugs/ nicotinic receptor antagonists: Two types.

1. Ganglion blockers (*Not clinically used now, now used for research purpose*)
2. NMJ blocker

Q. Classify ganglion blockers.

Q. Name the ganglion-blocking drugs. (RU-04J)

Ans.

Classification of ganglion blockers:

A. **Competitive / non-depolarizing blocker:** They compete with Ach for nicotinic receptor. So, interfere with the postsynaptic action of acetylcholine. Example—

1. Tetraethylammonium (TEA)
2. Hexamethonium
3. Mecamylamine
4. Pempidine

B. **Non-competitive / depolarizing blockers:** They prolong depolarization.

1. Nicotine
2. Lobeline

(Ref: Katzung-13th/130)

Indication: Use of the ganglion blockers is infrequent because more selective autonomic blocking agents are available.

Trimethaphan	1. Hypertensive emergencies 2. Dissecting aortic aneurysm 3. To produce controlled hypotension in <u>neurosurgery</u> to reduce bleeding in the operative field. 4. In patients undergoing <u>electroconvulsive therapy</u>. 5. Autonomic hyperreflexia due to- • Road traffic accident • Spinal cord injury (T4, T5)
Mecamylamine	Use in <u>reducing nicotine craving</u> in patients attempting to quit smoking and for some other central indications.

(Ref: Katzung-13th/131)

*(The ganglion-blocking drugs competitively block the action of acetylcholine and similar agonists at nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. The ganglion-blocking drugs are important and used in pharmacologic and physiologic research because they can block all autonomic outflow. However, their lack of selectivity confers such a broad range of undesirable effects that they have **limited clinical use**.)*

(Ref: Katzung-13th/130)

Neuromuscular junction blockers

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the neuromuscular end plate of skeletal muscle. These neuromuscular blockers are structural analogs of acetylcholine, and they act either as **antagonists (nondepolarizing type)** or **agonists (depolarizing type)** at the neuromuscular junction. Neuromuscular blockers are clinically useful during surgery for producing complete muscle relaxation, without having to employ higher anesthetic doses to achieve comparable muscular relaxation. Agents are also useful in facilitating intubation as well.

(Ref: Lippincott's-6th)

Q. Classify neuromuscular blocking drugs. (RU-08J)

Q. Classify skeletal muscle relaxants. (CU-17M)

Q. Name the clinically used skeletal muscle relaxants. (DU-02M, RU-07J,06S, SU-06M)

Q. Short note: Neuromuscular blockers. (DU-16Ju)

Ans.

Neuromuscular blocking (NMJ blocker) drugs:

1. **Non-depolarizing / competitive / reversible group:**

Isoquinoline derivatives	Steroid derivatives
• Atracurium • Cisatracurium • Doxacurium • Metocurine • Mivacurium • Tubocurarine	• Pancuronium • Pipecuronium • Rocuronium • Vecuronium

2. **Depolarizing / non-competitive / irreversible group:**

- ✓ Succinylcholine (also known as suxamethonium)
- ✓ Decamethonium

* *Suxamethonium*
apnoea

According to duration of action:

1. Short acting (5-15 minutes) <i>< 25 min</i>	✓ Mivacurium ✓ Succinylcholine
2. Intermediate acting (20-35 minutes) <i>25-35 min</i>	✓ Atracurium ✓ Vecuronium ✓ Rocuronium
3. Long acting (>35 minutes) <i>> 35 min</i>	✓ Doxacurium ✓ Pancuronium ✓ Pipecuronium ✓ Tubocurarine

OT to long time
→ Repeated dose

(Ref: Katzung-13th/459, Table: 27-1; Rang Dale-8th)

NON-DEPOLARIZING / COMPETITIVE / REVERSIBLE NMJ BLOCKERS:

Non-depolarizing: These NMJ blockers bind with nicotinic receptors but **produce no depolarization** in the skeletal muscle. So they are called non-depolarizing. They are **antagonist** to nicotinic receptor.

Competitive: As these NMJ blockers compete with acetylcholine at the receptor without stimulating the receptor, they are called competitive blockers.

Reversible: As **their action can be overcome** by increasing the concentration of acetylcholine in the synaptic gap, eg, by administration of cholinesterase inhibitors, such as neostigmine, pyridostigmine or edrophonium, they are called reversible.

Widely used: Pancuronium, Vecuronium, Atracurium

Rarely used: D-tubocurarine

(Ref: Lippincott's-6th)

Q. Describe the mechanism of action of pancuronium. (RU-07J)

Q. Explain the muscle action of atracurium. (SU-06M)

Q. What are the M/A of non depolarizing NMJ blockers?

Ans.

Mechanism of action of non-depolarizing NMJ Blockers / Atracurium / Pancuronium:

Non-depolarizing blocker at the NMJ



Competes with ACh for nicotinic receptor at post-synaptic membrane



Binds with nicotinic receptor and prevents binding of ACh



No depolarization by ACh



Flaccid type of skeletal muscle paralysis

(Ref: Lippincott's-6th)

(In general, larger muscles (eg, abdominal, trunk, paraspinal, diaphragm) are more resistant to blockade and recover more rapidly than smaller muscles (eg, facial, foot, hand). The first muscles to be effected are external eye muscles (double vision), small muscles of the face, pharynx. The diaphragm is usually the last muscle to be paralyzed. When administration of muscle relaxants is discontinued, recovery of muscles usually occurs in reverse order, with the diaphragm regaining function first.)

(Ref: Katzung-13th/462)

Q. How the action of atracurium can be reversed? (SU-06M)

Q. How could you overcome the toxicity of atracurium with explanation? (RU-16J)

Q. How will you manage a case of pancuronium toxicity? (RU-02M)

Ans.

Reversal of action of Atracurium / Pancuronium / non-depolarizing NMJ blocking drugs: The action of atracurium / pancuronium / non-depolarizing NMJ blocking drugs can be reversed by increasing the concentration of acetylcholine in the synaptic gap, eg, by administration of **cholinesterase inhibitors**, such as **neostigmine**, **pyridostigmine** or **edrophonium**. When concentration of ACh increases, it can displace the drug and bind with nicotinic receptors.

(Ref: Lippincott's-6th)

Q. Short note: Pancuronium. (RU-16Ju)

Ans. Write from above discussion.

DEPOLARIZING / NON-COMPETITIVE / IRREVERSIBLE NMJ BLOCKER

Depolarizing: These NMJ blockers bind with nicotinic receptors and **produce depolarization** in the skeletal muscle. So they are called depolarizing. They are **agonist** to nicotinic receptor.

Non-competitive: As these NMJ blockers **do not compete with ACh** to bind with nicotinic receptor, they are called non-competitive.

Irreversible: As their action **cannot be overcome** by increasing the concentration of acetylcholine in the synaptic gap, they are called irreversible.

(Ref: Lippincott's-6th)

Onset of action: Rapid (within 1 min)

Duration of action: Short (5-10 min)

Pharmacokinetics: The action of succinylcholine is short lived due to redistribution & rapid hydrolysis by plasma cholinesterase (Pseudo-cholinesterase & Butyrylcholinesterase)

Sequence of muscle paralysis: Muscles of eyes, jaw, larynx → Muscles of limbs, abdominal muscles & other muscles of trunks → Intercostal muscles & diaphragm (muscles of respiration)

(Ref: Goodman & Gilman's-12th)

Q. Explain the action of succinylcholine. (SU-16Ju,09J)

Q. Write the mechanism of action of succinylcholine. (DU-08J; SU-16J,06S)

Q. Explain the muscle relaxant action of succinylcholine. (SU-17J)

Q. Write the mechanism of action of depolarizing drugs.

Ans.

Mechanism of action of succinylcholine / depolarizing / non-competitive NMJ blockers:

Phase I block (Depolarizing)

Fig - Lippincott

Non-competitive NMJ blockers (eg, succinylcholine) at NMJ

↓
Binds with the nicotinic receptor

↓
Open Na^+ channels

↓
Depolarization of the motor end plate

↓
Depolarization spreads to the adjacent membrane which causes **transient contraction (twitching) of the muscle (fasciculation)**.

(spastic)

↓
As the depolarizing agent is not destroyed instantly, it persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively longer time and provides constant stimulation to the receptor

↓
The depolarized membrane remains depolarized & non responsive to subsequent impulse.

(Ref: Katzung-13th/460)

Phase II block (Desensitizing)

The continued binding of the depolarizing agent renders the receptors incapable of transmitting further impulses.

↓
With time, the continuous depolarization gives way to gradual repolarization as the Na^+ channel closes or is blocked.

↓
This causes a resistance to depolarization (desensitization) and a **flaccid paralysis**.

(Ref: Lippincott's-6th; Katzung-13th/461)

Q. What are the indications of NMJ blocker? (SU-04S, CU-02J)

Q. Outline the indications of pancuronium. (RU-08J)

Ans.

Indications of NMJ blocker / Pancuronium:

1. **In surgical anaesthesia:** To relax the skeletal muscles during surgery. This is especially important in intra-abdominal and intrathoracic procedures.
2. **In various orthopedic procedures** such as correction of dislocation, alignment of fracture, these drugs are used for skeletal muscle relaxation.
3. **During endotracheal intubation:** By relaxing the pharyngeal and laryngeal muscles, neuromuscular blocking drugs facilitate laryngoscopy and endotracheal tube intubation.
4. **To facilitate endoscopes**, e.g. laryngoscopy, bronchoscopy, esophagoscopy

5. **Convulsive disorders**, e.g. epilepsy, tetanus, eclampsia & convulsive drug poisoning.
6. **During electro-convulsive shock treatment.**

(Ref: Goodman & Gilman's-12th; Lippincott's-6th)

Q. Name the drugs that can potentiate the effects of muscle relaxants. (DU- 10J)

Ans.

Drugs that can potentiate the effects of muscle relaxants /Drug interactions of NMJ blocking drugs:

1. **Cholinesterase inhibitors:** Drugs such as neostigmine, physostigmine can overcome the action of non-depolarizing NMJ blocking drugs, but with increased dosage cholinesterase inhibitors can cause a depolarizing block as a result of elevated acetylcholine concentration at the end-plate membrane.

Halothane: Halothane enhances neuromuscular blockade by exerting a stabilizing action at the neuromuscular junction.

3. **Aminoglycosides:** They enhance neuromuscular blockade of competitive blockers.

4. **Ca²⁺ channel blockers:** Increase neuromuscular block.

(Ref: Lippincott's-6th)

Q. Mention the important adverse effects of depolarizing blockers. (DU-08J)

Q. Mention the adverse effects of Pancuronium (non-depolarizing agent). (RU-08J,06S,04J)

Q. Enumerate the adverse effects of succinylcholine / suxamethonium. (DU-99M,CU-02J)

Ans.

Adverse effects of NMJ blocker:

NMJ blocker	Adverse effects
Non-depolarizing drugs (e.g. pancuronium)	1. Hypotension: Due to ganglion block & histamine release 2. Bronchoconstriction: Due to histamine release 3. Tachycardia (Gallamine): Due to muscarinic block
Depolarizing drugs (eg, suxamethonium/ succinylcholine)	1. Bradycardia: Due to muscarinic agonistic effect 2. Potassium release: Increased cation permeability in motor end plate → Loss of K⁺ from muscle → ↑Plasma K⁺ 3. Cardiac arrhythmia: Ventricular dysrhythmia, cardiac arrest. 4. Increased intraocular pressure. 5. Malignant hyperthermia: due to increased release of Ca²⁺ from sarcoplasmic reticulum. (Rx: rapid cooling of the pt & administration of Dantrolene). 6. Suxamethonium apnea. 7. Post-operative muscle pain

(Ref: Rang & Dale's-8th; Lippincott's-6th)

Q. How will you manage a case of prolonged apnea due to succinylcholine? (DU-02M)

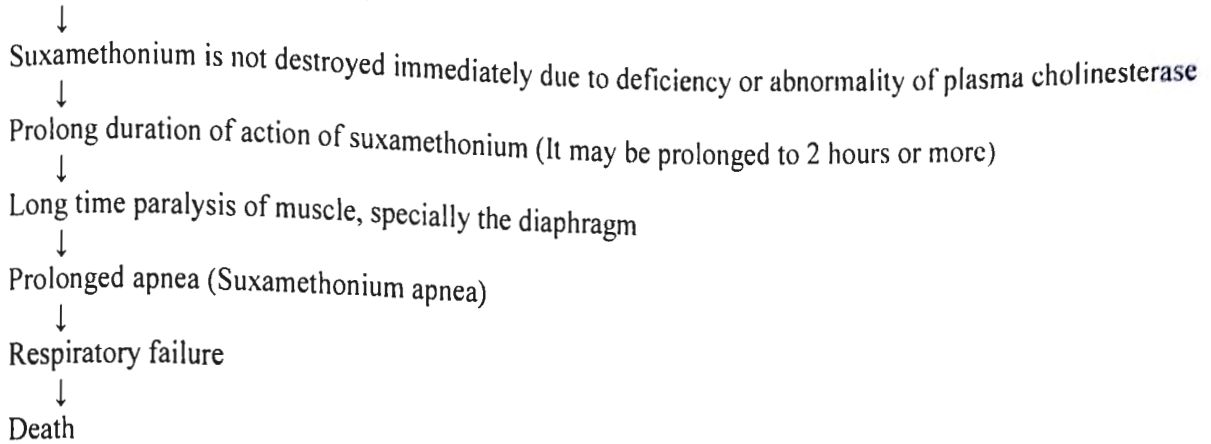
Q. How will you treat a case of suxamethonium apnea? (CU-15Ju)

Q. Short note: Suxamethonium apnea.

Ans.

Suxamethonium apnea: The normal duration of action of suxamethonium is less than 5 minutes, because it is hydrolyzed by plasma cholinesterase. Suxamethonium apnea occurs in patients with genetical deficiency of plasma cholinesterase or atypical form of the enzyme, or in administration of suxamethonium along with anticholinesterase drug.

Suxamethonium administration



Treatment:

- Assisted ventilation until recovery
- Fresh blood transfusion for pseudo-cholinesterase.

(+ve pressure ventilation)

(Ref: Lippincott's-6th; Rang & Dale's-8th)

Q. Compare & contrast between tubocurarine & gallamine. (CU-00M, SU-00M)

Ans.

Comparison between tubocurarine & gallamine:

Traits	D-Tubocurarine	Gallamine
1. Source	Natural (Alkaloid)	Synthetic (Dicholinester)
2. Route of administration	Enteral	Parenteral
3. Onset of action	10-15 min	5 min
4. Duration of action	30-40 min	40-50 min
5. Potency	More potent	Less potent
6. Atropine like effect	Absent	Present
7. M ₂ blocking property	No	Strongly blocked. So, it causes tachycardia.
8. Autonomic ganglia	Weakly blocked	No
9. Histamine release	Moderately releases histamine (So can cause bronchospasm & hypotension)	No histamine release
10. Use in anesthesia	Not preferable, because it causes hypotension, bronchoconstriction and increased bronchial secretion	Preferably used
11. Excretion	40% renal excretion.	100% renal excretion. (So, contraindicated in pt. with poor renal function)

(Ref: Rang Dale's-8th, Table: 10-7; Katzung-13th/463; Table 27-3)

Q. Write down the important differentiating features between non-depolarizing & depolarizing skeletal muscle relaxants with their clinical uses. (DU-10J, SU-12Ju)

Q. What are the differences between Tubocurarine & Suxamethonium? (CU-05S, SU-05M)

Q. Compare & contrast between gallamine and suxamethonium. (CU-12Ju, SU-01M)

Q. Compare & contrast between atracurium and suxamethonium. (SU-15J)

Q. Compare atracurium and succinylcholine as skeletal muscle relaxants. (SU-17M)

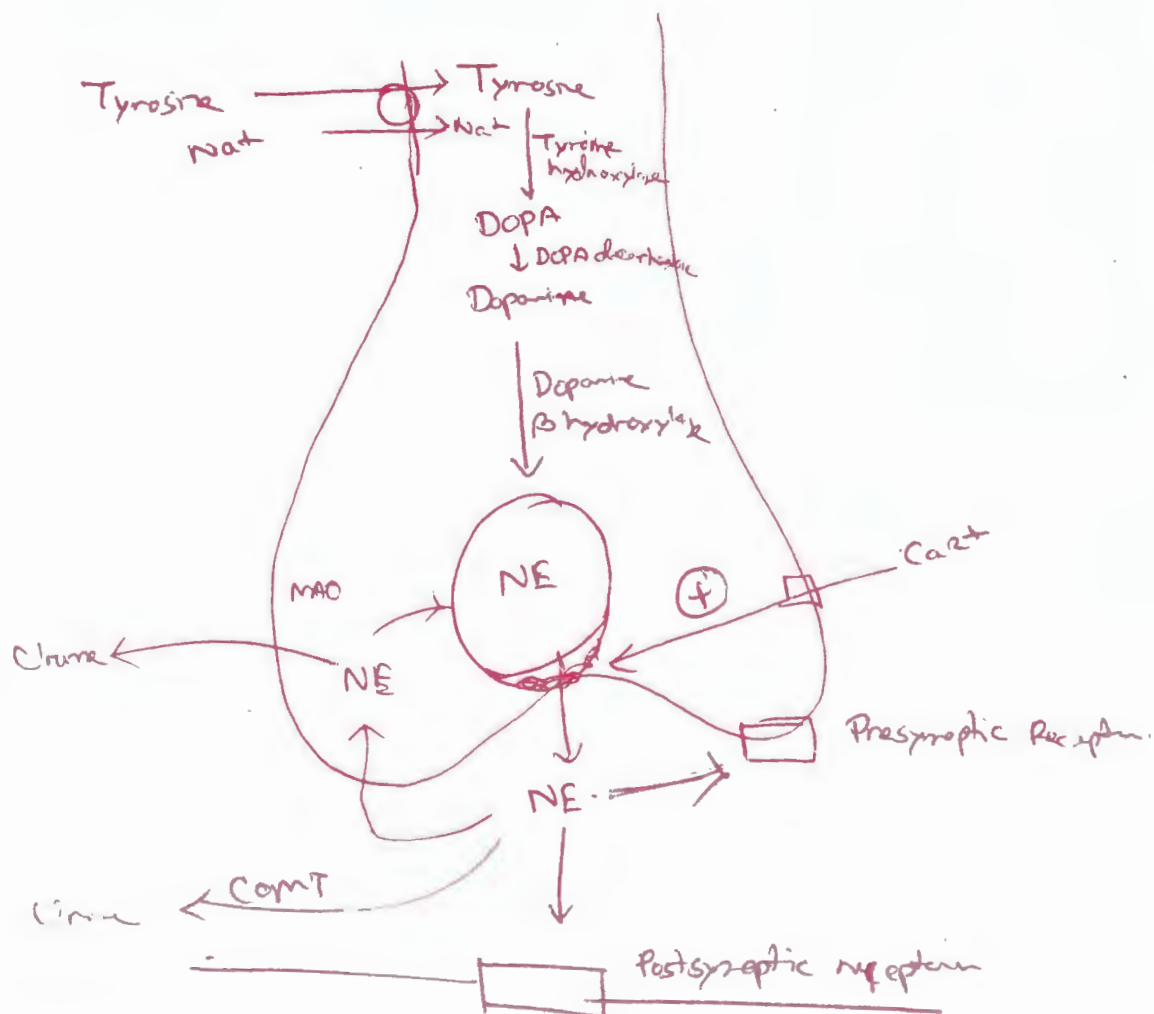
Q. Compare rocuronium and succinylcholine. (CU-17M)

Ans.

Differences between depolarizing & non depolarizing muscle relaxants

Traits	Non-depolarizing (Tubocurarine, gallamine, atracurium)	Depolarizing (Suxamethonium / suxamethonium)
1. Competes with ACh to bind with nicotinic receptor	Yes	No
2. Production of depolarization	No	Yes
3. Reversal of action by anticholinesterase	Yes	No
4. Type of muscle paralysis	Flaccid type	Transient fasciculation which is followed by flaccid paralysis
5. Side effects	▪ Hypotension ▪ Bronchoconstriction	▪ Bradycardia ▪ Arrhythmia ▪ Hyperkalemia ▪ Increased intraocular pressure ▪ Post-operative muscle pain
6. Antidote	Available (Neostigmine)	Not available

(Ref: Lippincott's-6th; Rang & Dale's-8th)



Adrenergic Pharmacology

- Q. Write down the steps of biosynthesis & fate of catecholamines. (DU-14J, RU-17J, SU-16J,15J)
 Q. Outline the steps of biosynthesis & fate of adrenaline. (DU-14Ju, SU-14J,09J, RU-16J,11J)
 Q. Outline the synthetic pathway of Noradrenalin. (CU-16J)
 Q. Outline the biosynthesis & fate of adrenergic neurotransmitters. (SU-17J)
 Q. Draw & label a diagram to show the synthesis, release & termination of action of noradrenaline. (CU-07Ju; RU-04M/S, SU-13J,12J)

Ans.

Biosynthesis & fate/metabolism of adrenaline/ noradrenaline:

Site of synthesis:

- **Noradrenaline:** Adrenergic nerve ending
- **Adrenaline:** Adrenal medulla.

DOPA = Dihydroxy phenyl alanine

Steps of synthesis:

Tyrosine
 ↓ Tyrosine hydroxylase
 DOPA
 ↓ DOPA decarboxylase
 Dopamine
 ↓ Dopamine β-hydroxylase
 Nor-adrenaline (NA)
 ↓ N-methyl transferase
 Adrenaline

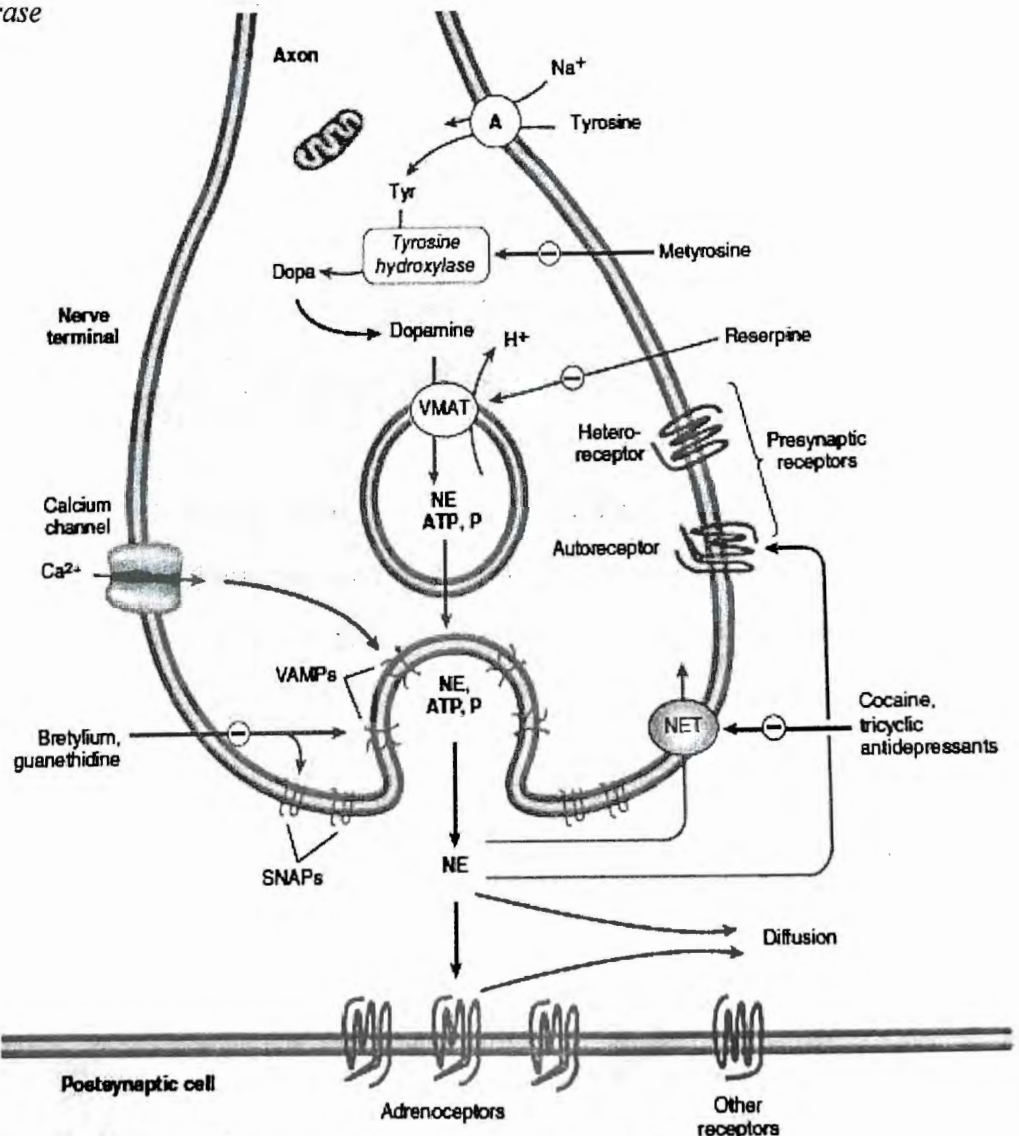
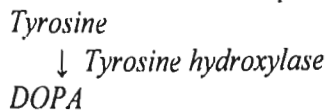


Fig: Schematic diagram of a generalized noradrenergic junction.

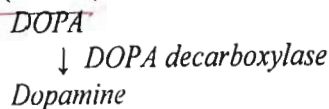
Nice to know

- **Step I:** Tyrosine is transported into the noradrenergic ending by a sodium-dependent carrier.
- **Step II:** Tyrosine is converted to dopa.

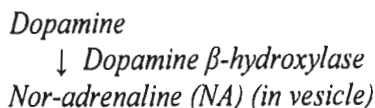


This is the rate-limiting reaction, ie, if we block *tyrosine hydroxylase* enzyme activity, NE synthesis will be blocked.

- **Step III:** Dopa is converted to dopamine which is transported into the vesicle by the vesicular monoamine transporter (VMAT).



- **Step IV:**



- **Step V:** Occurs in adrenal medulla.



PNMT is only present in adrenal medulla but absent in the adrenergic nerve ending. So, adrenaline is synthesized only in adrenal medulla but not in adrenergic nerve ending.

Storage of adrenaline & nor-adrenaline: In the vesicle of adrenergic nerve ending & adrenal medulla. The vesicles also store dopamine.

- **Adrenergic nerve ending:** 80% nor-adrenaline and 20% adrenaline. No adrenaline is synthesized in the storage vesicle of adrenergic nerve ending. The source of small amount adrenaline in the storage vesicle is reuptake from synaptic cleft.
- **Adrenal medulla:** 85% adrenaline and 15% nor-adrenaline.

Release of nor-adrenaline:

Arrival of nerve impulse (action potential) at the presynaptic nerve terminal

↓
Opening of voltage-gated Ca^{2+} channel

↓
Entry of Ca^{2+} into the presynaptic nerve terminal from synaptic cleft

↓
 Ca^{2+} causes fusion of synaptic vesicles with presynaptic membrane

↓
The vesicles burst and release nor-adrenaline & adrenaline into the synaptic cleft by exocytosis.

Adrenaline

Synthesis & release

1. Only synthesized & released from the adrenal medulla.
2. Circulates in the whole body via blood.
3. Comes to synaptic cleft.
4. Uptaken into adrenergic nerve ending along with nor-adrenaline (uptake I) by active process.
5. Stored in vesicle.

So, when adrenergic nerve is stimulated, both adrenaline & nor-adrenaline are released, although the nerve ending does not synthesize adrenaline.

Q. Why adrenaline is called pseudo neurotransmitter?

Ans.

Adrenaline is called pseudo neurotransmitter: All neurotransmitters (NT) must be synthesized within the nerve terminal but adrenaline is synthesized in adrenal medulla from noradrenaline by PNMT. This is why it is called pseudoneurotransmitter.

Nice to know

Fate / removal of adrenaline & nor-adrenaline: Nor-adrenaline can be removed from the synaptic cleft by one of the three ways:

1. **Uptake I:** About 70-80% of the released nor-adrenaline is transported into the cytoplasm of the terminal by the norepinephrine transporter (NET). This is known as uptake I. From cytoplasm, they are then transported by VMAT into the vesicles.
2. **Uptake II:** It may diffuse out of the synaptic space & enters into the general circulation. This uptake of adrenaline & nor-adrenaline in non-nervous tissue (muscle, liver, adipose tissue) is called uptake II.
3. **Metabolism:** By COMT (Catechol-O-Methyltransferase) & MAO (Monoamine oxidase)

Differences between uptake I & uptake II:

	Uptake I	Uptake II
1. Site	Occurs in the adrenergic nerve ending	Occurs in the non-nervous tissue (muscle, liver, adipose tissue, endothelium)
2. Type of the transport	Active process	Active or passive process
3. Rate of uptake	Low	High
4. Specificity	NA > A > ISO	A > NA > ISO
5. Requirement	Requires presence of Na and low K ⁺ concentration, which is energy, carrier and temperature dependant process.	Requires presence of Ca ²⁺ but not energy, carrier and temperature dependant process.
6. When occurs	When conc. of NA in circulation is 1-39 µg/dl.	When uptake I is saturated and conc. of NA in circulation is > 40 µg/dl.
7. Affinity	More affinity for noradrenaline	Less affinity for noradrenaline
8. Effective for	70-90% released noradrenaline.	Circulating adrenaline.
9. Inhibitor	May be blocked by TCA, cocaine, ouabain	Can be blocked by steroids.

Q. Describe the metabolism of adrenaline.

Ans.

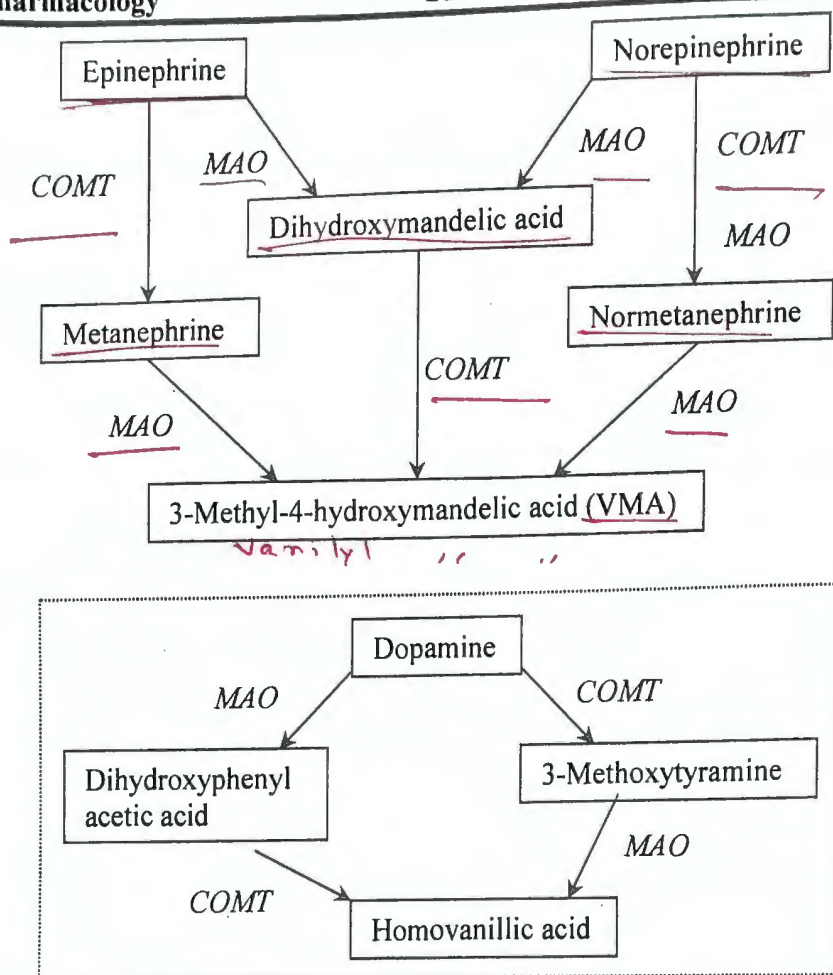
Metabolism of adrenaline:

Site of metabolism: Liver, kidney, GIT, neuron etc.

Enzymes of metabolism:

In neurons	MAO (Monoamine oxidase)
In liver, kidney, GIT, other organs	COMT (Catechol-O-Methyltransferase)
	MAO (Monoamine oxidase)

Degradation of catecholamines: The catecholamines are inactivated by oxidative deamination, catalyzed by monoamine oxidase (MAO) and O-methylation carried out by catechol-O-methyltransferase (COMT). The aldehyde products of the MAO reaction are oxidized to the corresponding acids. The metabolic products of these reactions are excreted in the urine as VMA (vanillyl mandelic acid), metanephrine and normetanephrine.



(Ref: Katzung-13th/95 & Lippincott's-6th)

Q. What is catecholamine? Why are they called so? (DU-13Ju,08Ju, RU-14J, SU-06S)

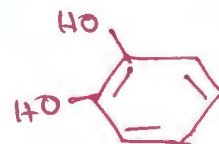
Q. What are the catecholamines? (DU-07J; RU-17J,14J,12J,06S, SU-03S)

Q. Enumerate the endogenous/ catecholamines. (RU-06J)

Ans.

Catecholamines: Sympathomimetic amines that contain the catechol nucleus (3,4-dihydroxybenzene ring) are called catecholamines.

Natural / Endogenous	Synthetic
1. Adrenaline	1. Isoprenaline
2. Nor-adrenaline	2. Dobutamine
3. Dopamine	3. Dopexamine
	4. Doxepine
	5. Fenoldopam
	6. Ibopamine



Properties:

- High potency:** The catecholamines show the highest potency in directly activating α or β receptors.
- Rapid inactivation:** Catecholamines are metabolized by COMT and MAO in the neuron, synapse, gut wall, and liver. Thus, catecholamines have only a brief period of action when given parenterally, and they are ineffective when administered orally because of inactivation.
- Poor penetration into the CNS:** Catecholamines are polar and, therefore, do not readily penetrate into the CNS. Nevertheless, most of these drugs have some CNS effects (anxiety, tremor, and headaches).

(Ref: Ganong's-24th/145; Lippincott's-6th)

Nice to know

Non-catecholamines: Sympathomimetic amines that lack the catechol nucleus (3,4-dihydroxybenzene ring) are called non-catecholamines.

Properties

1. Longer $t_{1/2}$.
2. Cross the blood brain barrier.
3. Not inactivated by COMT.
4. Poor substrate for MAO (so, long $t_{1/2}$)
5. May act indirectly by releasing of stored catecholamine.

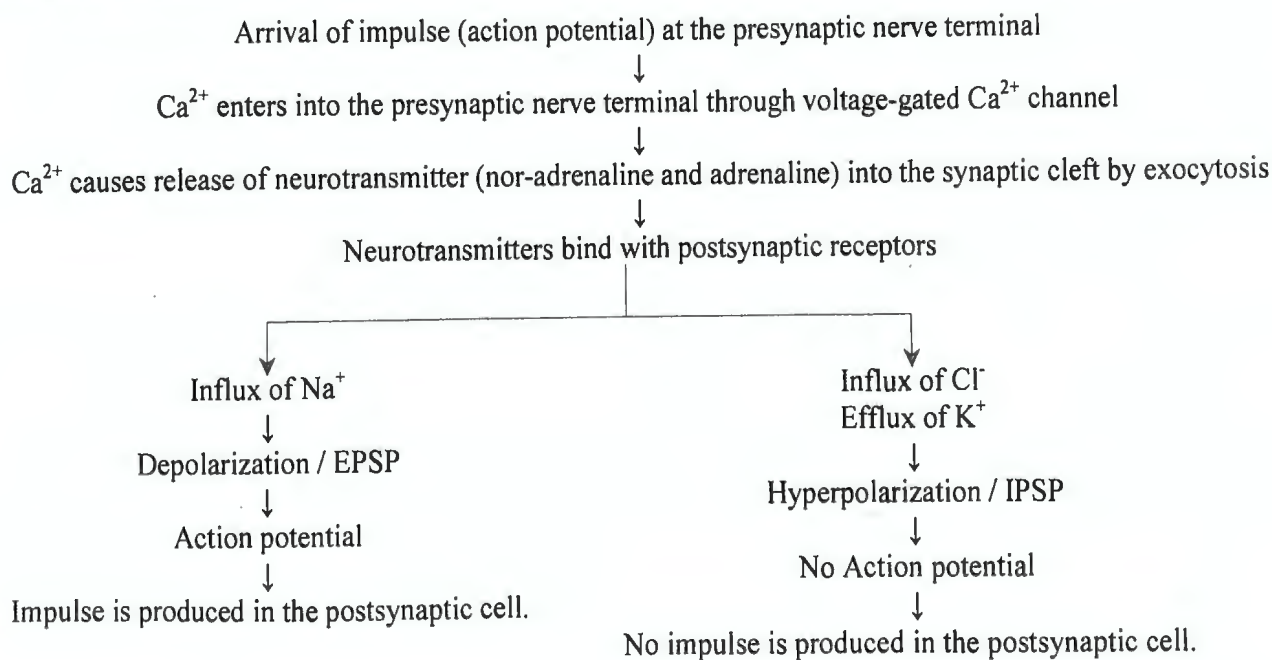
Ex. *Ephedrine*
Amphetamine

Difference between catecholamine and non-catecholamine

Traits	Catecholamine	Non-catecholamine
1. Structure	Contain the catechol nucleus (3,4-dihydroxybenzene ring)	Devoid of -OH group in 3,4 positions of benzene ring.
2. Onset	Rapid	Slow
3. Duration of action	Short	Prolonged
4. Effective route of administration	Injection	Oral
5. Effect on CNS	No effect as it cannot cross BBB.	Prominent as it crosses BBB.
6. Enzymatic metabolism	Occurs	Does not occur as they inhibit the enzyme.

Q. Outline the adrenergic neurotransmission. (DU-04M; CU-03J; RU-09J,07Ju, SU-06M)

Ans.

Adrenergic neurotransmission

(Ref: Ganong's-24th/120-123; Guyton-12th/546)

Q. What are the receptors present in heart & kidney? (CU-03S)

Q. Enumerate the autonomic receptors present in heart.

Q. Name the adrenergic receptors and outline relevant mechanisms that can influence cardiac function. (CU-12J)

Ans.

Receptors present in the heart:

Receptors present in the heart	Effect of stimulation of the receptor
1. M_2 receptor	Decreases heart rate & force of contraction
2. α_1 receptor	Vasoconstriction of the arterioles of heart
3. β_1 receptor	Increases heart rate & force of contraction
4. β_2 receptor	Coronary vasodilation
5. H_2 receptor	Increases heart rate & force of contraction

Receptor present on kidney:

1. β_1 receptor: Stimulation of this receptor increases renin secretion from kidney.

Q. Classify adrenoceptors with their important sites of distribution. (DU-09Ju, CU-12J, SU-10Ju)

Q. Classify adrenergic receptor sites with their physiological effects. (RU-05M, SU-15Ju, 07J, CU-11J, 08Ju)

Q. Mention the pharmacological effect of adrenaline. (RU-01S)

Q. List where β -adrenoceptors located & mention effects of their activation. (CU-06S)

Q. Show the distribution of various adrenergic receptor sites. (SU-13Ju/J, 12J)

Q. Explain the effects of adrenaline on blood vessel. (RU-16Ju)

Ans.

Adrenergic receptors / Adrenoceptors: The receptors on which epinephrine (adrenaline) and norepinephrine (noradrenaline) or the adrenergic agonists act are called adrenoceptors. Adrenoceptors are of 2 types-

1. α -adrenoceptors (α_1 , α_2)
2. β -adrenoceptors (β_1 , β_2 , β_3)

Pupil contraction - Miosis

Receptor	Result of ligand binding	Location	Effects
α_1	Formation of IP_3 and DAG, Increased intracellular calcium <i>Prostate - contraction</i> <i>Heart - ↑ Force</i> <i>Vascular smooth muscle</i>	- Eye: Iris radial muscle - Gut smooth muscle - Sphincter of the whole body (except pupil) - Penis, seminal vesicles - Pilomotor smooth muscle - Uterus, pregnant - Arteriole to skin, heart, kidney, skeletal muscle & abdominal viscera - Sweat gland - Salivary glands - Liver	- Contraction → Mydriasis (<i>Pupil dilation</i>) - Decreases motility and tone - Constriction (Urinary retention, constipation) - Ejaculation - Erection of hair - Contraction - Vasoconstriction - Slight, localized secretion - Thick, viscous secretion - Glycogenolysis - Gluconeogenesis
α_2	Inhibition of adenylyl cyclase, Decreased cAMP	- Pre-synaptic nerve terminal - Endocrine pancreas - Adipose tissue - Platelet - Arteriole to heart, skin, salivary glands	- Inhibits release of NA from adrenergic nerve ending by negative feedback mechanism - Inhibits secretion of insulin and glucagon - Lipolysis ↓ - Aggregation - Vasoconstriction
β_1	Stimulation of adenylyl cyclase, Increased cAMP	- Heart - JG cells of kidney	- Increases heart rate <i>↑ heart rate</i> - Increases force of contraction <i>↑ force</i> - Increases conduction velocity <i>↑ velocity</i> - Increases renin secretion

β_2	Stimulation of adenylyl cyclase and increased cAMP. Activates cardiac G_i under some conditions. <i>Smooth muscle</i>	- Arteriole to heart & skeletal muscle - Smooth muscle of bronchus - Smooth muscle of GIT - Smooth muscle of gall bladder - Smooth muscle of urinary bladder - Smooth muscle of uterus - Liver - Endocrine pancreas	- Vasodilation - Relaxation $\rightarrow$ Bronchodilation - Relaxation - Relaxation - Relaxation - Relaxation of mainly gravid uterus $\rightarrow$ delay premature labour pain - Glycogenolysis - Increases secretion of insulin and glucagon
β_3	Stimulation of adenylyl cyclase and increased cAMP	- Adipose tissue - Bladder	- Lipolysis - Relax detrusor

(Ref: Katzung-13th/141; Ganong-24th)

Q. Mention the CVS effects of adrenaline. (DU-12Ju, 10/07Ju; RU-08J, SU-11J)

Q. Describe the effect of adrenaline on CVS. (CU-04J; SU-03J)

Q. Mention the effect of adrenaline on blood vessels. (RU-12Ju)

Ans.

CVS effects of adrenaline:

Site	Receptor	Effects
On Heart	β_1	- Positive chronotropic effect: $\uparrow$ Heart rate - Positive inotropic effect: $\uparrow$ Force of contraction - Positive dromotropic effect: $\uparrow$ Conduction velocity - Net effect: $\uparrow$ CO $\rightarrow$ $\uparrow$ BP
On blood vessels	α_1	Vasoconstriction in the arterioles to skin, heart, kidney, skeletal muscle & abdominal viscera
	α_2	Vasoconstriction in the arterioles to heart, skin, salivary glands
	β_2	Vasodilation in the arterioles to heart & skeletal muscle

Q. Outline the pharmacological effects of adrenalin on blood pressure. (RU-08J)

Ans.

Effects of adrenaline on blood pressure:

- α_1 -mediated vasoconstriction $\rightarrow \uparrow$ TPR (Total peripheral resistance) $\rightarrow \uparrow$ BP
- β_1 -mediated increase in heart rate and force of contraction $\rightarrow \uparrow$ CO $\rightarrow \uparrow$ BP
- β_2 -mediated vasodilation $\rightarrow \downarrow$ TPR $\rightarrow \downarrow$ diastolic BP
- In small dose, adrenaline binds with β_2 receptor and in large dose, adrenaline binds with α_1 receptor
- Net effect:
 - Systolic BP: $\uparrow\uparrow$
 - Diastolic BP: $\downarrow$ (small dose), $\uparrow$ (large dose)
 - Mean pressure: $\uparrow$
 - Pulse pressure: $\uparrow\uparrow$

D_1 - Dilatation of renal blood vessels

D_2 - modulates NT release

(Ref: Katzung-13th/141)

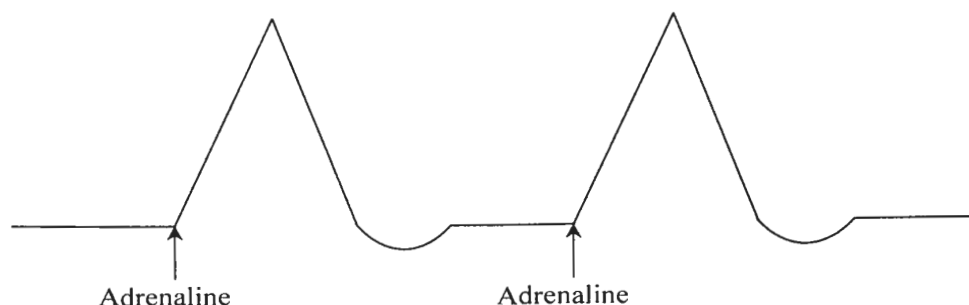
Q. Explain the effects of adrenalin on blood pressure.

Ans.

If we administer adrenaline, then there is a **sharp rise of BP** followed by **immediate return of BP** to baseline with a **secondary fall**.

- The sharp rise is because adrenaline acts on α_1 receptor causing vasoconstriction and β_1 receptor increasing heart rate & force of contraction. Both effects increase BP.

- BP sharply comes back to baseline due to the reuptake of Adrenaline by uptake-II mainly & some portion by uptake-I and metabolism of adrenaline by circulating MAO and COMT enzymes.
- The secondary fall is due to β_2 effect. Adrenaline also activates β_2 receptors in the blood vessels supplying skeletal muscles resulting in vasodilation in skeletal muscles and some decrease in BP.



Q. Compare the CVS effects of adrenaline, NA & isoprenaline. (DU-04J, CU-06S, SU-04M)

Q. Compare the CVS effect of adrenaline & NA. (DU-06J, CU-16J)

Ans.

CVS effects of adrenaline, NA & isoprenaline

Effects	Adrenaline	Noradrenaline	Isoprenaline (isoproterenol)
Cardiac			
▪ Heart rate	↑	↑	↑
▪ Force of contraction	↑	↑	↑
▪ Stroke volume	↑	↑	↑
▪ Cardiac output	↑	↑/0	↑
Peripheral circulation			
▪ TPR	↓	↑↑	↓
▪ Muscle blood flow	↑↑	0/↓	↓
▪ Renal blood flow	↓	↓	↓
▪ Cutaneous blood flow	↓	↓	0
Blood pressure			
▪ Systolic BP	↑↑	↑	↓
▪ Diastolic BP	↓(small dose), ↑(large dose)	↑	↓↓
▪ Mean BP	↑	↑	↓
▪ Pulse pressure	↑↑		↑↑

(Ref: Katzung-13th/142 (Table 9-4) Isoprenaline; Goodman & Gilman's-12th, Ad, NA)

Q. Mention its metabolic effects of adrenaline. (DU-07Ju)

Ans.

Metabolic effects of adrenaline

Site of action	Receptor	Action
Liver	β_2, α_1	▪ Glycogenolysis ▪ Gluconeogenesis
Adipose tissue	β_3	▪ Lipolysis
JG cells of kidney	β_1	▪ Increases rennin release
Endocrine pancreas	α_2	▪ Inhibits secretion of insulin and glucagon
(α_2 effect is predominant)	β_2	▪ Increases secretion of insulin and glucagon

Q. Mention the CNS effects of adrenaline. (RU-06J)

Ans.

CNS effects of adrenaline:

1. Mild restlessness
2. Tremor
3. Insomnia
4. Euphoria

Adrenergic drugs

Q. Classify sympathomimetic/ adrenergic drugs. (DU-16Ju, RU-09J; SU-10J, CU-05J)

Q. Classify sympathomimetics according to receptors on which they act. (SU-09Ju,06M)

Q. Classify adrenergic drugs according to receptor sensitivity. (DU-15Ju,14Ju,12J,11Ju,10Ju, RU-16J,13J,02J, SU-12J,11Ju,10Ju)

Q. List the directly acting sympathomimetics. (CU-17M)

Q. Lists different adrenergic receptor agonists & their pharmacological actions. (CU-11J,08Ju)

Q. Lists different adrenergic receptor agonists with their receptor activation. (SU-08J)

Ans.

Sympathomimetic / adrenergic drugs: A drug that mimics stimulation of the sympathetic nervous system is called sympathomimetic / adrenergic drugs.

A. **Direct-acting adrenergic / sympathomimetic drugs:** These drugs act directly on one or more adrenergic receptors. According to receptor selectivity they are two types-

Non-selective	Drugs which act on more than one receptor	1. Adrenaline (acts on all receptors) 2. Nor-adrenaline (acts on α_1, α_2, β_1) 3. Isoprenaline (isoproterenol) (acts on β_1, β_2, β_3) 4. Dopamine (acts on α_1, α_2, β_1 & D_1, D_2)	
Selective	Drugs which act on a single receptor only	α_1-selective	▪ Phenylephrine ▪ Methoxamine ▪ Oxymetazoline ▪ Midodrine
		α_2 selective	▪ α-Methyl dopa ▪ Oxymetazoline ▪ Clonidine
		β_1 selective	▪ Dobutamine
		β_2 selective	▪ Salbutamol (INN) or Albuterol (USAN) ▪ Salmeterol ▪ Formoterol ▪ Terbutaline ▪ Pirbuterol ▪ Fenoterol ▪ Reproterol ▪ Rimiterol ▪ Isoxsuprine ▪ Orciprenaline ▪ Ritodrine.

B. **Indirect-acting adrenergic / sympathomimetic drugs:**

1. **Increase release of NA from nerve ending (release promoter):**

- a. Amphetamine
- b. Tyramine

2. **Reuptake inhibitor:** An indirect-acting drug that increases the activity of transmitters in the synapse by inhibiting their reuptake into the presynaptic nerve ending.
- Tricyclic anti-depressant (TCA)
 - Cocaine
 - Ouabin
3. **Inhibitor of enzymes COMT & MAO:**
- MAO inhibitor: Pargyline, *Selegiline*
 - COMT inhibitor: Entacapone
- C. **Mixed-action agonist (both direct & indirect acting):** Stimulate adrenoceptors directly and also increase release of NA from the nerve ending.
- Ephedrine (α , β -agonist & release promoter)
 - Pseudoephedrine
 - Metaraminol.

(Ref: Goodman & Gilman's-12th; Katzung-13th/135-150; Lippincott's-6th, Bennett & Brown-11th)

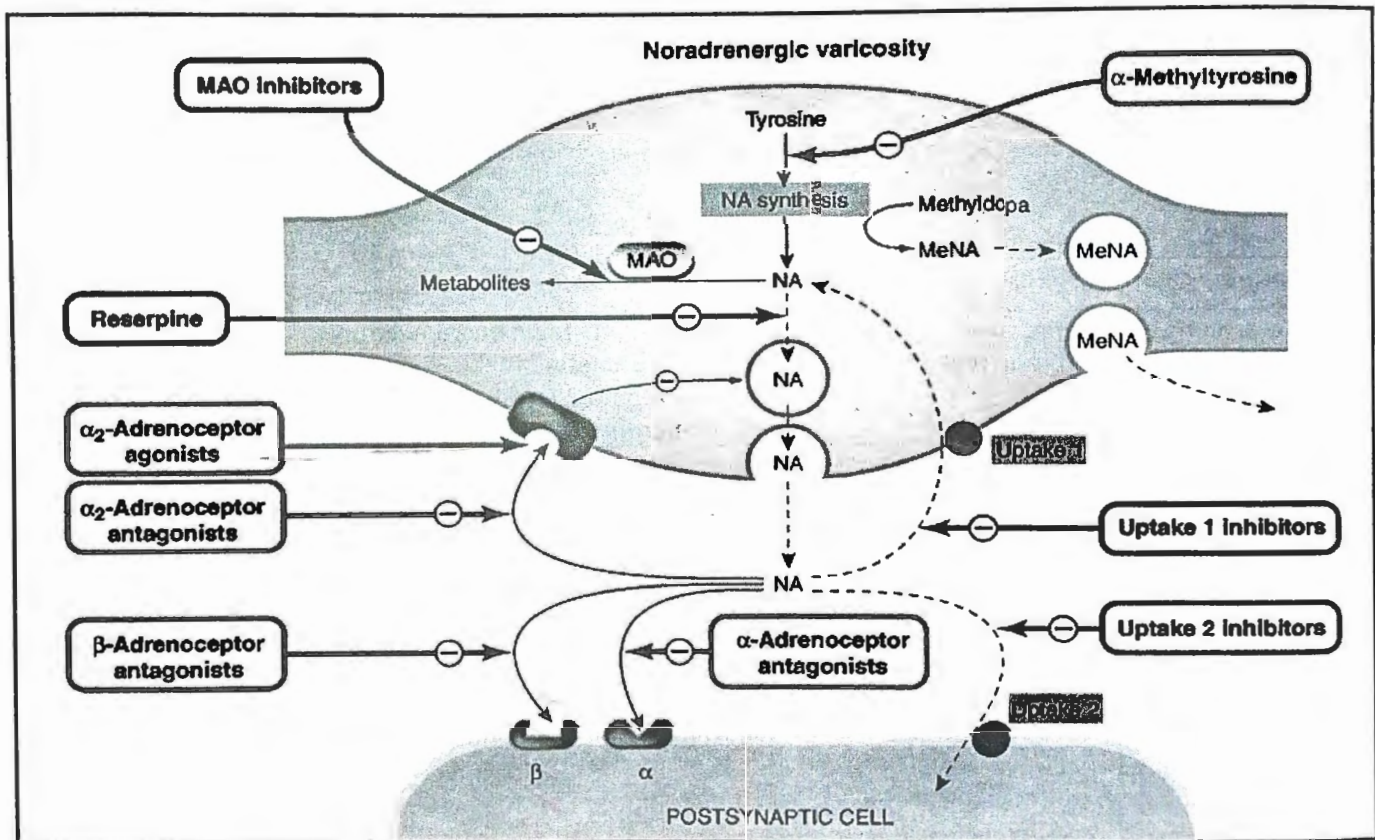


Figure. Generalised diagram of a noradrenergic nerve terminal, showing sites of drug action. MAO, monoamine oxidase; MeNA, methylnoradrenaline; NA, noradrenaline.

Q. Classify selective β_2 -agonists according to duration. (CU-15Ju, SU-06M)

Ans.

Selective β_2 -agonists:

Short acting (2-6 hours)	- Salbutamol - Terbutaline - Metaproterenol - Pirbuterol
Long acting (over 12 hours)	- Salmeterol - Formoterol

Q. Lists important clinical uses of adrenergic agonists. (SU-12J,08J,07Ju)

Ans.

Uses of adrenoceptor agonists:

Adrenaline α, β	- Anaphylactic shock - Cardiac arrest
Isoprenaline β	- Its nonselectivity is one of its drawbacks and the reason why it is rarely used therapeutically. - Now rarely used as bronchodilator in asthma (β_2 effect) - Can be used in cardiac arrest (β_2 effect) (Heart block 50-70%)
Phenylephrine α_1	- Acts as nasal decongestant as it produces prolonged vasoconstriction. - Used to raise BP in some emergency condition, eg, during spinal anaesthesia $\rightarrow$ sudden fall in BP $\rightarrow$ BP is raised by phenylephrine. - Used to terminate supraventricular tachycardia
Oxymetazoline α_2	As decongestant in nose and eyes
Clonidine α_2	- Hypertension - Used to minimize the symptoms that accompany withdrawal from opiates or benzodiazepines.
Dopamine α, β, γ	Cardiogenic shock
Dobutamine β_1	Cardiogenic shock
Salbutamol, pirbuterol and terbutaline β_2	Bronchial asthma
Salmeterol and formoterol β_2	Bronchial asthma
Ritodrine / Terbutaline β_2	Suppression of premature labour
Methoxamine α_1	- Paroxysmal supraventricular tachycardia. - Used to overcome hypotension during surgery involving halothane anaesthetics.
Metaproterenol	Useful as a bronchodilator in the treatment of asthma and to reverse bronchospasm.
Amphetamine RP	Treatment of hyperactivity in children, narcolepsy, and appetite control.
Ephedrine α, β, RP	- Has been used - In asthma - As a nasal decongestant (due to its local vasoconstrictor action) - To raise blood pressure. - The clinical use of ephedrine is declining due to the availability of better, more potent agents that cause fewer adverse effects.
Pseudoephedrine	- Nasal and sinus congestion - Congestion of the eustachian tubes.

(Ref: Lipincott's-6th)

Q. Explain the use of life saving catecholamines in different life threatening conditions. (RU-05M)

Ans.

Life saving catecholamines & their use in life threatening conditions:

1. Cardiogenic shock: Dopamine, dobutamine
2. Heart block: Isoprenaline (temporary use)
3. Heart failure: Dobutamine
4. Cardiac arrest: Adrenaline

(Ref: Katzung-13th; Rang Dale-8th)

Nasal Congestion — stuffiness, ↑ Thickness of m. mucosa, inflammation, ↑ Secretion, Allergy, Histamine release, Rhinitis, Vasodilation
Decongestion — 20-30%

Adrenergic agonists vasoconstriction and Decongestion
(50-70% mast cell stabilization 30-40%)

Adrenaline

General consideration

- **Synonym:** Epinephrine
- **Source:** Animal chromafin tissue.
- **Nature:** Neurohormone.
- **Class:** Catecholamine
- **Receptor:** Interacts with both α and β receptors.
 - α at high dose.
 - β at low dose.
- **Onset of action:** Rapid
- **Duration of action:** Short due to rapid inactivation by COMT & MAO.
- **Effective route of administration:** Injection

Pharmacokinetics

- **Route:** IV (emergency), subcutaneous, topical (eye), inhalation.
- **Onset of action:** Rapid
- **Duration of action:** Short due to rapid inactivation by COMT & MAO.
- **Metabolism:** By-
 1. COMT: Degrade circulating adrenaline.
 2. MAO: Degrade intracellular adrenaline.
- **Elimination:** Through urine as-
 1. Adrenaline – 1%
 2. Metanephrine – 7.6%
 3. VMA – 9%

Q. What are the indications of adrenaline? (DU-14J,08Ju,07J, RU-17J,16J,13J; SU-17J)

Ans.

Indications of adrenaline (Ad) / epinephrine:

1. **Anaphylactic shock:** To relieve bronchospasm, increased bronchial secretion, hypotension, angioedema.
2. **Status asthmaticus:** To relieve bronchospasm, increased bronchial secretion.
3. **Glaucoma:** 2% epinephrine solution may be used topically to reduce IOP in open-angle glaucoma. It reduces the production of aqueous humor by vasoconstriction of the ciliary body blood vessels.
4. **Cardiac arrest:** Epinephrine may be used to restore cardiac rhythm in patients with cardiac arrest regardless of the cause.
5. **Anesthetics:** To increase the duration of action of local anesthetic by vasoconstriction and delaying absorption of the local anesthetic.
6. As **nasal decongestant**.
7. To control nasal bleeding (epistaxis) in the form of nasal pack.

(Ref: Lippincott's-6th)

Q. What are the adverse effects of adrenaline? (CU-02J)

Ans.

Adverse effects of adrenaline:

1. **Cardiovascular:**
 - Hypertension & ↑cardiac work → Cardiac ischemia & failure
 - Sinus tachycardia
 - Ventricular arrhythmias.
2. **CNS adverse effects:**
 - Tremor
 - Restlessness
 - Insomnia

- Anxiety
 - Throbbing headache
 - Rarely, convulsion, cerebral hemorrhage, arrhythmias, or MI (by cocaine)
 - Euphoria (by Amphetamine)
3. Retention of urine
 4. Constipation
 5. May cause dyslipidaemia (↑FFA level)
 6. Hyperglycemia

(Ref: Katzung-13th edition)

Q. What are the contraindications of adrenaline? (CU-03J)

Ans.

Contradictions of adrenaline:

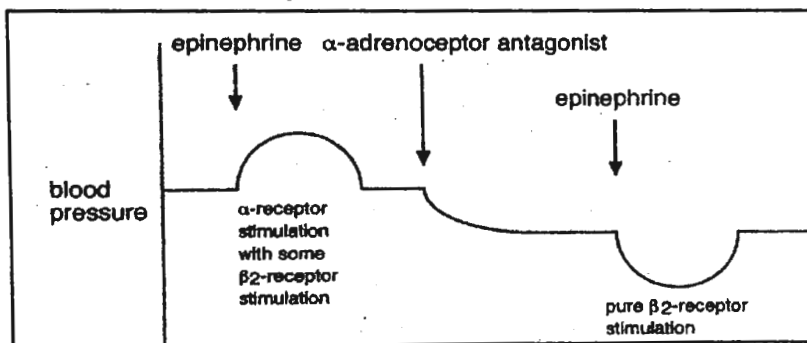
1. Hypertension (HTN)
2. Hyperthyroidism
3. Cardiac arrhythmia
4. Ischemic heart diseases (IHD)
5. Diabetes mellitus (DM)
6. Benign enlargement of prostate (BEP)
7. Patient taking non-selective β -blocking drugs.
8. Cerebral hemorrhage.

(Ref: Goodman & Gilman's-12th)

Q. Short note: Epinephrine reversal. (RU-15J)

Ans.

Epinephrine Reversal: Epinephrine reversal is characterized by a drop in blood pressure that is produced by epinephrine after the administration of α -blockers.



Mechanism:

1. If **adrenaline** is administered alone, it **increases BP** by stimulating α_1 receptor causing vasoconstriction and β_1 receptor increasing heart rate & force of contraction. But it also activates β_2 receptors in the blood vessels supplying skeletal muscles resulting in vasodilation in skeletal muscles and some decrease in BP. But the net effect is increased BP.
2. When we administer **α receptor blockers** such as phenoxybenzamine, it irreversibly blocks α receptors without causing vasoconstriction $\rightarrow$ $\downarrow$ BP.
3. If we again administer same dose of **adrenaline**, then there is gradual **fall of BP**. This is called **epinephrine reversal**. This time adrenaline stimulates β_2 -receptors situated in blood vessels of skeletal muscles causing vasodilatation that resulted in fall in PR and BP. This time adrenaline could not bind to α receptors, because they are already blocked by phenoxybenzamine.

Q. How will you manage a case of anaphylactic shock? (CU-14J)

Q. Give the management of penicillin induced anaphylactic shock. (RU-15J)

Q. Outline the drug therapy of penicillin induced hypersensitivity reaction. (CU-06M,07J, RU-14J)

- Q. What are the clinical features of anaphylactic shock? Discuss its management. (RU-07J,06M)
- Q. In anaphylactic shock, a) which drugs are used? b) Justify the combination. c) Mention their individual role. (SU-15Ju)
- Q. Short note: Anaphylactic shock. (SU-16J)

Ans.

Management of anaphylactic shock:

Clinical features:

1. Bronchospasm
2. Hypotension
3. Allergic reactions

General measures:

1. Should stop the drug immediately in case of penicillin induced hypersensitivity.
2. Patient should be kept in supine position with leg elevated for 30°
3. Respiratory resuscitation.
4. Monitoring of blood pressure.

Specific measures:

1. **Inj. Adrenaline:** To increase BP & cause bronchodilation. Adrenaline is the **drug of choice**, because it activates α , β_1 , and β_2 receptors, all of which may be important in reversing the pathophysiologic processes of anaphylaxis.
2. **Inj. Hydrocortisone:** To suppress inflammation.
3. **Antihistamine (H_1 & H_2 -blocker):** Antagonizes the action of histamine.
4. Bronchodilator
5. IV fluid.

Q. Explain the role of adrenaline in the treatment of anaphylactic shock. (DU-16Ju,15Ju, RU-15Ju,09J, CU-06J, SU-17J,14Ju)

Q. Explain the role of adrenaline in the treatment of allergic shock. (SU-12Ju)

Q. Discuss the role of adrenaline in penicillin induced anaphylactic shock. (CU-07J)

Ans.

Role of adrenaline in anaphylactic shock: In anaphylactic shock, there is bronchoconstriction & hypotension.

1. Adrenaline activates α_1 -receptors and causes **vasoconstriction and increases BP**.
2. Adrenaline activates $\beta_1 \rightarrow \uparrow$ Heart rate & force of contraction $\rightarrow \uparrow$ Systolic BP. Thus adrenaline reverses shock.
3. Adrenaline activates β_2 -receptors & causes **bronchodilatation**.
4. Adrenaline **stabilizes mast cell** and thus inhibits release of histamine and vasoactive amine.

Q. Explain the role of adrenaline in hypoglycemic shock. (DU-15Ju)

Ans.

In hypoglycemic shock, adrenaline increases blood glucose level by increasing glycogenolysis and gluconeogenesis.

Dopamine

General consideration

- **Source:** Synthetic
- **Class of drug:** Catecholamine
- **Nature:** Neurohormone
- **Receptor:** $D_1 - D_5$, α_1 , α_2 , β_1
- **Metabolism:** By MAO & COMT.
- **Mode of action:** Direct
- **Onset of action:** Within 5 minutes.

- **Duration of action:** Short (10 min), as it is a substrate for both MAO and COMT. So it requires continuous infusion.
- **Effective route:** Parenteral, continuous IV infusion due to shorter half life ($t_{1/2}$ 2 min).
- **Elimination:** Urine

Q. Enumerate the receptors of dopamine.

Ans.

Receptors of dopamine:

Receptor	Site	Effects
D ₁ (DA ₁), D ₅	Brain; effector tissues, especially smooth muscle of the renal vascular bed	Stimulation of adenylyl cyclase and increased cAMP
D ₂ (DA ₂)	Brain; effector tissues, especially smooth muscle; presynaptic nerve terminals	Inhibition of adenylyl cyclase; increased potassium conductance
D ₃	Brain	Inhibition of adenylyl cyclase
D ₄	Brain, cardiovascular system	Inhibition of adenylyl cyclase
Dopamine also acts on α_1 , α_2 , β_1		

Q. Describe the dose dependent effects of Dopamine on blood vessels. (CU-16Ju,15Ju)

Q. Enumerate the dose dependent effects of dopamine. (CU-07/06J,04S)

Q. Outline the receptor mediated actions of dopamine. (SU-07Ju)

Q. What are the pharmacological effects of dopamine? (SU-02M)

Ans.

Pharmacological effects / dose-dependent effects of dopamine:

Dose	Receptor	Effect
Low dose	D ₁	▪ Dopamine activates D₁ receptor in kidney & viscera → vasodilation → increased blood flow to kidney and viscera → increased GFR → improved renal function during shock.
Moderate dose	β_1 , D ₁	▪ Dopamine activates β_1 → ↑Heart rate & force of contraction → ↑Systolic BP. ▪ Dopamine does not increase diastolic BP due to dilation of renal & splanchnic vessels. ▪ Dopamine activates D₁ → improved renal function
High dose	D ₁ , α_1 , β_1	▪ Dopamine activates α_1 → vasoconstriction → ↑BP.

(Ref: Goodman & Gilman's-12th)

Q. What are the indications of dopamine? (DU-05S; RU-04M)

Ans.

Indications of dopamine:

1. **Cardiogenic & Septic shock:** Before dopamine is administered to patients in shock, hypovolemia should be corrected by transfusion of whole blood, plasma, or other appropriate fluid.
2. **Severe congestive cardiac failure (CCF)** particularly in patients with oliguria & low / normal peripheral resistance.

(Ref: Goodman & Gilman's-12th)

Q. What are the adverse effects of dopamine? (RU-05/04M)

Ans.

Adverse effects of dopamine: Adverse effects due to overdosage generally are attributable to excessive sympathomimetic activity.

1. **CVS adverse effects:**
 - Tachycardia
 - Precipitation of anginal pain
 - Arrhythmia
 - Hypertension

2. CNS: Headache, insomnia, excitement, restlessness
3. Nausea, vomiting.
4. Ischemic necrosis, sloughing due to extravasation of large amounts of dopamine during infusion.
5. Rarely, gangrene of the fingers or toes has followed prolonged infusion of the drug.

(Ref: Goodman & Gilman's-12th)

- Q. Illustrate the pharmacological role of dopamine in cardiogenic shock. (CU-17M,07J,06M, RU-16Ju,12Ju, SU-17J,15J,14Ju,13J,12Ju)
- Q. Why dopamine is preferred to noradrenaline in cardiogenic shock. (RU-10Ju, SU-16J,14J,11Ju,09J).
- Q. Justify dopamine, not adrenaline is the drug of choice in cardiogenic shock. (CU-03J; SU-17M)
- Q. Why adrenaline is not used in cardiogenic shock? (DU-09J)
- Q. Justify the priority of dopamine over adrenaline & noradrenaline as inotropic drugs in the Mx of circulatory shock. (DU-06M; SU-07J,06J/M)
- Q. Mention the role of adrenaline, dopamine in the management of shock. (DU-13Ju)

Ans.

Role of dopamine on cardiogenic shock:

- Dopamine activates β_1 receptor $\rightarrow$ $\uparrow$ Heart rate & force of contraction $\rightarrow$ $\uparrow$ Systolic BP. Thus dopamine reverses shock.
- Dopamine activates D_1 receptor $\rightarrow$ renal vasodilation $\rightarrow$ increases renal blood flow $\rightarrow$ increases GFR and Na^+ excretion $\rightarrow$ improves renal function during shock. In shock, renal blood flow is decreased and there is risk of renal damage. But by this effect, dopamine improves renal function.

Both effects of dopamine help to improve the condition of cardiogenic shock.

Effects of adrenaline and noradrenaline on cardiogenic shock:

- Adrenaline / noradrenaline activates β_1 receptor in heart $\rightarrow$ $\uparrow$ Heart rate & force of contraction $\rightarrow$ $\uparrow$ Systolic BP.
- Adrenaline / noradrenalin $\rightarrow$ binds with α_1 receptor (in cutaneous blood vessels) $\rightarrow$ Vasoconstriction $\rightarrow$ $\uparrow$ BP.
Both these effects of adrenaline and noradrenaline increase BP and reverse shock.
- Adrenaline / noradrenaline $\rightarrow$ binds with α_1 receptor (in the renal vascular smooth muscle) $\rightarrow$ renal vasoconstriction $\rightarrow$ decreases renal blood flow $\rightarrow$ renal damage $\rightarrow$ risk of renal failure (ARF / renal shut down).

Therefore, there is chance of renal failure in case of adrenaline or noradrenalin in cardiogenic shock, though it improves cardiac function. So, use of dopamine (not adrenaline / noradrenaline) in cardiogenic shock is more appropriate, rational, & justifiable.

Q. Short note: Dopamine. (DU-15Ju, RU-09J)

Ans. Write in short general consideration, mode of action, indication, adverse effects from above.

Q. Name the drugs used in the treatment of cardiogenic shock. (SU-07J)

Q. Mention some inotropic agents that can be used in circulatory shock.

Ans.

Drugs / inotropic agents used in the treatment of cardiogenic shock

1. Dopamine
2. Dobutamine
3. Adrenaline

(Ref: Rang-Dale-8th)

Q. How do you manage a case of cardiogenic shock? (RU-10J)

Ans.

Management of cardiogenic shock:

1. Patient should be transferred & managed in coronary care unit (CCU).
2. **Cardiotonic drugs: Dopamine &/or dobutamine** (mixed with normal saline) in continuous IV infusion.
3. **Use of IV fluid:** Should be avoided (if edema / congestion present) or should be used cautiously.
4. **Continuous catheterization:** To monitor urine output.
5. **Monitoring:** Pulse, blood pressure, temperature, dehydration, urine output, respiration etc.
6. **Treatment of the underlying cause.**

Dobutamine

Q. Mention the CVS effects of dobutamine. (DU-09J)

Ans.

CVS effects of dobutamine: Effects of dobutamine on heart (β_1 effect)

1. Positive inotropic effect: $\uparrow$ Force of contraction. It has relatively greater inotropic than chronotropic effect compared with isoproterenol.
 2. Positive chronotropic effect: $\uparrow$ Heart rate
 3. Positive dromotropic effect: $\uparrow$ Conduction velocity
- Net result:** Increased cardiac output $\rightarrow$ Increased blood pressure.

Q. Short note: Dobutamine. (DU-11Ju)

Ans.

Dobutamine: Dobutamine is a synthetic, direct-acting catecholamine. It was initially considered a relatively β_1 -selective agonist, but its actions are more complex. Its chemical structure resembles dopamine, but its actions are mediated mostly by activation of α and β receptors. Clinical preparations of dobutamine are a racemic mixture of (-) and (+) isomers, each with contrasting activity at α_1 and α_2 receptors.

- The (+) isomer is a potent β_1 agonist and α_1 antagonist.
- The (-) isomer is a potent α_1 agonist.

(Ref: Katzung-13th/145)

Indication / Therapeutic uses:

1. Shock (with dopamine)
2. Congestive heart failure (to increase cardiac output)
3. For inotropic support after cardiac surgery.

(Ref: Lippincott's-6th)

Adverse effects:

1. Nausea
2. Headache
3. Angina pain
4. Palpitation
5. Shortness of breath

Contraindication

1. Hypertrophic obstructive cardiomyopathy
2. Subaortic stenosis

Q. Mention the role of dobutamine in the management of shock. (DU-13Ju, RU-14J)

Ans.

Role of dobutamine in the management of shock: Dobutamine is used in combination with dopamine to increase cardiac output in congestive heart failure and cardiogenic shock. The drug increases cardiac output with little change in heart rate, and it does not significantly elevate oxygen demands of the myocardium - a major advantage over other sympathomimetic drugs.

(Ref: Lippincott's-6th)

Q. Compare dopamine with dobutamine. (CU-16Ju,15Ju)

Ans.

Comparison between dopamine and dobutamine:

Traits	Dopamine	Dobutamine
1. Source	Natural catecholamine	Synthetic catecholamine
2. Mechanism	Adrenergic + Dopaminergic	Pure adrenergic
3. Effect on BP	Increase, sustained	Increase / neutral / decrease
4. Effect on renal blood flow and diuresis	Improves at low doses by direct action	No direct action. May improve due to improved cardiac function.
5. Arrhythmogenicity	More	Less
6. Inotropic action	Less	More, consistent
7. Clinical utility	• Cardiogenic & Septic shock. • Severe congestive cardiac failure (CCF) particularly in patients with oliguria & low / normal peripheral resistance.	• Shock (with dopamine) • Congestive heart failure (to increase cardiac output) • For inotropic support after cardiac surgery.

Isoprenaline (Isoproterenol)

Indication

1. AV block
2. Cardiac arrest
3. Bronchial asthma

Adverse effect

1. Headache
2. Dizziness
3. Tachycardia
4. Arrhythmia
5. Sweating
6. Flushing
7. Tremor
8. Diarrhea

Contraindication

1. Acute coronary disease, eg, angina.
2. Hyperthyroidism
3. Liver congestion

Q. Explain the hazards of isoprenaline in angina.

Ans.

Hazards of isoprenaline in angina

- Isoprenaline → β_1 effect → Increased heart rate & force of contraction → Increased myocardial oxygen demand → Precipitate angina.
- Isoprenaline → β_2 effect → Vasodilation → Decreased BP → Decrease vital organ perfusion.

Both the effects may lead to death.

Xylometazoline and Oxymetazoline

These drugs are direct-acting synthetic adrenergic agonist that stimulates both α_1 - and α_2 - receptors.

Indication:

1. **Topical decongestants** in the **eye** or the **nose** because of their ability to cause vasoconstriction and decrease congestion.

Mechanism of action: Oxymetazoline directly stimulates α receptors on blood vessels supplying the nasal mucosa and the conjunctiva → vasoconstriction → Decreases blood flow → Decreases congestion.

Adverse effects: Oxymetazoline is absorbed in the systemic circulation regardless of the route of administration and may produce-

1. Nervousness
2. Headaches
3. Trouble sleeping.
4. Burning of the nasal mucosa and sneezing (when administered in the nose)
5. Rebound congestion is observed with long-term use.

(Ref: Lippincott's-6th; Katzung-13th/145)

Salbutamol / Albuterol

According to INN, it is Salbutamol. It is Albuterol according to USAN.

Important properties of salbutamol / Albuterol:

1. Route of administration:

- a. **Inhalation:** Salbutamol is usually given by the inhaled route for direct effect on bronchial smooth muscle. This is usually achieved through a metered dose inhaler (MDI), nebulizer.
 - b. Oral
 - c. Intravenous
2. **Onset of action:** Rapid. Bronchodilation is maximal within 15–30 minutes.
 3. **Duration of action:** Short acting (3 – 4 hours).
 4. Large safety margin; no or less CVS and CNS effects.
 5. Resistant to COMT as it has a modification in catechol –OH group.

(Ref: Katzung-13th/340)

Q. What are the indications of salbutamol. (CU-12Ju/J)

Ans.

Indications of salbutamol:

1. Acute and chronic bronchial asthma.
2. Chronic obstructive pulmonary disease (COPD)

Q. Outline the receptor mediated action of salbutamol. (CU-12Ju/J, SU-07Ju, RU-12J)

Q. Outline the mechanism of action of salmeterol. (SU-13J, 10Ju/J, 08Ju)

Q. How β_2 selective agonists (salbutamol / salmeterol) act? (CU-06S; RU-06J)

Ans.

Mechanism of action of selective β_2 selective agonists (salbutamol / salmeterol): Bronchial asthma is characterized by **bronchoconstriction** leading to severe respiratory distress. Selective β_2 agonist drugs (salbutamol / salmeterol) relieve asthma by producing **bronchodilatation**.

1. β_2 agonist drugs (salbutamol / salmeterol) bind with β_2 receptor of bronchial smooth muscle

↓
Relaxation of bronchial smooth muscle (**bronchodilatation**)

↓
Quick relief of acute bronchoconstriction and asthma.

(Ref: Katzung-13th/340)

2. Acts on β_2 receptor of mast cells → Decreased histamine release → Prevent bronchoconstriction.
3. Inhibits release of leukotrienes (bronchoconstrictor) → Relief of asthma.
4. Decreases microvascular permeability of lungs → No edema → Relief of asthma.

Q. What are the advantages of inhaled salbutamol?

Q. Discuss the beneficial role of salbutamol in bronchial asthma. (RU-13J,12J)

Ans.

Advantages of inhaled salbutamol:

1. Selective action on β_2 -receptor of bronchial smooth muscle.
2. Rapid onset of action (within 1-5 minutes).
3. Very low systemic absorption and so less / no CVS & CNS (tremor) adverse effects.
4. Easy to use; even if can be used in office or during walking.
5. Topical delivery (anatomical selectivity).

(Ref: Goodman & Gilman's-12th)

Q. What are the toxicities of inhaled β_2 -selective agonists?

Ans.

Toxicities of inhaled β_2 -selective agonists: Owing to their β_2 -receptor selectivity & topical delivery, they have relatively few side effects including irritation of the airway. A portion of inhaled drug is inevitably absorbed into the systemic circulation. At higher doses, they may lead to following toxicities-

- CVS: Palpitation & arrhythmia.
- CNS: Tremor, restlessness, insomnia, anxiety (CNS stimulatory effects).

(Ref: Goodman & Gilman's-12th)

Q. What are adverse effects of systemic β_2 -selective agonists? (RU-06J)

Q. What are adverse effects of salbutamol? (CU-12Ju/J)

Ans.

Adverse effects of systemic β_2 -selective agonists: The adverse effects of β_2 agonists are greatly increased by administering the drug orally or parenterally rather than by inhalation.

1. **CVS:**
 - Tachycardia
 - Worsening of arrhythmias or myocardial ischemia.
2. **CNS:** Tremor, restlessness, insomnia, anxiety (CNS stimulation).
3. Constipation
4. Urinary retention
5. **Metabolic:**
 - Glycogenolysis → Hyperglycemia
 - Gluconeogenesis → Hyperglycemia
 - Hypokalemia

(Ref: Goodman & Gilman's-12th)

Salmeterol

Q. What is the role of salmeterol in bronchial asthma? (SU-09Ju,08J)

Ans.

Role of salmeterol in long-term control of bronchial asthma:

1. Salmeterol and formoterol are long-acting β_2 agonists (LABA), providing bronchodilation for at least 12 hours.
2. Both salmeterol and formoterol have slower onsets of action and should not be used for quick relief of an acute asthma attack.
3. LABA should be prescribed for routine administration.
4. Because they have no anti-inflammatory action, they are not recommended as monotherapy for asthma.
5. They interact with inhaled corticosteroids to improve asthma control.
6. Whereas inhaled corticosteroids remain the long-term control drugs of choice in asthma, long-acting β_2 agonists are considered to be useful adjunctive therapy for attaining asthma control.

(Ref: Lippincott's-6th; Katzung-13th/340)

Q. Differentiate between salbutamol & salmeterol. (RU-12J)

Ans.

Difference between salbutamol, salmeterol & formoterol

Traits	Salbutamol	Salmeterol	Formoterol
1. Receptor selectivity	β_2 selective	β_2 selective	β_2 selective
2. Onset of action	Rapid (within 1-5 minutes)	Slow	Rapid
3. Duration of action	Short (2-6 hours)	Long (>12 hours)	Long (>12 hours)
4. Route	Inhalation, Oral	Inhalation	Inhalation
5. Use in asthma	Acute attack	Prophylaxis	Prophylaxis

α -methyl dopa and Clonidine

Discussed in the CVS chapter under Antihypertensive drugs.

Ephedrine

Ephedrine is both an α_1 and α_2 , β_2 receptor agonist; in addition, it enhances release of norepinephrine from sympathetic neurons and therefore is a **mixed-acting** sympathomimetic drug.

Source: Ephedrine and pseudoephedrine are plant alkaloids (ephedra) that are now made synthetically.

Route of administration: Oral, also injection.

Absorption: Ephedrine has excellent absorption orally and penetrates into the CNS.

Metabolism: Ephedrine is not catechols and are poor substrates for COMT and MAO; thus, these drugs have a long duration of action.

Excretion: Urine.

Tachyphylaxis: Produced

Duration of action: Prolong

CNS penetration: Can penetrate.

Pharmacological actions:

1. **Increases systolic and diastolic blood pressures** by vasoconstriction and cardiac stimulation.
2. **Bronchodilation**
3. Ephedrine enhances contractility and **improves motor function in myasthenia gravis**.
4. **Mild stimulation of the CNS**. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance.

Indication: The clinical use of ephedrine is declining due to the availability of better, more potent agents that cause fewer adverse effects. Ephedrine has been used to treat-

1. Asthma
2. As a nasal decongestant (due to its local vasoconstrictor action).
3. Hypotension that may occur with spinal anesthesia.
4. Complete heart block with Stokes Adams syndrome
5. Depression
6. Narcolepsy
7. As mydriatics

(Ref: Lippincott's-6th; Goodman & Gilman-12th edition)

Q. What are the adverse effects of ephedrine?

Ans.

Adverse effects of ephedrine:

1. **On CVS:**
 - Hypertension, particularly after parenteral administration or with higher-than-recommended oral dosing.
 - Headache
 - Flushing
 - Arrhythmia
 - Anginal pain
2. **On CNS:**
 - Insomnia
 - Restlessness
 - Tremor
 - Dizziness
 - Talkativeness
3. **Tachyphylaxis:** Gradual decrease of response due to repeated administration of the same dose of a drug at very short interval is called tachyphylaxis.

Phenylephrine

Properties

1. Phenylephrine is a direct-acting α -agonist that favors α_1 receptors over α_2 receptors.
2. It is a vasoconstrictor that raises both systolic and diastolic blood pressures.
3. It has no effect on the heart itself but rather induces reflex bradycardia when given parenterally.

Indication:

1. As decongestant on the nasal mucosa
2. As mydriatic in ophthalmic solutions.
3. Used to raise blood pressure and to terminate episodes of supraventricular tachycardia.

Adverse effect: Large doses can cause-

1. Hypertensive headache
2. Cardiac irregularities.

(Ref: Lippincott's-6th; Katzung-13th/145)

Q. Mention the cardiovascular effects of phenylephrine. (SU-11J)

Ans.

Cardiovascular effects of phenylephrine

1. Phenylephrine is a vasoconstrictor (by acting on α_1 receptors) that raises both systolic and diastolic blood pressures.
2. It has no effect on the heart itself but rather induces reflex bradycardia when given parenterally.

(Ref: Lippincott's-6th)

Amphetamine

Amphetamine, racemic b-phenylisopropylamine, has powerful **CNS stimulant actions** in addition to the peripheral α and β actions common to indirect-acting sympathomimetic drugs.

Q. Discuss the pharmacological effects of Amphetamine. (SU-16Ju)

Pharmacological action of Amphetamine:

A. **CNS:** Amphetamine is a powerful CNS stimulant. The main results of an oral dose of 10 to 30 mg include-

1. Wakefulness
2. Alertness
3. Elevation of mood, with increased initiative, self-confidence, and ability to concentrate;
4. Elation and euphoria;
5. Increase in motor and speech activities.
6. Performance of simple mental tasks is improved, but, although more work may be accomplished, the number of errors may increase.
7. Physical performance- in athletes, for example, is improved, and the drug often is abused for this purpose.
8. Prevents fatigue and sleep
9. Decreases appetite.
10. Prolonged use or large doses causes depression and fatigue.
11. Many individuals given amphetamine experience headache, palpitation, dizziness, vasomotor disturbances, agitation, confusion, dysphoria, apprehension, delirium, or fatigue.

B. **Cardiovascular Responses.**

1. Increases both systolic and diastolic blood pressure.
2. Heart rate often is reflexly slowed.
3. Cardiac arrhythmias (with large doses)

C. **Respiration.** Amphetamine stimulates the respiratory center, increasing the rate and depth of respiration.

D. **Others-**

1. Urinary retention

Q. What are the clinical uses of amphetamine? (NTK)

Ans.

Therapeutic Uses of Amphetamine: Amphetamine is used chiefly for its CNS effects.

1. **Obesity:** Dextroamphetamine with greater CNS action and less peripheral action, was used off-label for obesity (but no longer is approved for this purpose because of the risk of abuse).
2. **Narcolepsy** (characterized by hypersomnia)
3. Attention-deficit/hyperactivity disorder.
4. Minimal brain dysfunction
5. In fatigue to maintain wakeful state
6. As analeptic in barbiturate poisoning
7. In sport as abuse

Q. How does amphetamine produce anorexiant effect?

Ans.

Amphetamine produces anorexiant effect by the following way-**1. Central:**

- a. Amphetamine → (-) lateral hypothalamic center → Decreases food intake.
- b. Amphetamine → Increases release of NA and dopamine → ↑ Metabolism.

2. Peripheral:

- a. ↓ GIT motility.
- b. ↓ GIT secretion.

Note: Anorexiant effect persists only for 2-3 weeks.

Q. Why amphetamine is not used clinically?

Ans.

Amphetamine is not used clinically, because-

1. It causes euphoria.
2. It causes more alertness and more mood.
3. It decreases sleep.
4. It may produce addiction.

Nice to know

Toxicity and Adverse Effects of Amphetamine: The acute toxic effects of amphetamine usually are extensions of its therapeutic actions, and as a rule result from overdosage.

1. **CNS:** Restlessness, dizziness, tremor, hyperactive reflexes, talkativeness, tenseness, irritability, weakness, insomnia, fever, and sometimes euphoria. Confusion, aggressiveness, changes in libido, anxiety, delirium, paranoid hallucinations, panic states, and suicidal or homicidal tendencies occur, especially in mentally ill patients.
2. **CVS:** Headache, chilliness, pallor or flushing, palpitation, cardiac arrhythmias, anginal pain, hypertension or hypotension, and circulatory collapse. Excessive sweating occurs.
3. **GIT:** Dry mouth, metallic taste, anorexia, nausea, vomiting, diarrhea, and abdominal cramps.
4. Psychological dependence
5. Tolerance

Fatal poisoning usually terminates in convulsions and coma, and cerebral hemorrhages are the main pathological findings.

The abuse of amphetamine as a means of overcoming sleepiness and of increasing energy and alertness should be discouraged. The drug should be used only under medical supervision.

(Ref: Goodman & Gilman-12th edition)

Contraindication

1. Palpitation
2. Arrhythmia
3. HTN
4. Angina

Q. What is amphetamine psychosis?

Ans.

Amphetamine psychosis: As amphetamine block uptake I, there is increased secretion & decreased uptake of dopamine by presynaptic adrenergic nerve terminal. So long-term or short term abuse of amphetamine gives rise to visual hallucination as well as paranoid delusion in the setting of a clear sensorium and full orientation.

Q. Name some drugs that produce paradoxical effect.

Ans.

Drugs that produce paradoxical effect

1. Amphetamine → In hyperkinetic children.
2. Bromocriptine → In acromegaly.
3. Thiazide → In diabetes insipidus.

Q. How does Adrenaline differ from Ephedrine?

Ans.

Differences between Adrenaline and Ephedrine

Traits	Adrenaline	Ephedrine	Amphetamine
1. Source	Animal chromaffin tissue	Plant ephedra	Synthetic
2. Nature	Neurohormone	Alkaloid	Synthetic
3. Mode of action	Direct	Mixed	Indirect
4. Duration of action	Short	Prolong	Prolong
5. Vasopressor effect	More	Less	Less than ephedrine
6. CNS action	Less	More	More than ephedrine
7. Tachyphylaxis	Does not produce	Produce	Produce
8. Anorexient effect	No	No	Yes
9. Euphoria	No	No	Yes

Adrenergic antagonists / Sympatholytic drugs

- Q. Classify adrenoceptor antagonists. (CU-12Ju)
- Q. Name the adrenergic receptor blockers. (SU-06S)
- Q. Name the sympatholytics. (SU-06J)
- Q. Categorize the α -receptor blocking drugs. (DU-13Ju, CU-04M, RU-14Ju,13Ju,10Ju)
- Q. Classify sympatholytic drugs according to site of action. (CU-04S)

Ans.

Anti-adrenergic or sympatholytic drugs:

A. Receptor blockers

1. α -blocker: α -blockers may be reversible or irreversible.

Reversible α -blocker <i>(binds with receptor with weak bond, eg, H bond, van der Waals force)</i>			Irreversible α -blocker <i>(binds with receptor with strong covalent bond)</i>
α_1 blocker	α_2 blocker	α_1 and α_2 blocker	α_1 and α_2 blocker
Prazosin Terazosin Doxazosin Tamsulosin	Tolazoline Yohimbine	Phentolamine	Phenoxybenzamine Dibenzamine

2. β -blocker: All β blockers are competitive blockers.

Selective β -blocker <i>(blocks either β_1 or β_2)</i>		Non-selective β -blocker <i>blocks both β_1 and β_2 (cardio-nonselective)</i>
β_1 blocker (cardioselective)	β_2 blocker	β_1 and β_2 blocker
Atenolol Bisoprolol Metoprolol Acebutolol Alprenolol Esmolol Betaxolol Celiprolol Nevivolol	Butoxamine	Propranolol Timolol Pindolol Nadolol Sotalol Carteolol Penbutolol

(Ref: Bennet & Brown-11th; Katzung-13th/155)

3. Mixed antagonists: α and β blocker: $\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$

- Labetalol**
- Carvedilol**

B. Neuron blockers

- Centrally acting: α -methyl Dopa, Clonidine
- Peripherally acting: Reserpine, Guanethidine

NB: Commonly used drugs are shown in **BOLD** letters.

C. Ganglion blockers

- Hexamethonium
- Trimethaphan

α -blockers

Q. Explain the role of prazosin in hypertension. (SU-05J)

Q. Enumerate the pharmacological action of prazosin.

Q. What are the pharmacological actions of α -blockers? (SU-04/02M)

Ans.

Mechanism of action/ role of prazosin in hypertension:

Prazosin / α -blockers

Blocks α receptor on arteriole, pre-capillary sphincter, so noradrenaline cannot bind with that receptor

↓ Phospholipase-C (PLC)

↓ DAG & ↓ IP₃ & ↓ Ca²⁺ influx

Vasodilatation

↓ PR (Peripheral Resistance)

↓ BP

Pharmacological actions of α -blockers / Prazosin

Organ	Effect
1. CVS	Decreases BP
2. Eye	Miosis
3. GIT	Diarrhea
4. Male sex organ	Failure of ejaculation
5. Kidney	Increased blood flow
6. Pregnant uterus	Relaxation

Q. Lists clinical uses of α -blockers. (SU-09Ju)

Q. What are the indications of α -receptor blockers? (DU-13Ju, RU-14Ju, 13Ju, 11J, CU-04M; SU-06J/S)

Q. What are the clinical conditions where we can use Prazosin / selective α blockers? (DU-06S; CU-04M)

Ans.

Indications of α -receptor blockers:

1. **Hypertensive emergency:** Labetalol
2. **Chronic Hypertension:** α_1 -blockers (eg, prazosin) are effective in the treatment of mild to moderate systemic hypertension. But they are not usually recommended as monotherapy for hypertension because other classes of antihypertensives are more effective in preventing heart failure.
3. **Pheochromocytoma:** Phenoxybenzamine, Phentolamine.
4. **Benign prostatic hypertrophy** (to relax capsular smooth muscle that may contribute to urinary obstruction): Prazosin, terazosin, doxazosin, **tamsulosin**, and Alfuzosin are all efficacious in patients with BPH. These drugs are particularly useful in patients who also have hypertension.
5. **Erectile dysfunction:** Phentolamine may cause erection in men with erectile dysfunction.
6. **Peripheral vascular diseases (PVD):** Raynaud's phenomenon and other conditions involving excessive reversible vasospasm in the peripheral circulation do benefit from prazosin or phenoxybenzamine.
7. To reverse the local vasoconstrictor effect of noradrenaline (phentolamine).

(Ref: Katzung-13th/156-157)

Nice to know: Indications of individual drugs-

α -blockers	Indications
Prazosin	1. Mild to moderate HTN 2. HTN in Pheochromocytoma 3. HTN with BPH 4. Chill blain (frost bite)
Terazosin	1. Hypertension 2. Benign prostatic hyperplasia (BPH)
Doxazosin	1. Hypertension 2. Benign prostatic hyperplasia (BPH)
Alfuzosin	1. Benign prostatic hyperplasia (BPH)
Tamsulosin	1. Benign prostatic hyperplasia (BPH)
Tolazoline	1. Peripheral vascular diseases, eg, Berger's disease
Phenoxybenzamine	1. Pheochromocytoma. • Prior to surgical removal of the tumor, patients are treated with phenoxybenzamine to preclude the hypertensive crisis that can result from manipulation of the tissue. • This drug is also useful in the chronic management of these tumors, particularly when the catecholamine-secreting cells are diffuse and, therefore, inoperable. 2. Raynaud's disease. 3. Autonomic hyperreflexia, which predisposes paraplegics to strokes, can be managed with phenoxybenzamine.
Phentolamine	1. Short-term management of pheochromocytoma. 2. Impotence (Erectile dysfunction) (now rarely used)
Yohimbine	1. Orthostatic hypotension (because it promotes norepinephrine release through blockade of presynaptic α_2 receptors.) 2. Male erectile dysfunction (now phosphodiesterase-5 inhibitors like sildenafil are used)

(Ref: Lippincott's-6th; Katzung-13th/156-157; Goodman & Gilman-12th edition)Nice to know

Erectile dysfunction: Sildenafil and other cGMP phosphodiesterase inhibitors are drugs of choice for erectile dysfunction.

(Ref: Katzung-13th/158)

Q. What are the adverse effects of α receptor blockers? (CU-04J; RU-14Ju, SU-09Ju,06S)

Q. Mention the adverse effects of prazosin. (DU-13Ju)

Ans.

Adverse effects of α -receptor blockers / Prazosin:

1. **Cardiac:** Postural hypotension, reflex tachycardia (they are less marked in prazosin)
2. **Eye:** Miosis
3. **GIT:** Diarrhoea, vomiting.
4. **Others:** Ejaculatory failure, nasal decongestion, flushing, headache, dizziness.

(Ref: Goodman & Gilman's-12th)

Q. Describe the importance of use of prazocine at bed time. (CU-17M)

Viva Q. What is first-dose effect?

Ans.

First-dose effect: The first dose of the α_1 blocker drugs produces an exaggerated **orthostatic hypotensive response** that can result in syncope (fainting). This action, termed a first-dose effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug **at bedtime**.

(Ref: Lippincott's-6th)

Viva Q. A 25 years old male patient has come to you with HTN. Can you prescribe him α blockers?

Ans. No, I can't. Because it can cause ejaculatory failure although it may help in erection. So prazosin or other α -blocking drugs are contraindicated in young male patients.

Q. What is postural hypotension? What are drugs that cause postural hypotension?

Q. Briefly outline drug induced postural hypotension. (CU-12J)

Q. How will you prevent postural hypotension?

Q. Write short note on: Postural hypotension.

Ans.

Postural hypotension: A steep fall in blood pressure due to stasis of blood in the peripheral circulation resulting from sudden changes in posture (from lying to standing) is called postural hypotension.

***Or, A fall in BP of more than 20 mmHg (SBP) or more than 10 mmHg (DBP) 2 – 3 minutes after sudden change in posture from lying to standing is called postural hypotension.

(Ref: Davidson's Medicine-22nd edition)

Drugs causing postural hypotension:

α- blockers	▪ Phenoxybenzamine ▪ Phentolamine ▪ Prazosin ▪ Terazosin
Ganglion blockers	▪ Hexamethonium ▪ Trimethaphan
Adrenergic neuron blocker	▪ α-methyl Dopa ▪ Clonidine ▪ Guanethidine
Ca²⁺ channel blocker	▪ Nifedipine
TCA	▪ Amitryptilline
Vasodilator	▪ GTN ▪ Na-nitroprusside ▪ Diazoxide
ACE inhibitor	▪ Captopril

Prevention of postural hypotension:

1. Starting the drug with 1/3rd or 1/4th of the normal dose & then gradually increasing to normal dose.
2. Drugs at bed time with a usual dose.
3. Dose should be increased gradually.

(Ref: Davidson's Medicine-22nd edition; Lippincott's-6th)

Q. Explain postural hypotension after prazosin / α -receptor blocker administration. (CU-15J; SU-04M)

Q. What is the mechanism of postural hypotension?

Ans.

Postural hypotension after prazosin / α -blocker administration:

Prazosin administration to a hypertensive pt

↓

Blocks α_1 -receptor on peripheral vessels & causes vasodilatation

↓

BP goes back to normal range (usual antihypertensive effect of prazosin)

↓

During changing posture from lying to standing, **baroreceptor reflex-mediated vasoconstriction** facilitates venous return from the part of the body below the level of the heart. But after administration of α_1 -blocker, this vasoconstriction effect cannot take place and vasodilation persists.

↓

↑ Venous pooling of peripheral blood
 ↓
 ↓ Venous return
 ↓
 ↓ Cardiac output
 ↓
 ↓ BP (Hypotension)
 ↓
 Postural Hypotension

2nd & 2nd Technique

α agonist - Tachycardia (SVT)
 α antagonist - Tachycardia (RT)

Q. Explain reflex tachycardia after prazosin administration.

Ans.

Reflex tachycardia after prazosin administration:

Prazosin blocks α receptor
 ↓
 BP goes back to normal range (usual antihypertensive effects of prazosin)
 ↓
 Upon standing up, sudden fall of blood pressure (postural hypotension)
 ↓
 Reflex activation of sympathetic nerves in an attempt to increase BP
 ↓
 Ad / NA try to bind with α_1 and β_1 receptor
 ↓
 α_1 is already blocked
 ↓
 Postural hypotension persists.
 β_1 receptor is activated
 ↓
 ↑ Heart rate
 ↓
 Tachycardia (Reflex tachycardia).

on β_1 block
 or or
 RT

∴ Postural Hypotension → RT

Q. Compare reflex tachycardia of prazosin with that of phenoxybenzamine.

Ans.

Comparison of reflex tachycardia by prazosin & phenoxybenzamine: Reflex tachycardia is more marked with agents that block α_2 -presynaptic receptors in the heart, as augmented release of NA will further stimulate β_1 receptors in the heart.

(Ref: Katzung-13th edition)

Explanation:

Prazosin blocks α_1 receptor	Phenoxybenzamine blocks both α_1 & α_2 receptors
↓ Reflex tachycardia	α_1-receptor blockade cause reflex tachycardia as usual and α_2 receptor blockade on pre-synaptic nerve terminal inactivates negative feedback mechanism ↓ ↑ NA / Ad release from pre-synaptic nerve terminal ↓ NA / Ad bind with β_1-receptors on heart ↓ More increase of heart rate ↓ More marked reflex tachycardia than prazosin

So, reflex tachycardia after non-selective blocker (phenoxybenzamine) administration is more marked than that of selective α -blocker (prazosin) administration.

Q. Briefly assign reasons why prazosin, but not other α blockers are preferred as antihypertensive drug. (DU-06M)

Q. Why non-selective α -blockers are not used in HTN?

Ans.

Prazosin, but not other α blockers are preferred as antihypertensive drug:

1. Prazosin blocks α_1 receptor selectively.
2. Postural hypotension & reflex tachycardia is less marked amongst all α -blockers.
3. The nature of binding is reversible & the action can be overcome easily if needed.

(Ref: Goodman-12th)

Q. What are the differences between Prazosin & Phenoxybenzamine?

Q. Mention the difference between selective and non-selective α blocker. (SU-12Ju)

Ans.

Differences between selective (prazosin) and non-selective (phenoxybenzamine):

Traits	Selective α blocker (Prazosin)	Non-selective α blocker (Phenoxybenzamine)
1. Receptor selectivity	α_1 receptor only	Both α_1 & α_2 receptors
2. Nature of binding	Reversible	Irreversible
3. Antagonism	Competitive reversible	Competitive irreversible
4. Actions other than α -blockade	Some antagonism of ACh	No
5. Reflex Tachycardia	Less marked	More marked
6. Postural hypotension	Less	More than Prazosin

Q. Explain the role of Tamsulosin in the treatment of benign enlargement of prostate. (RU-10Ju,09J)

Q. Tamsulosin is preferred over prazosin in benign prostatic hyperplasia- Explain. (RU-13Ju)

Ans.

Role of Tamsulosin in the treatment of benign enlargement of prostate

1. Tamsulosin relaxes capsular smooth muscle of prostate and thus relieves urinary obstruction.
2. Tamsulosin has relatively minor effects on blood pressure at a low dose. This drug may be preferred in patients who have experienced orthostatic hypotension with other α_1 -blockers, eg, prazosin.

Q. Justify the use of Tamsulosin in a hypertensive patient with BPH. (CU-05J)

Q. Which one is the drug of choice amongst α -blockers in HTN with BPH?

Ans.

Drug of choice in HTN with BPH: Tamsulosin

Explanation: Tamsulosin is a competitive α_1 blocker. It has relatively greater potency in inhibiting contraction in prostate smooth muscle versus vascular smooth muscle compared with other α_1 -blockers. Furthermore, compared with other antagonists, tamsulosin has less effect on standing blood pressure in patients.

(Ref: Katzung-13th/155)

Q. Short note: Tamsulosin. (RU-16J)

Ans.

Tamsulosin:

Tamsulosin is a competitive α_1 antagonist.

Bioavailability: High

Half-life: 9–15 hours.

Metabolism: Liver

Indication: BPH

Handwritten note:
 α agonist $\rightarrow$ sympathetic
 $\rightarrow$ Urinary retention
 $\therefore$ antagonist $\rightarrow$ Relief

Adverse effects of Tamsulosin

1. Orthostatic hypotension
2. Increased risk of the intraoperative floppy iris syndrome (IFIS) in patients undergoing cataract surgery. (Ref: Katzung-13th/155)

Q. Explain the role of phenoxybenzamine in pheochromocytoma?

Ans.

Role of phenoxybenzamine in pheochromocytoma: Pheochromocytoma is the tumor of the adrenal medulla & sympathetic neurons that secretes enormous quantities of catecholamine into the circulation. The usual manifestation is severe hypertension (HTN), palpitation, headache & excess sweating.

The vast majority are treated surgically. However phenoxybenzamine is almost always used to treat the patient in preparations for surgery. Phenoxybenzamine controls episodes of severe HTN & other symptoms of catecholamine excess.

The advantage of using phenoxybenzamine is its irreversible binding with α -receptors. So, excess catecholamine cannot displace the phenoxybenzamine from α -receptors. On the other hand, due to reversible binding, prazosin can be easily displaced from α -receptors. So, Prazosin is ineffective in pheochromocytoma.

(Ref: Katzung-13th/156)

β-receptor blocking drugs

Q. Classify β blockers. (DU-17J, 16J, 13J, 12J, 11J, 09Ju; RU-08Ju, SU-11J)

Q. Categorize β-adrenoceptor blockers. (CU-17J)

Q. Name the cardio-selective beta-blockers. (DU-15J, 09/08J, RU-15J)

Q. How the β blockers are categorized? (SU-14J)

Ans.

β-receptor blocking drugs: β-blocker drugs are classified according to their receptor selectivity:

Selective β-blocker (blocks either β_1 or β_2)		Non-selective β-blocker blocks both β_1 and β_2 (cardio-nonselective)
β_1 blocker (cardioselective)	β_2 blocker	β_1 and β_2 blocker
• Atenolol • Bisoprolol • Metoprolol • Acebutolol • Esmolol • Alprenolol • Betaxolol • Celiprolol • Nebivolol	• Butoxamine	• Propranolol • Timolol • Pindolol • Nadolol • Sotalol • Carteolol • Penbutolol

(Ref: Bennet & Brown-11th; Katzung-13th/155)

Mixed antagonists: α and β blocker:

1. Labetalol
2. Carvedilol

According to generation:

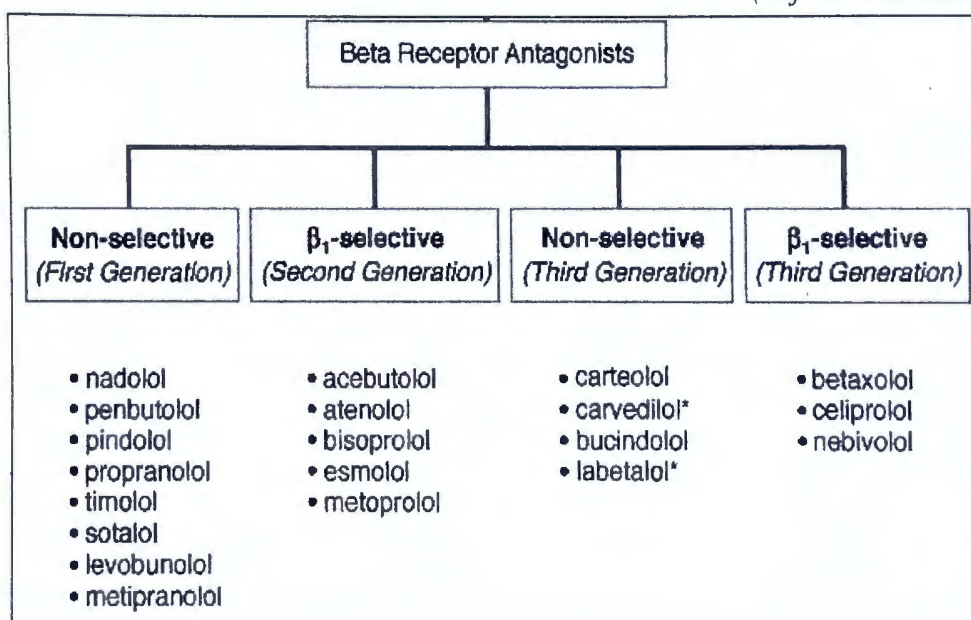
1. **1st generation β -blockers/ Cardio-nonselective β -blockers:** Classical non-selective β -blockers. Eg propranolol, timolol, pindolol, nadolol, sotalol.
2. **2nd generation β -blocker/ Cardioselective β -blockers:** β_1 -selective drugs, eg, atenolol, bisoprolol, metoprolol, acebutolol, esmolol.
3. **3rd generation non-selective β -blockers:** β -blocking drugs with additional cardiovascular actions.

NO production	β_2 -receptor agonism	α_1 -receptor antagonism	Ca^{2+} entry blockade	K^+ channel opening	Antioxidant activity
▪ Celiprolol ▪ Carteolol ▪ Nipradilol ▪ Bopindolol ▪ Nebivolol	▪ Celiprolol ▪ Carteolol ▪ Bopindolol	▪ Carvedilol ▪ Labetalol ▪ Nipradilol	▪ Carvedilol ▪ Betaxolol	▪ Tilisolol	▪ Carvedilol

4. **3rd generation β_1 blockers/ Cardioselective β -blockers:**

- a. Betaxolol
- b. Celiprolol
- c. Nebivolol.

(Ref: Goodman & Gilman's-12th)

Nice to know:

- **Cardioselective β -blockers:** Block only β_1 receptor.
- **Cardio-nonselective β -blockers:** Block both β_1 and β_2 receptors.

Q. Enlist the β -blockers with ISA (intrinsic sympathomimetic activity). (CU-16J)

Ans.

β -blockers with ISA (intrinsic sympathomimetic activity)

1. Acebutolol
2. Pindolol
3. Carteolol
4. Bopindolol
5. Oxprenolol
6. Celiprolol
7. Penbutolol

(Ref: Katzung-13th/162; Lippincott's-6th/102)

Nice to know: Explanation

Intrinsic sympathomimetic activity (ISA) characterizes a group of beta blockers that are able to stimulate beta-adrenergic receptors (agonist effect) and to oppose the stimulating effects of catecholamines (antagonist effect) in a competitive way.

Partial agonists are ligands that elicit a submaximal response when bound to beta receptors at maximal occupancy. (Ref: Internet)

Acebutolol and pindolol: Antagonists with partial agonist

Acebutolol (β_1 -selective blocker) and pindolol (nonselective β -blocker) are not pure antagonists. These drugs also have the ability to weakly stimulate both β_1 and β_2 receptors and are said to have intrinsic sympathomimetic activity (ISA). These partial agonists stimulate the β receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, epinephrine and norepinephrine. The **result** of these opposing actions is a **diminished effect** on cardiac rate and cardiac output compared to that of β -blockers without ISA.

(Ref: Lippincott's-6th/102)

Q. What are the advantages of selective beta blockers over non-selective? (DU-10Ju, 109/08J, RU-15J)

Q. Why bisoprolol is preferred to propranolol in hypertension with asthma? (SU-14Ju)

Ans.

Advantages of cardioselective beta blockers over cardio-nonselective beta blockers: Cardioselective beta blockers have some advantages over cardio-nonselective beta blockers. $\beta_2 \rightarrow$ Bronchodilation

1. Cardioselective beta blockers have **no unwanted bronchoconstrictor** effect of β_2 receptors. Hence they are useful in hypertensive patients with **impaired pulmonary function, eg, asthma, COPD**.
2. Because these drugs have **less effect on peripheral vascular β_2 receptors**, **coldness of extremity**, a common side effect of β blocker therapy, is less frequent.
3. These drugs are useful in **diabetic hypertensive patients** who are receiving insulin or oral hypoglycemic agents.

(Ref: Lippincott's-6th)

Q. Discuss the pharmacological effects of propranolol. (SU-16Ju)

Ans.

Pharmacological effects of propranolol**A. Effects on the Cardiovascular System**

- $\downarrow$ Heart rate (negative chronotropy)
- $\downarrow$ Force of contraction (negative inotropy)
- $\downarrow$ Conduction velocity (negative dromotropy), eg, Slowed atrioventricular conduction.
- Peripheral resistance $\rightarrow$ initially increases (acute effects), then falls (after chronic drug administration)
- Antagonize the release of renin by JG cells of kidney.

Result:

- Beta-blockers given chronically lower blood pressure in patients with hypertension.
- Do not usually cause hypotension in healthy individuals with normal blood pressure.

B. Effects on the Respiratory Tract

- Blockade of the β_2 receptors in bronchial smooth muscle may lead to an increase in airway resistance (**bronchoconstriction**), particularly in patients with asthma.
- Consequently, these drugs should generally be avoided in patients with asthma.

C. Effects on the Eye

- Reduce intraocular pressure by decreasing aqueous humor production.

D. Metabolic and Endocrine Effects

- Inhibit lipolysis.
- Glycogenolysis is partially inhibited after β_2 -receptor blockade. (β -blockers should be used with caution in insulin-dependent diabetic patients.)
- Chronic use of β -blockers has been associated with-
- Increased plasma VLDL-C

- Decreased HDL-C
- LDL-C generally do not change.
- HDL-C/LDL-C ratio increases that may increase the risk of coronary artery disease.
- These changes tend to occur with both selective and nonselective β blockers, though they may be less likely to occur with β blockers possessing intrinsic sympathomimetic activity (partial agonists).

E. Effects Not Related to Beta-Blockade

- Partial β -agonist activity is desirable to prevent precipitation of asthma or excessive bradycardia.
- Local anesthetic action, also known as "membrane-stabilizing" action, is a prominent effect of several β blockers.
- Sotalol has marked class III antiarrhythmic effects, reflecting potassium channel blockade.

(Ref: Katzung-13th/158-162)

Q. Write down the indications of β -adrenoceptor blockers. (CU-17J)

Q. Write down the indications of Propranolol. (DU-15J,13J,12J,09Ju, RU-04S, CU-08J,05J, SU-06/04J)

Ans.

Indications of propranolol:

CVS	1. Hypertension 2. IHD (angina pectoris, unstable angina, MI) 3. Cardiac arrhythmias (supra-ventricular & ventricular arrhythmias) 4. Obstructive cardiomyopathy 5. Dissecting aortic aneurysm 6. Fallot's tetralogy 7. Portal HTN and esophageal varices
Endocrine	1. Hyperthyroidism 2. Pheochromocytoma 3. Cushing's disease
CNS	1. Migraine 2. Acute alcohol and opioid withdrawal syndrome 3. Anxiety. For example, performance anxiety (stage fright).

(Ref: Katzung-13th/163-165; Goodman & Gilman's-12th)

Q. Write down the important clinical uses of Atenolol. (DU-07Ju)

Q. Short note: Atenolol. (DU-14J)

Ans.

Indications of cardioselective β -blockers, eg, atenolol / Metoprolol / Acebutolol / Bisoprolol

1. IHD (angina pectoris, unstable angina, MI)
2. Hypertension.
3. Arrhythmias
4. Heart failure

(Ref: Katzung-13th/163-164; Lippincott's-6th)

Q. What are the adverse effects of β -blocking drugs? (CU-16Ju,08J, RU-10Ju, SU-04M)

Ans.

Adverse effects of β -blocking drugs / propranolol:

CVS adverse effects	▪ Bradycardia ▪ Hypotension ▪ Cardiac conduction abnormalities (cardiac arrhythmias). ▪ Cold extremities due to decreased peripheral circulation. ▪ Exercise intolerance (β_2 blockade impairs vasodilation in skeletal muscles)
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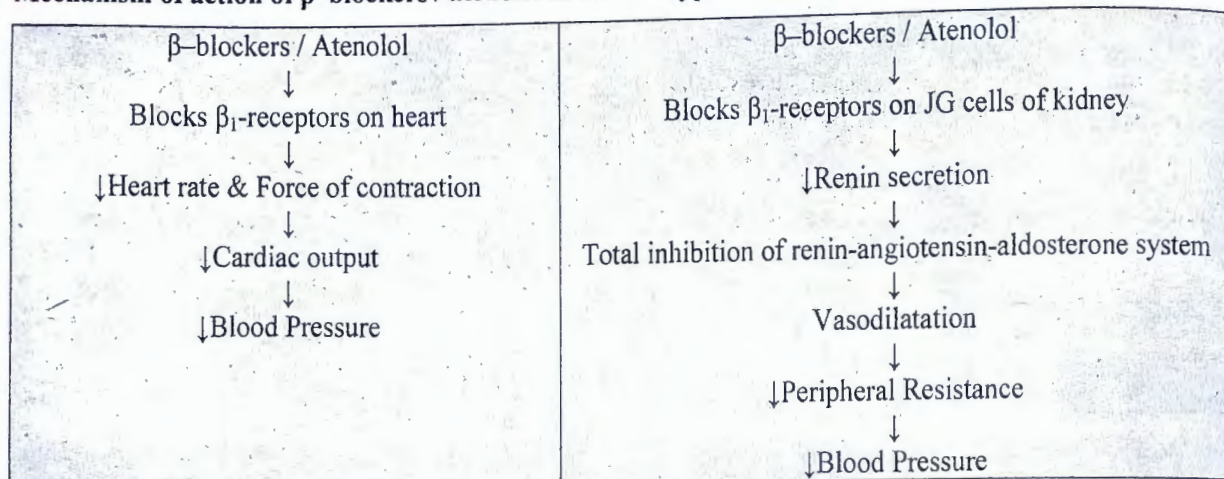
CNS adverse effects	▪ Sedation ▪ Sleep disturbance (Insomnia, Nightmares) ▪ Depression ▪ Suicidal tendency (in case of long term use)
Others	▪ Bronchoconstriction ▪ Dyslipidaemia ▪ Prolongation of hypoglycemia ▪ Sexual dysfunction in men

(Ref: Katzung-13th/165; Goodman & Gilman's-12th)**Q. Short note: Propranolol. (RU-17J)**

Ans. Write from above discussion.

Q. How does β -blockers lower elevated blood pressure? (RU-15J)**Q. How cardio-selective β blocking drug lowers the BP? (DU-04M, CU-05J)****Q. How does atenolol lower BP? (DU-14Ju, 11J, RU-09/08Ju)****Q. Justify the use of atenolol as anti-hypertensive. (SU-15J)**

Ans.

Mechanism of action of β -blockers / atenolol as an antihypertensive drug:**Q. Explain bronchospasm after propranolol therapy in asthmatic patient. (CU-15J)****Q. Justify preference of bisoprolol to propranolol in asthmatics. (SU-15Ju)**

Ans.

Role of propranolol / non-selective β blocker in asthmatic patient: Bronchial asthma is characterized by bronchoconstriction leading to severe respiratory distress.

Propranolol is a non-selective β blocker. It blocks β_2 receptor of bronchial smooth muscle

↓

Contraction of bronchial smooth muscle (**bronchoconstriction / bronchospasm**)

↓

Aggravation of bronchial asthma.

Role of bisoprolol in asthmatic patient:

Bisoprolol is a β_1 selective β -blocker. It does not block β_2 receptor of bronchial smooth muscle

↓

No contraction of bronchial smooth muscle (no bronchoconstriction / bronchospasm)

↓

No aggravation of bronchial asthma.

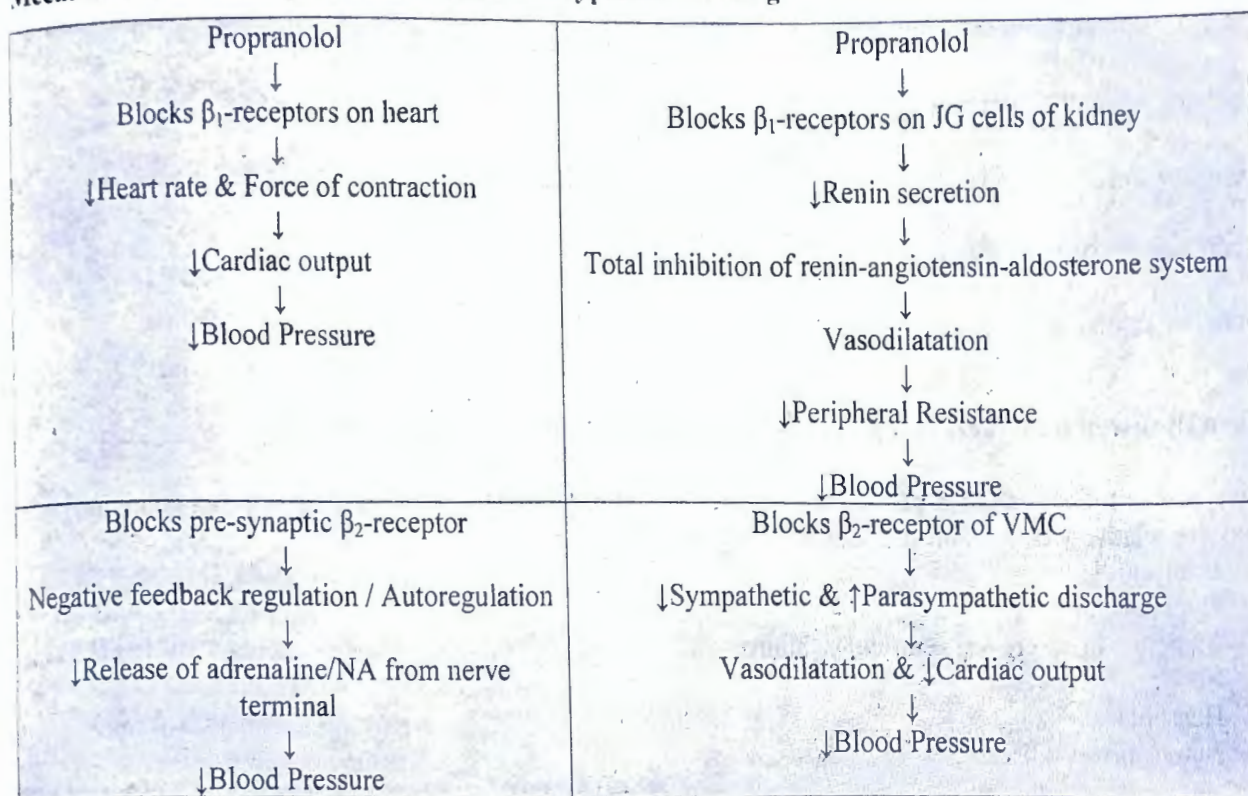
This is why; bisoprolol is preferred to propranolol in asthmatic patient.

Q. Write down the mechanism of action of propranolol. (DU-09Ju)

Q. Explain how propranolol reduces blood pressure. (DU-17J)

Q. How a non-selective β blocker lowers the BP? (CU-03S; RU04J)

Ans. Mechanism of action of propranolol as an antihypertensive drug:



Q. How to withdraw β blockers?

Ans.

β blocker withdraw phenomenon: β blocker should be withdrawn **slowly**. Sudden withdrawal of β blockers causes severe **rebound hypertension** which may be dangerous.

Chronic administration of β blockers for hypertension results in **up-regulation of β_1 receptor**.

↓

Sudden withdrawal of β blockers.

↓

Endogenous catecholamine now can act on more β_1 receptor than previous.

↓

Severe hypertension

β blocker withdraw phenomenon is more prominent in β_1 selective and least for drugs having partial agonist property.

How to withdraw β blockers: Reduce the dose over **10-14 days** and then withdraw it.

Q. What is the role of β blockers in angina/MI?

Q. Justify the use of atenolol as anti-anginal. (SU-15J)

Q. Explain the anti-anginal effects of propranolol. (DU-16J)

Ans.

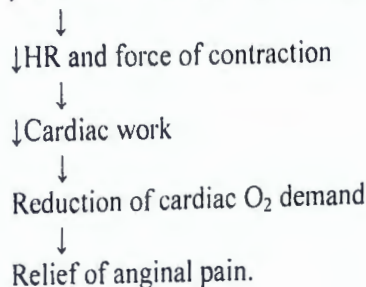
Role of β blockers (propranolol, atenolol) in angina / MI:

1. They reduce the severity and frequency of anginal attack.
2. They improve exercise tolerance in many patients with angina.

3. They are particularly effective in patient with MI. Long-term use of **timolol, propranolol, or metoprolol** in patients who have had a MI prolongs survival.
4. When combined with nitrate, they increase the exercise duration and tolerance.

Mechanism of anti-anginal action of β -blockers

β blockers block β_1 receptors on heart



(Ref: Katzung-13th/163)

Q. When the use of β -blockers in a patient with angina or MI is contraindicated?

Ans.
Relative contraindications of β -blockers: β -blockers are strongly indicated in acute myocardial infarction (MI). But they are relatively contraindicated in a pt. of MI with-

1. Bradycardia
2. Hypotension
3. Moderate or severe left ventricular failure
4. Shock
5. Heart block
6. Active airways disease.

(Ref: Katzung-13th/163-164)

Q. What is role of β blocker in heart failure?

Q. Explain the role of carvedilol on cardiac disease. (SU-12Ju)

Q. Discuss the role of β adrenoceptor antagonists in cardiovascular diseases. (CU-12Ju)

Ans.
Role of β blocker in heart failure:

1. At least three β blockers—**metoprolol, bisoprolol, and carvedilol**—are effective in **reducing mortality** in selected patients with **chronic heart failure**.
2. Although administration of these drugs may **worsen acute congestive heart failure**, cautious long-term use with gradual dose increments in patients who tolerate them may **prolong life**.
3. Although mechanisms are uncertain, there appear to be beneficial effects on **myocardial remodeling** and in decreasing the risk of **sudden death**.

(Ref: Katzung-13th/164)

Q. What are the roles of β -blockers / Propranolol in hyperthyroidism? (SU-12Ju)

Ans.
Role of β -blockers / Propranolol in hyperthyroidism:

1. β blockers control many of the CVS sign & symptoms caused by hyperthyroidism & thus are useful adjuvant to more definitive therapykj/
2. Inhibit peripheral conversion of T_4 into $T_3 \rightarrow \downarrow T_3$ in tissue level $\rightarrow$ less activity by T_3
3. β -blockers reduce sympathetic discharge from VMC & pre-synaptic nerve terminal (in hyperthyroidism there is increased sympathetic activity).

(Ref: Goodman & Gilman's-12th)

Caution of using: It should be used cautiously in patient with supra-ventricular tachycardia (SVT) that often precipitate heart failure.

(Ref: Katzung-13th/164)

Palpitations, AF, Atrial fibrillation, Angina, Dyspnoea

Q. Mention the mechanism of action of timolol in glaucoma. (RU-05M)

Ans.

Role of β blocker (Timolol) in glaucoma:

β blocker (Timolol)

↓
Reduces the formation of aqueous humor from the ciliary body

↓
↓ Intra ocular pressure (IOP)

↓
Improves the condition of glaucoma

(Ref: Katzung-13th/164)

Advantage of Timolol over other β -blockers:

1. It has no membrane stabilizing activity, ie, it has no local anesthetic effect.
2. It has no intrinsic sympathomimetic activity, ie, it is a true antagonist. So, it is more efficacious in reducing IOP

Q. What are the adverse effects of Timolol? (RU-03S)

Ans.

Adverse effects of Timolol: As Timolol is used topically (in glaucoma), so there is less chance of systemic adverse effects. If it absorbs sufficiently in the systemic circulation, then it causes systemic adverse effects, eg,

- CVS: Bradycardia, hypotension, palpitation, cold extremities
- CNS: Sedation, sleep disturbance, depression.
- Other: Bronchoconstriction

(Ref: Katzung-13th/165)

Q. Write down the contraindications of Propranolol. (DU-15J,13J,12J,09Ju)

Q. What are the contraindications of β_2 blockers / Propranolol / Atenolol? (DU-07Ju; SU-073u)

Ans.

Contraindications of β_2 blockers / Propranolol / Atenolol:

1. Hypertension is a common indication of β -blocker therapy. But patients of hypertension with following co-morbidity should not be given β -blocker-
 - a. bradycardia
 - b. heart block
 - c. bronchial asthma
 - d. acute heart failure
 - e. peripheral vascular diseases (eg, Raynaud's phenomenon)
 - f. diabetes in pt. who receives insulin
2. Hyperlipidemia
3. Pulmonary hypertension.
4. After prolong fasting.

(Ref: Katzung-13th/164-165)

MCQ

Q. Drugs with mixed α and β antagonist activity are- (DU-17M)

- a) prazosin
 - b) labetalol
 - c) atenolol
 - d) carvedilol
 - e) propranolol
- a.-F, b.-T, c.-F, d.-T, e.-F*

Q. Propranolol lowers blood pressure by- (DU-17M)

- a) blocking β -receptor
 - b) diuresis
 - c) blocking α receptor
 - d) reducing renin secretion
 - e) decreasing cardiac output
- a.-T, b.-F, c.-F, d.-T, e.-T*

Q. Atropine causes- (DU-17J)

- a) miosis
 - b) mydriasis
 - c) tachycardia
 - d) bronchoconstriction
 - e) increased lacrimation
- a.-F, b.-T, c.-T, d.-F, e.-F*

Q. Catecholamines comprise of- (DU-17J)

- a. ephedrine
 - b. adrenaline
 - c. nor-adrenaline
 - d. histamine
 - e. dobutamine
- a.-F, b.-T, c.-T, d.-F, e.-F*

Q. Features of OPC poisoning are- (DU-17J)

- a. increased lacrimation
 - b. bradycardia
 - c. miosis
 - d. decreased sweating
 - e. decreased salivation
- a.-T, b.-T, c.-T, d.-F, e.-F*

Q. Propranolol- (DU-16J)

- a) is a non selective β blocker
 - b) is lipid soluble
 - c) causes direct peripheral vasodilatation
 - d) is used in migraine prophylaxis
 - e) causes bronchodilatation
- a. T, b. T, c. F, d. T, e. F*

Q. Following drugs are selective β -blockers- (DU-15Ju)

- a. propranolol
 - b. metoprolol
 - c. phentolamine
 - d. prazosin
 - e. atenolol
- a. F, b. T, c. F, d. F, e. T*

Q. Stimulation of cholinergic system causes- (DU-14Ju)

- a. intraocular pressure to rise
 - b. sweating
 - c. tachycardia
 - d. reduced gut motility
 - e. urinary incontinence
- a. F, b. T, c. F, d. F, e. T*

Q. β -blockers are contraindicated in- (DU-14Ju)

- a. bronchial asthma
 - b. heart failure
 - c. hypothyroidism
 - d. migraine
 - e. diabetes mellitus
- a. T, b. T, c. F, d. F, e. T*

Q. Remedies for nasal stuffiness often contain following drugs: (CU-14Ju)

- a) Albuterol.
 - b) Atropine
 - c) Epinephrine
 - d) Norepinephrine.
 - e) Phenylephrine.
- a. F, b. F, c. T, d. F, e. T*

Q. The systemic side effects of Pilocarpine include: (CU-14Ju)

- a) Constipation
 - b) Excessive sweating
 - c) Urinary urgency
 - d) Bronchial spasm
 - e) Dry mouth.
- a. F, b. T, c. T, d. T, e. F*

Q. The followings are β blockers- (DU-14J)

- a. propranolol
- b. atenolol
- c. tamsulosin
- d. nadolol

- e. prazosin
a. T, b. T, c. F, d. T, e. F

Q. Features of OPC poisoning are- (DU-14J)

- a. increased lacrimation
- b. bradycardia
- c. miosis
- d. constipation
- e. decreased salivation.
a. T, b. T, c. T, d. F, e. F

Q. Adverse effects of salbutamol include- (DU-14J)

- a. postural hypotension
- b. palpitations
- c. tremor
- d. edema
- e. hyperkalemia.
a. F, b. T, c. T, d. F, e. F

Q. Rocuronium- (DU-13Ju)

- a. is a synthetic steroid derivatives.
- b. produce full neuromuscular blockade within 3 minutes.
- c. causes hepatic necrosis.
- d. is a powerful histamine releaser.
- e. potent inducer of hepatic microsomal enzyme.
a. T, b. T, c. F, d. F, e. F

Q. Competitive neuromuscular blocking drugs are- (DU-13J)

- a. atracurium.
- b. mivacurium.
- c. suxamethonium.
- d. tubocurarine.
- e. baclofen.
a. T, b. T, c. F, d. T, e. F

Q. Features of OPC poisoning include- (DU-13J)

- a. increased bronchial secretion.
- b. tachycardia.
- c. miosis.
- d. constipation.
- e. urinary urgency.
a. T, b. F, c. T, d. F, e. T

Q. Atropine causes- (DU-13J)

- a. cycloplegia.
- b. bradycardia.
- c. decrease intraocular pressure.

- d. urinary retention.
- e. bronchodilatation.
a. T, b. F, c. F, d. T, e. T

Q. Stimulation of beta-2 receptor causes- (SU-13J)

- a. Bronchodilatation
- b. Vasoconstriction
- c. Glycogenolysis in liver
- d. Increase blood pressure
- e. Relaxation of gravid uterus
a. T, b. F, c. T, d. F, e. T

Q. Catecholamines are:- (SU-13J)

- a) Adrenaline
- b) Ephedrine
- c) Dopamine
- d) Isoprenaline
- e) Salbutamol
a. T, b. F, c. T, d. T, e. F

Q. Atenolol is indicated- (SU-13J)

- a) Migraine prophylaxis
- b) Arrhythmia
- c) Anxiety neurosis
- d) Hyperthyroidism
- e) Hypertension
a. F, b. T, c. F, d. F, e. T

Q. Pancuronium- (DU-12/11Ju)

- a. Is a synthetic agent. (T)
- b. Is steroidal in nature. (T)
- c. Is more potent than tubocurarine. (T)
- d. Causes bradycardia. (F)
- e. Releases histamine. (F)

Q. Following are β_1 selective antagonists- (DU-12Ju)

- a. Propranolol (F)
- b. Doxazocin (F)
- c. Celiprolol (?)
- d. Phentolamine (F)
- e. Bisoprolol (T)

Q. Poisoning by OPC causes- (DU-12J)

- a. Increasing bronchial secretion. (T)
- b. Constipation (F)
- c. Miosis (T)
- d. Tachycardia (F)
- e. Convulsion (T)

Q. Indications of adrenaline are- (DU-12J)

- a. Anaphylactic shock. (T)
- b. Ischemic heart disease. (F)
- c. Hypertension (F)
- d. Status asthmaticus (T)
- e. In combination with local anesthetics. (T)

Q. Following drugs are selective beta blockers- (DU-12J)

- a. Propranolol (F)
- b. Metoprolol (T)
- c. Phentolamine (F)
- d. Prazosin (F)
- e. Atenolol (T)

Q. Adverse effects of salmeterol include- (DU-12J)

- a. Tremor (T)
- b. Palpitations (T)
- c. Hyperkalemia (F)
- d. Interstitial nephritis. (F)
- e. Seizure (F)

Q. Catecholamine comprises- (DU-12J)

- a. Ephedrine (F)
- b. Noradrenaline (T)
- c. Adrenaline (T)
- d. Dobutamine (T)
- e. Salbutamol (F)

Q. Features of OPC poisoning are- (DU-11Ju)

- a. Increased bronchial secretion. (T)
- b. Tachycardia (F)
- c. Miosis (T)
- d. Constipation (F)
- e. Urinary urgency (T)

Q. Competitive NMJ blockers- (DU-11J)

- a. Atracurium (T)
- b. Mivacurium (T)
- c. Suxamethonium (F)
- d. Tubocurarine (T)
- e. Baclofen (F)

Q. Adrenaline is indicated in- (DU-11J)

- a. Anaphylactic shock (T)
- b. IHD (F)
- c. HTN (F)
- d. Status asthmaticus (T)
- e. In combination with local anesthetic (T)

Q. β_2 -blockers are present in- (DU-11J)

- a. Heart (F)
- b. JG cells of kidney (F)
- c. Dilator pupillae muscle (T)
- d. Bronchus (T)
- e. Liver (T)

Q. Acetylcholine- (DU-10Ju)

- a. is released from preganglionic sympathetic neurons (T)
- b. is synthesized in adrenal medulla (F)
- c. causes tachycardia (F)
- d. causes bronchospasm (T)
- e. is metabolized by MAO (F)

Q. Atropine causes- (DU-10J)

- a. cycloplegia (T)
- b. bradycardia (F)
- c. decrease of intraocular pressure (F)
- d. urinary retention (T)
- e. bronchodilatation (T)

Q. The followings are β_1 selective antagonists- (DU-10J)

- a. dobutamine (F)
- b. atenolol (T)
- c. propranolol (F)
- d. phenoxybenzamine (F)
- e. metoprolol (T)

Q. Dopamine- (DU-10Ju)

- a. Is a catecholamine (T)
- b. Causes vasodilatation in viscera (T)
- c. Enhances prolactin release (?)
- d. Produces EPS if concentration is decreased in basal ganglia. (T)
- e. Causes Psychosis if concentration is decreased in limbic system (F)

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Chapter 3

Ocular pharmacology

Formation of aqueous humour: The aqueous humour is formed by active process and by diffusion from the capillaries of the ciliary processes.

Circulation of aqueous humour: Ciliary process → Posterior chamber of eye → Through pupil → Anterior chamber of eye → Iridocorneal angle → Canal of Schlemm → Episcleral vein → Aqueous vein → Ophthalmic vein.

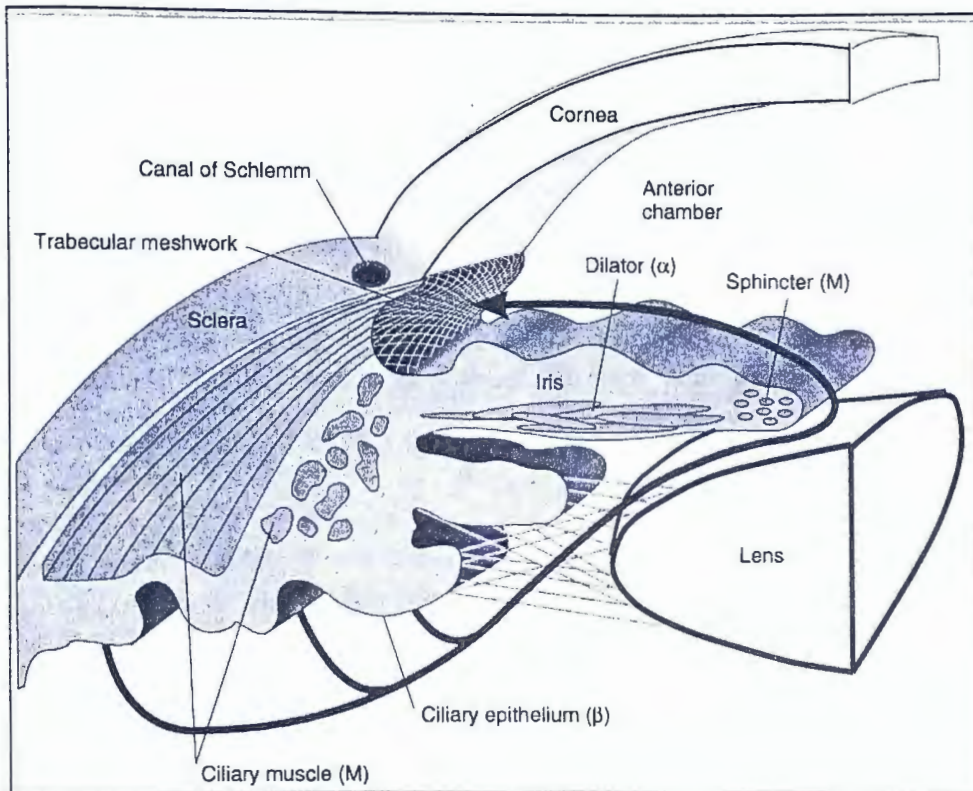


Fig. Formation & circulation of aqueous humour.

Intraocular pressure: Intraocular pressure (IOP) is the fluid pressure of the aqueous humor inside the eye.

Normal intra-ocular pressure: About 15-20 mm of Hg.

Q. Mention the clinical importance of Canal of Schlemm. (CU-15Ju)

Ans.

Clinical importance of Canal of Schlemm: Obstruction of canal of Schlemm leads to interference with the drainage of the aqueous humor. This increases IOP, resulting in glaucoma.

Glaucoma

Glaucoma: Glaucoma is a neurodegenerative disease of the optic nerve caused by a group of ocular conditions which lead to optic nerve damage and eventual visual field loss. It is frequently but not invariably associated with **raised intraocular pressure**.

(Ref- Kanski-6th/382 + Parsons-20th/270)

Diagnostic criteria of glaucoma: Any two of the followings are diagnosed as glaucoma-

1. **Raised intra-ocular pressure** (measured by tonometer).
2. **Structural damage:** Cupping of optic disc (measured by ophthalmoscope).
3. **Functional damage:** Changes in the visual field and visual acuity (measured by automated perimetry).

Causes of raised intraocular pressure (IOP):

1. Over-production of aqueous humour, or
2. Interference with the drainage of the aqueous humour into canal of Schelmm, or
3. Combination of both.

Types of glaucoma: Two major types of glaucoma are recognized:

1. **Closed-angle (or narrow-angle) glaucoma:** The closed-angle form is associated with a shallow anterior chamber, in which a dilated iris can occlude the outflow drainage pathway at the angle between the cornea and the ciliary body. This form is associated with acute and painful increases of pressure, which must be controlled on an emergency basis with drugs or prevented by surgical removal of part of the iris (iridectomy).
2. **Open-angle glaucoma:** The open-angle form of glaucoma is a chronic condition, and treatment is largely pharmacologic. Because intraocular pressure is a function of the balance between fluid input and drainage out of the globe, the strategies for the treatment of open-angle glaucoma fall into two classes:
 - Reduction of aqueous humor secretion and
 - Enhancement of aqueous out-flow.

Q. Categorize drugs used in the management of glaucoma. (CU-13Ju,12J,10Ju)

Q. Name the drugs used to treat glaucoma. (DU-16Ju,11Ju,10Ju, RU-12Ju,08J, SU-10J)

Q. Name the drugs for glaucoma with their mechanism of action. (DU-17M,11Ju,09J, CU-07Ju, RU-06/05M)

Q. Name five drugs used to treat glaucoma. (DU-15Ju)

Q. Mention the pharmacotherapy of acute painful glaucoma. (CU-15Ju)

Ans.

Drugs for glaucoma: Five general groups of drugs have been found to be useful in reducing intraocular pressure. Of the five drug groups, the prostaglandin analogs and the β -blockers are the most popular.

Groups	Name of drugs	Mechanism of action
Cholinomimetic	• Pilocarpine • Carbachol • Physostigmine • Echothiophate • Demecarium	Ciliary muscle contraction → Opening of trabecular meshwork → ↑ Outflow of aqueous humor.
α-agonists	Non-selective: • Epinephrine • Dipivefrin	↑ Outflow of aqueous humor.
	α_2-Selective: • Apraclonidine • Brimonidine	↓ Aqueous humor secretion
β blockers.	• Timolol • Betaxolol • Carteolol • Levobunolol • Metipranolol	Reduces formation of aqueous humour → ↓ IOP

Diuretics (Carbonic anhydrase inhibitors)	• Dorzolamide • Brinzolamide • Acetazolamide • Methazolamide • Dichlorphenamide	↓ Aqueous humor secretion due to lack of HCO_3^- .
Prostaglandins	• Latanoprost • Bimatoprost • Travoprost • Unoprostone	↑ Outflow of aqueous humor

(Ref: Katzung-13th/162; Table: 10-3)

Q. Name the drugs used in glaucoma. (DU-14Ju)

Q. Categorize anti-glaucoma drugs according to their mechanism of action. (CU-09Ju,07J)

Q. Enlist the drugs that can influence aqueous humor drainage. (CU-15Ju)

Ans.

Anti-glaucoma drugs according to their mechanism of action:

1. Anti-glaucoma drugs that act by increasing aqueous humor outflow	▪ Cholinomimetic drugs ▪ Non-selective α-agonists ▪ Prostaglandins
2. Anti-glaucoma drugs that act by decreasing aqueous secretion	▪ β-Blockers ▪ Diuretics (Carbonic anhydrase inhibitors) ▪ Selective α_2-agonists

(Ref: Katzung-13th/162; Table: 10-3)

Q. Compare the role of anti-glaucoma drugs in reducing intra-ocular pressure. (RU-12Ju)

Q. List the drugs that can be used to treat glaucoma. Compare the listed drugs in brief. (SU-10J)

Q. Write the role of pilocarpine in glaucoma. (CU-13Ju, RU-16Ju)

Ans.

Comparison of anti-glaucoma drugs:

Traits	Pilocarpine	Timolol	Acetazolamide	Latanoprost
1. Group	Directly acting cholinergic drug	Non-selective β -receptor blocker	Low-efficacy diuretics	Prostaglandin analogue
2. Mechanism of action	Contracts ciliary muscle → opening of trabecular meshwork → ↑outflow of aqueous humour → ↓IOP.	Reduces formation of aqueous humour → ↓IOP	Inhibit carbonic anhydrase enzyme → ↓secretion of aqueous humour → ↓IOP	↑Outflow of aqueous humour via uveo-scleral pathway.
3. Use in acute angle closure glaucoma	Used very effectively	Can be used	Can be used	Less effective in acute case. Used in POAG
4. Adverse effects	1. Bronchospasm 2. Bradycardia 3. Diarrhoea 4. Urinary urgency 5. Sweating & salivation 6. Tremor	1. Bradycardia 2. Hypotension 3. Palpitation 4. Cold extremities 5. Sedation 6. Sleep disturbance 7. Depression 8. Bronchospasm	1. Metabolic acidosis 2. Hypokalemia 3. Paraesthesia 4. CNS depression	1. Nausea 2. Vomiting 3. Diarrhea 4. Flushing 5. Bradycardia 6. Hypotension 7. Bronchospasm 8. Irregular menstruation

Q. Give the mechanism of action of Brinzolamide. (DU-15Ju)

Ans. **Brinzolamide** → Inhibit carbonic anhydrase enzyme → ↓secretion of aqueous humour → ↓IOP

Q. Compare Physostigmine and Acetazolamide. (CU-11J)

Ans.

Comparison between Physostigmine and Acetazolamide

Traits	Physostigmine	Acetazolamide
1. Group	• Anticholinesterases	• Carbonic anhydrase inhibitor
2. Mechanism of action	• Act by inhibiting acetylcholinesterase, thereby increasing local concentration of Ach.	• Acts by inhibiting carbonic anhydrase.
3. Indication	• Glaucoma • Overdoses of anticholinergic drugs, such as atropine overdose. • Atony of bladder and bowel.	• Glaucoma • Urinary alkalinization • Metabolic alkalosis • Acute mountain sickness
4. Adverse effects	• Bradycardia, hypotension. • Bronchoconstriction • Diarrhea, vomiting, hyperacidity. • Urinary urgency. • Severe salivation & sweating.	• Metabolic acidosis • Hypokalemia • Renal stone
5. Effect on CNS	• Excitation	• Depression

Mydriatics

Q. Name some important drugs used as mydriatics. (DU-09Ju, CU-04M; RU-06J)

Q. Name some atropine substitute used as mydriatics. (CU-06M)

Q. Name the antimuscarinic mydriatic drugs. (DU-17M)

Ans.

Mydriasis: Dilatation of pupil is called mydriasis.

Mydriatics: Drugs that cause mydriasis are called mydriatics.

Classification of mydriatics:

1. Parasympathoplegic /M₃-receptor blocker/Antimuscarinic mydriatics:

Drugs	Duration of action
1. Atropine	5 - 6 days
2. Scopolamine	3 - 7 days
3. Homatropine	12 - 24 hours
4. Cyclopentolate	3 - 6 hours
5. Tropicamide	15 - 60 min

2. Sympathomimetic mydriatics:

- Adrenaline (1 in 10,000)
- Phenylephrine (2.5 - 10%)
- Cocaine hydrochloride.

3. General anesthetics:

- Halothane
- Ether

4. Local anesthetics:

- Cocaine

(Ref: Katzung-13th/127, Table: 8-2; Basak ophthalmology-4th/103)

Q. What is the contraindication atropine in ocular use?

Ans.

Contraindication of atropine in ocular use: All types of glaucoma, as it causes raised IOP (except glaucoma secondary to uveitis).

Q. Mention the role of timolol in glaucoma. (SU-13J)

Q. Explain the mechanism of action of timolol in glaucoma. (DU-07Ju, CU-03S, RU-05M, SU-03S/J)

Q. What are the adverse effects of timolol? (CU-03S)

Ans.

Mechanism of action of timolol in glaucoma: Timolol decreases aqueous humour secretion from the ciliary epithelium.

Adverse effect of timolol:

1. Bradycardia
2. Bronchoconstriction
3. Cardiac failure
4. Heart block

Miotics

Miosis: Constriction of the pupil is called miosis.

Miotics: Drugs that cause miosis are called mydriatics.

(Ref: Basak ophthalmology-4th/102)

Classification of miotics:

A. **Systemic miotics:** Morphine (It is a strong miotic but is not used as a miotic due its systemic adverse effects).

B. **Topical (local) miotics:**

1. **Cholinomimetic miotics:**

Group	Drugs
Direct acting cholinomimetic	Pilocarpine (1-4%) Methacholine
Indirect acting cholinomimetic	Eserine (0.25-1%) Neostigmine
Combination	Carbachol & urecholine

2. **Sympatholytic miotics:** Rarely used topically (Thymoxamine- 0.5%)

3. **Histamine:** Miosis can be induced by direct stimulation by histamine

(Ref: Basak ophthalmology-4th/ 102)

Q. What are the differential diagnoses in a case of pin-point pupil?

Ans.

Differential diagnoses of pin-point pupil

1. Morphine poisoning: Bilateral pin-point pupil.
2. Physostigmine overdose

3. Head injury: Contralateral miosis
4. Pontine hemorrhage

Q. Name some drugs causing cataract.

Ans.

Drugs causing cataract

1. Corticosteroids
2. Miotics
3. Anticancer drugs
4. Chlorpromazine
5. Busulphan

MCQ

Q. Drugs used in glaucoma include- (DU-17J)

- a. atropine
 - b. physostigmine
 - c. pralidoxime
 - d. pilocarpine
 - e. acetazolamide
- a.-F, b.-T, c.-F, d.-T, e.-T*

Q. Drugs used in glaucoma include- (DU-14Ju,14J)

- a. eucatropine
 - b. pilocarpine
 - c. tropicamide
 - d. physostigmine
 - e. acetazolamide.
- a. F, b. T, c. F, d. T, e. T*

Q. Drugs used in glaucoma include- (DU-13J)

- a. pilocarpine.
 - b. tropicamide.
 - c. physostigmine.
 - d. acetazolamide.
 - e. frusemide.
- a. T, b. F, c. T, d. T, e. F*

Chapter 4

Drugs acting in CNS

Q. Name the central neurotransmitters. (RU-09J,07Ju/J)

Ans.

Neurotransmitters (NT) of CNS:

Truly excitatory NT	Truly inhibitory NT	Mixed NT
▪ Glutamate ▪ Aspartate	▪ GABA ▪ Glycine	Amine NT: ▪ 5HT ▪ Dopamine ▪ Nor-adrenaline ▪ Adrenaline

Sedative & hypnotic drugs

Anxiety: Anxiety is an unpleasant state of tension, apprehension or uneasiness- a fear that seems to arise from an unknown source. Disorders involving anxiety are the most common mental disturbances. The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, the symptoms of severe, chronic, debilitating anxiety may be treated with antianxiety drugs (sometimes called **anxiolytic** or **minor tranquilizers**) and/or some form of behavioral or psychotherapy. Because many of the antianxiety drugs also cause some sedation, the same drugs often function clinically as both anxiolytic and **hypnotic** (sleep-inducing) agents.

(Ref: Lippincott's-6th/121)

There are two kinds of sleep: **rapid eye movement (REM) sleep** and **nonREM (NREM)**, or **slow-wave sleep**. REM sleep is so named because of the characteristic eye movements that occur during this stage of sleep.

(Ref: Ganonog-25th/273)

Q. Describe the stages of NREM sleep. (CU-17J)

Ans.

Stages of NREM sleep / slow-wave sleep: NREM sleep is divided into four stages.

1. As a person begins to fall asleep and enters **stage 1**, the EEG shows a low-voltage, mixed frequency pattern. A **theta rhythm** (4–7 Hz) can be seen at this early stage of slow-wave sleep. Throughout NREM sleep, there is some activity of skeletal muscle but no eye movements occur.
2. **Stage 2** of NREM sleep is marked by the appearance of sinusoidal waves called **sleep spindles** (12–14 Hz) and occasional high voltage biphasic waves called **K complexes**.
3. In **stage 3** of NREM sleep, a high-amplitude **delta rhythm** (0.5–4 Hz) dominates the EEG waves.
4. Maximum slowing with large waves is seen in **stage 4** of NREM sleep. Thus, the characteristic of deep sleep is a pattern of rhythmic slow waves, indicating marked **synchronization**; it is sometimes referred to as slow-wave sleep.

While the occurrence of theta and delta rhythms is normal during sleep, their appearance during wakefulness is a sign of brain dysfunction.

(Ref: Ganonog-25th/273)

Q. Define sedation.

Q. Define sedative or anxiolytic. (DU-16J,11Ju,07J; RU-10J, SU-16Ju)

Ans.

Sedation: This is a state of CNS depression characterized by drowsiness, calmness, quietness and reduction of anxiety without producing actual sleep.

Sedative / anxiolytic drugs: The drugs which reduce anxiety & exert a calming effect are called sedative or anxiolytic drugs.

(Ref: Katzung-13th/369)

Q. Define hypnosis. (SU-05M)

Q. Define hypnotics. (DU-16J, 11Ju, 07J, RU-10/09J, SU-16Ju)

Ans.

Hypnosis: The state of CNS depression resembling natural sleep from which the recipient can be aroused by ordinary stimulus is called hypnosis.

Hypnotic drugs: The drugs which produce drowsiness & encourage the onset & maintenance of sleep are called hypnotic drugs.

(Ref: Katzung-13th/369)

Q. What are the common sleep disorders? (SU-16Ju)

Ans.

Sleep disorders:

1. **Insomnia:** not enough sleep or sleep of poor quality; problems of falling asleep (initial insomnia) or staying asleep (maintenance insomnia), or waking too early.
2. **Hypersomnia:** excessive daytime sleepiness.
3. **Parasomnia:** unusual happenings in the night
 - a. nightmares
 - b. night terrors
 - c. sleepwalking
 - d. REM behaviour disorder.
4. **Other**
 - a. sleep scheduling disorders (circadian rhythm disorder)
 - b. restless legs syndrome
 - c. periodic leg movements of sleep.

(Ref: Bennet & Brown-11th edition)

Nice to know

Insomnia: Insomnia may be defined as the subjective problem of insufficient, non-restorative sleep despite an adequate opportunity for sleep.

Stages of CNS depression:

Anxiolysis / Tranquilization

↓
Sedation

↓
Hypnosis

↓
Narcosis

↓
Anesthesia

↓
Coma

↓
Death

Q. Classify hypnotics. (RU-09J)

Q. Classify sedatives and hypnotics. (DU-16J, SU-17J)

Q. Enlist anxiolytic drugs. (RU-13Ju)

Q. Enumerate sedative & hypnotic drugs. (DU-15J, CU-11J, 08J, RU-07M, SU-16Ju)

Q. Enumerate the new generation sedative hypnotic drugs. (RU-08J)

Q. Classify benzodiazepine. (CU-06M, RU-11J, SU-11Ju)

Q. List the benzodiazepines according to duration of action. (DU-13J, 12J, CU-15J)

Q. How benzodiazepines are subgrouped? (SU-17M)

Q. Name clinically important anxiolytic drugs. (DU-10J)

Q. What are the drugs used in anxiety disorders. (DU-09Ju)

Q. Name four non-benzodiazepine drugs used as anxiolytics. (DU-13Ju)

Ans.

Sedatives & hypnotics/ Drugs for insomnia (hypnotics) & anxiety (sedatives):**A. Benzodiazepine (BDZ):** (May act as both sedative & hypnotic)Benzodiazepines may be divided into four categories based on their elimination $t_{1/2}$:

Ultra-short-acting	Short acting ($t_{1/2}$ < 6 hours)	Intermediate acting ($t_{1/2}$ 6-24 hours)	Long acting ($t_{1/2}$ > 24 hours)
Clorazepate	- Midazolam - Triazolam - Oxazepam	- Alprazolam - Estazolam - Lorazepam - Temazepam	- Diazepam - Flurazepam - Quazepam - Nitrazepam - Parazepam - Chlordiazepoxide

(Ref: Goodman & Gillman-12th edition)**B. Barbiturates:** (May act as both sedative & hypnotics)

Ultra-short acting ($t_{1/2}$ < 15 min)	- Thiopental sodium - Methohexital
Short acting ($t_{1/2}$ 1-3 hours)	Pentobarbital (tens) Hexo Secobarbital
Intermediate acting ($t_{1/2}$ 4-6 hours)	Amobarbital (tens) Aprobarbital - Butobarbital - Butalbital
Long acting ($t_{1/2}$ > 6 hours)	- Phenobarbital / Phenobarbitone - Mephobarbital

C. Non-barbiturate Sedatives:

- Antipsychotics
- Antidepressants
- Antihistamines including hydroxyzine and promethazine.
- Melatonin receptor agonist
 - Ramelteon
 - Tasimelteon
- 5-HT receptor agonist
 - Buspirone
- Chloral hydrate
- Ethanol
- Meprobamate

(Ref: Lippincott's-6th/126-131 + Katzung-13th/369-373; Goodman & Gillman-12th edition)**D. Newer Hypnotics / Novel benzodiazepine receptor agonists:** Hypnotics in this class are commonly referred to as "Z compounds". They include-

- Zopiclone
- Eszopiclone
- Zolpidem
- Zaleplon

(Ref: Goodman & Gillman-12th edition; Katzung-13th/373)**E. Orexin receptor antagonists:** Orexin receptor antagonists are new class of hypnotic drugs. They include-

- Almorexant
- Suvorexant

(Ref: Katzung-13th/378)

Nice to know

Phenobarbital / Phenobarbitone are the same drug. Phenobarbital is the aldehyde form & phenobarbitone is the ketone form. You can use any one name in the answer script.

Z compounds

1. Z compounds are structurally unrelated to each other and to benzodiazepines.
2. Their therapeutic efficacy as hypnotics is due to agonist effects on the benzodiazepine site of the GABA_A receptor.
3. Compared to benzodiazepines, Z compounds are less effective as anticonvulsants or muscle relaxants.
4. Over the last decade, Z compounds have **largely replaced** benzodiazepines in the treatment of insomnia.
5. They have less potential for dependence and abuse than traditional benzodiazepines.

(Ref: Goodman & Gillman-12th edition)

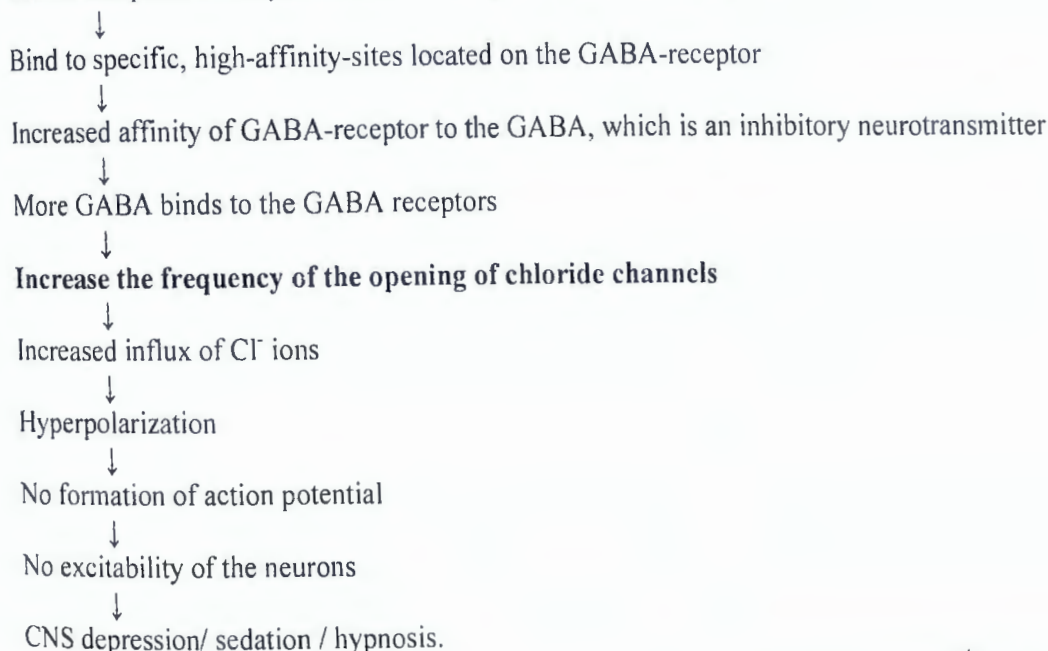
Benzodiazepine

- Q. Explain the mechanism of action of Benzodiazepines. (DU-13Ju, CU-06M, SU-01J)
- Q. Discuss the molecular action / mechanism of action of diazepam. (DU-15J,14Ju,13J,12/10J, SU-16J,15J,08Ju, RU-09J)
- Q. How does diazepam produce anxiolytic action? (DU-11Ju)
- Q. Explain sedative action of clonazepam. (SU-10J,07Ju)
- Q. Outline the sedative action of diazepam. (SU-17J)
- Q. Discuss the sedative effect of clobazam. (SU-14J,04S)
- Q. Discuss the sedative/hypnotic effect of nitrazepam. (SU-12Ju)
- Q. Discuss the hypnotic effects of BDZs & barbiturates. (RU-07J/Ju,04M;CU-06M/S,SU-04M/S)
- Q. Explain the neurotransmitter involved action of diazepam/clonazepam. (SU-17M,11Ju)

Ans.

Mechanism of action of benzodiazepines/diazepam/ clonazepam/ nitrazepam/ clobazam: GABA is a major inhibitory neurotransmitter in the CNS. Benzodiazepines potentiate GABAergic inhibition at all levels of the neuraxis, including the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex, and cerebral cortex. Benzodiazepines **increase efficiency of GABAergic synaptic inhibition** without directly activating GABA_A receptors or opening the associated chloride channels.

Benzodiazepines /diazepam/ clonazepam/ nitrazepam/ clobazam



(Ref: Katzung-13th/374; Lippincott's-6th/121)

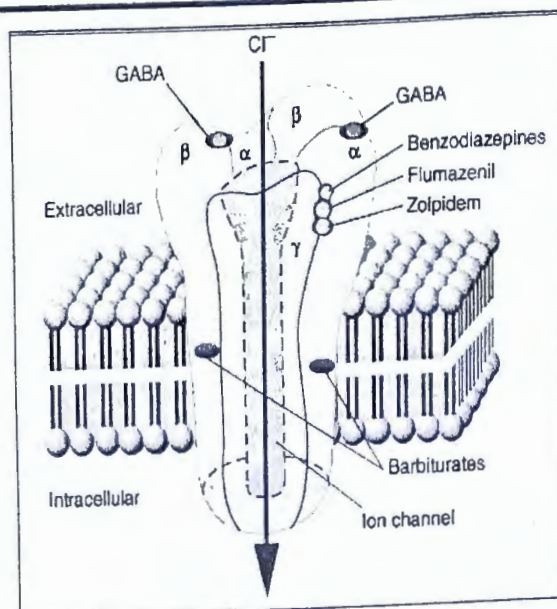


Fig. Mechanism of action of benzodiazepine and barbiturates on GABA receptor

Q. Name the drugs which enhance the GABAergic activity in CNS. (SU-10/08J)

Ans.

Drugs that enhance GABAergic action / facilitate GABA-mediated Cl^- channel opening:

1. Benzodiazepines (diazepam, lorazepam, clonazepam, nitrazepam, clobazam etc.)
2. Barbiturates (phenobarbitone)
3. Vigabatrin
4. Tiagabine
5. Gabapentin
6. Valproate

(Ref: Tripathi-6th/404 (fig-30.2))

Q. Write down the pharmacological actions of benzodiazepines/ diazepam. (DU-10/08J; CU-08J,05S/J; RU-13Ju, SU-16J)

Q. How does diazepam produce skeletal muscle relaxation? (RU-16Ju,06J,04M)

Q. Enumerate the effects caused by diazepam. (DU-07J, CU-07Ju, SU-06M, RU-09J,05M)

Q. Mention the dose-dependent pharmacological effects of diazepam. (RU-16Ju)

Ans.

Pharmacological actions of benzodiazepines / diazepam:

Organ level effects	Descriptions
1. Sedation	- Reduction of anxiety - Euphoria - Impaired judgment - Loss of self control Anterograde amnesia (inability to remember events occurring during the drug's duration of action).
2. Hypnosis	By definition, all of the sedative-hypnotics induce sleep if high enough doses are given. - Latency of sleep onset is decreased (<i>time to fall asleep</i>); - Duration of stage 2 NREM sleep is increased; - Duration of REM sleep is decreased; and - Duration of stage 4 NREM slow-wave sleep is decreased.
3. Anesthesia	- High doses of certain sedative-hypnotics depress the CNS to the point known as stage III of general anesthesia. - Diazepam, lorazepam, and midazolam—are used IV in anesthesia often in combination with other agents.

4. Anticonvulsant effect	Clonazepam, nitrazepam, lorazepam, and diazepam—are used to treat epilepsy (status epilepticus) and other seizure disorders.
5. Muscle relaxation.	- Inhibits polysynaptic reflexes and internuncial transmission. - At high doses, depress transmission at the skeletal neuromuscular junction.
6. Cardio-respiratory depression.	- At hypnotic doses in healthy patients, no significant cardio-respiratory changes. Respiratory depression in patients with pulmonary diseases (asthma, COPD) even at therapeutic doses. Respiratory depression is the usual cause of death due to overdose of sedative-hypnotics. - In hypovolemic states, heart failure, normal doses of sedative-hypnotics may cause cardiovascular depression. - At toxic doses, circulatory collapse. Cardio-respiratory depression is more marked when sedative-hypnotics are given IV.

(Ref: Katzung-13th/376-377; Lippincott's-6th/122)

Q. Mention the advantages of BDZs over barbiturates. (DU-06M)

Q. Mention the advantages of BDZs as hypnotics. (RU-15J)

Q. Justify nitrazepam as a better hypnotics / sedatives than phenobarbitone. (DU-06M)

Q. Compare the CNS depressive effects of BDZs with that of barbiturates.

Q. Why BDZs are preferred to barbiturates? (RU-05J)

Q. How BDZs differ from barbiturates in respect of their TI (therapeutic index)?

Ans.

Advantages of benzodiazepines (BDZs) over barbiturates:

1. Benzodiazepines (BDZs) have **higher TI** (therapeutic index). So, BDZs need more dose than barbiturates to produce cardio-respiratory depression. That's why, BDZs are **safer**.

On the other hand, barbiturates have **lower TI**. At doses higher than TI, these drugs may depress respiratory and vasomotor centers in the medulla, leading to coma and death.

2. BDZS has competitive antagonist i.e. antidote (flumazenil). So, in case of accidental or suicidal overdose, effects of BDZs can be opposed by flumazenil. But, barbiturates have no antagonists or antidote.
3. BDZs don't induce drug metabolizing enzyme. So, no drug interaction occurs. But, barbiturates induce drug metabolizing enzyme & cause drug interaction.
4. BDZS has minimal effects on CVS & autonomic functions.

(Ref: Katzung-13th/370)

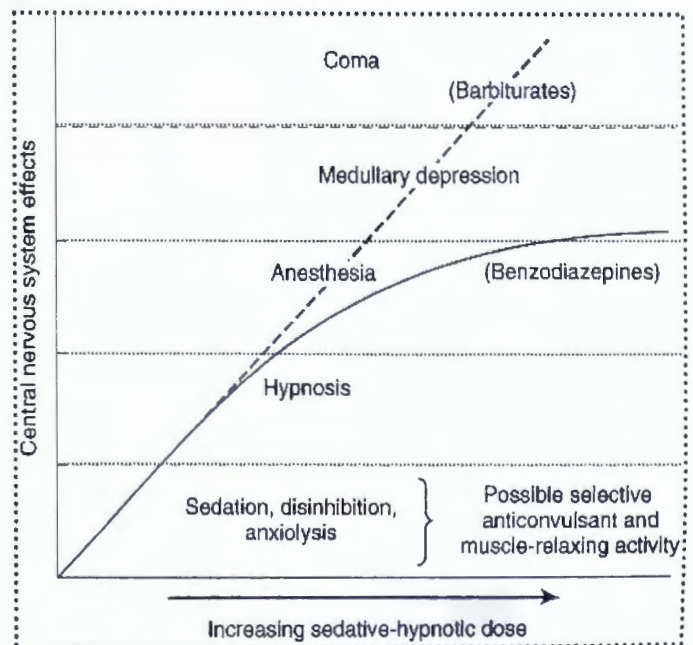


Figure: Relationships between dose of benzodiazepines and barbiturates and their CNS effects.

Q. Describe the metabolism of benzodiazepines. (CU-15Ju)

Ans.

Metabolism of benzodiazepines

Site of metabolism: Liver.

Phase I reactions: Most benzodiazepines undergo microsomal **oxidation**, including N- dealkylation and aliphatic hydroxylation catalyzed by cytochrome P450 isozymes, especially CYP3A4.

Phase II reactions: The metabolites are subsequently **conjugated** to form **glucuronides** that are excreted in the urine.

Many phase I metabolites of benzodiazepines are pharmacologically active, some with long half-lives. For example, desmethyldiazepam has an elimination half-life of more than 40 hours.

Alprazolam and triazolam undergo α -hydroxylation, and the resulting metabolites have short half-life due to rapid conjugation to inactive glucuronides.

(Ref: Katzung-13th/372)

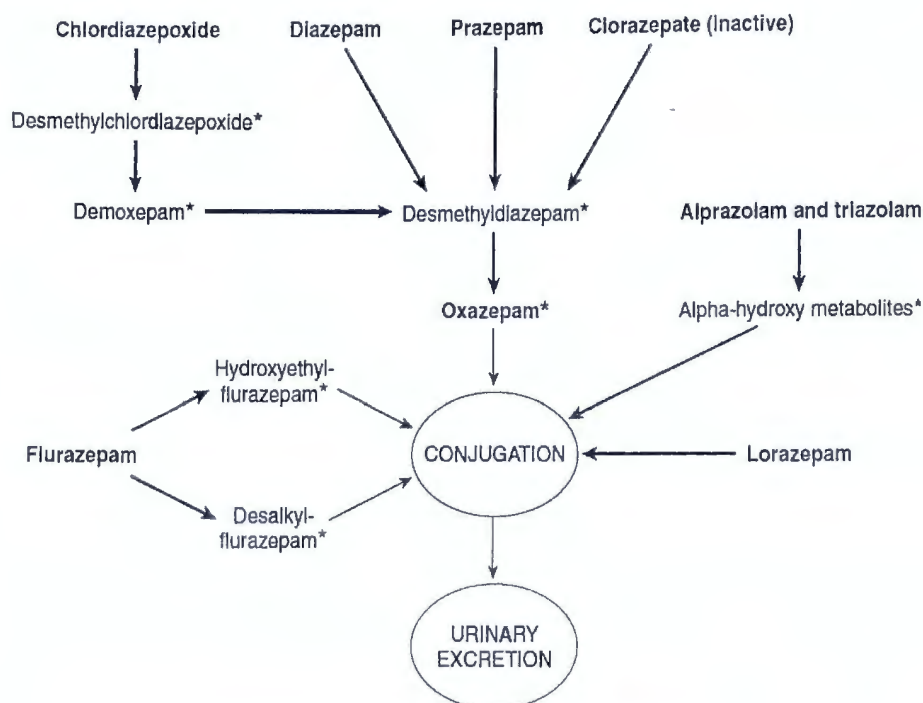


Fig. Biotransformation of benzodiazepines.

Nice to know

Pharmacokinetic profile of sedatives & hypnotics:

Absorption & distribution:

1. **Route:** Oral or I/V
2. **Lipid solubility:** Sufficient
3. **Absorption from GIT:** Well
4. **Plasma Protein Binding:** No significant PPB.
5. Sedative & hypnotic drugs are also detectable in the breast milk & may exert their effects in the nursing baby.

Biotransformation:

Benzodiazepine compounds:

1. **Phase-I:** Oxidation
2. **Phase-II:** Glucuronidation
3. Don't induce enzymes.

Barbiturates:

1. **Phase-I:** Oxidation
2. **Phase-II:** Glucuronidation
3. Induce hepatic drug metabolizing enzymes & increase the metabolism of other concomitant drugs.

Excretion: Renal excretion. In most cases changes in renal function don't have any marked effect on the elimination of parent drugs.

Q. What are the criteria of an ideal hypnotic drug? (CU-17J,13J,07J,06S)

Q. What should be the selection criteria of an ideal hypnotic? (SU-12Ju)

Ans.

Criteria of an ideal hypnotic drug:

1. Should reduce / relieve the anxiety properly (i.e. efficacy is good).
2. Should not alter the normal REM sleep pattern.
3. Should not hamper normal daily activity or reduce strength or motor skills.
4. Should not hamper learning or memory.
5. Should not produce dependence.
6. Should not produce "hang-over effects".
7. Should not produce tolerance.
8. Should not produce "cardio-respiratory depression" even in a gross overdose or poisoning.
9. Should be devoid of "extra-pyramidal symptoms".

Q. What are the indications of benzodiazepine? (DU-13Ju,07J/Ju, CU-12J,08Ju, RU-07Ju, SU-07Ju)

Q. Mention the indications/clinical uses of diazepam. (DU-15J,14Ju,13J,12J,09Ju; RU-15J,12Ju/J,11J,08J)

Q. Mention 4 clinical indications of diazepam. (DU-16J)

Q. What are the indications of sedatives & hypnotics? (RU-10J)

Q. List the clinical uses of clonazepam. (SU-06M/J)

Q. Name the clinical uses of zopiclone. (RU-05M)

Ans.

Indications of benzodiazepine / clonazepam / diazepam:

1. **Anxiety disorders:** Benzodiazepines are effective for the treatment of the anxiety symptoms secondary to panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, performance anxiety, posttraumatic stress disorder, obsessive-compulsive disorder, and extreme anxiety associated with phobias, such as fear of flying. The benzodiazepines are also useful in treating anxiety related to depression and schizophrenia.
2. **Sleep disorders:** Insomnia.
3. **Amnesia:** The shorter-acting agents are often employed as premedication for anxiety-provoking and unpleasant procedures, such as endoscopic, bronchoscopic, and certain dental procedures as well as angioplasty. **Midazolam** is an injectable-only benzodiazepine also used for the induction of anesthesia.
4. **Seizure:**
 - a. **Clonazepam** is useful in the chronic treatment of epilepsy.
 - b. **Diazepam** is the drug of choice in terminating grand mal epileptic seizures and status epilepticus.
5. **As muscle relaxants:** **Diazepam** is useful in the treatment of skeletal muscle spasms, such as occur in muscle strain, and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.
6. **Management of alcohol withdrawal:** Long-acting drugs such as **chlordiazepoxide** and **diazepam**.
7. **As Preanesthetic medication.**
8. **Delirium tremens:** Parenteral **lorazepam**.
9. **Psychiatric uses:** Treatment of mania, drug-induced hyperexcitability states (eg, phencyclidine intoxication), and major depressive disorders with **alprazolam**.

10. Diagnostic aids in neurology and psychiatry.

(Ref: Katzung-13th/378-379; Lippincott's-6th/123-124)Nice to know

The individual benzodiazepines show small differences in their relative anxiolytic, anticonvulsant, and sedative properties. However, the duration of action varies widely among this group, and pharmacokinetic considerations are often important in choosing one benzodiazepine over another.

Q. What are the adverse effects of diazepam? (DU-09Ju, CU-06J, RU-07J, SU-16J)

Q. Mention the adverse effects of benzodiazepines. (DU-08J)

Ans.

Adverse effects of benzodiazepines/ diazepam:In case of low dose:

1. Hangover effect
2. Somnolence
3. Drowsiness
4. Impaired judgment
5. Diminished motor skill, such as—
 - a. Driving ability.
 - b. Job performance.
 - c. Personal relationship.
6. **Anterograde amnesia:**
 - a. It can hamper learning.
 - b. Can be used in date-rape by criminals. -- midazolam

In larger dose:

1. Lethargy
2. **Cardiac failure:** especially in pt with MI.
3. **Respiratory centre depression:** especially in patients with chronic pulmonary disease and in those with symptomatic sleep apnea and asthma.
4. May cause total memory loss, in long term use.
5. Rhabdomyolysis.
6. Can lead to serious aggressive behavior.

Other adverse effects:

1. Addiction.
2. Abnormal sleepiness of the breastfeed baby.
3. Development of tolerance and dependency due to prolonged use.
4. Hypersensitivity reactions
5. Teratogenicity

(Ref: Katzung-13th/380 & Goodman & Gilman's-12th)

Q. What are the contraindications of diazepam? (RU-06J,05J)

Ans.

Contraindications of diazepam:

1. **Pulmonary insufficiency:** Severe bronchial asthma, Chronic obstructive pulmonary disease (COPD)
2. Obstructive sleep apnea
3. Hepatic impairment

Q. What are the effects of benzodiazepines in pregnancy? (CU-15Ju)

Ans.

Effects of benzodiazepines in pregnancy: All sedative-hypnotics cross the placental barrier during pregnancy. If sedative-hypnotics are given during the predelivery period, they may contribute to the depression of neonatal vital

functions. Sedative-hypnotics are also detectable in breast milk and may exert depressant effects in the nursing infant.

(Ref: Katzung-13th/371)

Q. Why diazepam should not continue for prolong period? (CU-07/05J)

Q. Enumerate the consequences of long time use of diazepam. (CU-12J,08J)

Ans.

Hazards / consequences of prolong use of diazepam: Prolong & continuous use of diazepam (more than 10 days) causes **pharmacodynamic tolerance** by down-regulation of GABA receptors. The response of the drug reduces & dose of the drug should be increased gradually to get desired therapeutic effect. As a result the frequency & intensity of **adverse effects** & the chance of **dependence** are increased subsequently. So, diazepam should not use more than 7 days & there should be a 3 days interval between two consecutive schedules.

Q. Name some newer non-benzodiazepines with advantages over benzodiazepines. (RU-10J)

Ans.

Newer non-benzodiazepines:

- **Hypnotics:** Zopiclone, eszopiclone, zolpidem, zaleplon.
- **Sedatives:** Buspirone, meprobamate.

Advantages of non-benzodiazepines over benzodiazepines:

1. No hangover effect, somnolence, lethargy, drowsiness.
2. No diminished motor skills.
3. No chance of amnesia.
4. No chance of cardio-respiratory depression.
5. No / less chance of developing addiction.
6. No down-regulation & development of tolerance.

Q. How can you treat in a case of diazepam toxicities? (DU-04J)

Ans.

Management of benzodiazepine / diazepam toxicities: In general, death from benzodiazepine overdose is rare unless the drugs are combined with other CNS-depressant agents such as ethanol, opioids, or barbiturates.

Diagnosis

History: This is often difficult to elicit as patients are frequently comatose.

Clinical presentation: Onset of CNS depression may be observed within 30–120 minutes of ingestion, depending on the compound.

- **Typical presentation** is coma with **normal vital signs**.
- Hyporeflexia
- Midposition or small pupils
- Hypothermia
- **Respiratory depression** is exceedingly **unusual** in oral overdose of benzodiazepines.

Laboratory investigations

- A. **Drug levels** in blood and urine (confirmatory test).
- B. **Other tests:** Glucose, arterial blood gases, and pulse oximetry.

Treatment

1. **Emergency and supportive measures**
 - a. Protect the airway and assist ventilation if necessary.
 - b. Treat coma, hypotension, and hypothermia if they occur.
 2. **Specific antidotes:** Flumazenil rapidly reverses coma.
 3. **Decontamination** by activated charcoal if the ingestion occurred within the previous 30 minutes.
- (Ref: Poisoning & Drug Overdose by Olson-5th edition; Washington manual-33rd/982-983)

Benzodiazepine Antagonists: Flumazenil

Flumazenil is an antagonist at benzodiazepine binding sites on the GABA_A receptor that can rapidly reverse the effects of benzodiazepines.

Pharmacokinetics: The drug is available for intravenous administration only. Onset is rapid but duration is short, with a half-life of about 1 hour. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine.

Mechanism of action: Flumazenil binds with high affinity to specific sites on the GABA_A receptor, where it competitively antagonizes the binding and allosteric effects of benzodiazepines and other ligands

Effects: It blocks many of the actions of benzodiazepines, zolpidem, zaleplon, and eszopiclone, but does not antagonize the CNS effects of other sedative-hypnotics, ethanol, opioids, or general anesthetics.

Indication:

- Management of benzodiazepine overdose.

Adverse effects of flumazenil

1. Agitation
2. Confusion
3. Dizziness
4. Nausea.
5. It may induce seizures in patients with tricyclic antidepressant overdose.
6. It may induce acute withdrawal, including seizures and autonomic instability, in patients who are addicted to benzodiazepines.

(Ref: Katzung-13th/377; Lippincott's-6th.125)

Barbiturates

Q. Briefly describe the pharmacodynamics of phenobarbitone. (CU-00J, SU-00J)

Q. Briefly discuss the hypnotic effect of barbiturates. (RU-07Ju,04M, CU-06M)

Q. Explain the neurotransmitter involved in the action of barbiturates. (SU-11Ju)

Q. Explain the neurotransmitter involved in the action of phenobarbitone. (SU-17M)

Ans.

Mechanism of hypnotic effect of barbiturates/ phenobarbitone: The sedative-hypnotic action of the barbiturates is due to their interaction with GABA_A receptors, which **enhances GABAergic transmission**. The binding site is distinct from that of the benzodiazepines.

In addition, barbiturates can **block excitatory glutamate receptors**. Anesthetic concentrations of pentobarbital also **block high-frequency sodium channels**. All of these molecular actions lead to **decreased neuronal activity**.

1. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings.

Barbiturates/Phenobarbitone



Bind to specific, high-affinity-sites located on the GABA-receptor

↓
 Increased affinity of GABA-receptor to the GABA, which is an inhibitory neurotransmitter
 ↓
 More GABA binds to the GABA receptors
 ↓
 Increase the **duration of the opening** of chloride channels
 ↓
 Increased influx of Cl^- ions into the neurons
 ↓
 Hyperpolarization
 ↓
 No formation of action potential
 ↓
 No excitability of the neurons
 ↓
 CNS depression/ sedation / hypnosis.

(Ref: Lippincott's-6th/127)

2. At high conc. barbiturates may also be **GABA mimetic**, i.e. directly activates Cl^- channels

↓
 Increased influx of Cl^- ions into the neurons
 ↓
 Hyperpolarization
 ↓
 CNS depression/ sedation / hypnosis.

(Ref: Katzung-13th/374-375)

Q. "Barbiturates cause more pronounced CNS depression compared with benzodiazepines"- Explain why.

Ans.

Barbiturates cause more pronounced CNS depression compared with benzodiazepines: Barbiturates are less selective in their actions than benzodiazepines, because they also **depress the actions of the excitatory neurotransmitter glutamic acid**. Barbiturates also exert nonsynaptic membrane effects in parallel with their effects on GABA and glutamate neurotransmission. This multiplicity of sites of action of barbiturates may be the basis for their ability to induce full surgical anesthesia and for their more pronounced central depressant effects (which result in their low margin of safety) compared with benzodiazepines and the newer hypnotics.

(Ref: Katzung-13th/375)

Q. Mention the clinical uses of barbiturates. (CU-09Ju)

Q. What are the indications of barbiturates? (SU-03M, CU-01M)

Ans.

Indications of barbiturates:

1. Induction of general anesthesia (Thiopental-Na)
2. Congenital hyperbilirubinemia (phenobarbitone)
3. In epilepsies (phenobarbitone):
 - Partial seizures.
 - GTCS (Generalized Tonic Clonic Seizures).
 - Status epilepticus (Thiopental-Na).
4. **Anticonvulsant:** Barbiturates are used in the emergency treatment of convulsions, such as occur in-
 - Tetanus
 - Eclampsia
 - Status epilepticus
 - Cerebral hemorrhage.
 - Poisoning by convulsant drugs.

(However, benzodiazepines generally are superior in these uses. Phenobarbital sodium is used most frequently because of its anticonvulsant efficacy.)

5. Used in diagnosis (Narcoanalysis) & treatment in psychiatry (Narcotherapy).
6. For sedation & hypnosis.
7. For control of alcohol withdrawal syndrome.

(Ref: Katzung-13th/378-379; Goodman & Gillman's-12th)

Nice to know

Indications of individual barbiturates:

Drugs	Therapeutic uses	Route of administration
<i>Amobarbital</i>	Insomnia, preoperative sedation, emergency management of seizures	IM, IV
<i>Butabarbital</i>	Insomnia, preoperative sedation	Oral
<i>Butalbital</i>	Marketed in combination with analgesics	Oral
<i>Mephobarbital</i>	Seizure disorders, daytime sedation	Oral
<i>Methohexital</i>	Induction and maintenance of anesthesia	IV
<i>Pentobarbital</i>	Insomnia, preoperative sedation, emergency management of seizures	Oral, IM, IV, rectal
<i>Phenobarbital</i>	Seizure disorders, status epilepticus, daytime sedation	Oral, IM, IV
<i>Secobarbital</i>	Insomnia, preoperative sedation	Oral
<i>Thiopental</i>	Induction and/or maintenance of anesthesia, preoperative sedation, emergency management of seizures	IV

(Ref: Goodman & Gillman's-12th)

Q. Explain the role of phenobarbitone in congenital hyperbilirubinemia.

Ans.

Role of phenobarbitone in congenital hyperbilirubinemia: Phenobarbitone → Induces hepatic drug-metabolizing enzyme → Increased concentration of "glucuronyl transferase" enzyme → Increased conjugation of bilirubin → Increased metabolism bilirubin → Decreased serum bilirubin level.

Q. Mention the adverse effects barbiturate therapy. (CU-09Ju)

Q. Mention the adverse effects thiopental sodium. (SU-13J)

Ans.

Adverse effects of barbiturates:

1. Drowsiness, impaired concentration, and mental and physical sluggishness.
2. **Hangover effect:** Hypnotic doses of barbiturates produce a drug "hangover" that may lead to impaired ability to function normally for many hours after waking.
3. Addiction
4. Tolerance
5. Dependence.
6. **Enzyme induction:** Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are metabolized by the CYP450 system.
7. Allergy
8. Skin lesion
9. Histamine release
10. Asthma
11. Oliguria

(Thiopental Na, morphine antagonist)

(Ref: Lippincott's-6th, 12th)

Q. Compares & contrasts between BDZs & Barbiturates. (SU-04M,03S/J)

Q. Compare Clobazam with Phenobarbitone. (SU-01S)

Ans.

Compare & contrast between BDZs & Barbiturates:

Traits	Benzodiazepine	Barbiturate
1. Effect	Cause less pronounced & relatively specific CNS depression.	Cause more pronounced & non-specific CNS depression.
2. Therapeutic index (TI)	High, so safer.	Low, so dangerous.
3. Effect on hepatic enzymes	Does not induce hepatic microsomal enzymes	Induce hepatic microsomal enzymes
4. Physical dependency	Less	More
5. Respiratory depression	Less	More
6. Suicidal tendency	Less	More
7. Sleep pattern	Does not alter normal sleep pattern.	Alter normal sleeping pattern.
8. Hang over effect	Does not produce morning hangover	Produce morning hangover.
9. Withdrawal syndrome	Less	Severe

Q. How does atracurium differ from diazepam? (DU-02M)

Ans.

Difference between atracurium & diazepam: Both atracurium & diazepam are muscle relaxants but differ in the following points:

Traits	Atracurium	Diazepam
1. Mechanism of action	Non-depolarizing neuromuscular blocker	Facilitate the action of GABA in CNS
2. Muscle relaxation	During general anesthesia	- Skeletal muscle spasm, eg- muscle strain - Spasticity from degenerative disorder such as multiple sclerosis & cerebral palsy
3. Antidote	Neostigmine	Flumazenil
4. Sedation	No	Yes

Q. Contrast diazepam, zolpidem, phenobarbitone. (SU-13Ju)

Q. Compare and Contrast diazepam with phenobarbitone. (SU-17J,14J)

Q. Contrast sedative hypnotic action of diazepam, zopiclone and phenobarbitone mentioning mode of action & safety. (SU-10Ju)

Ans.

Difference among diazepam, zopiclone and phenobarbitone

Traits	Diazepam	Zolpidem/ zopiclone	Phenobarbitone
1. Group	Benzodiazepine	Cyclopyrrolones	Barbiturate
2. CNS depression.	More than zopiclone but less than barbiturate.	Marked sedative	More than diazepam & zopiclone.
3. $t_{1/2}$	>24 hours	5-6 hours	1-3 hours
4. Therapeutic index (TI)	High, so safer.	Higher, so much safer.	Low, so dangerous.
5. Induction of hepatic enzymes	No	No	Yes
6. Addiction	Less	Least	More
7. Cardio-respiratory depression	Less	Less	More
8. Sleep pattern	Does not alter normal sleep pattern.	Does not alter normal sleep pattern.	Alter normal sleeping pattern.
9. Hang over effect	More	Absent	More
10. Withdrawal syndrome	Less	Least	Severe
11. Antidote	Flumazenil	No	No

Nice to know

- **Tolerance of benzodiazepines:** It is caused by down-regulation of GABA receptor. It is called pharmacodynamic tolerance.
- **Tolerance of barbiturates:** It is caused by induction of hepatic drug-metabolizing enzymes. It is called pharmacokinetic tolerance.
- **Hang over effect** is the drowsiness, dysphoria and mental or motor depression in the following day.

Q. Barbiturate + OCP =?

Q. Barbiturate + Warfarin =?

Ans.

Drug combination	Mechanism of interaction
Barbiturate + OCP	Barbiturates induce hepatic microsomal enzyme → ↑Metabolism of OCP → Failure of contraception.
Barbiturate + Warfarin	Barbiturates induce hepatic microsomal enzyme → ↑Metabolism of warfarin → ↓Anti-coagulation effect → ↑coagulation (thrombosis).

Q. Write about withdrawal syndrome of barbiturates.

Ans.

Withdrawal syndrome of barbiturates: With the long-term use of barbiturates, especially if doses are increased, a state of physiologic dependence can occur. Abrupt withdrawal from a barbiturate can have severe and life-threatening manifestations, leading to death.

Withdrawal symptoms include-

1. **CVS:** Palpitation, orthostatic hypotension, cardiac arrest.
2. **CNS excitation:** Anxiety, insomnia, tremor, restlessness, altered mental function, hyperactive reflexes, and convulsion.

Treatment: Phenobarbitone (long-acting barbiturate), tapering dose by 15-25%, later by 5-10% within 2 weeks.

(Ref: Katzung-13th/381, Lippincott's-6th)

Q. What are the s/s of barbiturate poisoning?

Q. How can you treat a case of Phenobarbital poisoning?

Ans.

Barbiturate / Phenobarbital poisoning:

Clinical presentation: The onset of symptoms depends on the drug and the route of administration.

A. **With mild to moderate intoxication-**

1. Lethargy
2. Slurred speech
3. Nystagmus
4. Ataxia

B. **With higher doses-**

1. Hypotension
2. Hypothermia
3. Bradycardia
4. Coma
5. Respiratory arrest
6. Pupils are usually small or midposition
7. The patient may lose all reflex activity and appear to be dead.

Diagnosis

1. **Diagnosis** is usually based on a history of ingestion and should be suspected in any epileptic patient with stupor or coma.

2. **Serum & urine levels** of phenobarbital
3. **Other tests** include electrolytes, glucose, BUN, creatinine, arterial blood gases or pulse oximetry, and chest x-ray.

Treatment

A. **Emergency and supportive measures**

1. Protect the airway and assist ventilation if necessary.
2. Treat coma, hypothermia, and hypotension if they occur.

B. **Specific antidotes.** There is **no specific antidote**.

C. **Decontamination:** By activated charcoal and gastric lavage.

D. **Enhanced elimination**

1. **Alkalinization of the urine** increases the urinary elimination of phenobarbital but not other barbiturates.
2. **Repeat-dose activated charcoal**- decreases the half-life of phenobarbital.
3. **Hemodialysis or hemoperfusion**- for severely intoxicated patients.

(Ref: *Poisoning & Drug Overdose* by Olson-5th edition)

Q. Short note: Buspirone.

Ans.

Buspirone

Buspirone has selective anxiolytic effects. Buspirone relieves anxiety without causing marked sedative, hypnotic, or euphoric effects. Unlike benzodiazepines, the drug has no anticonvulsant or muscle relaxant properties. Buspirone does not interact directly with GABAergic systems.

Mechanism of action: It may exert its anxiolytic effects by acting as a partial agonist at brain 5-HT_{1A} receptors, but it also has affinity for brain dopamine D₂ receptors.

Indication:

1. Generalized anxiety states.

Elimination half-life: 2–4 hours

Pregnancy category: B

Adverse effects:

1. Nonspecific chest pain
2. Tachycardia
3. Palpitations
4. Dizziness
5. Nervousness
6. Headache
7. Tinnitus
8. Gastrointestinal distress
9. Paresthesias and a dose-dependent pupillary constriction
10. Blood pressure may be significantly elevated in patients receiving MAO inhibitors.

Advantages:

1. No rebound anxiety or withdrawal signs on abrupt discontinuance.
2. Minimal abuse liability.
3. Dependence is unlikely.
4. Causes less psychomotor impairment than benzodiazepines and does not affect driving skills.
5. Does not potentiate effects of conventional sedative-hypnotic drugs, ethanol, or tricyclic antidepressants.
6. Elderly patients do not appear to be more sensitive to its actions.

Disadvantages:

1. Slow onset (1-2 weeks) of anxiolytic effects.
2. Unsuitable for management of acute anxiety states.
3. Not effective in acute withdrawal syndrome of benzodiazepines.
4. Less effective in panic disorders.

(Ref: Katzung-13th/372,382)

Q. Short note: Ramelteon.

Ans.

Ramelteon: It is a melatonin receptor agonist.

Mechanism of action: It activates MT1 and MT2 melatonin receptors located in the suprachiasmatic nuclei of the brain. Melatonin receptors are thought to be involved in maintaining circadian rhythms underlying the sleep-wake cycle.

Indication:

1. Sleep disorders, especially those characterized by difficulty in falling asleep.

Contraindication: Ramelteon should be used with caution in patients with **liver dysfunction**.

Adverse effects

1. Dizziness
2. Somnolence
3. Fatigue
4. Endocrine changes.

(Ref: Katzung-13th/372,382)

Nice to know

Orexin receptor antagonists: Orexin receptor antagonists are new class of hypnotic drugs. They include-

1. Almorexant
2. Suvorexant

Mechanism of action: Orexin A and B are peptides found in hypothalamic neurons that are involved in the control of wakefulness; their levels increase in the day and decrease at night. Loss of orexin neurons is associated with narcolepsy, a disorder characterized by daytime sleepiness and cataplexy. Animal studies show that orexin receptor antagonists have sleep-enabling effects.

(Ref: Katzung-13th/378)

Opioid Analgesic

Q. What is Pain?

Ans.

Pain: Pain is an unpleasant sensory & emotional experience associated with actual or potential tissue damage or described in terms of such damage.

(Ref: Bennett & Brown-11th)

Types of pain:

1. *According to nature:*
 - a. Acute pain / fast pain
 - b. Chronic pain / slow pain
 2. *According to involvement of nerve fibers:*
 - a. Neuropathic pain
 - b. Non-neuropathic pain
- **Acute pain:** Acute pain is experienced after trauma or surgery, typically resolves with healing of the injured tissue, and can usually be managed effectively with the appropriate use of pharmacotherapy. It is transmitted principally by fast conducting A-delta fibers and has major nociceptive input (physical trauma, pleurisy, myocardial infarct, perforated peptic ulcer).
 - **Chronic pain:** Chronic pain is commonly defined as pain that persists beyond the period expected for healing, or pain that is associated with progressive or persistent non-malignant disease. e.g. chronic pain due to rheumatoid arthritis. Chronic pain can persist long after the healing of damaged tissue. It is transmitted principally by slow conducting type C fibers.
 - **Neuropathic pain:** Neuropathic pain is defined as a chronic pain resulting from damage to the nervous system. Eg, trigeminal neuralgia.
 - **Cancer-related pain** refers to pain that is the result of primary tumour growth, metastatic disease, or the toxic effects of chemotherapy and radiation, such as neuropathies due to neurotoxic antineoplastic drugs.
 - **Features associated with neuropathic pain** including:
 1. **Allodynia** - pain caused by a stimulus that would not normally provoke pain, e.g. light touch.
 2. **Hyperalgesia** - an increased response to a stimulus that would normally be painful.
 3. **Paraesthesia** - abnormal sensation, e.g. 'pins and needles'.
 4. **Dysaesthesia** - a painful paraesthesia, e.g. burning foot pain in diabetic neuropathy.

(Ref: Bennett & Brown-11th/280-281)

Fast pain & slow pain:

Acute pain / Fast pain	Chronic pain / Slow pain
1. It is felt within about 0.1 second after the pain stimulus is applied.	1. It is felt 1 (one) second or more after the pain stimulus is applied.
2. It is described by the patient as sharp pain, acute pain, pricking pain and electric pain.	2. It is described by the patient as burning pain, aching pain, throbbing pain, nauseous pain and chronic pain.
3. It produces bright, sharp localized sensation.	3. It produces dull, intense, diffuse, and unpleasant feeling.
4. It is conducted to the spinal cord by Aδ fibers.	4. It is conducted to the spinal cord by C fibers.

Various aspects of pain: Pain has 4 steps to develop-

1. **Nociception:** Nociception is a consequence of tissue injury (trauma, inflammation) causing the release of chemical mediators which activate *nociceptors* (free nerve endings).
2. **Pain perception:** It is the appreciation & interpretation of pain.
3. **Pain reaction (suffering):** Suffering is a consequence of pain and of lack of understanding by patients of the meaning of the pain; it comprises anxiety and fear (particularly in acute pain) and depression (particularly in chronic pain).

4. **Pain behavior:** e.g. such immediate and obvious aspects as facial expression, restlessness, seeking isolation (or company), medicine-taking, as well as, in chronic pain, the development of querulousness, depression, despair and social withdrawal.

(Ref: Bennett & Brown-11th)

- **Noxious stimuli:** Histamine, Bradykinin, prostaglandin, adenosine, and lactate are produced in response to trauma, injury, inflammation or any other tissue injury or pathological condition.
- **Importance of knowing pain nociception:** By interfering, the nociception we can reduce the somatic pain. NSAIDs interfere pain nociception & exert its analgesic effects.

Q. Describe the pathway of pain perception. (CU-16Ju)

Ans.

Pathway of pain perception: Mechanical, electrical, thermal or chemical pain stimuli → Stimulation of pain receptor (Free nerve ending) → Afferent nerve fibers: **Fast pain by Aδ fibers, slow pain by C fibers** → Enters into the spinal cord → Synapse with posterior horn cell → Ascend as lateral spinothalamic tract → Pons → Ventral posterolateral nucleus of the thalamus. (*Here crude pain is appreciated & emotional reactions are initiated*) → Internal capsule → Corona radiate → Somesthetic area in the postcentral gyrus (*Here the exact & meaningful interpretation of pain occurs*).

(Ref: Neuroanatomy-5th/146,149; Ganong-24th)

- **Importance of pain perception / reaction / behavior:** By interfering pain perception or reaction or behavior we can relieve from pain. Opioid analgesics cause such type of interference & used in visceral pain.

Q. Define analgesic. (DU-17M, SU-07J,05M)

Ans.

Analgesic drug: An analgesic is defined as a drug that relieves pain. e.g. paracetamol, morphine. Analgesics are classified as opioids and non-opioids.

(Ref: Bennett & Brown-11th/281)

Nice to know

- *Drugs that relieve pain due to a single cause or specific pain syndrome only, e.g. ergotamine (migraine), carbamazepine (neuralgias), glyceryl trinitrate (angina pectoris), are not classed as analgesics; nor are adrenocortical steroids that suppress pain of inflammation of any cause.*

(Ref: Bennett & Brown-11th)

- *The word **opium** is derived from opos, the Greek word for "juice," the drug being derived from the juice of the opium poppy, **Papaver somniferum**. After incision, the poppy seed pod exudes a white substance that turns into a brown gum that is crude opium. Opium contains many alkaloids.*
- *Narcotic was originally used to describe sleep-inducing medications.*

(Ref: Katzung-13th/531)

Q. Define opioid, opiate and opioid analgesic?

Ans.

Opiate: The term opiate specifically describes the naturally occurring alkaloids: morphine, codeine, thebaine, and papaverine. Opiates are derived from alkaloids of the opium poppy.

(Ref: Katzung-13th/531)

Opioid / Opioid analgesic: The term opioid describes all compounds that work at opioid receptors.

(Ref: Katzung-13th/531)

Or, The term opioid refers broadly to all compounds related to opium. The class of drugs that includes opiates, opiopeptins, and all synthetic and semisynthetic drugs that mimic the actions of the opiates

(Ref: Goodman & Gilman-12th edition, Katzung & Trevor's-10th edition)

Q. Name the endogenous opioid peptides. (DU-07J, CU-14J)

Ans.

Endogenous opioid peptides: Endogenous peptides that act on opioid receptors are called endogenous opioid peptides.

(Ref: Katzung & Trevor's-10th edition)

Types: 3 types-

1. Endorphins
2. Enkephalin
 - Methionine-enkephalin (met-enkephalin)
 - Leucine-enkephalin (leu-enkephalin)
3. Dynorphins
 - Dynorphin A
 - Dynorphin B

(Ref: Katzung-13th/532)

Mechanism of action: Endogenous opioid peptides bind with opioid receptor → Activation of opioid receptors prevents the release of substance P (a neurotransmitter and local hormone involved in pain transmission) → Pain transmission is inhibited.

(Ref: Bennett & Brown-11th)

Q. Continuous wear and tear running on the body. But we do not feel pain. Why?

Ans.

There are continuous wear and tear running on the body, eg, millions of intestinal epithelial cells are shed in each second. But we do not feel pain. This is due to the presence of endogenous opioid peptides. Endogenous opioid peptides bind with opioid receptor → Activation of opioid receptors prevents the release of substance P → Pain transmission is inhibited.

(Ref: Bennett & Brown-11th)

Q. Name opioid receptor with their distribution & gross function. (DU-14Ju,12Ju, RU-13Ju,08Ju, CU-08J)

Ans.

Opioid Receptor Subtypes, Their Functions, and Their Endogenous Peptide Affinities:

Receptor Subtype	Functions	Endogenous Opioid Peptide Affinity
μ (mu)	Supraspinal and spinal analgesia; sedation; <u>inhibition of respiration</u> ; slowed GI transit; modulation of hormone and neurotransmitter release	Endorphins > enkephalins > dynorphins
δ (delta)	Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release	Enkephalins > endorphins and dynorphins
κ (kappa)	Supraspinal and spinal analgesia; psychotomimetic effects; slowed GI transit	Dynorphins >> endorphins and enkephalins

(Ref: Katzung-13th/532)

Distribution of opioid receptors:

1. Brainstem
2. Thalamus
3. Spinal cord
4. Hypothalamus
5. Limbic system
6. Peripheral sensory nerve fiber & their terminal.

Q. Classify analgesics. (DU-17J,11J,08J,06S; CU-15J; RU-04S, SU-15Ju,07J)

Q. Classify analgesics according to mechanism of action. (SU-16Ju)

Ans.

Analgesic drugs:

1. **Opioid / narcotic analgesics:** They act in the CNS and cause drowsiness. (See below)
2. **Non-opioid / non-narcotic analgesics:** They act chiefly peripherally, eg, NSAIDs.

(Ref: Katzung-13th & Bennett & Brown-11th)

Q. Classify/Mention opioid analgesics. (DU-16Ju,10Ju, RU-06S)

Q. Enlist narcotic analgesics. (DU-08J,06S; CU-04M)

Q. Name the opioids. (RU-05M, SU-08Ju)

Q. Classify opioid analgesics categorically. (RU-16J)

Q. Classify opioid analgesics according to their efficacy?

Q. Enumerate two opioid analgesics from each group. (RU-17J)

Ans.

Classification of opioid analgesics

A. According to their efficacy:

High efficacy	Moderate efficacy	Low efficacy
• Morphine • Hydromorphone • Oxymorphone • Methadone • Meperidine • Heroin (dimorphine) • Fentanyl • Sufentanil • Alfentanil • Remifentanil • Levorphanol • Nalbuphine • Buprenorphine • Butorphanol	• Hydrocodone • Oxycodone • Pentazocine	• Codeine

(Ref: Katzung-13th/533)

B. According to chemical structure

Phenanthrenes	Morphinans	Benzmorphans	Phenylpiperidines	Diphenylheptane
• Morphine • Codeine • Oxycodone • Oxymorphone • Hydromorphone • Hydrocodone • Buprenorphine • Nalbuphine	• Levorphanol • Butorphanol	• Pentazocine	• Fentanyl • Alfentanil • Sufentanil • Remifentanil • Meperidine	• Methadone

(Ref: Lippincott's-6th/192; Katzung-13th/544-547)

C. According to origin:

Natural	Semisynthetic	Synthetic
• Morphine • Codeine	• Hydromorphone • Hydrocodone • Oxycodone • Oxymorphone	• Methadone • Meperidine • Fentanyl • Tapentadol • Tramadol

(Ref: Lippincott's-6th/192)

D. Functional classification:

• Pure agonists	Morphine, codeine
• Partial agonists	Buprenorphine
• Mixed action	Pentazocine, nalbuphine, butorphanol
• Antagonists	Naxolone, naltrexone

(Ref: Bennett & Brown-11th/283)

Morphine and Pethidine (Meperidine)

The word *Morphine* comes from *Morphious* which means the *Goddess of dream* in Greek mythology.

Source: Opium is the source of morphine. Poppy plant *Papaver somniferum* and *P album* → Unripe seed capsule → longitudinal parallel incision → milky exudates → dried in air → brown gum that is crude opium.

Chemical nature: Alkaloids.

- Q. Describe the mechanism of action (M/A) of morphine. (CU-15Ju)
 Q. Write the mechanism of action (M/A) of pethidine. (SU-15J)
 Q. How does morphine produce analgesia? (DU-14Ju, 12Ju, CU-17J, 08J, RU-08J)
 Q. Explain analgesic effect of pethidine. (DU-10Ju, 00J, SU-14Ju, 10J, 09Ju)
 Q. Shortly discuss the molecular mechanism of morphine. (SU-08J)
 Q. Explain the analgesic action of morphine mentioning receptor-neurotransmitter involved. (DU-06/04S, RU-07J, 06J/S, CU-14J, 12Ju, SU-17M)

Ans.

Mechanism of action of morphine / pethidine / opioids: Opioid agonists produce analgesia by binding to specific G protein-coupled opioid receptors that are located in brain and spinal cord regions involved in the transmission and modulation of pain. Morphine binds to all the opioid receptors (μ , δ , κ). Pethidine is predominantly a μ receptor agonist.

1. Morphine binds to opioid receptors (μ , δ , κ) in the presynaptic nerve terminal.

↓
 Closure of voltage-gated Ca^{2+} channels
 ↓
 $\downarrow \text{Ca}^{2+}$ influx
 ↓
 Decreases the release of neurotransmitters (substance P, acetylcholine, norepinephrine, serotonin, glutamate)
 ↓
Pain transmission is inhibited.

2. Morphine binds to opioid receptor (μ) in the postsynaptic nerve terminal

↓
 Open K^+ channels
 ↓
 K^+ conductance, causing increased K^+ efflux
 ↓
 Hyperpolarization
 ↓
 Inhibitory postsynaptic potential (IPSP)
 ↓
Pain transmission is inhibited.

(Ref: Katzung-13th/534)

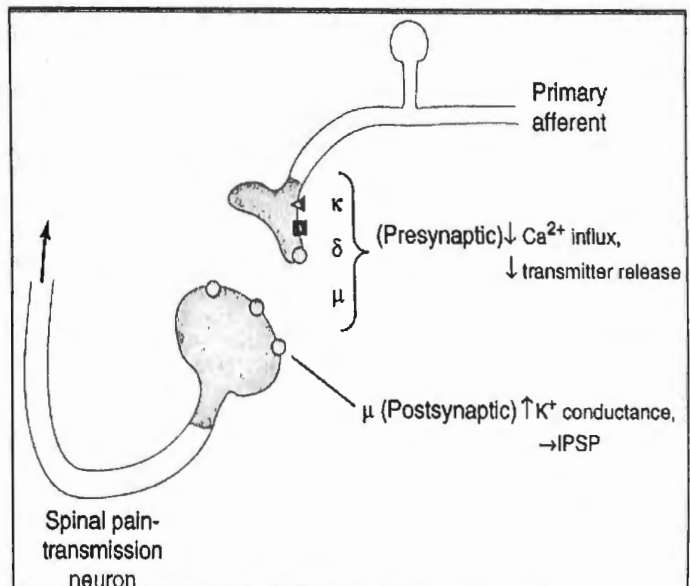


Fig. Spinal sites of action of opioids.

- Q. What are the pharmacological effects of morphine or opioid analgesics? (DU-09Ju, CU-13J, 11Ju, 08J, SU-16Ju, 11J, 08Ju)
- Q. Mention the central pharmacological effects of morphine. (DU-13J, 12J, CU-17M, SU-16J, 12J, RU-12J)
- Q. Mention the central nervous system effects of morphine. (DU-15J)
- Q. List the central and peripheral effects of morphine. (CU-05M, SU-15Ju)
- Q. Discuss in brief the pharmacological action of morphine on CNS. (DU-11J, 07J; RU-16J, 14J)
- Q. State the effects of morphine on respiratory and GIT. (RU-17J)
- Q. Lists the central & GIT effects of pethidine. (SU-07Ju)
- Q. List the pharmacological effects of meperidine on CNS.
- Q. Name the depressor effects of morphine on CNS. (RU-09Ju)

Ans.

Pharmacological effects of morphine / pethidine / opioid analgesics:

CNS effects	
1. Selective depression of CNS	▪ Analgesia ▪ Sedation ▪ Sleep ▪ Respiratory depression ▪ Cough suppression (<i>morphine, not pethidine</i>) ▪ Inhibition of heat regulatory center (hyperthermia)
2. Selective stimulation of CNS	▪ Vomiting ▪ Miosis / pinpoint pupils. (<i>Pethidine does not cause pinpoint pupils but, rather, causes the pupils to dilate because of an atropine-like action.</i>) ▪ Hyperactive spinal cord reflexes (some only) ▪ Convulsions (very rare)
3. Changes in mood	▪ Euphoria ▪ Dysphoria
4. Dependence	▪ Affects other systems too.

(Ref: Bennett & Brown-11th)

Peripheral effects	
Peripheral nervous system	▪ Analgesia, some anti-inflammatory effect
CVS	▪ Bradycardia (<i>except meperidine, pethidine which cause tachycardia due to its anti-muscarinic action</i>) ▪ Hypotension (<i>due to vasodilation</i>)
Respiratory system	▪ Bronchosecretion ▪ Bronchospasm (<i>by releasing histamine</i>)
GIT	▪ ↓GIT motility & ↑GIT tone → Constipation (<i>morphine, not pethidine</i>)
Biliary tract	▪ Contracts biliary smooth muscle → Biliary colic ▪ Constricts sphincter of Oddi → ↑Plasma amylase & lipase.
Renal	▪ Urinary retention. (<i>Pethidine produces less urinary retention than does morphine.</i>) ▪ Decreased renal blood flow → Renal hypoperfusion ▪ Anti-diuretic effects (<i>due to release of ADH</i>)
Uterus	▪ May prolong labour. ▪ Morphine may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions. (Ref: Lippincott's-6th/195) ▪ Fentanyl and pethidine inhibit uterine contractility but only at supraclinical concentrations.

Neuro-endocrine	▪ Increase release of ADH, prolactin, somatotropin ▪ Inhibit LH surge
Pruritus	▪ Flushing, warming of the skin accompanied by sweating, urticaria and itching.
Immune	▪ Opioids modulate immune system by effects on lymphocyte proliferation, antibody production and chemotaxis.

(Ref: Katzung-13th/539-540)

Q. How morphine produce miosis? (CU-14Ju)

Ans.

Mechanism of miosis caused by morphine: Morphine produces miosis by μ and κ receptor-mediated stimulation of the oculomotor nucleus.

(Ref: Rang & Dale's-8th)

Nice to know

Importance of miosis caused by morphine: Pinpoint pupils are an important diagnostic feature in opioid poisoning, because most other causes of coma and respiratory depression produce pupillary dilatation. Tolerance does not develop to the pupillary constriction induced by opioids and therefore can be observed in opioid-dependent drug users who may have been taking opioids for a considerable time.

(Ref: Rang & Dale's-8th)

Q. Briefly discuss the clinical uses of opioid analgesics/morphine. (CU-14J,09/08Ju)

Q. What are the indications of morphine or other opioids? (DU-06S, CU-08J, RU-11Ju, SU-16Ju,15J)

Q. Write important indications of morphine & pethidine. (DU-08J)

Ans.

Indications of morphine & other opioids:

1. **Analgesia:**

- **Acute MI**
- Severe somatic pain, eg, extreme burn, fracture, post-operative pain, acute pancreatitis.
- Chronic pain in terminal cancer patient.
- **Obstetric labor:** Opioid analgesics (eg, meperidine) are often used during obstetric labor.
- **Renal and biliary colic:** The acute, severe pain of renal and biliary colic often requires a strong agonist opioid for adequate relief.

2. **Acute pulmonary edema:** IV morphine relieves dyspnea from pulmonary edema associated with left ventricular failure.

3. **In pre-anesthetic medication** (for analgesia & anxiolysis)

4. **Shivering** (pethidine has anti-shivering effect due to its α_2 -receptor blocking property)

5. **Cough suppression** (dextromethorphan & codeine are used as they are synthetic opioid with few or no CNS effects at lower dose than that of anesthesia)

6. **Non-infective diarrhea** (Diphenoxylate is used for its more selective GIT effects with no / less CNS effect)

(Ref: Katzung-13th/540-541)

Q. Enlist the antitussive Morphine like drugs. (CU-16J)

Ans.

Antitussive Morphine like drugs: The opioid analgesics are among the most effective drugs available for the suppression of cough. The opioid derivatives most commonly used as antitussives are-

1. Dextromethorphan
2. Codeine
3. Levopropoxyphene
4. Noscapine

(Ref: Katzung-13th/547)

Nice to know

Due to increasing reports of death in young children taking **dextromethorphan** in formulations of over-the-counter "cold/cough" medications, its use in children younger than 6 years of age has been **banned** by the FDA.

(Ref: Katzung-13th/547)

Q. Justify the Role / Use of morphine in acute myocardial infarction. (DU-16Ju, SU-15Ju, 14J)

Q. Explain the pharmacological basis of using morphine in the Mx of MI. (CU-06M)

Ans.

Pharmacological basis of using morphine in acute myocardial infarction (MI): Morphine is used in MI-

1. For adequate **analgesia** and thus to relieve severe distress.
2. To lower adrenergic drive and thereby reduce pulmonary and systemic vascular resistance and susceptibility to **ventricular arrhythmias**.

Intravenous opioids (initially morphine sulphate 5-10 mg or diamorphine 2.5-5 mg) should be administered through an intravenous cannula and titrated by giving repeated small aliquots until the patient is comfortable.

(Ref: Davidson's medicine-21st)

Q. Explain the pharmacological basis of using morphine in left ventricular failure. (CU-17J, 16J, 15Ju, 14Ju)

Q. Mention the beneficial role of morphine in pulmonary edema due to LVF. (DU-17M)

Q. Why morphine is used in acute pulmonary edema with acute LVF?

Ans.

Role of morphine in pulmonary edema due to ALVF: Pulmonary edema due to acute left ventricular failure (ALVF) present with breathlessness. Intravenous morphine relieves breathlessness by reducing pulmonary edema.

Proposed mechanisms include-

1. Reduced anxiety (*perception* of shortness of breath)
2. Reduced cardiac preload (reduced venous tone) and
3. Reduced afterload (decreased peripheral resistance).

However, if **respiratory depression** is a problem, **furosemide** may be preferred for the treatment of pulmonary edema. Morphine can be particularly useful when treating painful myocardial ischemia with pulmonary edema.

(Ref: Katzung-13th/541)

Q. What are the adverse effects of opioid analgesics? (DU-04S; CU-04M, SU-04J)

Q. Write down the adverse effects of morphine. (CU-13Ju)

Ans.

Adverse effects of opioid analgesics / morphine:

Adverse Effects with Acute Use	Adverse Effects with Chronic Use
1. Respiratory depression	1. Hypogonadism
2. Nausea / vomiting	2. Immunosuppression
3. Pruritus	3. Increased feeding
4. Urticaria	4. Increased growth hormone secretion
5. Constipation	5. Withdrawal effects
6. Urinary retention	6. Tolerance, dependence
7. Delirium	7. Abuse, addiction
8. Sedation	8. Hyperalgesia
9. Myoclonus	9. Impairment while driving
10. Seizures	

(Ref: Katzung-13th/542)

Other adverse effects of opioid analgesics / morphine:

1. **Increased intracranial pressure (ICP):** The elevation of ICP, particularly in head injury, can be serious.

(Ref: Lippincott's-6th/196)

Q. What are the contraindications of opioid analgesics / morphine? (DU-07J, SU-16Ju, 15J, 11J, CU-00S)

Ans.

Contraindications of morphine / opioid analgesics:

1. **Head injury** (as morphine increases ICP which deteriorate the condition)
2. **Pregnancy** (risk of teratogenesis and physical dependence of the fetus)
3. **Impaired pulmonary function:** In patients with borderline respiratory reserve, the depressant properties of the opioid analgesics may lead to acute respiratory failure.
4. **Impaired hepatic or renal function.**
5. **Impaired endocrine function:** Patients with adrenal insufficiency (Addison's disease), hypothyroidism (Myxedema) may have prolonged and exaggerated responses to opioids.
6. **Combining a pure agonist (morphine) with a weak partial agonist (pentazocine)** should be avoided. In this combination, there is a risk of diminishing analgesia or even inducing a state of withdrawal.
7. **Undiagnosed acute visceral pain** (eg, undiagnosed acute abdominal pain)

(Ref: Katzung-13th/544)

Q. Why morphine is contraindicated in undiagnosed acute abdomen / acute visceral pain?

Ans.

Morphine is contraindicated in undiagnosed acute abdomen / acute visceral pain: Elaboration of pain (e.g. site, nature, severity, radiation etc.) is one of the important clues for the diagnosis of any acute visceral (e.g. abdominal) pain. By interpreting or elaborating the pain, an expert physician or surgeon can diagnose the disease even without any investigation.

If we suppress the pain or reduce the intensity or severity of visceral pain before a proper & complete history and physical examination, it is very difficult to diagnose the cause of pain properly. So, opioid analgesics should be given after a proper & complete evaluation of pain.

Q. A 35 years aged lady has admitted in the medicine ward with complaints of abdominal pain suspected to be biliary stone origin. How you will treat pharmacologically? Explain role of these drug(s). (SU-10J)

Ans.

Pharmacological intervention of abdominal pain due to biliary stone:

1. **Analgesic:** According to the severity (as it is a visceral pain, there is a little role of NSAIDs)
 - **Mild-moderate pain:** Anti-spasmodic (hyoscine butyl bromide oral or parenteral)
 - **Severe pain:** Opioid analgesic (pethidine or nalbuphine or tramadol) ± An anti-spasmodic
2. **Anti-emetic:** If there is associated vomiting → Prochlorperazine or ondansetron.
3. **Anti-ulcerant:** If the patient has history of PUD or patient is kept nothing by mouth (ranitidine or omeprazole)
4. **Antibiotic:** Should only be used where indicated. Not necessary to use routinely.

Q. Why morphine is contraindicated in head injury? (RU-15Ju, 12J)

Q. Explain the consequence: Morphine given in head injury. (DU-13Ju)

Ans.

Morphine is contraindicated in head injury: Morphine causes respiratory depression. Carbon dioxide retention caused by respiratory depression results in cerebral vasodilation. Morphine also increases intracranial pressure (ICP). In patients with elevated ICP, cerebral vasodilation may lead to lethal alterations in brain function.

(Ref: Katzung-13th/544)

Q. Which opioid is preferred in obstetric analgesia and why? (DU-10Ju)

Q. Why pethidine is preferred to morphine in obstetric case? (DU-13J, 12J)

Q. Why pethidine is preferred to morphine in labor pain? (SU-17J, 14Ju)

Ans.

Pethidine is preferred in obstetric analgesia/ Morphine is potentially more harmful: Opioid analgesics are often used during obstetric labor for analgesia. Because opioids cross the placental barrier and reach the fetus care must be taken to minimize neonatal cardio-respiratory depression.

Pethidine is widely used in obstetrics because-

1. It does not delay labour like morphine;
2. It causes less cardio-respiratory depression in the fetus.

(Ref: Bennett & Brown-11th + Katzung-13th)

(Explanation: Morphine undergoes glucuronidation for its metabolism & excretion. But placenta is lack of glucuronyl transferase enzyme. So, Morphine is not metabolized in placenta and its concentration & duration of action increases. So there is more chance of fetal cardio-respiratory depression. Moreover, morphine may prolong labor.

On the other hand, pethidine does not require glucuronidation; rather it requires alkylation for its metabolism & excretion. So pethidine is metabolized in the placenta and its concentration & duration of action is less than morphine. So there is less chance of fetal cardio-respiratory depression. That's why pethidine is safer & preferred in obstetric use.)

(Ref: Rang-Dale-8th + Katzung-13th edition)

Q. Why is morphine contraindicated in pregnancy?

Ans.

Morphine is contraindicated in pregnancy or at least should be used carefully: In pregnant women who are chronically using opioids, the fetus may become physically dependent in utero and manifest withdrawal symptoms in the early postpartum period.

Opioid analgesics can cross blood-placental barrier & may cause fetal respiratory depression & ultimately teratogenesis or intra-uterine fetal death occurs.

(Ref: Katzung-13th/544)

Q. Why morphine should not be used in impaired pulmonary function?

Ans.

Morphine should not be used in impaired pulmonary function: In patients with borderline respiratory reserve, the depressant properties of the opioid analgesics/morphine may lead to acute respiratory failure.

(Ref: Katzung-13th/544)

Q. Why morphine should not be used in impaired hepatic function?

Ans. Morphine is metabolized primarily in the liver. So, should be used cautiously in hepatic impairment (e.g. hepatitis) or patients with hepatic coma.

(Ref: Katzung-13th/544)

Q. Why morphine should not be used in impaired renal function?

Ans. Morphine is excreted through kidney. So in patients with impaired renal function, the half-life of morphine is prolonged and morphine & its active glucuronide metabolites may accumulate in the body producing toxicities.

(Ref: Katzung-13th/544)

Q. How does Morphine produce tolerance and withdrawal effects? (CU-16Ju)

Ans.

Tolerance to morphine: With frequently repeated therapeutic doses of morphine or its surrogates, there is a gradual loss in effectiveness; this loss of effectiveness is termed tolerance. To reproduce the original response, a larger dose must be administered.

Withdrawal or abstinence syndrome / Dependence: Along with tolerance, physical dependence develops. Physical dependence is defined as a characteristic withdrawal or abstinence syndrome when a drug is stopped or an antagonist is administered.

Mechanism of opioid tolerance and physical dependence: It is poorly understood, but persistent activation of μ receptors such as occurs with the treatment of severe chronic pain appears to play a primary role in its induction and maintenance.

Current concepts have shifted away from tolerance being driven by a simple up-regulation of cAMP system. Although this process is associated with tolerance, it is not sufficient to explain it.

Concept of receptor recycling: Normally, activation of μ receptors by endogenous ligands results in receptor endocytosis followed by resensitization and recycling of the receptor to the plasma membrane. However, using genetically modified mice, research now shows that the failure of morphine to induce endocytosis of the μ -opioid receptor is an important component of tolerance and dependence.

Concept of receptor uncoupling: Under this hypothesis, tolerance results from a dysfunction of structural interactions between the μ receptor and G proteins, second-messenger systems, and their target ion channels.

(Ref: Katzung-13th/537)

Nice to know

Degrees of tolerance that may develop to some of the effects of the opioids.

High	Moderate	Minimal or None
Analgesia Euphoria, dysphoria Mental clouding Sedation Respiratory depression Antidiuresis Nausea and vomiting Cough suppression	Bradycardia	Miosis Constipation Convulsions

(Ref: Katzung-13th/539)

Q. How will you manage a case of morphine addict? (CU-17M, SU-15Ju)

Ans.

Pharmacological approaches to treating a case of morphine addict

Mechanism	Example(s)
1. To alleviate withdrawal symptoms	• Methadone. • Ibogaine. • α_2 agonists (e.g. clonidine, lofexidine). • β blocker (e.g. propranolol) to diminish excessive peripheral sympathetic activity.
2. Long-term substitution	• Methadone, buprenorphine or legal heroin to maintain opioid-dependent patients
3. Blocking response	• Naltrexone to block opioid effects in drug-withdrawn patients
4. Reducing continued drug use (may act by reducing craving)	• Baclofen • Ibogaine

(Ref: Rang-Dale-8th)

Q. Enumerate post-operative analgesia. (RU-12Ju)

Ans.

Post-operative analgesia: The analgesic drugs used in post-operative period is called post-operative analgesia.

Drugs used in post-operative analgesia

- Analgesics used in immediate post-operative period (first 24-48 hours):**
 - Opioid analgesics** are preferred especially in IM route. Eg, morphine, pethidine, nalbuphine, tramadol.
 - NSAIDs** (eg, ketorolac, diclofenac, ibuprofen) are used in selective cases such as elderly patient, patient with cardiorespiratory compromise.
- Regular analgesic in post-operative period (after 48 hours to onward): NSAIDs** are used mostly in oral or per-rectal route. Eg,
 - Diclofenac
 - Ketorolac

c. Naproxane

(Ref: Bennett & Brown-11th/297)

Q. Why morphine is called the restricted drug? (RU-13Ju)

Ans.

Morphine causes addiction. Therefore, many governments regulate the manufacture, distribution, marketing, and sale of morphine, for instance through a prescription system. This is why; morphine is called the restricted drug.

Q. Mention the differences between morphine & pethidine. (DU-14J,07M; SU-17M,11Ju,09/08Ju, RU-10Ju)

Q. How does morphine differ from mepiridine? (RU-04S)

Q. Compare & contrast morphine & pethidine. (DU-15J, CU-15J,07Ju, RU-06M, SU-16J,13Ju)

Q. What are the advantages of pethidine over morphine? (DU-08J)

Ans.

Differences between morphine & pethidine:

Traits	Morphine	Pethidine
1. Source	Natural (opium)	Synthetic (phenylpiperidine)
2. Onset of action	Late	Immediate
3. Duration of analgesia	4 - 5 hours	2 - 3 hours
4. Potency	More than pethidine	Less
5. Biotransformation	Glucuronidation	Alkylation
6. Hypnotic effect	More	Less
7. Respiratory depression	More	Less
8. Cough suppression	Causes	Does not cause
9. Constipation	Causes	Does not cause
10. Urinary retention	Present	Absent
11. Pre-anesthetic medication	Now not used	Used
12. Safety in obstetric use	No	Safe
13. Anti-muscarinic effects	No	Yes
14. Histamine release	Yes, causes bradycardia & hypotension	No

(Ref: Bennett & Brown-11th)

Tramadol

Tramadol is a synthetic codeine analog that acts as a centrally acting **analgesic**. Its mechanism of action is predominantly based on blockade of serotonin reuptake.

Mechanism of action:

1. Inhibition of uptake of **norepinephrine** and **serotonin**.
2. **Weak μ -opioid receptor** agonist.

Indications of tramadol:

1. As a post-operative analgesia.
2. Chronic neuropathic pain (as an adjunct with pure opioid agonists).
3. Treatment of labor pain.

Adverse effects: Common side effects of tramadol include-

1. Seizures, especially in patients taking SSRI, TCA, or in overdose.
2. Serotonin syndrome
3. Nausea
4. Vomiting

5. Dizziness
6. Dry mouth
7. Sedation
8. Headache.
9. Anaphylaxis.

Contraindication

1. Relatively contraindicated in patients with a **history of epilepsy** and for use with other drugs that lower the seizure threshold.
2. Tramadol should also be avoided in patients taking monoamine oxidase inhibitors.
3. Patients with a **history of addiction**.

(Ref: Katzung-13th & Goodman & Gilman-12th edition)

Q. Mention the advantages of tramadol over morphine. (DU-17M)

Ans.

Advantage of tramadol over morphine:

1. Respiratory depression is less than with equianalgesic doses of morphine.
2. Less degree of constipation.
3. In the treatment of mild-to-moderate pain, tramadol is as effective as morphine or meperidine. However, for the treatment of severe or chronic pain, tramadol is less effective.
4. Tramadol is as effective as meperidine in the treatment of labor pain and may cause less neonatal respiratory depression.

Tapentadol

Newer **analgesic** with modest μ -opioid receptor affinity and significant norepinephrine reuptake inhibiting action.

Advantage: Less gastrointestinal complaints such as nausea.

Indications of tapentadol: Mild to moderate pain

Adverse effects of tapentadol: Common side effects include

1. Seizures, especially in patients with seizure disorders
2. Serotonin syndrome

(Ref: Katzung-13th)

Mixed Agonist-Antagonists and Partial Agonists

Drugs that stimulate one receptor but block another are termed mixed agonist-antagonists. The effects of these drugs depend on previous exposure to opioids. In individuals who have not recently received opioids, mixed agonist-antagonists show agonist activity and are used to relieve pain. In the patient with opioid dependence, the agonist-antagonist drugs may show primarily blocking effects-that is, produce withdrawal symptoms.

(Ref: Lippincott's-6th)

Examples

- Drugs such as *nalbuphine* and *butorphanol* are competitive μ -receptor antagonists but exert their analgesic actions by acting as agonists at κ -receptors.
- *Pentazocine* qualitatively resembles these drugs, but it may be a weaker μ -receptor antagonist or partial agonist while retaining its κ -agonist activity.
- *Buprenorphine*, on the other hand, is a partial agonist at μ -receptors.

(Ref: Goodman & Gilman-12th edition)

Nalbuphine

Nalbuphine is a strong κ -receptor *agonist* and a μ -receptor *antagonist*; it is given parenterally.

(Ref: Katzung-13th)

Pharmacological Actions

1. **Analgesia:** An intramuscular dose of 10 mg nalbuphine is equianalgesic to 10 mg morphine, with similar onset and duration of analgesic and subjective effects.
2. **Respiratory depression:** Nalbuphine depresses respiration as much as do equianalgesic doses of morphine. However, nalbuphine exhibits a **ceiling effect** such that increases in dosage beyond 30 mg produce no further respiratory depression. Unfortunately, when respiratory depression does occur, it may be relatively resistant to naloxone reversal.
3. Nalbuphine does not affect the heart or increase blood pressure.

Adverse effects:

- **At doses of 10 mg or less:** sedation, sweating, and headache.
- **At much higher doses (70 mg):** Psychotomimetic side effects (e.g., dysphoria, racing thoughts, and distortions of body image).
- **Tolerance and Physical Dependence**

Therapeutic Uses: Nalbuphine is used to produce **analgesia**. The usual adult dose is 10 mg parenterally every 3 to 6 hours.

(Ref: Goodman & Gilman-12th edition; Katzung-13th)

Q. Compare between pathidine and tramadol. (DU-17J)

Ans.

Comparison between pathidine and tramadol

Traits	Tramadol	Pethidine
1. Source	Synthetic codeine analog	Synthetic (phenylpiperidine)
2. Mechanism of analgesia	Blockade of serotonin reuptake.	It is predominantly a μ receptor agonist.
3. Oral bioavailability	Good	Poor
4. Onset of action	Late	Immediate
5. Duration of analgesia	More	Less
6. Potency	Less	More
7. Respiratory depression	Less or no	Less
8. Effects on cardiovascular system	No	Yes
9. Seizures association	Yes	No
10. Serotonin syndrome	Yes	No
11. Constipation	Less	No
12. Safety in obstetric use	Yes	Safe
13. Anti-muscarinic effects	No	Yes
14. Hypnotic effect	No	Less
15. Histamine release	No	No

Q. How does ketorolac differ from mepiridine? (DU-09J,07Ju)

Q. Contrast analgesic action of ketorolac and pethidine. (SU-05M)

Q. Write the differences between opioids & NSAIDs. (DU-07Ju, CU-07J,05J/S)

Q. Compare & contrast between ibuprofen & pethidine as analgesic. (CU-05S)

Q. Compare & contrast between diclofenac & pethidine/morphine as analgesic. (CU-11J,10Ju, RU-12Ju)

- Q. Compare & contrast between ketoprofen & pethidine as analgesic. (SU-05J)
 Q. Compare between aspirin & morphine as analgesic.
 Q. Write the differences between morphine and ibuprofen. (SU-12J)
 Q. Compare analgesic action of pethidine and paracetamol in respect to their mechanism of action, indication and adverse effects. (SU-13J, 12Ju)

Ans.
 Differences between opioids & NSAIDs:

centrally

peripherally

Traits	Opioids / morphine / pethidine	NSAIDs/Ketorolac/Aspirin/ diclofenac/ ketoprofen/ ibuprofen
1. Type of drug	Opioids	NSAID
2. Mechanism of action	Inhibits pain transmission by presynaptic neurotransmitter release and post-synaptic hyperpolarization.	Inhibits cyclo-oxygenase enzyme, thus inhibits PG synthesis.
3. Interference in pain pathway	Pain perception, behavior & reaction	Pain nociception
4. Degree of analgesia	More	Less
5. Type of pain relieved	Visceral pain	Somatic pain
6. Anti inflammatory effect	No	Yes
7. Anti platelet effects	No	Yes
8. Anti pyretic effects	No	Yes
9. Gastric irritation	No	Yes
10. Sedative effect	Strong sedative & hangover effect	No sedative effect
11. Bronchoconstriction	Marked	Moderate
12. Addiction tendency	Yes	No
13. Physical dependency	Physical dependency & withdrawal symptoms may occur	No
14. Respiratory depression	Occurs	No
15. Intracranial pressure	Increases ICP	No
16. Miosis	Occurs	No

Opioid antagonists

Pure opioid / morphine antagonists are:

1. Naloxone
2. Naltrexone
3. Nalmefene

These drugs are morphine derivatives. These agents have a relatively high affinity for μ -receptor opioid binding sites. They have lower affinity for δ and κ receptors but can also reverse agonists at these sites. Administration of opioid antagonists produces no profound effects in normal individuals. However, in patients dependent on opioids, antagonists **rapidly reverse the effect of agonists**, such as **heroin**, and precipitate the symptoms of opiate withdrawal.

Pharmacokinetics

- Naloxone is usually given by injection and has a short duration of action (1–2 hours).
- Naltrexone is well absorbed orally. It has a half-life of 10 hours, and a single oral dose of 100 mg blocks the effects of injected heroin for up to 48 hours.

- Nalmefene, the newest of these agents, is a derivative of naltrexone but is available only for IV administration. Like naloxone, nalmefene is used for opioid overdose but has a longer half-life (8–10 hours).

Clinical uses:

- **Naloxone:** Treatment of acute opioid/morphine overdose.
- **Naltrexone:**
 1. Treatment of opioid addiction. A single dose given on alternate days blocks virtually all of the effects of a dose of heroin.
 2. Treatment of chronic alcoholism
- **Nalmefene** is used for acute opioid overdose but has a longer half-life (8–10 hours).

(Ref: Katzung-13th)

Q. Why methadone, not naloxone, is used in initial treatment of opioid dependence? (SU-14Ju)

Ans.

Methadone, not naloxone, is used in initial treatment of opioid dependence

1. Administration of **naloxone** or another antagonist results in a transient, explosive abstinence syndrome—**antagonist-precipitated withdrawal** in a subject physically dependent on opioids.
2. **Methadone** is a synthetic opioid with long duration of action, due to high protein binding and slow liver metabolism. The elimination $t_{1/2}$ is 7 h after a single IM dose, 15 h after an oral dose, but 25 h after repeated dosing.
3. The long duration of action favours its use for the treatment of opioid withdrawal in addicted patients.
 - a. Methadone occupies opioid receptors, thus reducing the desire to take other opioids and the intensity of euphoria.
 - b. The slow offset also diminishes the severity of the withdrawal.
 - c. Methadone reduces craving and less 'kick/buzz/rush' from IV heroin or morphine, because their opioid receptors are already occupied by methadone.

(Ref: Bennet & Brown-11th edition)

Nice to know

For patients receiving long-term opioid therapy, naloxone should be used only to reverse respiratory depression, with care taken to avoid precipitating withdrawal or severe pain.

(Ref: Bennet & Brown-11th edition)

Q. Short note: Co-analgesic. (RU-17J,15J,13Ju,12Ju)

Q. Short note: Analgesic adjuvant. (RU-16Ju)

Ans.

Coanalgesic / Adjuvant drugs

Coanalgesic, or adjuvant drugs, are medications whose primary indication is for a purpose other than pain relief, but that demonstrate some analgesic effects. They are not themselves analgesics but are used alongside analgesics in the management of pain.

Examples of co-analgesics:

1. **Corticosteroids:** Most widely used adjuvant analgesics in palliative care..
2. **Neuroleptics:** Levomepromazine is very useful in bedridden patients with advanced cancer who experience pain associated with anxiety, restlessness or nausea.
3. **Benzodiazepines:** Used as a short-term treatment for painful muscle spasm.
4. **Adjuvant analgesics used for neuropathic pain**
 - a. Local anaesthetics
 - b. Antidepressants
 - c. Anticonvulsants
 - d. Capsaicin

- e. Clonidine
- f. Cannabinoids
- g. Ziconotide
- h. Ketamine

5. **Adjuvants used for bone pain**

- a. Bisphosphonates.

Indications of co-analgesics

1. Cancer-related pain
2. Chronic non-malignant pain
3. Neuropathic pain associated with many cancers.

Pharmacological role:

1. They may modify the perception or the concomitants of pain that make it worse (anxiety, fear, depression), e.g. psychotropic drugs.
2. They may modify underlying causes, e.g. spasm of smooth or voluntary muscle.
3. Most coanalgesics have a slower onset of analgesic action.
4. Most experience with coanalgesics has been in the treatment of **chronic pain**.

(Ref: Bennett & Brown-11th/290; Websites)

Anti-depressant drugs

Depression: Depression is defined as disorders of mood rather than disturbances of thought or cognition.

(Ref: Rang & Dale's-8th)

Q. Classify depression. (CU-15Ju,14J)

Ans.

Classification of depression: There are two distinct types of depressive syndrome:

1. **Unipolar depression**, in which the mood changes are always in the same direction.
2. **Bipolar affective disorder**, in which depression alternates with mania.

(Ref: Rang & Dale's-8th)

Nice to know

Mania: Mania is in most respects exactly the opposite, with excessive exuberance, enthusiasm and self-confidence, accompanied by impulsive actions, these signs often being combined with irritability, impatience and aggression, and sometimes with grandiose delusions of the Napoleonic kind.

Antimanic drug - Li (Ref: Rang & Dale's-8th)

Q. What are the characteristics of unipolar depression? (CU-15Ju)

Ans.

Characteristics of unipolar depression: Unipolar depression is characterized by-

1. Feelings of intense sadness & despair (loss of hope)
2. Mental slowing & loss of concentration
3. Pessimistic worry (always expect bad things to happen)
4. Lack of pleasure
5. Self deprecation
6. Variable agitation & hostility.
7. Some physical changes in severe or melancholic depression:
 - Insomnia or hypersomnia.
 - Altered eating pattern with anorexia & wt. loss or sometimes overeating.
 - Decreased energy & libido.
 - Disruption of the normal circadian & ultradian rhythms of activity, body temperature & many endocrine functions.

(Ref: Goodman & Gilman's-12th)

Nice to know

Symptoms of depressive disorders

<i>Psychological</i>	<i>Somatic</i>
1. Depressed mood	1. Reduced appetite
2. Reduced self-esteem	2. Weight change
3. Pessimism	3. Disturbed sleep
4. Guilt	4. Fatigue
5. Loss of interest	5. Loss of libido
6. Loss of enjoyment (anhedonia)	6. Bowel disturbance
7. Suicidal thinking	7. Motor retardation (slowing of activity)

(Ref: Davidson's-22nd/235)

Q. What do you know about mono-amine theory of depression? (RU-10)

Q. What is the basis of pharmacological intervention of depressive illness? (CU-17M,11J,09J)

Q. Outline the biological basis of depression. (SU-17M,16J,15Ju,13J,12J,11Ju)

Q. What do you know about amine hypothesis? (DU-09J)

Q. Write down the chemical basis of depression. (DU-07Ju)

Ans.

Pathophysiology of Major Depression: In addition to the older idea that a deficit in function or amount of monoamines (**monoamine hypothesis**) is central to the biology of depression, there is evidence that neurotrophic and endocrine factors play a major role (**neurotrophic hypothesis**).

Neurotrophic hypothesis: According to this hypothesis, major depression is associated with the loss of neurotrophic factors (especially **brain-derived neurotrophic factor, BDNF**) and endocrine factors. BDNF is critical in the regulation of neural plasticity, resilience, and neurogenesis.

(Ref: Katzung-13th/511-512)

Mono-amine hypothesis of depression: This hypothesis suggests that depression is related to a deficiency in the amount or function of cortical and limbic **serotonin (5-HT), norepinephrine, and dopamine.** (monoamines)

Evidence supporting the monoamine hypothesis: All available antidepressants appear to have significant effects on the monoamine system. All classes of antidepressants appear to enhance the synaptic availability of 5-HT, norepinephrine, or dopamine.

The monoamine hypothesis, like the neurotrophic hypothesis, is at best incomplete.

(Ref: Bennett & Brown-11th; Katzung-13th/511-512)

Q. Classify anti-depressants. (DU-17J, 15Ju, 14J, 08J; CU-11J, 10Ju, 05J; RU-06J, 04M, SU-09Ju)

Q. Name the selective serotonin reuptake inhibitors. (RU-13J, SU-10J)

Q. Name commonly used drugs to treat depressive disorder. (DU-14Ju, 13J, 12J, RU-08J)

Q. Categorize the drugs for depressive disorders according to their mechanism of action. (CU-10J)

Q. Name the clinically useful antidepressants. (RU-15Ju)

Q. Name 04 (four) antidepressant drugs. (DU-16Ju)

Ans.

Anti-depressant drugs:

1. Selective serotonin reuptake inhibitors (SSRI)	▪ Citalopram ▪ Escitalopram ▪ Fluoxetine ▪ Fluvoxamine ▪ Paroxetine ▪ Sertraline
2. Selective Serotonin-Norepinephrine reuptake inhibitors (SNRIs)	▪ Venlafaxine ▪ Desvenlafaxine ▪ Duloxetine ▪ Milnacipran ▪ Levomilnacipran
3. Tricyclic antidepressants	▪ Amitriptyline ▪ Nortriptyline ▪ Protriptyline ▪ Imipramine ▪ Desipramine ▪ Clomipramine ▪ Trimipramine ▪ Doxepin
4. 5-HT ₂ receptor modulator	▪ Nefazodone ▪ Trazodone ▪ Vortioxetine } 5-HT₂ antagonists
5. Tetracyclics and unicyclic	▪ Amoxapine ▪ Bupropion ▪ Maprotiline ▪ Mirtazapine ▪ Vilazodone

6. Monoamine oxidase (MAO) inhibitors*Used in BPD***Hydrazine derivatives**

- Phenelzine
- Isocarboxazid

Non-hydrazines

- Tranylcypromine
- Selegiline
- Moclobemide

(Ref: Katzung-13th/514-517)

[NB: *Vortioxetine*: It is antagonist of 5-HT₃, 5-HT₇, 5-HT_{1D}, partial agonist of 5-HT_{1B} and agonist of 5-HT_{1A} receptor.]

Tricyclic antidepressants

Pharmacokinetic properties of TCAs:

1. Most TCAs are incompletely absorbed & undergoes significant 1st pass metabolism.
2. Large volume of distribution: This is due to -
 - High tissue protein binding.
 - Relatively high lipid solubility.
3. TCAs are metabolized by two major routes:
 - Transformation of the tricyclic nucleus.
 - Alteration of the aliphatic side chain.
4. 'Ring-hydroxy' metabolites are relatively cardio-toxic.

(Ref: Katzung-13th/519, Goodman & Gilman's-12th)

Q. What are the molecular actions of amitriptyline? (SU-08Ju)

Q. What is the mechanism of action of TCAs? (CU-07Ju, 05M; RU-02M)

Q. Mention the mechanism of action of imipramine. (DU-14Ju, 13J, 12J, CU-05M)

Ans.

Mechanisms of actions of TCAs/ Amitriptyline/ Imipramine:

Mechanisms of actions of TCAs	Effects
Block reuptake of 'amine NT, eg, serotonin, nor-adrenaline' into the pre-synaptic nerve terminal. ↓ Increased conc. of 'amine NT' into the synaptic cleft. ↓ Prolong duration of action amine NT.	▪ Relief of depression
Block muscarinic receptors (atropine like action)	▪ Tachycardia ▪ Urine retention ▪ Constipation ▪ Dry mouth & skin ▪ Blurred vision
Block α adrenergic receptors.	▪ Postural hypotension ▪ Reflex tachycardia ▪ Ejaculatory failure ▪ Constipation.
Block pre-synaptic α ₂ receptors ↓ No auto-inhibitory effect of NA ↓ Increased NA release from pre-synaptic nerve endings (i.e. TCAs has sympathomimetic effects)	▪ Tachycardia ▪ Tremor ▪ Insomnia etc.
Block central H ₁ -receptors	▪ Sedation

↓
Down ↓
Regulation
of
receptor
Old age
↑ Tachycardia
20-25%
Drinking
from air
(55R) 4-20

Q. Mention the indications of amitriptyline. (RU-10J,06J)

Q. What are the clinical uses / indications of TCAs or SSRIs? (DU-17J, CU-12J, RU-13J)

Ans.

Indications of anti-depressants / Amitriptyline:

1. Depression.
2. Anxiety disorders: (e.g. SSRIs, venlafaxine, duloxetine)
 - Panic disorder
 - Generalized anxiety
 - Social phobia.
3. Obsessive-compulsive disorders.
4. Bipolar depression (e.g. fluoxetine in conjunction with olanzepine)
5. Enuresis
6. Insomnia
7. Chronic pain (elevated mood causes increased pain tolerability)
8. Neuropathic pain (e.g. amitriptyline, nortriptyline)
9. Other uses:
 - Bulimia (eating disorder)
 - Pre-menstrual dysphoric disorder.
 - Fibromyalgia (e.g. duloxetine, venlafaxine, SSRIs, TCAs)
 - Obesity (e.g. sibutramine)
 - Smoking cessation (e.g. bupropion)
 - Attention-deficit hyperactivity disorder (e.g. atomoxetine).

(Ref: Katzung-13th/521-523; Rang & Dale's-8th)

Nice to know

Current status of TCA: At the present time, the TCAs are used primarily in depression that is unresponsive to more commonly used antidepressants such as the SSRIs or SNRIs. Their loss of popularity stems in large part from relatively poorer tolerability compared with newer agents, difficulty of use, and lethality in overdose.

(Ref: Katzung-13th/515)

Q. Why there is delay in producing therapeutic effect after administration of TCA? (CU-13Ju)

Ans.

Delay in producing therapeutic effect after administration of TCA: Following administration of TCA, amine levels increase immediately, but maximum beneficial effects of antidepressants are not seen for many weeks. The time required to synthesize **neurotrophic factors** has been proposed as an explanation for this delay of antidepressant effects. Appreciable protein synthesis of products such as BDNF typically takes 2 weeks or longer and coincides with the clinical course of antidepressant treatment.

(Ref: Katzung-12th/525)

Q. Write down the adverse effects of TCAs? (DU-17J, CU-17M,14J,07Ju,05M; RU-10J,09Ju)

Q. Write down the adverse effects of amitriptyline? (CU-08Ju, RU-16Ju)

Q. Write down the adverse effects of imipramine. (DU-14Ju,13J,12J)

Ans.

Adverse effects of TCAs/ amitriptyline:

1. Due to anti-muscarinic effects (atropine like action)	▪ Tachycardia ▪ Urine retention ▪ Constipation ▪ Dry mouth & skin ▪ Blurred vision
2. Due to α_2 receptor blocking property	▪ Postural hypotension ▪ Reflex tachycardia ▪ Cardiac arrhythmias ▪ Ejaculatory failure.

3. Due to pre-synaptic α_2 -adrenoceptors blocking property (i.e. sympathomimetic)	▪ Tachycardia ▪ Tremor
4. Due to central H_1 -blocking property.	▪ Sedation
5. Neurologic adverse effects	▪ Seizures
6. Psychiatric adverse effects	▪ Aggravation of psychosis
7. Metabolic-endocrine adverse effects	▪ Withdrawal syndrome. ▪ Sexual disturbances ▪ Weight gain.

(Ref: Katzung-13th/525)

Q. Write short note on: Imipramine. (DU-12Ju,10J)

Ans. Write M/A, indication, adverse effects from above.

Selective serotonin reuptake inhibitors (SSRI)

Pharmacokinetic properties of SSRI:

- Oral bioavailability is equal or relatively higher than that of TCAs.
- Fluoxetine is notable for the long half life for its active metabolite norfluoxetine (7-9 days at steady state). This long t_{1/2} has allowed the introduction of a formulation for once weekly dosing.

(Ref: Katzung-13th/517)

Q. Short note: Selective serotonin reuptake inhibitors. (CU-14Ju)

Ans. Write from below.

Q. Explain the mechanism of action of citalopram. (RU-15Ju)

Q. How does fluoxetine produce anti-depressant effects? (RU-09J)

Q. Short note: Sertraline. (DU-09Ju)

Ans.

Anti-depressant effects of SSRI / fluoxetine:

Fluoxetine / Paroxetine / SSRIs

↓
 Selectively block the reuptake of serotonin
 ↓
 Increased concentration of the serotonin in the synaptic cleft
 ↓
 Greater post-synaptic neuronal activity
 ↓
 Anti-depressant effect

(Ref: Lippincott's-6th/135)

Q. What are the indications of SSRIs / Fluoxetine?

Ans.

Indications of SSRI:

1. Major depression.
2. Anxiety disorders:
 - Panic disorder
 - Generalized anxiety disorder (GAD)
3. Obsessive-compulsive disorders (OCD) (*the only approved indication for fluvoxamine*)
4. Other uses:
 - Bulimia (eating disorder, *only fluoxetine is approved for this indication*).
 - Pre-menstrual dysphoric disorder (PMDD)
 - posttraumatic stress disorder (PTSD)

(Ref: Katzung-13th/521-522; Lippincott's-6th/136)

Q. What are the adverse effects of SSRIs/ Fluoxetine? (CU-12J)

Ans.

Adverse effects of SSRIs: The adverse effects of the SSRIs can be predicted from their potent inhibition of serotonin reuptake. SSRIs enhance serotonergic tone, not just in the brain but throughout the body.

A. **GIT: Increased serotonergic activity in the gut is commonly associated with**

1. Nausea
2. Gastrointestinal upset
3. Diarrhea

GI adverse effects usually emerge early in the course of treatment and tend to improve after the first week.

B. **Increasing serotonergic tone at the level of the spinal cord and above is associated with diminished sexual function and interest-**

1. Loss of libido
2. Delayed orgasm
3. Diminished arousal.

The sexual effects often persist as long as the patient remains on the antidepressant but diminish with time.

C. **Other adverse effects**

1. Headaches
2. Insomnia or hypersomnia.
3. Weight gain (particularly paroxetine)
4. **Discontinuation syndrome** in some patients characterized by dizziness, paresthesias beginning 1 or 2 days after stopping the drug (paroxetine and sertraline) and persisting for 1 week or longer.

(Ref: Katzung-13th/524-525)

Q. Short note: Fluoxetine. (DU-17M)

Ans. Write from above discussion.

Q. What are the differences between TCA (Amitriptyline) & SSRI (Fluoxetine)? (DU-10Ju,09J,SU-15J,12J)

Q. Compare TCA & SSRI. (DU-08J; SU-16J,14J,12Ju,10J,09Ju; RU-13J; CU-13Ju)

Q. Compare TCAs & SSRIs with respect to their mechanism of action & side effects. (CU-06M)

Q. Compare and contrast Imipramine and Citalopram. (SU-13Ju)

Q. Compare Amitriptyline & Fluoxetine. (SU-13J,09J)

Q. Why sertraline is better than amitriptyline? (SU-11Ju)

Q. Differentiate sertraline from nortriptyline? (DU-15Ju)

Ans.

Differences between TCA (Amitriptyline, Imipramine) & SSRI (Fluoxetine, Citalopram):

Traits	TCA (Amitriptyline, Imipramine)	SSRI (Fluoxetine, Citalopram)
1. Chemistry	Tricyclic i.e. 3 benzene rings.	Dicyclic i.e. 2 benzene rings.
2. Mechanism of action	Blocks reuptake of both noradrenaline & serotonin	Blocks reuptake of serotonin
3. Absorption	Incompletely absorbed	Well absorbed than TCAs
4. Bioavailability	Less	More.
5. 1 st pass metabolism	Significant 1 st pass metabolism occurs.	No 1 st pass metabolism.
6. Half life	Relatively short (31-46 hours).	Long (7-9 days)
7. Anti-muscarinic action	Present	Absent
8. Blocks α adrenoceptor	Yes	No
9. Blocks α_2 -adrenoceptor	Yes, so it has sympathomimetic adverse effects.	No
10. Blocks central H ₁ -receptors.	Yes, so causes sedation.	No, so it causes less or no sedation
11. Weight gain	Yes	No
12. Effects on Libido	Less	More

Q. What are the advantages & disadvantages of SSRIs as anti-depressant? (SU-04M)

Q. Mention the advantages of selective serotonin reuptake inhibitors. (RU-08J)

Q. Discuss the advantages of SSRIs over tricyclic antidepressants (TCA). (DU-14J, CU-15Ju, RU-15Ju, SU-14Ju)

Ans.

Advantages of SSRIs as anti-depressants:

A. Pharmacokinetic advantages:

1. Absorbed well & thus bioavailability is more.
2. No 1st pass metabolism.
3. Long half life & thus less frequent dosing

B. Pharmacodynamic advantages:

1. Blocks only 5HT receptors (i.e. more selective effect. Hence, it is named SSRIs)
2. No anti-muscarinic blocking adverse effects.
3. No anti-adrenergic blocking adverse effects.
4. No anti-histaminergic blocking adverse effects.
5. No sympathomimetic adverse effects.

Disadvantages of SSRIs as anti-depressant:

1. More effects on libido & more chance of sexual dysfunction.
2. Paroxetine has teratogenic effect; so should be avoided in pregnancy.
3. Less chance of weight gain.
4. It causes transient nausea & insomnia.

Q. Name the newer anti-depressant drugs which are preferred clinically. (DU-10Ju)

Ans.

Newer anti-depressant drugs which are preferred clinically: Selective serotonin reuptake inhibitors (SSRI)

Selective Serotonin-norepinephrine reuptake inhibitors (SNRIs)

The SNRIs include venlafaxine, desvenlafaxine, duloxetine, milnacipran.

Mechanism of action: These drugs selectively inhibit the re-uptake of both serotonin and norepinephrine.

Effects: Acute increase in serotonergic and adrenergic synaptic activity, otherwise like SSRIs.

Indications:

1. Major depression
2. Chronic pain disorders
3. Fibromyalgia
4. Perimenopausal symptoms.

Toxicity:

1. Sedation
2. Serotonergic adverse effects associated with SSRIs.
3. Noradrenergic effects, including increased blood pressure and heart rate, and CNS activation, such as insomnia, anxiety, and agitation. The hemodynamic effects of SNRIs tend not to be problematic in most patients.
4. Cardiac toxicity (venlafaxine overdose)
5. Discontinuation syndrome.

Advantage over TCAs: The SNRIs differ from the TCAs in that they lack the potent antihistamine, α -adrenergic blocking, and anticholinergic effects of the TCAs. As a result, the SNRIs tend to be favored over the TCAs in the treatment of MDD and pain syndromes because of their better tolerability.
(Ref: Katzung-13th/520-525; Goodman & Gilman's-12th)

Atypical anti-depressants

Q. What are the atypical anti-depressants? Why are they called so?

Ans.

Atypical anti-depressants: The atypical anti-depressants are a mixed group of agents that have actions at several different sites. They include-

1. Bupropion
2. Mirtazapine
3. Nefazodone
4. Trazodone
5. Vilazodone
6. Vortioxetine

(Ref: Lippincott's-6th/138)

Bupropion

Mechanism of action: This drug acts as a weak dopamine and norepinephrine reuptake inhibitor to alleviate the symptoms of depression.

Properties

1. Its short half-life may require more than once-a-day dosing.
2. Assists in decreasing the craving and attenuating the withdrawal symptoms for nicotine in tobacco users trying to quit smoking.

Indication:

1. Depression
2. Treatment for smoking cessation.

Side effects

1. Dry mouth
2. Sweating
3. Nervousness
4. Tremor
5. A very low incidence of sexual dysfunction, and
6. Increased risk for seizures at high doses.

Contraindication

1. Patients at risk for seizures
2. Eating disorders such as bulimia.

(Ref: Lippincott's-6th/139)

Q. Elaborate the therapeutic approach to depression. (SU-15Ju)

Ans.

Therapeutic approach to depression: (make the answer short as per your need)

SELECTION:

- An antidepressant should be selected to match individual **patients' requirements**, such as the need for a sedative effect, or the avoidance of antimuscarinic effects (especially in the elderly).
- The choice rests on tolerability, safety in overdose etc.
- SSRIs, lofepramine, mirtazapine, reboxetine and venlafaxine are highlighted as best fulfilling these needs.

MODE OF USE

- Antidepressants usually require **3-4 weeks** for effect.
- Patients may experience **unwanted effects** immediately on starting treatment (they should be warned), but such symptoms often diminish with time.
- **Titrating** from a generally tolerable starting dose, e.g. amitriptyline 30-75 mg/day, with **weekly increments** to a recognized '**minimum therapeutic**' dose, usually around 125 mg/day, lessens the impact of adverse symptoms before a degree of tolerance (and therapeutic benefit) develops.
- **Low starting doses** are particularly important for **elderly patients**.
- Only when the drug has reached the minimum therapeutic dose and been taken for at least 4 weeks can response or non-response be considered **adequate**.
- **TCAs** are given either in divided doses or, for the more sedative compounds, as a single evening dose.
- **SSRIs** have advantages over tricyclics in simplicity of introduction and use.
 - Dose titration is often unnecessary as the minimum therapeutic dose can usually be tolerated as a starting dose.
 - Divided doses are not required, and administration is by a single morning or evening dose.
- Response to **reboxetine, venlafaxine and mirtazapine** may occur at the starting dose, but some dose titration is commonly required.
- **Venlafaxine** is licensed for treatment-resistant depression by gradual titration from 75 to 375 mg/day.

CHANGING AND STOPPING ANTIDEPRESSANTS

- **When an antidepressant fails** despite an adequate trial or due to unacceptable adverse effects, a **change** to a drug of a different class is generally advisable.
- For a patient who has not responded to an **SSRI** it is logical to try a **TCA** or a **novel compound** such as venlafaxine, reboxetine or mirtazapine.
- Evidence also suggests that patients failing on one SSRI may respond to a different drug within the class.
- When changing between SSRIs and/or TCAs, doses should be **reduced progressively** over 2-4 weeks, and where a new drug is to be introduced it should be '**cross-tapered**', i.e. the dose **increased** gradually as that of the substituted drug is **reduced**.
- Changes to or from **MAOIs** must be handled with great caution due to the dangers of **interactions** between antidepressants. Therefore MAOIs cannot safely be introduced within 2 weeks of stopping SSRIs and TCAs and not until 5 weeks after stopping fluoxetine. Similarly, TCAs and SSRIs should not be introduced until 2-3 weeks have elapsed from discontinuation of MAOI.
- When a patient achieves **remission**, the antidepressant should be continued for at least **9 months** at the dose that returned mood to normal. Premature dose reduction or withdrawal is associated with increased risk of **relapse**.
- In cases where three or more depressive episodes have occurred, evidence suggests that **long-term continuation** of an antidepressant offers protection.
- When ceasing use of an antidepressant, the dose should be **reduced gradually** to avoid a **discontinuation syndrome** (symptoms include anxiety, agitation, nausea and mood swings).

AUGMENTATION

- Augmentation, i.e. the addition of another drug, is used to enhance the effects of standard antidepressants when two or more have successively failed to alleviate depressive symptoms despite treatment at an adequate dose for an adequate time.
- **Drugs used for augmentation:**
 1. Mood stabiliser, lithium carbonate (*most commonly used. 50% of patients who have not responded to standard antidepressants can respond after lithium augmentation.*)
 2. Tri-iodothyronine (T3).
 3. Amino acid L-tryptophan
 4. β -blocker pindolol.
 5. Atypical antipsychotics - olanzapine, quetiapine and risperidone.

(Ref: Bennet & Brown-12th)

Anti-psychotic drugs

Psychosis: The term "psychosis" denotes a variety of **mental disorders**: the presence of **delusions** (false beliefs), various types of **hallucinations**, usually auditory or visual, but sometimes tactile or olfactory, and grossly disorganized thinking in a clear sensorium.

(Ref: Katzung-13th/491)

The psychotic disorders include

1. Schizophrenia
2. Manic phase of bipolar (manic-depressive) illness
3. Acute idiopathic psychotic illnesses, and other conditions marked by severe agitation.

(Ref: Goodman & Gilman's-12th)

Schizophrenia: Idiopathic psychoses characterized by chronically disordered thinking & emotional withdrawal & often associated with delusions & auditory hallucinations, are called schizophrenia.

(Ref: Goodman & Gilman's-12th)

Symptoms of Schizophrenia

Positive symptoms:

1. **Hallucinations:** most commonly auditory (i.e. voices) in the third person, which patients may find threatening. The voices may also give commands. Visual hallucinations are rare.
2. **Delusions:** most commonly persecutory. 'Passivity phenomena' include delusions of thought broadcasting, thought insertion or thought withdrawal, made actions, impulses or feelings.
3. **Bizarre behaviours** including agitation, sexual disinhibition, repetitive behaviour, wearing of striking but inappropriate clothing.
4. **Thought disorder** manifest by failure in the organization of speech such that it drifts away from the point (tangentiality), never reaches the point (circumstantiality), moves from one topic to the next illogically (loosened associations, knight's move thinking), breaks off abruptly only to continue on an unrelated topic (derailment) or moves from one topic to the next on the basis of a pun or words that sound similar (clang association).

Negative symptoms:

1. **Affective flattening** manifest by unchanging facial expression with lack of communication through expression, poor eye contact, lack of responsiveness, psychomotor slowing.
2. **Alogia** (literally 'absence of words', manifesting clinically as a lack of spontaneous speech (poverty of speech).
3. **Anhedonia** (inability to derive pleasure from any activity) and **associality** (eg. withdrawal from social contacts)
4. **Apathy/avolition** involving lack of energy, lack of motivation to work, participate in activities or initiate any goal-directed behaviour, and poor personal hygiene.
5. **Attention problems** involving an inability to focus on any one issue or engage fully with communication.

(Ref: Bennet & Brown-11th edition)

Delusions: Delusions means **false beliefs**. Eg, the belief that one has special powers or status or that one has cancer. Examples of the most extreme form of delusion are- 'My head is missing,' 'I have no body,' 'I am dead.'

(Ref: Davidson's-22nd edition)

Hallucinations: These are perceptions without external stimuli, ie, **false sensation**. They can occur in any sensory modality, most commonly visual or auditory. Typical examples are hearing voices when no one else is present, or seeing demonic faces on a blank white wall.

(Ref: Davidson's-22nd edition)

Antipsychotic drugs: The term *antipsychotic drugs*- previously known as **neuroleptic drugs**, **antischizophrenic drugs** or **major tranquillisers**- conventionally refers to those used to treat **schizophrenia**.

(Ref: Rang & Dale's-8th)

A **neuroleptic** is a subtype of antipsychotic drug that produces a high incidence of **extrapyramidal side effects** (EPS) at clinically effective doses, or catalepsy in laboratory animals.

(Ref: Katzung-13th/490)

Q. Write down the chemical basis of psychosis. (DU-08/07Ju)

Q. Briefly outline biological basis of schizophrenia. (SU-13J,12Ju)

Q. Elaborate the biological basis of psychosis. (SU-17M,16Ju,15Ju)

Ans.

Biological / Chemical basis of schizophrenia: Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly a **dysfunction of the mesolimbic or mesocortical dopaminergic neurons**.

Serotonin hypothesis of Schizophrenia: According to this hypothesis, **increased serotonin activity** in the brain could be involved in schizophrenia. Atypical antipsychotic drugs such as clozapine and quetiapine act by blocking 5-HT_{2A}-receptor.

(Ref: Katzung-13th/491 + Rang & Dale's-8th)

Dopamine hypothesis of schizophrenia: It is the most fully developed of several hypotheses and is the basis for much of the rationale for drug therapy. According to this hypothesis "**excessive dopaminergic activity in the brain is responsible for schizophrenia**". Increased dopaminergic activity is brought about by-

1. Increase in brain dopamine D₂-receptors
2. Dopamine receptor (D₂) supersensitivity
3. Increased dopamine level due to overproduction or reduced destruction.

(Ref: Katzung-13th/491 + Bennett & Brown-11th)

Glutamate hypothesis of schizophrenia: Glutamate is the major excitatory neurotransmitter in the brain. Hypofunction of NMDA receptors, located on GABAergic interneurons, leading to diminished inhibitory influences on neuronal function, contributed to schizophrenia.

(Ref: Katzung-13th/492)

[NB: N-methyl-d-aspartate (NMDA)]

Q. Classify/Enlist anti-psychotic drugs. (DU-17M,15J,11J,09J,07M, CU-17J, SU-11J, RU-06M)

Q. Enumerate typical & atypical anti-psychotic drugs. (CU-06M)

Q. Name the atypical anti-psychotic drugs. (DU-13Ju,10J, RU-16Ju,11/10Ju)

Q. Name the newer anti-psychotic drugs. (RU-13Ju)

Q. Classify anti-schizophrenia drugs.

Q. Classify antipsychotic drugs according to their potency. (CU-16J)

Q. Enlist D₂ receptor antagonist in CNS. (CU-15Ju)

Q. What are the drugs used for major psychosis? (SU-16Ju)

Q. Short note: Atypical anti-psychotic drugs. (DU-11Ju)

Ans.

Anti-psychotic drugs / drugs for schizophrenia / D₂ receptor antagonist in CNS:

A. **Traditional or typical neuroleptic drugs** (also called **conventional** or **first-generation antipsychotics**) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive **blocking of dopamine receptors**.

According to chemical nature:

1. <u>Phenothiazine derivatives</u>	- Chlorpromazine - Prochlorperazine - Thioridazine - Perphenazine - Trifluoperazine - Fluphenazine
2. <u>Thioxanthene derivatives</u>	Thiothixene
3. <u>Butyrophenone derivatives</u>	Haloperidol
4. <u>Miscellaneous structure</u>	- Pimozide - Molindone

According to potency: (The first-generation drugs are further classified as "low potency" or "high potency" based on the affinity for the dopamine D2 receptor.)

Low potency	- Chlorpromazine - Thioridazine
High potency	- Fluphenazine - Haloperidol - Loxapine - Perphenazine - Pimozide - Prochlorperazine - Thiothixene - Trifluoperazine

(Ref: Lippincott's-6th/147)

B. Atypical (or second-generation antipsychotics):

Atypical (or second-generation antipsychotics): The newer antipsychotic drugs are referred to as atypical (or second-generation antipsychotics), because they have **fewer extrapyramidal adverse effects** than the older, traditional agents.

These drugs appear to owe their unique activity to **blockade of both serotonin and dopamine** (and, perhaps, other) receptors.

The "atypical" antipsychotic drugs are now the **most widely used** type of antipsychotic drug.

1. Loxapine
2. Clozapine
3. Asenapine
4. Olanzapine
5. Quetiapine
6. Paliperidone
7. Risperidone
8. Sertindole
9. Ziprasidone
10. Zotepine
11. Aripiprazole

(Ref: Katzung-13th/493-494; Lippincott's-6th/147-148)

C. Glutamatergic antipsychotics: Glycine transporter 1 receptor inhibitor-

1. Bitopertin
2. Sarcoserine

(Ref: Katzung-13th/494)

Nice to know

- Investigational antipsychotic agents includes the metabotropic glutamate receptor agonists.
- Dopamine receptors:
 1. $D_1, D_5 \rightarrow G_s \rightarrow (+) \text{ Adenylyl cyclase enzyme} \rightarrow \uparrow cAMP$
 2. $D_2, D_3, D_4 \rightarrow G_i \rightarrow (-) \text{ Adenylyl cyclase enzyme} \rightarrow \downarrow cAMP$

Q. What is the mechanism of action of anti-psychotics? (CU-06M)

Q. Mention the anti-psychotic mechanism of action of chlorpromazine. (DU-16Ju,08Ju)

Q. Mention the mechanism of action of central dopamine receptor blocker. (CU-11J)

Q. Mention the mechanism of action of haloperidol. (DU-12Ju)

Q. Explain the anti-psychotic effects of chlorpromazine. (DU-15J,09J,07M), RU-11Ju

Q. Explain anti-psychotic actions of haloperidol. (DU-11J, RU-13Ju,06M,04J, SU-08J)

Q. Which pathway of dopaminergic neurotransmission is utilized to treat schizophrenia? (CU-07Ju)

Q. How Phenothiazine acts as anti-psychotic? (CU-17M,06M)

Q. How does chlorpromazine produce anti-psychotic effect? (DU-12J)

Ans.

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Mechanism of action of typical anti-psychotic drugs (eg, chlorpromazine/ haloperidol): The typical anti-psychotic drugs produce their antipsychotic action by blocking D₂ dopamine receptors in the mesolimbic and mesocortical systems of the brain.

Chlorpromazine / haloperidol
 ↓
Block dopamine D₂ receptor in the mesolimbic-mesocortical pathway
 ↓
 Open K⁺ channel
 ↓
 K⁺ influx into neuron
 ↓
 Hyperpolarization of neuron
 ↓
 Decreases excitability of neurons
 ↓
 ▪ No hallucination, delusion, aggressive behavior
 ▪ Calmness
 ▪ Tranquility
 ▪ Normal sleep pattern
 ↓
Anti-psychotic action.

(Ref: Katzung-13th/495; Lippincott's-6th/148)

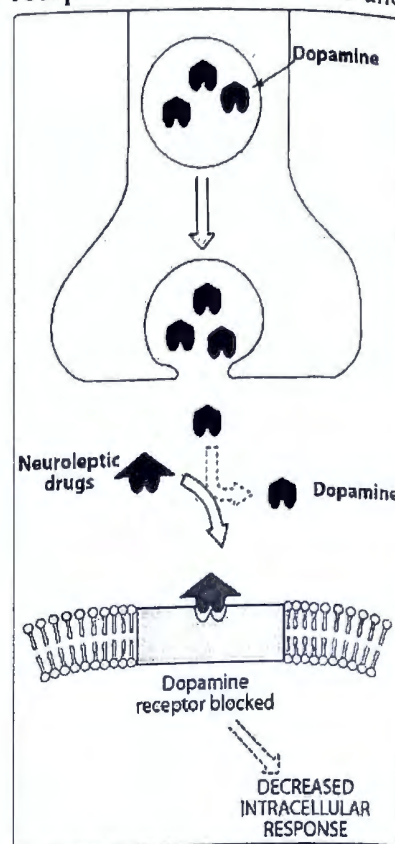


Figure. Dopamine-blocking actions of neuroleptic drugs.

Mechanism of action of atypical anti-psychotic drugs (eg, clozapine): Most of the newer atypical agents appear to exert part of their unique action by blocking serotonin receptor (5-HT_{2A}-receptor). The atypical drugs also **block D₂ receptor** but they have lower affinity for the D₂ receptor, which may partially explain its minimal ability to cause extrapyramidal side effects (EPS).

(Ref: Katzung-13th/495; Lippincott's-6th/148)

Nice to know

Relative receptor-binding affinities of anti-psychotic drugs

- Chlorpromazine: $\alpha_1 = 5\text{-HT}_{2A} > D_2 > D_1$
- Haloperidol: $D_2 > \alpha_1 > D_4 > 5\text{-HT}_{2A} > D_1 > H_1$
- Clozapine: $D_4 = \alpha_1 > 5\text{-HT}_{2A} > D_2 = D_1$
- Olanzapine: $5\text{-HT}_{2A} > H_1 > D_4 > D_2 > \alpha_1 > D_1$
- Aripiprazole: $D_2 = 5\text{-HT}_{2A} > D_4 > \alpha_1 = H_1 \gg D_1$
- Quetiapine: $H_1 > \alpha_1 > M_{1,3} > D_2 > 5\text{-HT}_{2A}$

(Ref: Katzung-13th/496)

Q. Enlist D₂ receptor antagonist in CNS. (CU-15Ju)

Ans. D₂ receptor antagonist in CNS: Anti-psychotic drugs are D₂ receptor antagonist in CNS.

Q. Enlist the pharmacological effects of anti-psychotics. (CU-07S)

Q. Discuss the effects of chlorpromazine on CNS. (DU-10J)

Q. Outline the consequences of dopamine receptor blockade in the CNS. (CU-13/12J,09Ju,08Ju)

Q. Enumerate the central effects of chlorpromazine. (CU-06J)

Q. Enumerate the therapeutic actions of chlorpromazine that are related to its blockade of dopaminergic receptor. (CU-07Ju;RU-07Ju)

Q. Enumerate effects of dopaminergic receptor stimulation in different sites of the body. (CU-04S)

- Q. Mention the dopaminergic pathway/tract in the brain. Describe the effects of dopamine in various dopaminergic tracts. (DU-12Ju, CU-14Ju)
- Q. Describe the behavioral effects of chlorpromazine. (CU-15Ju)
- Q. Write short note on: Chlorpromazine. (DU-09Ju, SU-13J)

Ans.
Pharmacological effects of anti-psychotics/chlorpromazine:

- A. **Effects of dopaminergic receptor blocking:** There are 5 important dopaminergic pathways recognized in the brain.

Dopaminergic pathways in the brain	Effects on blocking the pathway
1. Mesolimbic-mesocortical pathway: Closely related to behavior	Antipsychotic action- - No hallucination - No delusion - No aggressive behavior - Calmness - Tranquility - Normal sleep pattern.
2. Nigrostriatal pathway: Involved in the coordination of voluntary movements.	Extra-pyramidal syndromes (EPS): - Parkinson's syndrome - Akathisia - Acute dystonic reactions - Tardive dyskinesia - Seizure
3. Tuberoinfundibular pathway: Inhibits prolactin secretions.	Increased prolactin secretion, which causes in- Women: - Amenorrhea - Galactorrhea. - False +ve pregnancy tests. - Increased libido. Men: - Gynecomastia. - Decreased libido.
4. Medullary-periventricular pathway: May be involved in eating behavior.	Weight gain (due to altered eating behavior).
5. Incertohypothalamic pathway: Regulates copulatory behavior in rats.	It appears to regulate the anticipatory motivational phase of copulatory behavior in rats.

(Ref: Katzung-13th/495) Hpc

- B. **Effects of other receptors blocking property:**

Types of blocking	Effects of blocking
1. Muscarinic receptor blocking	- Tachycardia - Urine retention - Constipation - Dry mouth & skin - Blurred vision
2. α-adrenergic blocking	- Postural hypotension - Reflex tachycardia - Cardiac arrhythmias - Ejaculatory failure.
3. Histaminergic blocking	- Sedation - Anti-allergic action. - Anti-emetic effect

4. Voltage gated Na ⁺ channel blocking	▪ Anti-epileptic effects. ▪ Local anesthetics. ▪ Arrhythmia.
5. Peripheral conversion of androgen to estrogen	Women: ▪ Amenorrhea. ▪ Galactorrhea. ▪ False +ve pregnancy tests. ▪ Increased libido. Men: ▪ Gynecomastia. ▪ Decreased libido.
6. Serotonin (5-HT ₂) receptor blocking.	▪ Antipsychotic action

(Ref: Katzung-13th/497)

Q. List the indications of anti-psychotics / chlorpromazine. (DU-07Ju)

Q. Mention the clinical uses of central dopamine receptor blocker. (CU-11J)

Ans.

Indications of chlorpromazine:

Psychiatric Indications

1. **Schizophrenia:** It is the primary indication for antipsychotic agents.
2. **Schizoaffective disorders** (characterized by both schizophrenia & affective disorder)
3. **Mood disorders:**
 - a. **Psychotic depression** (along with anti-depressant)
 - b. **Treatment-resistant depression**
 - c. **Acute bipolar depression**
 - d. **Unipolar depression** (adjunctive use of antipsychotics with antidepressants).
 - e. Acute phase of **mania** in **bipolar affective disorder**
 - f. Control of **agitation** associated with bipolar disorder and schizophrenia (**haloperidol**).
4. **Tourette's syndrome**
5. Disturbed behavior in patients with **Alzheimer's disease**

Nonpsychiatric Indications

1. **As anti-emetic** (*prochlorperazine and benzquinamide. Most older typical antipsychotic drugs have a strong antiemetic effect. This action is due to dopamine-receptor blockade*)
2. **For relief of pruritus** (H₁-receptor-blocking action)
3. **Preoperative sedatives** (promethazine)
4. **Neuroleptanesthesia** (droperidol + fentanyl)

(Ref: Katzung-13th/497-498)

Q. Elaborate the therapeutic approach to psychosis. (SU-15Ju)

Ans.

Therapeutic approach to psychosis

1. Patients who are 'neuroleptic naive', i.e. have never previously taken any antipsychotic agent, should start at the **lowest available dose**, e.g. haloperidol 0.5 mg/day or chlorpromazine 25 mg/day.
2. The **dose is increased** at intervals, until the desired effect on psychotic symptoms, calming disturbed behaviour or effecting sedation, is achieved.
3. They take **2–4 weeks** to be maximally effective. Treatment is then ideally continued to prevent relapse.
4. The benefits of prolonged treatment must be weighed against the adverse effects, which include extrapyramidal side-effects.
5. For long-term use, antipsychotic agents are often given in slow-release (depot) injected form to improve patient adherence.
6. The longer a psychosis is left untreated, the less favourable is the outcome.

7. Prescription of atypical antipsychotics follows similar rules to those for classical drugs, starting at low doses in neuroleptic-naïve patients.

(Ref: Bennet & Brown-11th edition; Davidsons-22nd/248)

Nice to know

Pharmacokinetics of anti-psychotic drugs:

- Most anti-psychotic drugs are readily but incompletely absorbed.
- Chlorpromazine: 25-35% bioavailability.
- Haloperidol: 65% bioavailability
- Many of them undergo significant 1st pass metabolism.
- Most of them are highly lipid soluble & protein bound (92-99%).
- They tend to have more volume of distribution.
- Standard elimination half lives: 20-40 hours.
- Metabolized almost completely.

(Ref- Katzung-13th/495 & Goodman & Gilman's-12th)

- Q. What are the adverse effects of anti-psychotics with underlying mechanism? (SU-11J, RU-05S, 03M)
- Q. Mention the adverse effects of chlorpromazine. (DU-15J, 12J, 08J, CU-17J, SU-16Ju)
- Q. Mention the three important adverse effects of chlorpromazine. (DU-16Ju)
- Q. What are the adverse effects of phenothiazines? Explain the underlying mechanism. (CU-17M, 06M; SU-14Ju)
- Q. Mention the adverse effects of haloperidol. (DU-12Ju, 11J, RU-06M, 04S, 03J)
- Q. Enumerate the motor and endocrine adverse effects of typical antipsychotic drugs. (SU-15Ju)
- Q. What are the endocrine adverse effects of chlorpromazine? (RU-09Ju)
- Q. Mention the adverse effects of central dopamine receptor blocker. (CU-12/11J)
- Q. Outline the CNS adverse effects of conventional antipsychotics and how could they be prevented? (RU-16Ju)

Ans.

Adverse effects of antipsychotics/ chlorpromazine/ haloperidol:

Type	Adverse effects	Mechanisms
ANS	▪ Tachycardia ▪ Urine retention ▪ Constipation ▪ Dry mouth & skin ▪ Blurred vision	Muscarinic receptor blockade.
	▪ Postural hypotension ▪ Reflex tachycardia ▪ Cardiac arrhythmias ▪ Ejaculatory failure.	α -adrenergic blocking
CNS	Extra-pyramidal symptoms: ▪ Parkinson's syndrome. ▪ Akathisia. ▪ Acute dystonic reactions. ▪ Tardive dyskinesia. ▪ Seizures.	Dopamine receptor blocking.
	▪ Toxic confusional state	Muscarinic receptor blockade.
	▪ Sedation.	H ₁ -receptor blockade.
	▪ Weight gain	Both H ₁ & 5-HT ₂ blockade.

Endocrine	Women: ▪ Amenorrhea. ▪ Galactorrhea. ▪ False +ve pregnancy tests. ▪ Increased libido. Men: ▪ Gynecomastia. ▪ Decreased libido.	Hyperprolactinemia.
Cardiac	▪ Ventricular arrhythmia. ▪ Cardiac conduction block. ▪ Abnormalities in T-wave.	In case of overdose.
Ocular	▪ Deposition in the anterior portion of the (eye & lens).	Common in chlorpromazine therapy
Others	▪ Agranulocytosis. ▪ Cholestatic jaundice. ▪ Skin eruption.	Allergic reaction.

(Ref: Katzung-13th/497 (Table: 29-2), 500)

Extra-pyramidal symptoms (EPS)

Mechanism of EPS: Extra-pyramidal symptoms result directly or indirectly from **D₂-receptor blockade** in the nigrostriatal pathway. They are called so because they involve extrapyramidal motor system.

Table: Extra-pyramidal symptoms of Neuroleptic Drugs

Reaction	Features
1. Acute dystonia (spastic retrocollis or torticollis)	Spasm of muscles of tongue, face, neck, back; may mimic seizures; <i>not</i> hysteria
2. Akathisia	Motor restlessness; <i>not</i> anxiety or "agitation"
3. Parkinsonism	Bradykinesia, rigidity, variable tremor, masked facies, shuffling gait
4. Neuroleptic malignant syndrome	Catatonia, stupor, fever, unstable blood pressure, myoglobinemia; can be fatal
5. Perioral tremor ("rabbit syndrome")	Perioral tremor (may be a late variant of parkinsonism)
6. Tardive dyskinesia	Oral-facial dyskinesia; widespread choreoathetosis or dystonia

(Ref: Goodman & Gillman-12th edition)

Drugs causing EPS: Extrapyramidal symptoms are mainly caused by first-generation/typical antipsychotic drugs because of more D₂ dopamine receptor blockade by these drugs. The atypical antipsychotic drugs exhibit a lower incidence of these symptoms because they have lower affinity to D₂ dopamine receptor.

1. <u>Drugs causing severe EPS</u>	▪ Haloperidol ▪ Fluphenazine.
2. <u>Drugs causing moderate EPS</u>	▪ Chlorpromazine ▪ Perphenazine ▪ Loxapine ▪ Risperidone ▪ Molindone
3. <u>Drugs causing less EPS</u>	▪ Clozapine ▪ Aripiprazole ▪ Olanzapine ▪ Mesoridazine ▪ Thioridazine

(Ref: Goodman & Gillman-12th edition)

Q. Mrs. Camelia attended a psychiatrist; following treatment she developed rigidity, bradykinesia and tremor. Mention her newly developed disease condition and enlist the offending drugs which may cause such unwanted effects. What are the underlying causes and how will you manage it? (SU-13Ju)

Ans.

Diagnosis: Extra-pyramidal symptoms of anti-psychotic drugs

Drugs causing such unwanted effects: Write drugs causing moderate and severe EPS from above.

Underlying causes: D₂-receptor blockade in the nigrostriatal pathway by the offending drug.

Management: Reduce dose or change drug; antiparkinsonian agents may help

Q. A patient aged 35 years suffering from psychosis & is given chlorpromazine. He develops tremor & rigidity. Explain the causes & give treatment. (SU-09Ju)

Ans. The patient has developed chlorpromazine-induced Parkinsonism.

Cause: D₂-receptor blockade in the nigrostriatal pathway by chlorpromazine.

Treatment: Antiparkinsonism drugs.

Q. Mention the advantages of atypical anti-psychotics over classical ones. (RU-16Ju,07Ju)

Q. Mention the advantages of newer anti-psychotics over older. (RU-13Ju,12Ju,11Ju)

Q. Why clozapine is better than chlorpromazine? (SU-17M)

Ans.

Advantages of atypical / 2nd generation anti-psychotics:

1. Extra-pyramidal side effects are minimal. So, tolerability and thus compliance is better for atypical agents.
2. They are more effective than older ones in treating **negative symptoms** of schizophrenia.
3. Clozapine (but not the newer atypicals) is more effective than classical agents in treatment-resistant schizophrenia.
4. They may improve the impaired cognitive function.
5. H₁-receptor blockade activity (sedation) is minimal.

Typical - High potency, low cost

(Ref: Bennet & Brown-11th edition)

Clozapine

Criteria of clozapine:

1. **Half life:** Average 12 hours.
2. **Clinical potency:** Medium
3. Suppress both positive & negative symptoms of schizophrenia.
4. Many patient refractory to typical anti-psychotics respond to clozapine.
5. **Extra-pyramidal symptoms:** Few or no.
6. **Anti-muscarinic activity:** Moderate to high.
7. **Incidence of agranulocytosis:** High.
8. Prolactin level does not rise.

(Ref: Tripathi-6th/429)

Adverse effects of clozapine:

1. Agranulocytosis.
2. Anti-muscarinic adverse effects:
 - Mydriasis
 - Tachycardia
 - Dry mouth
 - Dry skin
 - Blurred vision
 - Urine retention
 - Constipation
3. Unstable blood pressure.

Q. What are the differences between chlorpromazine & haloperidol?

Q. Compare chlorpromazine with haloperidol as antipsychotic. (CU-15J,14J)

Ans.

Differences between chlorpromazine & haloperidol:

Traits	Chlorpromazine	Haloperidol
1. Chemistry	Phenothiazine derivatives	Butyrophenone derivatives
2. Clinical potency	Low	High
3. Extra pyramidal symptoms	Medium	Severe
4. Anti-muscarinic effects.	More	Less
5. Sedation	High	Low
6. Hypotensive actions	More common	Less common

(Ref: Katzung-13th edition)

Q. Compare classical and atypical antipsychotics. (RU-14Ju)

Q. Write down the differences between Chlorpromazine & Olanzapine. (DU-14Ju)

Ans.

Comparison between classical and atypical antipsychotics

Traits	Classical antipsychotics (eg, Chlorpromazine)	Atypical antipsychotics (eg, Olanzapine)
1. Mechanism of action	Block dopamine D ₂ receptor.	Block serotonin receptor (5-HT _{2A}) and D ₂ receptor.
2. D ₂ -blocking activity	Strong	Weak
3. Tolerability and thus compliance	Less	More
4. Extra pyramidal symptoms	Severe	Little
5. Efficacy against negative symptoms of schizophrenia	Less effective	More effective
6. H ₁ -receptor blockade activity (sedation)	More	Less
7. Anti-emetic effect	Present	Absent
8. Hyperprolactinemia	Present	Absent
9. Efficacy against Treatment-resistant schizophrenia	Less	More (Clozapine, but not the newer atypicals)

(Ref: Katzung-13th edition; Bennet & Brown-11th)

Q. Compare haloperidol & clozapine? (SU-14J,13J,10Ju)

Q. How haloperidol differs from clozapine? (SU-09J,08J)

Ans.

Differences between haloperidol & clozapine:

Traits	Haloperidol	Clozapine	Olanzapine
1. Chemistry	Butyrophenone	Dibenzodiazepine	Thienobenzodiazepine
2. D ₂ -blocking activity	Strong	Weak	Weak
3. Clinical potency	High	Medium	High
4. Extra pyramidal symptoms	Severe	Little	Little or no
5. Hypotension	Less common	More common	Less common
6. Anti-emetic effect	Present	Absent	Absent
7. Hyperprolactinemia	Present	Absent	Absent
8. Efficacy against Treatment-resistant schizophrenia	Less	More	Less

(Ref: Katzung-13th edition)

Q. Compare between chlorpromazine & risperidone. (DU-17M, 13Ju)

Ans.

Comparison between chlorpromazine & risperidone

Traits	Chlorpromazine	Risperidone
1. Clinical potency	Low	Medium
2. Extra pyramidal symptoms	Severe	Little
3. Hypotension	Less common	More common
4. Anti-emetic effect	Present	Absent
5. Hyperprolactinemia	Present	Absent

(Ref: Katzung-13th edition)

Q. Compare anti-psychotic action of haloperidol & olanzapine. (SU-07Ju)

Ans.

Anti-psychotic action of haloperidol & olanzapine: *Write from below*

Drug	Advantages	Disadvantages
Chlorpromazine	Generic, inexpensive	Many adverse effects, especially autonomic
Haloperidol	Parenteral form also available; generic	Severe extrapyramidal syndrome
Clozapine	May benefit treatment-resistant patients; little extrapyramidal toxicity	May cause agranulocytosis in up to 2% of patients; dose-related lowering of seizure threshold
Risperidone	Broad efficacy; little or no extrapyramidal system dysfunction at low doses	Extrapyramidal system dysfunction and hypotension with higher doses
Olanzapine	Effective against negative as well as positive symptoms; little or no extrapyramidal system dysfunction	Weight gain; dose-related lowering of seizure threshold

(Ref: Katzung-13th edition)

Q. Compare Imipramine with Chlorpromazine. (CU-16J)

Ans.

Comparison between Imipramine and Chlorpromazine:

Traits	Imipramine	Chlorpromazine
1. Chemistry	Tricyclic i.e. 3 benzene rings.	Phenothiazine derivatives
2. Mechanism of action	Blocks reuptake of both noradrenaline & serotonin	Block dopamine D ₂ receptor.
3. Anti-muscarinic action	Yes	Yes
4. Blocks α adrenoceptor	Yes	Yes
5. H ₁ -receptor blockade activity (sedation)	Yes	Yes
6. Can cause Seizure	Yes	Yes
7. Anti-emetic effect	No	Yes
8. Hyperprolactinemia	No	Yes
9. Extrapyramidal side effects	No	Yes

Q. A male patient of 26 years of age has been suffering from mental illness. Doctor prescribed him clozapine & Procyclidine. Discuss their action. (SU-10J)

Ans.

Mechanism of action of clozapine:

- Clozapine blocks 5HT₂ receptor and also D₂ receptors for anti-psychotic action.
- Procyclidine is used in patients to reduce the extrapyramidal side effects of antipsychotic treatment.

Anti-convulsants / Antiepileptics

Seizure: A seizure or convulsion is any clinical event caused by an **abnormal electrical discharge in the brain**. Major seizures cause loss of consciousness, with the patient falling to the ground and presenting with a history of 'blackouts'. Minor seizures causing alteration of consciousness, without the patient falling to the ground, may also be described by patients as 'blackouts'.

(Ref: Davidson's-22nd)

Mechanism of seizure: It is due to sudden, excessive depolarization of some or all cerebral neurons. This may remain localized (focal seizure) or may spread to cause a secondary generalized seizure, or affect all cortical neurons simultaneously (primary generalized seizure).

(Ref: Bennet & Brown-11th edition)

Seizures are thought to arise from cerebral cortex; not from the other CNS structures such as the thalamus, brainstem or cerebellum. Seizures can be "nonepileptic" when evoked in a normal brain by treatments such as electroshock or chemical convulsants or "epileptic" when occurring without evident provocation.

(Ref: Goodman & Gilman's-12th)

Epilepsy: Epilepsy means a tendency to have recurrent seizures. It is a symptom of brain disease rather than a disease itself. A single seizure is not epilepsy but an indication for investigation.

(Ref: Davidson's-22nd)

Epilepsy: The term *epilepsy* refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures.

(Ref: Goodman & Gilman's-12th)

Classification of seizures/epilepsy:

Seizure types	Features
Partial seizures:	
1. Simple partial	Diverse manifestations determined by the region of cortex activated by the seizure (e.g., if motor cortex representing left thumb, clonic jerking of left thumb results; if somatosensory cortex representing left thumb, paresthesia of left thumb results), lasting approximating 20 to 60 seconds. <i>Key feature is preservation of consciousness.</i>
2. Complex partial	Impaired consciousness lasting 30 seconds to 2 minutes, often associated with purposeless movements such as lip smacking or hand wringing.
3. Partial with secondarily GTCS	Simple or complex partial seizure evolves into a tonic-clonic seizure
Generalized seizures:	
1. Absence (petit mal) seizure	Abrupt onset of impaired consciousness associated with staring and cessation of ongoing activities typically lasting less than 30 seconds. The pt stares and exhibits rapid eye-blinking.
2. Myoclonic seizure	A brief (perhaps a second), shock-like contraction of muscles which may be restricted to part of one extremity or may be generalized.
3. Generalized tonic-clonic (grand mal) seizures (GTCS)	The patient first becomes rigid and unconscious, falling down heavily if standing. This is followed by sustained contractions (tonic) of muscles throughout the body followed by periods of muscle contraction alternating with periods of relaxation (clonic), typically lasting 1 to 2 minutes.
4. Atonic seizures	These are seizures involving brief loss of muscle tone, usually resulting in heavy falls with or without loss of consciousness.
5. Tonic seizures	
6. Infantile spasms	

(Ref: Goodman & Gilman's-12th, Davidson's-22nd, Lippincott's-6th; Katzung-13th)

Q. What are the causes of seizures other than epilepsy? (CU-16Ju,14Ju)

Ans.

Causes of seizures other than epilepsy

1. **Febrile convulsions**
2. **Cerebrovascular disease**
 - a. Intracerebral hemorrhage
 - b. Cerebral infarction
 - c. Arteriovenous malformation
 - d. Cavernous hemangioma
3. **Tumours** (primary and secondary)
4. **Trauma** (including neurosurgery)
5. **Infective**
 - a. Meningitis
 - b. Encephalitis
 - c. Cerebral abscess (pyogenic)
 - d. Toxoplasmosis
 - e. Cysticercosis
 - f. Tuberculoma
 - g. Subdural empyema
 - h. HIV
 - i. Post-infectious encephalopathy
6. **Inflammatory**
 - a. Sarcoidosis
 - b. Vasculitis
 - c. SLE
7. **Cerebral birth injury**
8. **Hydrocephalus**
9. **Cerebral anoxia**
10. **Drugs**
 - a. **Antibiotics:** penicillin, isoniazid, metronidazole
 - b. **Antimalarials:** chloroquine, mefloquine
 - c. Ciclosporin
 - d. **Cardiac anti-arrhythmics:** lidocaine, disopyramide
 - e. **Psychotropic agents:** phenothiazines, tricyclic antidepressants, lithium
 - f. Amphetamines (withdrawal)
11. **Alcohol (especially withdrawal)**
12. **Toxins**
 - a. Heavy metals (lead, tin)
 - b. Organophosphates
13. **Metabolic disease**
 - a. Hypocalcaemia
 - b. Hyponatremia
 - c. Hypomagnesaemia
 - d. Hypoglycaemia
 - e. Renal failure
 - f. Liver failure

(Ref: Davidson's-22nd/1180-1181)

Q. Describe pathophysiology of epilepsy. (CU-16J)

Q. Describe the neurochemical basis of origin of epilepsy. (CU-16Ju)

Q. Discuss the role of GABA in the pathogenesis of epilepsy. (CU-17J,12J)

Ans.

Pathophysiology /neurochemical basis of epilepsy: To function normally, the brain must achieve an ongoing balance between excitation and inhibition, in order to remain responsive to the environment without

continued unrestrained spontaneous activity. The inhibitory transmitter GABA is particularly important, acting on ion channels to enhance chloride inflow and reduce the chances of action potential formation. Excitatory amino acids (glutamate and aspartate) allow influx of sodium and calcium, producing the opposite effect. It is likely that many seizures result from an imbalance between this excitation and inhibition.

During seizures, epileptic cortex shows repetitive discharges involving large groups of neurons. Seizures may be related to a localized disturbance in the cortex, becoming manifest as **focal seizures**. If focal seizures remain localized, the symptoms experienced depend on which cortical area is affected. When both hemispheres are involved, either at onset or after spread, the seizure becomes **generalized**.

In seizures that are generalized at onset, the abnormal activity probably originates in the central mechanisms controlling cortical activation and spreads rapidly.

(Ref: Davidson's-22nd/1179)

Q. Name the anti-epileptic drugs. (DU-09Ju, RU-08Ju, CU-08Ju)

Q. Enumerate anti-seizure drugs. (SU-13Ju)

Q. Name the important anti-convulsant drugs. (RU-10J, CU-13J)

Q. Categorize anti-epileptic drugs incorporating their mechanism of action. (CU-12Ju, 09J)

Q. Name newer anti-epileptic drugs. (RU-14Ju)

Q. Name 5 anti-epileptic drugs. (DU-16J)

Ans.

Anti epileptic drugs / Anti-convulsant drugs / Antiseizure Drugs: / Mechanism of action

Mechanism of action	Drugs
1. Enhancement of GABA-ergic (inhibitory) transmission / facilitation of GABA-mediated Cl⁻ channel opening 3) GABA potentiator (γ-amino butyric acid = GABA)	▪ Barbiturate: Phenobarbitone — Children ▪ Benzodiazepine: ☉ Diazepam. ☉ Lorazepam ☉ Clonazepam ☉ Nitrazepam ☉ Clobazam ▪ Tiagabine ▪ Gabapentin ▪ Pregabalin ▪ Vigabatrin ▪ Valproate
2. Blockage of voltage sensitive Na⁺-channel / prolongation of Na⁺-channel inactivation 1) Na ⁺ channel modulation	▪ Carbamazepine → Pregnancy ▪ Oxcarbazepine ▪ Eslicarbazepine ▪ Phenytoin ▪ Fosphenytoin ▪ Mephenytoin ▪ Ethotoin ▪ Valproic acid ▪ Na-valproate ▪ Lamotrigine ▪ Topiramate ▪ Zonisamide ▪ Lacosamide ▪ Primidone

3. Blockage of T-type Ca^{2+} -channel 2 Ca^{2+} channel modulators	▪ Ethosuximide ▪ Phensuximide ▪ Methsuximide ▪ Trimethadione ▪ Valproate
4. Other drugs	▪ Levetiracetam ▪ Retigabine (ezogabine in the USA) ▪ Rufinamide ▪ Perampanel ▪ Felbamate ▪ Stiripentol ▪ Acetazolamide

(Ref: Tripathi-6th/404 (fig-30.2) + Katzung-13th/400-419)

Q. Classify anti-epileptic drugs according to their clinical use. (RU-04S, SU-04S)

Q. Name the drugs used in generalized tonic clonic seizures. (DU-07J)

Q. Categorize anti-epileptic drugs incorporating their clinical uses. (CU-09J)

Ans.

Anti-epileptic drugs according to their clinical use:

clinical

Seizure types	Drugs of choice	Alternative drugs
A. Generalized seizures		
1. Primary generalized tonic-clonic (grand mal) seizures, GTCS	• Na-valproate • Lamotrigine Carbamazepine	• Clonazepam • Topiramate • Carbamazepine • Phenytoin
2. Absence (petit mal) seizures	• Ethosuximide • Na-valproate	• Clonazepam • Lamotrigine
3. Atypical absence 4. Myotonic 5. Atonic	• Na-valproate • Clonazepam • Lamotrigine • Phenytoin • Ethosuximide • Phenobarbital	
6. Myoclonic	• Na-valproate • Clonazepam	• Lamotrigine
B. Partial &/or secondary generalized seizures	• Levetiracetam • Na-valproate • Lamotrigine Carbamazepine	• Phenytoin • Carbamazepine • Vigabatrin • Gabapentin

(Ref: Bennett & Brown-11th/355 (Table: 21.2))

Nice to know

Principles of epilepsy management: These call for attention to conservative as well as drug measures:

1. Any causative factor must, of course, be treated, e.g. cerebral neoplasm.
2. Educate the patient about the disease, duration of treatment and need for compliance.
3. Avoid precipitating factors, e.g. alcohol, sleep deprivation, emotional stress.
4. Anticipate natural variation, e.g. fits may occur particularly or exclusively around periods in women (catamenial epilepsy).
5. Give antiepilepsy drugs only if seizure type and frequency require it.

(Ref: Bennett & Brown-11th edition)

Q. Write down the general principles of anti-epileptic therapy. (DU-17M)

Q. Enumerate the guide-lines of anti-epileptic therapy. (DU-03J)

Q. What are the principal guide-lines for prescribing anti-epileptic drug? (DU-10Ju)

Ans.

Guide-lines of anti-epileptic drug therapy:

1. **When to initiate:** Majority of first seizures are provoked by a reversible and recognizable factor, eg, infection, drug toxicity, surgery. For these reasons, following a single seizure anticonvulsants are not generally prescribed, whereas after two or more distinct seizure episodes, they generally are prescribed.
2. Start with one **first-line drug**. The majority of patients (70%) can be controlled on one drug (**monotherapy**).
3. Start at a **low dose**; gradually increase dose until effective control of seizures is achieved or side-effects develop (drug levels may be helpful).
4. Optimize **compliance** (use minimum number of doses per day).
5. **If first drug fails** (seizures continue or side-effects develop), start **second first-line drug**, followed if possible by gradual withdrawal of first.
6. **If second drug fails** (seizures continue or side-effects develop), start second-line drug in **combination** with preferred first-line drug at maximum tolerated dose (**polytherapy**).
7. **If this combination fails** (seizures continue or side-effects develop), replace second-line drug with **alternative second-line drug**.
8. If this combination fails, check compliance and reconsider diagnosis (Are events seizures? Occult lesion? Treatment compliance/alcohol/drugs confounding response?)
9. Consider alternative, **non-drug treatments** (e.g. epilepsy surgery, vagal nerve stimulation).
10. Use minimum number of drugs in combination at any one time.
11. Choice of drug is also determined by the patient's **age, sex** and **pregnancy**.
12. **Abrupt withdrawal:** Effective therapy must never be stopped suddenly either by the doctor (carelessness) or by the patient (carelessness, intercurrent illness or ignorance), or status epilepticus may occur.

(Ref: Davidson's-22nd/1183; Bennett & Brown-11th/350)

Q. Write down the treatment of status epilepticus. (RU-14Ju,09J)

Ans.

Status epilepticus: Status epilepticus exists when a series of seizures occurs without the patient regaining awareness between attacks over a period of 30 minutes. Most commonly, this refers to recurrent tonic clonic seizures (major status) and is a life-threatening medical emergency.

Treatment of status epilepticus in adults

Airway clearing (Ref: Davidson's-medicine-20th/1173)
O₂ → prevent hypoxia

Status	Treatment
Early	▪ Lorazepam 4 mg IV; repeat once after 10 minutes if necessary or ▪ Clonazepam 1 mg IV over 30 seconds, repeat if necessary or ▪ Diazepam 10-20 mg over 2-4 min; repeat once after 30 minutes if necessary.
Established	▪ Phenytoin 15-18 mg/kg IV at a rate of 50 mg/minute and/or ▪ Phenobarbitone 10-20 mg/kg IV at a rate of 100 mg/minute
Refractory	▪ Thiopental or ▪ Propofol or ▪ Midazolam with full intensive care support.

(Ref: Bennett & Brown-11th/353)

Q. Name four drugs for petitmal seizures. (DU-17M)

Ans.

Drugs for petitmal seizures

1. Ethosuximide
2. Na-valproate
3. Clonazepam

4. Lamotrigine

Nice to know

- **Lorazepam** i.v. is now the preferred initial choice.
- **Diazepam** i.v. was widely used as the first line drug, but it is more likely to cause hypotension and respiratory depression, and its antiepilepsy effect wears off after about 20 minutes, so that **phenytoin** i.v. must also be given at the same time to suppress further fitting (with ECG and blood pressure monitoring, since cardiac arrhythmias and further hypotension may result). For this reason some consider **phenobarbitone** to be safer. If resuscitation facilities are not immediately available, diazepam can be given by rectal solution.
- **Midazolam** (nasally) may be preferred in institutions, e.g. mental hospitals, rather than diazepam rectally because patient and carer compliance are better.

(Ref: Bennett & Brown-10th/376)Pharmacokinetic properties of anti-epileptic drugs:

1. **Route:** Oral, I/V.
2. **Absorption:** Good.
3. **Oral bioavailability:** 80-100%
4. Most anti-seizure drugs are not highly bound to plasma proteins.
5. Anti-seizure drugs are chiefly cleared by hepatic mechanisms.
6. Many of them are converted into active metabolites that are also cleared by the liver.
7. Plasma clearances are relatively slow.
8. Many of the older anti-seizure drugs are potent hepatic microsomal enzyme inducers. e.g.
 - Carbamazepine
 - Phenytoin
 - Phenobarbital.
 - Oxcarbazepine
9. Many of the anti-seizure drugs are teratogenic.

(Ref: Katzung-13th edition)**Phenytoin**

(Non-epileptic use = Trigeminal neuralgia, Arrhythmia)

Phenytoin is the oldest nonsedative antiseizure drug, introduced in 1938. It was known for decades as diphenylhydantoin.

- Q. Write the mechanism of actions of Phenytoin & mention its adverse effects. (RU-10J; CU-14Ju,07J,06J)
- Q. A 5 years old boy suffers from repeated attack of seizures. What are the drugs of choice? Explain their actions. (SU-08Ju)
- Q. Short note: Phenytoin. (DU-15J)

Ans.

Mechanism of action of phenytoin: It exerts anti-seizure effects without any generalized CNS depression. It alters Na^+ , K^+ , and Ca^{2+} conductance, membrane potentials, and the concentrations of amino acids and the neurotransmitters norepinephrine, acetylcholine, and GABA.

At therapeutic concentrations, the major action of phenytoin is to **block sodium channels**

↓
Inhibits generation of rapidly repetitive action potentials
↓
Anti-epileptic effect

Adult dose = 300mg/daily
(Ref: Katzung-13th/400)

T. Dose = 40-80 mg/kg

Indication of phenytoin:

1. Partial seizures.
2. Primary or secondary GTCS.

(Ref: Katzung-13th/400)

3. Anxiety

4. Trigeminal neuralgia

Analgia 1200 mg 2020

Q. Mention the important adverse effects of phenytoin. (DU-16J,07J, RU-10J, CU-17J,09J)

Ans.

Adverse effects of phenytoin:

1. Nystagmus.
2. Diplopia & ataxia.
3. In case of long term use:
 - Osteomalacia (due to abnormal vitamin-D metabolism)
 - Megaloblastic anemia (due to low folate level)
 - Mild peripheral neuropathy → Diminished deep tendon reflexes.
 - Coarsening of facial features.
4. Gingival hyperplasia.
5. Hirsutism in women.
6. Sedation.
7. Teratogenicity (**fetal hydantoin syndrome**)
8. Hypersensitivity.

(Ref: Katzung-13th/402)

Contraindications of phenytoin

1. Hepatitis
2. Pregnancy
3. History of hypersensitivity
4. Febrile convulsion

Q. Why phenytoin is not an ideal drug in young women while taking oral contraceptive pills? (DU-10Ju)

Ans.

Phenytoin is not an ideal drug in young women while taking oral contraceptive pills:

Phenytoin induces steroid metabolizing enzymes → Increased metabolism of oral contraceptives → Decreased action of oral contraceptives → Contraception failure → Unwanted pregnancy.

Phenytoin and some other antiepilepsy drugs (carbamazepine, barbiturates, topiramate, oxcarbazepine) induce steroid metabolizing enzymes and can cause hormonal contraception to fail. Patients who are taking phenytoin, need a higher dose of estrogen (least 50 micrograms/day) if they wish to continue on the pill, although this does not guarantee complete protection from pregnancy with the associated risks to the fetus. This is why phenytoin is not an ideal drug in young women while taking oral contraceptive pills. Lamotrigine and sodium valproate are not enzyme inducers and their use is not reason to alter the dose of oral contraceptive.

(Ref: Bennett & Brown-10th/375)

Nice to know

Drug interactions of phenytoin:

1. As plasma protein binding of phenytoin is 90%, other highly bound drugs, such as phenylbutazone & sulfonamides can displace phenytoin from its binding site.
2. Phenytoin is a potent hepatic microsomal enzyme inducer. So, it can increase metabolism of other drugs, which are metabolized by microsomal enzymes; e.g. OCP, warfarin, steroids (adrenal & gonadal), thyroxine, TCAs, doxycycline etc.
3. Drugs that can increase concentration of phenytoin by inhibiting its metabolism are- INH, co-trimoxazole, Na-valproate, some NSAID, disulfiram, cimetidine etc.

(Ref: Bennett & Brown-10th/378)

Pharmacokinetic properties of phenytoin:

1. Phenytoin provides a good example of the application of pharmacokinetics for successful prescribing. The important aspects are —

Zero order kinetics:

- Low dose phenytoin → Exhibits 1st order kinetics.
- Therapeutic plasma conc. → Exhibits zero order kinetics.

(Ref: Bennett & Brown-10th/378)

2. Absorption of Phenytoin is highly dependent on the formulation of the dosage form. Particle size & pharmaceutical additives affect both the rate & the extent of absorption. IM absorption is unpredictable.

(Ref: Katzung-13th/401)

Carbamazepine

Teratogenic 2M
(Pregnant 7 to 12, 2M)
7 to regularly 12, 3M
2M 2M 2M addition
2M)

Q. What is the mechanism of action of carbamazepine? (CU-16J, 15J, 11Ju)

Ans.

Mechanism of action of carbamazepine:

1. Blocks voltage sensitive Na^+ -channels (like phenytoin) $\rightarrow$ Inhibits generation of rapidly repetitive action potentials $\rightarrow$ Anti-epileptic effect.
2. Decreases synaptic transmission (at pre-synaptic junction) $\rightarrow$ Anti-convulsant action.

(Ref: Katzung-13th/402)

Q. Enlist the clinical uses of carbamazepine. (CU-02M)

Ans.

Indications of carbamazepine:

1. Partial seizures.
2. Generalized tonic-clonic seizures (GTCS).
3. Trigeminal neuralgia.
4. Mania in some patients with bipolar disorder.

(Ref: Katzung-13th/403)

Q. What are the adverse effects of carbamazepine? (DU-03J, CU-11Ju)

Ans.

Adverse effects of carbamazepine:

1. Diplopia (double vision)*
2. Ataxia*
3. Mild GIT upset
4. Unsteadiness
5. Drowsiness (at higher doses)
6. Hyponatremia & water intoxication.
7. Aplastic anemia (*need routine blood film exam & stop the drug if anemia appears*).
8. Agranulocytosis (*need routine blood film exam & stop the drug if anemia appears*).
9. Mild & persistent leucopenia (*need careful monitoring*).

(Ref: Katzung-13th/403)

*Most common dose-related adverse effects are diplopia, ataxia. The diplopia often occurs first and may last less than an hour during a particular time of day. Rearrangement of the divided daily dose can often remedy this complaint.

Drug interactions: Drug interactions are exclusively related to its 'drug-inducing properties'.

- It can increase the metabolism of OCP, phenytoin, ethosuximide, valproic acid, clonazepam, primidone etc. & may cause therapeutic failure.
- Enzyme inhibiting drugs cause increased concentration of carbamazepine & chance of more toxicity.

(Ref: Katzung-13th/403)

Valproic acid & Na-valproate

Q. Explain the anti-epileptic role of sodium valproate. (SU-14J, 12Ju)

Ans.

Mechanism of action of Na-valproate & Valproic acid:

1. Blocks voltage sensitive Na^+ channels $\rightarrow$ Inhibits generation of rapidly repetitive action potentials $\rightarrow$ Anti-epileptic effect.
2. **Increased GABA concentration** in the brain $\rightarrow$ $\uparrow$ GABA mediated CNS depression $\rightarrow$ anti-epileptic effect.

Q. Write down the indications of sodium valproate.

Ans.

Indications of sodium valproate:

1. Valproate is unique in its ability to control certain types of myoclonic seizures; in some cases the effect is dramatic.
2. Absence seizures (very effective)
3. GTCS
4. Other uses:
 - Atonic seizures.
 - Partial seizures.
 - Management of bipolar disorder.
 - Migraine prophylaxis.

Q. Write down the adverse effects of sodium valproate. (DU-16J)

Ans.

✓ x **Adverse effects of sodium valproate:**

1. GIT upset: Nausea, vomiting, abdominal pain, heart burn.
2. Sedation (especially along with phenobarbital)
3. Fine tremor.
4. Hepatotoxicity (idiosyncratic reaction which may be severe specially <2 children).
5. Thrombocytopenia
6. Teratogenesis during pregnancy:
 - Spina bifida.
 - CVS defects.
 - Orofacial abnormalities.
 - Digital abnormalities.

(Ref: Katzung-13th/412-413)

Ethosuximide

Mechanism of action: Blocks T-type Ca^{2+} current in the thalamic neurons.

Indications: Highly efficacious & safe drug for absence seizures. But it has a very narrow spectrum of clinical activity.

Adverse effects:

1. GIT upsets: Nausea, vomiting & abdominal pain (most common but dose related).
2. Transient lethargy or fatigue.
3. Other dose-related adverse effects: Headache, dizziness, hiccup, euphoria (less common)
4. Skin rashes—Stevens-Johnson Syndrome (SJS)

(Ref: Katzung-13th/411)

Phenobarbitone / Phenobarbital

Phenobarbital is the oldest of the currently available antiseizure drugs. Although it has long been considered one of the safest of the antiseizure agents, the use of other medications with lesser sedative effects has been urged. Many consider the barbiturates the drugs of choice for seizures only in infants.

Mechanisms of action:

1. Binds to an allosteric regulatory site on the GABA receptor → Prolongs the openings of Cl^- channels & increase the GABA receptor-mediated currents → Hyperpolarization & anti-epileptic effect
2. Blocks excitatory responses induced by glutamate.
3. Decreases Na^+ conductance (at higher conc.)

4. Blocks some Ca^{2+} -currents (at higher conc.).

Indications: Useful in the treatment of partial seizures & GTCS.

(Ref: Katzung-13th/404)

Lamotrigine

Mechanism of action:

1. Lamotrigine, like phenytoin, suppresses sustained rapid firing of neurons and produces a voltage- and use-dependent blockade of Na^+ channels.
2. Lamotrigine also inhibits voltage-gated Ca^{2+} channels.
3. Lamotrigine also decreases the synaptic release of glutamate.

Indications:

1. Effective as monotherapy for partial seizures & is now widely prescribed.
2. Absence and myoclonic seizures in children
3. Seizure control in the Lennox-Gastaut syndrome.
4. Bipolar disorder.

Adverse effects:

1. Diplopia
2. Dizziness
3. Headache
4. Nausea
5. Somnolence
6. Skin rash
7. Life-threatening dermatitis (in 1–2% of pediatric patients.)

(Ref: Katzung-13th/407)

Levetiracetam

Mechanism of Action

1. Levetiracetam binds selectively to the synaptic vesicular protein SV_2A .
2. It modifies the synaptic release of glutamate and GABA through an action on vesicular function.
3. It inhibits N-type calcium channels and inhibits calcium release from intracellular stores.

Clinical Uses: Adjunctive treatment of

1. Partial seizures in adults and children
2. Primary GTCS
3. Myoclonic seizures of juvenile myoclonic epilepsy.

Adverse effects

1. Somnolence
2. Asthenia
3. Ataxia
4. Dizziness
5. Less common- mood and behavioral changes; psychotic reactions are rare.

(Ref: Katzung-13th/407,408)

Gabapentin & Pregabalin

Both are analogs of GABA, but don't act directly on GABA-receptors.

(Non-epileptic
use
= Analgesic)

Mechanism of actions:

1. Modify the synaptic or non-synaptic release of GABA.
2. Pre-synaptically decrease the release of glutamate.

Indications:

1. Effective as an adjunct against partial seizures & GTCS.
2. Effective in the Rx of neuropathic pain.
3. Post-herpetic neuralgia.

Adverse effects:

1. Somnolence
2. Dizziness
3. Ataxia
4. Tremor
5. Headache.

(Ref: Katzung-13th/406)

Q. Short note: Febrile convulsion. (RU-15Ju)

Ans.

Febrile convulsion / seizure:

Definition: Febrile seizure is defined as a seizure in association with a febrile illness in the absence of a central nervous system (CNS) infection or acute electrolyte imbalance in children older than 1 month of age without prior afebrile seizures.

Age: 6 months to 4 years, with a peak incidence at 18 months.

(Ref: Current pediatric therapy-18th edition)

Clinical features of simple febrile convulsion-

1. It is usually associated with a core temperature that increases rapidly to $\geq 39^{\circ}\text{C}$.
2. Is initially generalized and tonic-clonic in nature.
3. Lasts a few seconds and rarely up to 15 min.
4. Brief postictal period of drowsiness.
5. Occurs only once in 24 hr.

Treatment:

1. Control the fever:

- Antipyretics (paracetamol).
- Cooling with sponge soaks.

2. Control of seizure:

- Oral diazepam: 0.3 mg/kg 8 hourly (1 mg/kg/24 hr)
- Rectal diazepam: 0.5 mg/kg.

(Ref: Nelson textbook of pediatrics-18th edition; Bennet & Brown-11th/353)

Q. Explain the pharmacological basis of using- Diazepam in febrile convulsion. (SU-15Ju, 15J, 14Ju)

Ans.

Diazepam in febrile convulsion: Diazepam is capable of inhibiting the development and spread of epileptiform electrical activity in the CNS. This is why; it is the drug of choice the treatment of acute attack of febrile convulsion.

Nice to know

A febrile seizure is described as complex or complicated-

1. when the duration is >15 min.
2. when repeated convulsions occur within 24 hr.
3. when focal seizure activity or focal findings are present during the postictal period.

Teratogenicity of Anti-epileptic drugs

Anti-epileptic drugs	Teratogenic effects
▪ Phenytoin ▪ Phenobarbital ▪ Carbamazepine	Fetal hydantoin syndrome
▪ Valproate	Spina bifida
▪ Topiramate	some teratogenicity in animal testing and in the human male fetus.

(Ref: Katzung-13th/417)

Antiseizure drugs in development: Three potential new antiseizure drugs are in phase 2 or phase 3 development; these are brivaracetam, YKP3089, and ganaxolone.

(Ref: Katzung-13th/417)

Antiparkinsonism drugs

Parkinsonism: Parkinsonism is a degenerative disease affecting the **basal ganglia** and is characterized by a combination of rigidity, bradykinesia, tremor, and postural instability that can occur for a variety of reasons but is usually idiopathic.

(Ref: Katzung-13th/473)

Q. Describe the neural network of parkinsonism. (CU-16J)

Q. Draw and describe the neural network of Parkinson's disease. (CU-14J)

Ans.

Pathogenesis of Parkinsonism: In basal ganglia, dopamine and acetylcholine balance each other to control movement. In Parkinsonism, there is loss of dopaminergic neurons in the **substantia nigra** of the **basal ganglia**. As a result, there is **decreased dopamine activity** and **increased cholinergic activity** in the basal ganglia. Reduced dopaminergic output from the substantia nigra to the globus pallidus leads to reduced inhibitory effects on the subthalamic nucleus, neurons of which become more active than usual in inhibiting activation of the cortex. This in turn results in bradykinesia.

(Ref: Katzung-13th/473 + Davidson's medicine-22nd/1195)

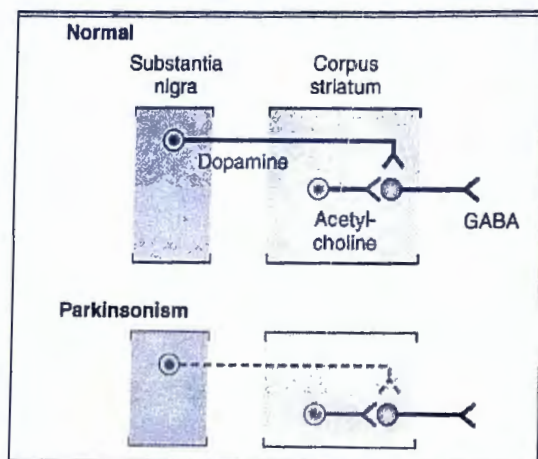


Fig. Schematic representation of the sequence of neurons involved in parkinsonism. Dopaminergic neurons originating in the substantia nigra normally inhibit the GABAergic output from the striatum, whereas cholinergic neurons exert an excitatory effect. In parkinsonism, there is a selective loss of dopaminergic neurons (dashed).

(Ref: Katzung-13th/474)

Nice to know

Principles of treatment:

1. To increase dopamine activity in the basal ganglia
2. To decrease cholinergic activity in the basal ganglia with antimuscarinic drugs.

(Ref: Katzung-13th/474)

Causes of parkinsonism

- a. Idiopathic Parkinson's disease (at least 80% of parkinsonism)
- b. Cerebrovascular disease
- c. Drugs and toxins
 1. Antipsychotic drugs (older and 'atypical')
 2. Metoclopramide, prochlorperazine
 3. Tetrabenazine
 4. Sodium valproate
 5. Lithium
 6. Manganese
 7. MPTP
- d. Other degenerative diseases
 1. Dementia with Lewy bodies

2. Progressive supranuclear palsy
3. Multiple system atrophy
4. Corticobasal degeneration
5. Alzheimer's disease

e. Genetic

1. Huntington's disease
2. Fragile X tremor ataxia syndrome
3. Dopa-responsive dystonia
4. Spinocerebellar ataxias (particularly SCA 3)
5. Wilson's disease

f. Anoxic brain injury

(MPTP = methyl-phenyl-tetrahydropyridine)

(Ref: Davidson's medicine-22nd/1195)

Q. Outline the role of anti-parkinsonism drugs in modifying pathophysiology of Parkinsonism. (SU-08J)

Ans.

Role of anti-parkinsonism drugs in modifying the pathophysiology of Parkinsonism: In Parkinsonism, there is loss of dopaminergic neurons in the basal ganglia. So there is decreased dopamine activity and increased cholinergic activity. Anti-parkinsonism drugs increase dopamine activity in the basal ganglia and decrease cholinergic activity in the basal ganglia with antimuscarinic drugs. This restores the normal balance of cholinergic and dopaminergic influences on the basal ganglia and improves the symptoms of Parkinsonism.

Q. Name important anti-parkinsonism drugs. (DU-14J)

Q. Name the drugs used for Parkinsonism? (DU-15Ju, RU-04S, SU-08J,06S)

Q. Categorize anti-Parkinsonian drugs. (CU-11Ju)

Ans.

Drugs used for Parkinsonism:

A. Drugs that increase central dopaminergic activity:

1. Dopamine precursor	▪ Levodopa
2. Dopamine agonists	▪ Bromocriptine ▪ Pergolide ▪ Pramipexole ▪ Ropinirole ▪ Rotigotine ▪ Apomorphine
3. Increased synthesis, release & reuptake of dopamine	▪ Amantadine
4. Decreased dopamine metabolism	MAO inhibitors: ▪ Selegiline ▪ Rasagiline COMT inhibitors: ▪ Tolcapone ▪ Entacapone

(Ref: Katzung-13th/474-481)

B. Drugs that decrease cholinergic activity (Anti-muscarinic drugs):

1. Procyclidine
2. Orphenadrine
3. Benztropine
4. Biperiden
5. Trihexyphenidyl

Benzhexol

(Ref: Katzung-13th/481)

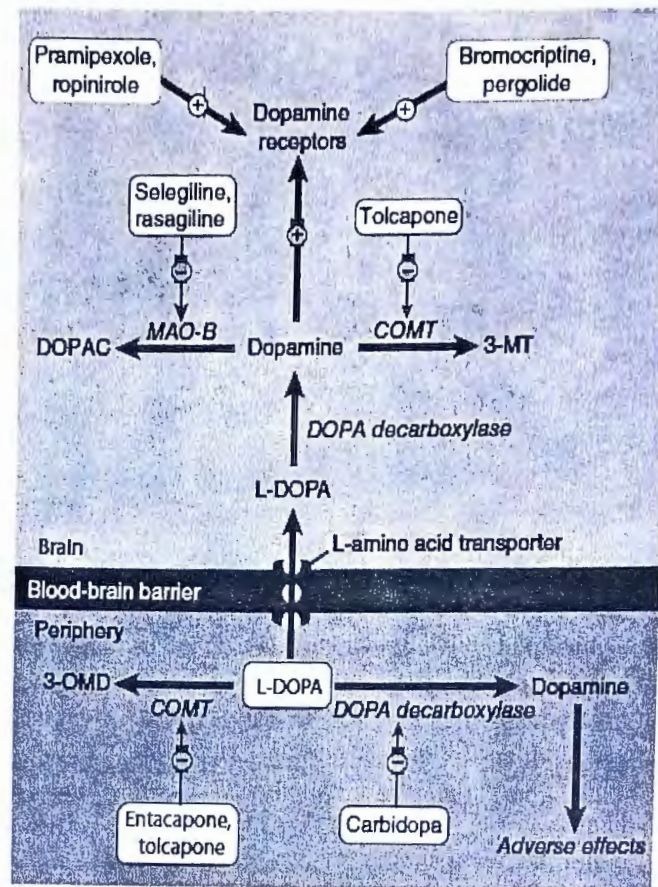


Fig. Pharmacologic strategies for dopaminergic therapy of Parkinson's disease. L-DOPA, levodopa.

Levodopa

Q. Explain the pharmacological basis of using Levodopa in Parkinsonism. (CU-05S)

Ans.

Mechanism of action of levodopa: Levodopa, the immediate metabolic precursor of dopamine, enters the brain, where it is decarboxylated to dopamine.

Levodopa enters the brain
 ↓
 Levodopa is decarboxylated to dopamine
 ↓
 Dopamine stimulates dopamine receptors
 ↓
 Increased dopamine activity
 ↓
 Antiparkinsonism effect.

The benefits of dopaminergic antiparkinsonism drugs appear to depend mostly on stimulation of the **D₂ receptors**. However, **D₁-receptor** stimulation may also be required for maximal benefit.

(Ref: Katzung-13th/474)

- Q. Discuss the role of carbidopa used along with levodopa. (DU-14J)**
Q. What is the role of carbidopa in the treatment of Parkinson's disease? (CU-14J)
Q. Justify the combined use of Levodopa & Carbidopa. (DU-15Ju, RU-12/11J, CU-16J, SU-06S)
Q. Explain the principle of administering carbidopa with levodopa. (DU-11Ju, CU-05S)
Q. Describe the fate of Levodopa after its oral administration. (CU-16Ju)
Q. Short note: Levodopa & Carbidopa combination. (SU-15Ju)

Ans.

Pharmacological basis of using combination of Levodopa & Carbidopa in Parkinsonism

- **Levodopa alone:** Unfortunately, only about 1–3% of orally administered levodopa actually enters the brain unaltered; the remainder is metabolized extracerebrally, predominantly by **decarboxylation** to **dopamine**, which does not penetrate the blood-brain barrier (BBB). This is why, levodopa must be given in large amounts when used alone.
- **Levodopa + dopa decarboxylase inhibitor (eg, Carbidopa):** When levodopa is given in combination with carbidopa, carbidopa reduces the peripheral metabolism of levodopa by inhibiting **dopa decarboxylase enzyme**. So the plasma level of levodopa is higher, & more levodopa is available for entry into brain. Carbidopa cannot enter the brain and it cannot metabolize levodopa in the brain. As a result, more levodopa is available in the brain to be converted to dopamine and exert anti-parkinsonism effect.
- Indeed, concomitant use of carbidopa may reduce the daily requirements of levodopa by approximately 75%.
(Ref: Katzung-13th/475)

Q. Describe the limitations and therapeutic effectiveness of levodopa in the treatment of Parkinson's disease. (CU-14Ju)

Ans.

Therapeutic effectiveness of levodopa

1. Levodopa provides the biggest improvement in motor symptoms of Parkinson's disease.

Limitations of levodopa

1. Development of **dyskinesias**, which are inevitable after some 5-10 years,
2. **Extensive metabolism** of levodopa to dopamine in peripheral tissues so that only 1-3% of an oral dose of levodopa reaches the brain.
3. Significant **adverse effects** by peripheral actions: Nausea, cardiac arrhythmia and postural hypotension.
4. Cannot alter the progressive course of the disease.

(Ref: Bennet & Brown-11th edition)

Q. Write the adverse effects of levodopa. (CU-12Ju)

Ans.

Adverse effects of levodopa:

1. Gastro-intestinal effects	When Levodopa is given without a peripheral decarboxylase inhibitor: ▪ Anorexia ▪ Nausea ▪ Vomiting
2. Cardio-vascular effects	▪ Tachycardia ▪ Ventricular extra-systoles ▪ Postural hypotension (often asymptomatic) ▪ Atrial fibrillation (very rarely) ▪ Hypertension (with MAO inhibitors)
3. Dyskinesia	▪ Chorea-athetosis of the face & distal extremities (Occurs in up to 80% of patients).
4. CNS effects / behavioral effects	▪ Depression ▪ Anxiety ▪ Agitation ▪ Insomnia ▪ Somnolence ▪ Confusion ▪ Nightmare ▪ Delusion ▪ Hallucination ▪ Euphoria

5. Fluctuation in clinical responses	- Occurs due to continued use. Wearing-off reactions or end-of-dose akinesia: Fluctuations in clinical state that are related to timing of levodopa intake. On-off phenomenon: Fluctuations in clinical state that are unrelated to the timing of doses.
6. Miscellaneous adverse effects	- May causes mydriasis & hence causes precipitation of Glaucoma - Blood dyscrasias

(Ref: Katzung-13th/476)**Q. Short note: On-off phenomenon.**

Ans.

On-off phenomenon:

After long-term treatment of Parkinson's disease with levodopa, there develops fluctuations in clinical response to levodopa which is called on-off phenomenon. In the on-off phenomenon, **off-periods** of marked **akinesia** alternate with **on-periods** of **improved mobility** but with **dyskinesia**.

Mechanism: Unknown.**Management:** Subcutaneous injection of **apomorphine** may provide temporary benefit.(Ref: Katzung-13th/476)**Nice to know**

Drug Holidays: A drug holiday (discontinuance of the drug for 3–21 days) may temporarily improve responsiveness to levodopa and alleviate some of its adverse effects but is usually of little help in the management of the on-off phenomenon. Furthermore, a drug holiday carries the risks of aspiration pneumonia, venous thrombosis, pulmonary embolism, and depression resulting from the immobility accompanying severe parkinsonism. For these reasons and because of the temporary nature of any benefit, drug holidays are not recommended.

(Ref: Katzung-13th/477)**Q. Enlist the Levodopa induced dyskinesias. (CU-16Ju)**

Ans.

Levodopa induced dyskinesias: Levodopa-induced dyskinesia is a form of dyskinesia associated with long-term treatment of Parkinson's disease with levodopa (LD). It often involves hyperkinetic movements, including chorea, dystonia, and athetosis. Based on the relationship with levodopa dosing, dyskinesia most commonly occurs in the following ways-

1. **Biphasic phenomenon:** Dyskinesia occurring at the time of peak LD plasma concentrations.
2. **Peak-dose phenomenon:** Dyskinesia occurs when the drug concentration rises or falls.

(Ref: Davidson's-22nd; Wikipedia)**Q. Mention of contraindications of levodopa.**

Ans.

Contraindications of levodopa

1. **Schizophrenia:** Levodopa should not be given to psychotic patients because it may exacerbate the mental disturbance.
2. Angle-closure glaucoma
3. Active peptic ulcer.
4. History of melanoma or with suspicious undiagnosed skin lesions.

(Ref: Katzung-13th/477)**Q. Short note: Levodopa. (DU-13J,12J,10Ju)**

Ans. Write in short from above.

Viva Q. Why dopamine is not effective in the treatment of Parkinsonism?

Ans. Dopamine does not cross the blood-brain barrier & if given into the peripheral circulation has no therapeutic effects in Parkinsonism.

Selegiline

Mechanism of action: Selegiline is a selective irreversible inhibitor of monoamine oxidase B at normal doses (at higher doses it inhibits MAO-A as well). It retards the breakdown of dopamine; in consequence, it enhances and prolongs the antiparkinsonism effect of levodopa (thereby allowing the dose of levodopa to be reduced) and may reduce mild on-off or wearing-off phenomena.

Clinical use:

- It has only a minor therapeutic effect on parkinsonism when given alone.
- It is used as adjunctive therapy for patients with a declining or fluctuating response to levodopa.

Dose: 5 mg with breakfast and 5 mg with lunch.

Adverse effect: Selegiline may cause insomnia when taken later during the day.

(Ref: Katzung-13th/479)

Amantadine

Amantadine, an antiviral agent, was by chance found to have antiparkinsonism properties.

Mechanism of action: Its mode of action in parkinsonism is unclear, but it may potentiate dopaminergic function by influencing the synthesis, release, or reuptake of dopamine.

Clinical Use:

- Less efficacious than levodopa.
- Its benefits may be short-lived, often disappearing after only a few weeks of treatment.
- It may favorably influence the bradykinesia, rigidity, and tremor of Parkinsonism.

Adverse Effects

1. **CNS effects:** Restlessness, depression, irritability, insomnia, agitation, excitement, hallucinations, and confusion.
2. Acute toxic psychosis (with overdosage)
3. Convulsions (with overdosage)
4. Livedo reticularis
5. Peripheral edema
6. Others: Headache, heart failure, postural hypotension, urinary retention, and GI disturbances (eg, anorexia, nausea, constipation, and dry mouth).

Caution: Amantadine should be used with caution in patients with a history of seizures or heart failure.

(Ref: Katzung-13th/480)

Q. How can you treat a case of drug induced Parkinson's syndrome? (RU-14Ju)

Q. How will you treat a case of iatrogenic parkinsonism? (CU-16J,15Ju)

Ans.

Treatment of drug induced Parkinson's syndrome

1. Stopping the offending drug:

- The first approach to treatment will be stopping the offending drug for a sufficient length of time, reducing it, or changing it to another drug that may be less likely to cause drug-induced parkinsonism.
- Generally, 60% of people will recover within two months of stopping the offending drug.

2. Antiparkinsonian agents:

- Anticholinergic drugs
- Amantadine
- Levodopa plus carbidopa.

Q. Mention the treatment of chlorpromazine induced Parkinson's syndrome. (RU-04J)

Ans.

Treatment of chlorpromazine induced Parkinson's syndrome: Chlorpromazine causes Parkinson's syndrome by blocking dopamine receptor in nigrostriatal pathway. Chlorpromazine should be stopped and levodopa should be given to the patient. As levodopa is a dopamine precursor & increases central dopaminergic activity, it is the drug of choice in chlorpromazine induced Parkinsonism.

Nice to know

Other therapies of Parkinson's disease

1. **Surgery**

- a. Thalamotomy
- b. Posteroventral pallidotomy
- c. Deep brain stimulation

2. **Neuroprotective therapy:** Among the compounds under investigation as potential neuroprotective agents that may slow disease progression are antioxidants, antiapoptotic agents, glutamate antagonists, glial-derived neurotrophic factor, rasagiline and anti-inflammatory drugs. Coenzyme Q10 and creatine have not been found effective
3. **Gene therapy:** Several phase 1 (safety) or phase 2 trials of gene therapy for Parkinson's disease have been completed in the USA.

(Ref: Katzung-13th/481)

General anesthesia

Types of anesthesia: There are two types of anesthesia.

1. General anesthesia or G/A
2. Local anesthesia or L/A

Q. Define general anesthesia. (DU-06M, RU-06M,05S)

Ans.

General anesthesia: General anesthesia may be defined as a global but reversible CNS depression characterized by five primary effects: analgesia, amnesia (loss of memory), loss of consciousness, loss of autonomic reflexes and skeletal muscle relaxation.

(Ref: Katzung-13th/421)

Q. Mention the objectives of general anesthesia. (DU-07J, SU-10/09J)

Ans.

Objectives / characteristics / cardinal features of general anesthesia:

1. Analgesia
2. Amnesia (loss of memory) (sleep/hypnosis)
3. Loss of consciousness (reversible unconsciousness)
4. Loss of autonomic reflexes
5. Skeletal muscle relaxation

Balanced anesthesia means to use drugs 5 points to ensure an easier field of operation for the surgeon
(Ref: Katzung-13th/421)

Q. Enlists the principles of general anesthesia. (SU-08J)

Ans.

General Principles of Surgical Anesthesia: Administration of general anesthesia, as well as the development of new anesthetic agents and physiologic monitoring technology, has been driven by three general objectives:

1. Minimizing the potentially deleterious direct and indirect effects of anesthetic agents and techniques.
2. Sustaining physiologic homeostasis during surgical procedures that may involve major blood loss, tissue ischemia, reperfusion of ischemic tissue, fluid shifts, exposure to a cold environment, and impaired coagulation.
3. Improving postoperative outcomes by choosing techniques that block or treat components of the surgical stress response, which may lead to short- or long-term sequelae.

(Ref: Goodman & Gilman-12th edition)

Nice to know

Depth of anesthesia: The depth of anesthesia has been divided into four sequential stages. Each stage is characterized by increased CNS depression, which is caused by accumulation of the anesthetic drug in the brain. These stages were discerned and defined with ether, which produces a slow onset of anesthesia. However, with halothane and other commonly used anesthetics, the stages are difficult to characterize clearly because of the rapid onset of anesthesia.

1. **Stage I Analgesia:** Loss of pain sensation results from interference with sensory transmission in the spinothalamic tract. The patient is conscious and conversational. Amnesia and a reduced awareness of pain occur as Stage II is approached.
2. **Stage II Excitement:** The patient experiences delirium and possibly violent, combative behavior. There is a rise and irregularity in blood pressure. The respiratory rate may increase. To avoid this stage of anesthesia, a short-acting barbiturate, such as thiopental, is given intravenously before inhalation anesthesia is administered.
3. **Stage III Surgical anesthesia:** Regular respiration and relaxation of the skeletal muscles occur in this stage. Eye reflexes decrease progressively, until the eye movements cease and the pupil is fixed. Surgery may proceed during this stage.
4. **Stage IV Medullary paralysis:** Severe depression of the respiratory and vasomotor centers occurs during this stage. Death can rapidly ensue unless measures are taken to maintain circulation and respiration.

(Ref: Lippincott's-5th/135,136)

Anatomic sites of anesthetic action: General anesthetics could interrupt nervous system function at-

1. Peripheral sensory neurons
2. The spinal cord
3. The brainstem &
4. The cerebral cortex

(Ref: Goodman & Gilman-11th/345)

Mechanism of action of general anesthetics:

Cellular mechanism of anesthesia: General anesthetics produce two important physiologic effects at the cellular level -

1. The inhalation anesthetics can **hyperpolarize neurons**.
2. Both inhalation & intravenous anesthetics have substantial effects on **synaptic transmission** & much smaller effects on **action potential generation or propagation**.

Molecular mechanism of anesthesia:

1. Ligand-gated ion channels are important targets for anesthetic action
2. Chloride channels gated by the inhibitory GABA_A-receptors are sensitive to clinical conc. of a wide variety of anesthetics, including the halogenated inhalation agents & many intravenous agents
3. At clinical concentration, general anesthetics increase the sensitivity of the GABA_A-receptors to GABA.

(Ref: Goodman & Gilman-11th/345)

Drugs used before surgery (pre-operative):

Pre-anesthetic medication

Before surgery, an assessment is made of:

- the patient's physical and psychological condition
- any intercurrent illness
- the relevance of any existing drug therapy.

All of these may influence the choice of anesthetic drugs.

(Ref: Bennet & Brown-10th edition)

Q. Define pre-anesthetic medication. (DU-16Ju,12/11Ju,CU-05S; RU-13Ju)

Q. Name the pre-anesthetic medications with their objectives/rationale/justification. (DU-17J,16Ju,15Ju,13Ju,12/11/09Ju, RU-16Ju,15Ju,13Ju,11J, SU-17J,16J,15J,14J,10/09J)

Q. Explain the role of individual drugs used in pre-anesthetic medication. (DU-07J; CU-07J)

Q. Discuss the pre-anesthetic medications. (CU-05S)

Q. Enlist the principles of pre-anesthetic medication. (SU-08J)

Q. Write the pharmacological basis of using diazepam in pre-anesthetic medication. (CU-13Ju)

Q. Short note: Pre-anesthetic medication. (SU-15Ju)

Ans.

Pre-anesthetic medication / anesthetic adjunct: Use of drugs before anesthesia to make it more pleasant & safe, is called anesthetic adjunct / pre-anesthetic medication.

(Ref: Tripathi-6th/378)

Pre-anesthetic medication/ Objectives of pre-anesthetic medication:

1. **To reduce anxiety:** Benzodiazepines, such as diazepam, midazolam, clonazepam, bromazepam, temazepam provide anxiolysis and amnesia for the immediate presurgical period.
2. **For analgesia:** Analgesia is indicated if the patient is in pain preoperatively or it can be given pre-emptively to prevent postoperative pain.
 - Severe preoperative pain is treated with a parenteral **opioid analgesic** such as morphine pethidine, fentanyl, nalbuphine.
 - **NSAIDs**, eg, ketorolac are commonly given orally preoperatively to prevent postoperative pain after minor surgery.

3. **To reduce bronchial, salivary secretion and to inhibit bronchospasm, bradycardia:** Antimuscarinic drugs such as atropine, scopolamine. Use of this premedication is rarely undertaken these days.
4. **To reduce gastric acid secretion:** Omeprazole, pantoprazole, esomeprazole, ranitidine.
5. **Antiemetic to prevent vomiting and possible aspiration of stomach contents:** Ondansetron, metoclopramide.
6. **For prevention of allergic reactions:** Antihistamines (chlorpheniramine, diphenhydramine)
7. **To prevent infection (in general / pelvic surgery):** Broad-spectrum antibiotics.
8. **For emptying GIT (in general/pelvic surgery):** Laxatives / glycerine / enema.

These agents facilitate smooth induction of anesthesia, and when administered continuously, they also lower the dose of anesthetic required to maintain the desired level of surgical (Stage III) anesthesia. However, such coadministration can also enhance undesirable anesthetic effects (eg, hypoventilation), and it may produce negative effects.

(Ref: Lippincott's-6th/172; Bennet & Brown-11th edition)

Drugs used during surgery (per-operative): Balanced anesthesia

During surgery, drugs will be required to provide:

- unconsciousness
- analgesia
- muscular relaxation when necessary
- control of blood pressure, heart rate, and respiration.

2) Anesthesia
Pre-

3) Recovery
(in recovery)

(Ref: Bennet & Brown-11th edition)

Q. What do you mean by induction and maintenance and recovery of anesthesia?

Q. Name the general anesthetics used for induction of anesthesia. (RU-17J)

Ans.

Stages of general anesthesia (GA): Anesthesia can be divided into 3 stages —

1. Induction
2. Maintenance &
3. Recovery

A. **Induction:** Induction is defined as the period of time from the onset of administration of the anesthetic to the development of effective surgical anesthesia in the patient. Induction of anesthesia depends on how fast effective concentrations of the anesthetic drug reach the brain. During induction, it is essential to avoid the dangerous excitatory phase (Stage II delirium).

1. Induction is usually done by **intravenous anesthetic** (eg, **thiopental** or **propofol** or **etomidate**).
2. For children, without IV access, **nonpungent agents**, such as **halothane** or **sevoflurane**, are used to induce GA. This is termed **inhalation induction**.

B. **Maintenance of anesthesia:** Maintenance is the period during which the patient is surgically anesthetized. Anesthesia is usually maintained by-

1. **Inhaled anesthetics** (eg, nitrous oxide and oxygen, plus a volatile agent, e.g. halothane or sevoflurane or isoflurane).
2. Additional doses of a **neuromuscular blocker** or **opioid** are given as required.
3. A **continuous IV infusion of propofol**. (This technique of total IV anesthesia is becoming more popular because the quality of recovery may be better than after inhalational anesthesia.)

C. **Recovery:** Recovery is the time from discontinuation of administration of the anesthesia until consciousness and protective physiologic reflexes are regained. Recovery is the reverse of induction and depends on how fast the anesthetic drug diffuses from the brain. Postoperatively, the anesthesiologist withdraws the anesthetic.

mixture and monitors the return of the patient to consciousness. The anesthesiologist continues to monitor the patient to be sure that he or she is fully recovered with normal physiologic functions (for example, is able to breathe on his/her own).

Drugs given during recovery are- (Note: Drugs mentioned below are given after surgery)

1. **Withdrawal of inhalation anesthetic** (eg, nitrous oxide and halothane) that was used for maintenance of anesthesia.
 2. **Neostigmine** to **reverse** muscle relaxation. → 4 hr ago + a blood
 3. **Analgesic** to prevent post-operative pain, eg, opioid analgesic (eg, morphine, pethidine), NSAID (eg, ketorolac, diclofenac).
 4. **Anti-emetic** to prevent post-operative nausea and vomiting: Ondansetron, cyclizine, metoclopramide.
- (Ref: Lippincott's-6th/173; Bennet & Brown-11th edition)

Q. What do you mean by balanced anesthesia? (DU-09Ju, RU-04J, SU-11J)

Q. State features of balanced anesthesia? (RU-11Ju)

Q. Name the drugs to produce balanced anesthesia. (RU-04J)

Q. Categorize the drugs used for induction & maintenance of anesthesia. (CU-06J)

Q. Write down four peripheral muscle relaxants used during surgery. (DU-13Ju)

Q. Short note: Balanced anesthesia? (DU-13J, 11Ju, CU-14Ju, SU-16J)

Ans.

Balanced anesthesia: It is defined as the achievement of surgical anesthetic state including unconsciousness with adequate analgesia & skeletal muscle relaxation with the combinations of intravenous and inhaled drugs.

(Ref: Katzung-12th/438-edited)

Induction:

- General anesthesia is normally induced with an **intravenous anesthetic** (eg, **thiopental** or **propofol**)
- However, volatile anesthetics (eg, sevoflurane) can also be used for induction of anesthesia. For children, without intravenous access, **nonpungent agents**, such as **halothane** or **sevoflurane**, are used to induce general anesthesia. This is termed **inhalation induction**.

Maintenance of anesthesia:

- Anesthesia is usually maintained by the administration of **inhaled anesthetics** (eg, volatile agents, **nitrous oxide**, **halothane**).
- However, intravenous anesthetics (eg, propofol) can be infused for maintenance of anesthesia.

Analgesic:

- During maintenance of anesthesia, **Opioids**, such as fentanyl, are often used for pain along with inhalation agents, because the latter are not good analgesics.

Skeletal muscle relaxant:

- Currently used muscle relaxants include **pancuronium**, **doxacurium**, **rocuronium**, **vecuronium**, **cisatracurium**, **atracurium**, **mevacurium** and **succinylcholine**.

(Ref: Katzung-13th; Lippincott's-6th/173)

Importance of balanced anesthesia:

1. To reduce the amount of drug used and thereby to reduce the adverse effects of each drugs.
2. To increase safety.

Q. Combination of drugs are required to achieve balanced anesthesia- Explain and justify. (DU-17M, 09J, RU-12Ju)

Ans.

Combinations of drugs are required to achieve balanced anesthesia: The neurophysiologic state produced by general anesthetics is characterized by five primary effects: unconsciousness, amnesia, analgesia, inhibition of autonomic reflexes, and skeletal muscle relaxation. None of the currently available anesthetic agents when used alone can achieve all five of these desired effects well. An ideal anesthetic drug should induce rapid, smooth loss of consciousness, be rapidly reversible upon discontinuation, and possess a wide margin of safety.

The modern practice of anesthesiology relies on the use of combinations of intravenous and inhaled drugs (balanced anesthesia techniques) to take advantage of the favorable properties of each agent while minimizing their adverse effects.

(Ref: Katzung-13th/421)

Q. Classify general anesthetics. (DU-05J; CU-11Ju,06S; RU-04M)

Q. Mention the drugs used during general anesthesia with their specific indications. (DU-10Ju)

Q. Name the general anesthetics used now a days. (RU-06M)

Q. Mention the intravenous / IV general anesthetics. (DU-11J, RU-14Ju,04J)

Ans.

Drugs for general anesthesia: General anesthetics are typically administered by IV injection or by inhalation.

IV or parenteral anesthetics	Inhaled anesthetics
1. Barbiturates: - Thiopental sodium - Methohexital	1. Halothane 2. Isoflurane 3. Enflurane 4. Desflurane 5. Sevoflurane 6. Methoxyflurane 7. Nitrous oxide (NO) - Gaseous 8. Xenon
2. Benzodiazepines: - Diazepam - Lorazepam - Midazolam	
3. Opioid analgesics: - Morphine - Pethidine - Fentanyl - Sufentanil - Alfentanil - Remifentanil	
4. Miscellaneous: - Propofol → ↑ GABA_A - Fospropofol - Ketamine → ↓ Glutamate - Etomidate - Dexmedetomidine	

(Ref: Goodman & Gilman's-12th & Katzung-13th/422)

Q. List the adverse effects / hazards of general anesthesia? (DU-08Ju, RU-07J)

Ans.

Adverse effects / hazards of general anesthesia:

A. **During anesthesia:**

1. Prolongation of post-operative period
2. Respiratory depression.
3. Salivation & respiratory secretion
4. Cardiac arrhythmias, asystoles
5. Hypotension
6. Aspiration of gastric contents (acid pneumonitis)
7. Laryngospasm & asphyxia
8. Delirium, convulsion & other excitatory effects (generally seen with IV anesthetics)

B. **After anesthesia:**

1. Nausea & vomiting
2. Persisting sedation
3. Pneumonia & atelectasis
4. Organ toxicities: Liver, Kidney damage.
5. Nerve palsies due to faulty positioning.

6. Emergence delirium
7. Cognitive defects: Prolonged excess cognitive decline has been observed in some patient.

(Ref: Tripathi-6th/377-378)Nice to know**Table: Pharmacologic Characteristics of Intravenous Anesthetics.**

Drug	Induction and Recovery	Comments
Etomidate	Rapid onset and moderately fast recovery	Provides cardiovascular stability; causes decreased steroidogenesis and involuntary muscle movements
Ketamine	Moderately rapid onset and recovery	Causes cardiovascular stimulation, increased cerebral blood flow, and emergence reactions that impair recovery
Midazolam	Slow onset and recovery; flumazenil reversal available	Used in balanced anesthesia and conscious sedation; provides cardiovascular stability and marked amnesia
Propofol	Rapid onset and rapid recovery	Used in induction and for maintenance; can cause hypotension; has useful antiemetic action
Thiopental	Rapid onset and rapid recovery (bolus dose)—slow recovery following infusion	Standard induction agent; causes cardiovascular depression; avoid in porphyrias
Fentanyl	Slow onset and recovery; naloxone reversal available	Opioid used in balanced anesthesia and conscious sedation; produces marked analgesia

(Ref: Katzung-12th edition)

Thiopental-Na**Q. Describe briefly the pharmacokinetics of thiopental sodium. (DU-11J)**

Ans.

Pharmacokinetics of thiopental sodium

- **Route of administration:** Intravenous.
- **Onset of action:** Rapid. (15-20 sec)
- **Distribution:** When thiopental is administered IV, it quickly enters the CNS because of high lipid solubility and depress function, often in less than 1 minute. However, diffusion out of the brain can occur very rapidly as well because of **redistribution** of the drug to other body tissues, including skeletal muscle and, ultimately, adipose tissue.
- **Duration of action:** Very short, due to the decrease of its concentration in the brain to a level below that necessary to produce anesthesia.
- **Metabolism:** Thiopental is metabolized slowly in the liver at the rate of only 12–16% per hour in humans following a single dose.
- **Excretion:** Less than 1% of the administered dose of thiopental is excreted unchanged by the kidney.

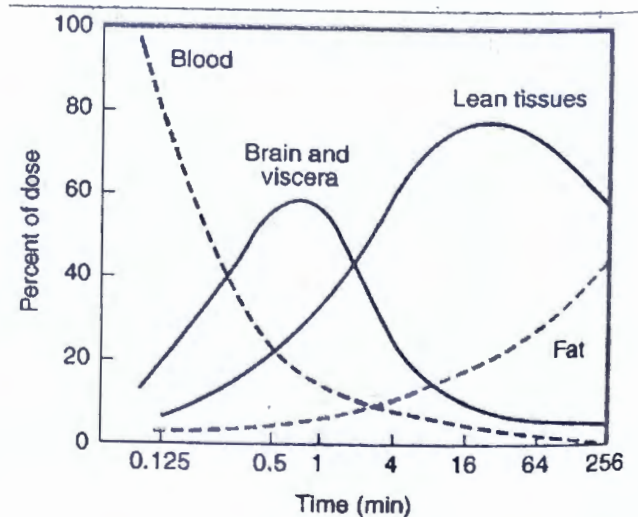
(Ref: Katzung-13th/433; Lippincott's-6th/183)

Fig. Redistribution of thiopental after an intravenous bolus administration. Note that the time axis is not linear.

Q. Explain the anesthetic action of thiopental-Na. (SU-13J)

Ans.

Cellular mechanism of anesthesia: At anaesthetizing concentrations, thiopental-Na has substantial effects on synaptic transmission & much smaller effects on action potential generation of propagation.

Molecular mechanism of anesthesia:

1. Ligand-gated ion channels are important targets for anesthetic action
2. Chloride channels gated by the inhibitory GABA_A-receptors are sensitive to clinical conc. of thiopental-Na.
3. At clinical concentration, thiopental-Na increases the sensitivity of the GABA_A-receptors to GABA.

(Ref: Goodman & Gilman-12th)

Q. Why Thiopental-Na is preferred for induction of general anesthesia? (CU-15Ju,14J)

Ans.

Thiopental-Na is preferred for induction of general anesthesia: Thiopental is a potent anesthetic. It has a high lipid solubility. When thiopental is administered intravenously, they quickly enter the CNS and depress function and induce anesthesia often in less than 1 minute. This is why thiopental-Na is preferred for induction of anesthesia.

(less than 20 sec)

(Ref: Lippincott's-6th/183)

Q. Mention the advantages & disadvantages of Thiopental-Na as IV general anesthesia. (DU-06M).

Ans.

Advantages of thiopental sodium:

1. Produces unconsciousness within minute (15-20 seconds)
2. Rapid recovery (6-10 minutes) (3-5 min)
3. It is a quick muscle relaxant.
4. Non-irritant to air passages.

low cost

easily available

less cardiorespiratory depression

Disadvantages of thiopental sodium:

1. It is a poor analgesic.
2. Large & repeated dose → Redistribution of the drugs to the pharmacological sanctuary space such as fatty tissues → Subsequent slow & sustained release of thiopental Na → Cardio-respiratory depression may occur. (cumulative defect) 2nd & 3rd are hangover effect (Nausea, vomiting, hypotension)
3. Extravasation of the solution or inadvertent intra-arterial injection produces intense pain & necrosis & gangrene may occur.

(Ref: Tripathi-6th/374)

Rebound
phenomenon

BP ↓ → Shock X

X Asthma → Bronchospasm

X children

X COPD

Inhaled anesthetics

Pharmacokinetic profile: The concentration of an inhaled anesthetic in a mixture of gases is proportional to its partial pressure (or tension). The rate at which a therapeutic concentration of the anesthetic is achieved in the brain depends on the following factors:

- 1. Solubility
- 2. Anesthetic conc. in the inspired air
- 3. Pulmonary ventilation
- 4. Pulmonary blood flow
- 5. Arterio-venous concentration gradient

(Ref: Katzung-13th/422)

Q. Define 'minimum alveolar concentration' (MAC). (RU-05M)

Q. What is the significance of MAC? (RU-05M)

Ans.

Minimum alveolar concentration / MAC:

Definition: MAC is the lowest conc. of the anesthetic in pulmonary alveoli needed to produce immobility in response to a painful stimulus (e.g. surgical incision) in 50% individuals.

Definition: MAC is defined as the median concentration that results in immobility in 50% of the patients when exposed to a noxious stimulus (e.g. surgical incision).

Significance of MAC:

- 1. Provides comparison of potencies of different inhaled anesthetic.
- 2. The more the percentage of MAC, the less the potency is.
- 3. The dose of the anesthetic gas can be calculated by using MAC.

Examples:

Anesthetic agent	MAC (%)
• Nitrous Oxide	> 100
• Halothane	0.75
• Isoflurane	1.40

(Ref: Katzung-13th/425; Tripathi-6th/365)

Q. Mention the advantages & disadvantages of halothane. (RU-17J)

Q. Write down the advantage of halothane over ether as general anesthetic agent. (CU-15J)

Ans.

Advantages of halothane:

- 1. Highly potent anesthetic
- 2. Induction is reasonably quick & pleasant.
- 3. Particularly suitable for induction & maintenance in children and as maintenance in adults.
- 4. Quick recovery
- 3. Non-irritant & non-inflammable
- 4. Potentiate competitive neuromuscular blockade
- 5. Relatively cheap.

Disadvantages / adverse effects of halothane:

- 1. It is not a good analgesics or muscle relaxants (but potentiates competitive NMJ blockade).
- 2. Concomitant use of N₂O / opioids / NMJ blockers is needed with halothane.
- 3. Liver damage
- 4. Cardiac arrhythmia
- 5. Low safety margin

(Ref: Tripathi-6th/372)

Q. Mention the advantages & disadvantages of nitrous oxide (N_2O). (CU-07S)

Ans.

Advantages of nitrous oxide (N_2O):

1. It is a good analgesic.
2. Non-irritating, non-inflammable anesthetics
3. Onset of action is quick & smooth.
4. Recovery is rapid.
5. Non toxic to the liver, kidney & brain.

Disadvantages of Nitrous Oxide (N_2O)

1. Low potency anesthetic.
2. It is a poor muscle relaxants.
3. Concomitant use of other potent anesthetic & NMJ blockers is required.
4. Quite expensive.

(Ref: Tripathi-6th/371)

Q. Mention rationale of using combination of halothane and nitrous oxide. (SU-14Ju)

Ans.

Rationale of using combination of halothane and nitrous oxide: Anesthesia is usually maintained by the combined administration of inhaled anesthetics such as **nitrous oxide** and **halothane**.

- **Nitrous oxide:** It provides good analgesia but lacks anesthesia.
- **Halothane:** It provides good anesthesia but lacks analgesia.

Thus, combined use of nitrous oxide and halothane provides good analgesia and anesthesia.

*O₂ → Respiration
20%, anesthetic 20% immobility
20%*

Q. What are the adverse effects of inhaled anesthetics?

Q. What are the adverse reactions of halothane? (CU-11Ju)

Ans.

Adverse effects of inhaled anesthetics:

1. **Acute toxicity**
 - a. Nephrotoxicity
 - b. Hematotoxicity
 - c. Hepatotoxicity (halothane hepatitis)
 - d. Malignant hyperthermia
2. **Chronic toxicity**
 - a. Mutagenicity
 - b. Teratogenicity
 - c. Increased incidence of miscarriages.
 - d. Carcinogenicity

(Ref: Katzung-13th/429-430)

Nice to know

Malignant Hyperthermia: It is an autosomal dominant genetic disorder of skeletal muscle that occurs in susceptible individuals undergoing general anesthesia with volatile agents and muscle relaxants (eg, succinylcholine).

Clinical features

1. Rapid onset of tachycardia and hypertension
2. Severe muscle rigidity
3. Hyperthermia
4. Hyperkalemia
5. Acidosis.

Malignant hyperthermia is a rare but important cause of anesthetic morbidity and mortality.

Specific biochemical abnormality: Increase in free calcium concentration in skeletal muscle cells.

Treatment

1. Dantrolene (to reduce calcium release from the sarcoplasmic reticulum).
2. Measures to reduce body temperature.
3. Restore electrolyte and acid-base balance.

(Ref: Katzung-13th/430)

Q. Short note: Halothane. (CU-16Ju)

Ans. Write in short from above discussion.

Q. Differentiate between the nitrous oxide and halothane. (DU-10Ju)

Ans.

Differences between the nitrous oxide and halothane

Nitrous oxide, NO	Halothane
1. It is a potent analgesic but a weak anesthetic	1. It is a potent anesthetic but a weak analgesic
2. It is used in GA for analgesia	2. It is used in GA for maintenance of anesthesia.
3. It does not produce muscle relaxation	3. It relaxes both skeletal & uterine muscle
4. It does not cause cardiac arrhythmia	4. It causes cardiac arrhythmia
5. It does not cause hepatotoxicity	5. It causes hepatotoxicity
6. It has moderate or no effect on cardiovascular system.	6. It causes dose-dependent hypotension

(Ref: Lippincott's-6th)

Q. Compare thiopental sodium and nitrous oxide as general anesthetic drugs. (CU-12Ju)

Ans.

Comparison between thiopental sodium and nitrous oxide

	Thiopental sodium	Nitrous oxide, NO
1. Mechanism of action	Increases sensitivity of GABA _A receptors to the neurotransmitters.	Increases duration of GABA-gated Cl ⁻ channel opening.
2. General anesthetic potency	High	Low
3. Analgesic potency	Low	High
4. Cardio-respiratory depression	May occur	No
5. Muscle relaxation	Yes	No
6. Diffusional hypoxia during recovery	No	Yes (Rx: O ₂ therapy during recovery)
7. Pneumothorax	No	Yes
8. Pressure on air sinuses	No	Increases the pressure.
9. Apnea, coughing, chest wall spasm, laryngospasm & bronchospasm	Yes	No
10. Excretion	Less quick than NO	Quicker

Same action as thiopental Na, but no cumulative action

rich blood flow

Propofol

Drug of choice

(O₂ + 100% + must)

Q. Short note: Propofol. (DU-17J,12Ju)

Ans.

Propofol

Propofol has become the most popular IV anesthetic. Propofol is widely used and has replaced thiopental as the first choice for anesthesia induction and sedation, because it produces a euphoric feeling in the patient and does not cause postanesthetic nausea and vomiting.

Pharmacokinetics:

- **Route of administration:** Intravenous
- **Onset of action:** Onset is smooth and occurs within about 40 seconds.

- **Distribution:** After IV administration, distribution half-life is 2–8 minutes, and redistribution half-life is 30–60 minutes.
- **Metabolism:** Liver.
- **Excretion:** Excreted in the urine as glucuronide and sulfate conjugates.

Mechanism of action: Through potentiation of the chloride current mediated through the GABA_A receptor complex.

(Ref: Katzung-13th/430-431)

Q. Write down the advantages & disadvantages of propofol. (DU-07M)

Ans.

Advantages of propofol:

1. More rapid recovery.
2. Patients subjectively feel better in the immediate postoperative period because of the reduction in postoperative nausea and vomiting and a sense of well-being.
3. It is used for both **induction** and **maintenance** of anesthesia, and is the agent of choice for **ambulatory surgery**. (Emergency)
4. Used for IV sedation in the operating room as part of a monitored anesthesia care technique and in diagnostic suites for procedural sedation.
5. Effective in producing prolonged sedation in patients in ICU.
6. Useful in patients with impaired ability to metabolize other sedative-anesthetic drugs.

Disadvantages of propofol

- Day case surgery → circumscription, abortion
1. Prolonged infusion for sedation or ventilatory management in the ICU may cause-
 - a. Delayed arousal due to cumulative effects.
 - b. Elevation of serum lipid levels.
 - c. Severe acidosis
 - d. Neurologic sequelae upon withdrawal.
 2. Dose-related depression of central ventilatory drive and transient apnea.
 3. Marked hypotension during induction of anesthesia.
 4. Pain at the site of injection is the most common adverse effect of bolus administration.
 5. Muscle movements, hypotonus, and (rarely) tremors.
 6. Clinical infections due to bacterial contamination of the propofol.
 7. Expensive.

(Ref: Katzung-13th/430-433; Lippincott's-6th/182)

Q. Compare propofol with thiopental sodium as general anesthetics. (RU-14Ju)

Ans.

Comparison between propofol & thiopental sodium

Traits	Propofol	Thiopental sodium
1. Onset of action	Rapid	Rapid
2. Metabolism	Rapid	Slow
3. Redistribution outside CNS	No	Yes
4. Accumulation with continuous infusion	No	Yes
5. Cardio-respiratory depression	Profound	Profound
6. Anesthetic effect	Potent	Potent
7. Analgesic effect	No	No
8. Recovery	More rapid	Rapid
9. Use in outpatient surgical procedures	Yes	No
10. Pain at injection site and systemic hypotension	Yes	No
11. Suitable for monitored anesthesia care	Yes	No
12. Postoperative nausea and vomiting	Minimal	Minimal

Ketamine

Street Drug

Q. Short note: Dissociative anesthesia. (RU-16J)

Ans.

Dissociative anesthesia is a state of profound **analgesia** and **anterograde amnesia** with minimal hypnosis during which the eyes may remain open; it can be produced by ketamine. It is particularly useful where modern equipment is lacking or where access to the patient is limited, e.g. at major accidents or on battlefields.

(Ref: Bennet & Brown-11th edition)

Nice to know

Dissociative anesthesia: Ketamine, a short-acting, nonbarbiturate anesthetic, induces a dissociated state in which the patient is unconscious (but may appear to be awake) and does not feel pain. This dissociative anesthesia provides sedation, amnesia, and immobility.

(Ref: Lippincott's-6th/184)

Q. Write short note on Ketamine. (DU-17M, 16Ju, 15J, 10J, SU-15J)

Q. Explain the anesthetic action of ketamine. (SU-17J, 14J, 13J, 10Ju)

Q. Write down the indications and adverse effects of ketamine. (DU-17J, RU-16Ju, SU-13J)

Ans.

Ketamine: Ketamine is a partially water-soluble and highly lipid soluble phencyclidine derivative. It produces significant analgesia. Patients have profound **analgesia**, unresponsiveness to commands, and **amnesia**, but may have their **eyes open**, move their limbs involuntarily, and breathe spontaneously. This cataleptic state has been termed **dissociative anesthesia**.

(Ref: Goodman & Gilman-12th; Ktzung-13th/436)

Pharmacokinetic property:

1. Highly lipid-soluble.
2. **Route of administration:** IV, IM, oral, rectal and epidural.
3. **Distribution:** Rapidly distributed into well-perfused organs, including the brain, liver, and kidney.
4. **Redistribution** to less well perfused tissues.
5. **Metabolism:** Liver
6. **Excretion:** Urinary and biliary excretion.

Mechanism of action:

Ketamine



Blockade of the membrane effects of the glutamate (excitatory NT) at the NMDA receptor.



Anesthetic action.

(Ref: Katzung-13th/436)

Indications / Clinical uses

1. Useful for anesthetizing patients at risk for hypotension and bronchospasm and for certain pediatric procedures.
2. Popular alternative to opioid analgesics to minimize respiratory depression.
3. Reduce the development of tolerance to long-term opioid use.
4. Ketamine can be administered by multiple routes (IV, IM, oral, rectal, epidural), thus making it a useful option for premedication in mentally challenged and uncooperative pediatric patients.
5. For outpatient anesthesia in combination with propofol (eg, as part of a monitored anesthesia care technique).
6. Painful procedures (eg, dressing changes for burns) in children.
7. Topical preparation for arthritic pain.

(Ref: Goodman & Gilman-11th/352; Katzung-13th/436; Lippincott's-6th/184)

X Abdominal Surgery

✓ Skeletal Muscle Surgery

Adverse effects:

1. Increases in blood pressure, heart rate, and cardiac output, presumably by centrally mediated sympathetic stimulation.
2. **Emergence delirium**: Characterized by hallucination, vivid dreams, illusions (very common). (Emergence phenomenon)
3. Increased cerebral blood flow.
4. Increases intracranial pressure (ICP). Ketamine is a potentially dangerous drug when ICP is elevated.
5. Increased intraocular pressure.

(Ref: Katzung-13th/436-437)**Contraindications**

1. Hypertension
2. Stroke

BP ↑

Long term surgery → multiple dose → muscle spasm
(Ref: Lippincott's-6th/184)

Q. Compare thiopentone and ketamine. (CU-15Ju)

Ans.

Comparison between Ketamine & Thiopental sodium

Traits	Ketamine	Thiopental sodium
1. Onset of action	Rapid	Rapid
2. Metabolism	Rapid	Slow
3. Redistribution outside CNS	Yes	Yes
4. Cardio-respiratory depression	Minimal	Profound
5. Cardiovascular stimulation	Yes (increases BP, heart rate, cardiac output)	No
6. Dissociative anesthesia	Yes	No
7. Anesthetic effect	Less potent	Potent
8. Analgesic effect	Profound	No
9. Protein binding	Low	High
10. Useful for mentally challenged and uncooperative pediatric patients.	Yes	No
11. Increases intracranial pressure (ICP)	Yes	No
12. Bronchodilation	Yes	No

(Ref: Katzung-13th/436-437)**Q. Discuss two advantages of ketamine over thiopental sodium. (DU-15Ju)**

Ans.

Advantages of ketamine over thiopental sodium: Ketamine causes-

1. Minimal cardio-respiratory depression.
2. Profound analgesic effect.
3. Bronchodilation (thus, it is useful for patients at risk for bronchospasm)
4. Increases blood pressure (thus, it is useful for patients at risk for hypotension)
5. Reduce the development of tolerance to long-term opioid use.
6. Ketamine can be administered by multiple routes (IV, IM, oral, rectal, epidural), thus making it a useful option for premedication in mentally challenged and uncooperative pediatric patients.

(Ref: Katzung-13th/436-437)**Q. What is monitored anesthesia care?**

Ans.

Monitored Anesthesia Care

Many diagnostic and minor therapeutic surgical procedures can be performed without general anesthesia using sedation-based anesthetic techniques. In this setting, regional or local anesthesia supplemented with midazolam or propofol and opioid analgesics (or ketamine) may be a more appropriate and safer approach than general anesthesia for superficial surgical procedures. This anesthetic technique is known as monitored anesthesia care.

Drugs used: The technique typically involves-

1. IV midazolam for premedication (to provide anxiolysis, amnesia, and mild sedation)
2. Propofol infusion (to provide moderate to deep levels of sedation)
3. A potent opioid analgesic or ketamine (to minimize the discomfort associated with the injection of local anesthesia and the surgical manipulations).

(Ref: Katzung-13th edition)

Nice to know

Conscious sedation: This technique refers to drug-induced alleviation of anxiety and pain in combination with an altered level of consciousness associated with the use of smaller doses of sedative medications. In this state the patient retains the ability to maintain a patent airway and is responsive to verbal commands. It is used primarily by nonanesthesiologists.

Drugs used: A wide variety of IV anesthetic drugs are useful in conscious sedation-

1. Diazepam
2. Midazolam
3. Propofol
4. Opioid analgesics (eg, meperidine, fentanyl)

} Non-potant 2nd

(Ref: Katzung-13th edition)

Deep sedation: It is similar to a light state of general (intravenous) anesthesia involving decreased consciousness from which the patient is not easily aroused. Because deep sedation is often accompanied by a loss of protective reflexes, an inability to maintain a patent airway, and lack of verbal responsiveness to surgical stimuli, this state may be indistinguishable from intravenous anesthesia. Drugs used in deep sedation protocols include thiopental, methohexital, midazolam, or propofol, potent opioid analgesics, and ketamine.

(Ref: Katzung-13th edition)

Local anesthesia

Q. Define local anesthesia. (RU-11J,06J,03S)

Ans.

Local anesthesia:

Definition: Local anesthesia is the loss of sensation in a body part without the loss of consciousness or the impairment of central control of vital functions.

(Ref: Goodman & Gilman-12th edition)

Definition: Local anesthesia is the condition that results when sensory transmission from a local area of the body to the CNS is blocked.

(Ref: Katzung & Trevor's-10th edition)

Q. Discuss about ideal anesthetic. (SU-13Ju)

Ans.

Properties of an ideal anesthetic:

1. Potent
2. Reversible
3. Rapid onset and adequate duration of action.
4. Short induction period
5. Minimal adverse reactions.
6. Non-irritating to nerve
7. Low systemic toxicity
8. No post anesthetic side effects
9. Sufficient tissue penetration.

10. Inexpensive
11. Sterilizable
12. Water soluble/stable in solution

- Q. Classify local anesthetics on chemical standpoint. (DU-08J, RU-06J, 05M, SU-11J)
 Q. Classify local anesthetics according to duration of action. (CU-13J, 12Ju, 05Ju)
 Q. Classify local anesthetics according to route of administration. (DU-15J, 07Ju, CU-08J, 06S)
 Q. Enlist/Name the local anesthetics. (CU-17J, SU-13Ju)
 Q. Name some important / clinically useful local anesthetics. (DU-13J, 11Ju, 10Ju, SU-04M, CU-05J)
 Q. Name the amide group of local anesthetics. (RU-16J, 15J, 13J, 12/09J)
 Q. Write the name & ways of application of local anesthetic agents. (CU-14J, 08J)
 Q. Explain with appropriate example different techniques of producing local / regional anesthesia. (CU-05M)
 Q. What are the different routes of administration of lidocaine? (DU-11Ju)
 Q. Name the drugs used in spinal anesthesia with advantages. (CU-13Ju, RU-14J)
 Q. Short note: Local anesthetics. (DU-16J)

Ans.

Local anesthetics:

A. According to chemical nature:

Esters <i>use 20% 2</i>	Procaine Tetracaine Benzocaine Cocaine
Amides	Lidocaine (Xylocaine) Mepivacaine Bupivacaine Levobupivacaine Ropivacaine Articaine

(Ester)
 ↓ metabolism
 ⇒ Allergy 25%
 p- amino - benzoic acid

(Ref: Katzung-13th/442)

B. According to duration of action:

Short acting	Procaine Cocaine <i>30-60 min</i>
Intermediate acting	Lidocaine/Xylocaine/Lignocaine: Most common. Widely used. Mepivacaine Prilocaine <i>60-120 min</i>
Long acting	Tetracaine Bupivacaine Ropivacaine <i>>120 min</i>

C. According to route of administration: (05-)

1. Surface anesthesia: Anesthesia of mucous membranes of the nose, mouth, throat, tracheobronchial tree, esophagus, and genitourinary tract can be produced by direct application of local anesthetics as solution, cream, jelly or lozenge. <i>spray - 2</i>	Tetracaine (2%) Lidocaine (2% - 10%) Cocaine (1% to 4%) <i>> 20 min - 20 min</i>
2. Infiltration anesthesia: To paralyze the sensory nerve endings and small cutaneous nerves. Infiltration anesthesia is the injection of local anesthetic directly into tissue without taking into consideration the course of cutaneous nerves. <i>circumcision, vasectomy, local burn</i>	Lidocaine (0.5% - 1%) Procaine (0.5% - 1%) Bupivacaine (0.125% - 0.25%)
3. I/V regional anesthesia: This technique relies on using the vasculature to bring the local anesthetic solution to the nerve trunks and endings. Eg, anesthesia of arm. <i>nerve specific - area / limb</i>	Lidocaine (0.5%) Prilocaine (0.5%)

4. Nerve block anesthesia: Injection of a solution of a local anesthetic into or about individual peripheral nerves or nerve plexuses is called nerve block anesthesia.	Lidocaine
5. Spinal anesthesia: Spinal anesthesia follows the injection of local anesthetic into the CSF in the lumbar space. <i>(cesarean section)</i> <i>caesarian sec. - a peripheral?</i>	Lidocaine Tetracaine Bupivacaine
6. Epidural anesthesia: Epidural anesthesia is administered by injecting local anesthetic into the epidural space. The primary site of action of epidural anesthetic is on the <u>spinal nerve roots</u> . However, epidural anesthetics also may act on the spinal cord and on the paravertebral nerves. It is widely used in obstetrics.	Lidocaine, Bupivacaine.
7. Field Block Anesthesia: Field block anesthesia is produced by subcutaneous injection of a solution of local anesthetic in order to anesthetize the region distal to the injection.	

(Ref: Goodman & Gilman-12th edition)Nice to know

Nerve Block Anesthesia: Injection of a solution of a local anesthetic into or about individual **peripheral nerves or nerve plexuses** produces even greater areas of anesthesia than do the other techniques. This is called nerve block anesthesia. Blockade of mixed peripheral nerves and nerve plexuses also usually anesthetizes somatic motor nerves, producing skeletal muscle relaxation, which is essential for some surgical procedures. The areas of sensory and motor block usually start several centimeters distal to the site of injection.

Example:

1. Brachial plexus blocks are particularly useful for procedures on the upper extremity and shoulder.
2. Intercostal nerve blocks are effective for anesthesia and relaxation of the anterior abdominal wall.
3. Cervical plexus block is appropriate for surgery of the neck.
4. Sciatic and femoral nerve blocks are useful for surgery distal to the knee.
5. Blocks of individual nerves such as the median or ulnar at the elbow, and blocks of sensory cranial nerves.

(Ref: Goodman & Gilman-12th edition)

Spinal Anesthesia: Spinal anesthesia follows the injection of local anesthetic into the CSF in the lumbar space. For a number of reasons, including the ability to produce anesthesia of a considerable fraction of the body with a dose of local anesthetic that produces negligible plasma levels, spinal anesthesia remains one of the most popular forms of anesthesia. In most adults, the spinal cord terminates above the second lumbar vertebra; between that point and the termination of the thecal sac in the sacrum, the lumbar and sacral roots are bathed in CSF. Thus, in this region there is a relatively large volume of CSF within which to inject drug, thereby minimizing the potential for direct nerve trauma.

Complications of Spinal Anesthesia

1. **Persistent neurological deficits**- extremely rare.
2. High concentrations of local anesthetic can cause **irreversible block**.
3. **Postural headache:** The incidence of headache decreases with increasing age of the patient and decreasing needle diameter. Treatment usually is conservative, with bed rest and analgesics.

(Ref: Goodman & Gilman-12th edition)Infiltration Anesthesia:

- **Advantage:** It can provide satisfactory anesthesia without disrupting normal bodily functions.
- **Disadvantage:** Relatively large amounts of drug must be used to anesthetize relatively small areas.

(Ref: Goodman & Gilman-12th edition)

Epidural Anesthesia: Epidural anesthesia is administered by injecting local anesthetic into the epidural space—the space bounded by the ligamentum flavum posteriorly, the spinal periosteum laterally, and the dura anteriorly. Epidural anesthesia can be performed in the sacral hiatus (caudal anesthesia) or in the lumbar, thoracic, or cervical regions of the spine. The primary site of action of epidural anesthetic is on the **spinal nerve roots**. However, epidural anesthetics also may act on the spinal cord and on the paravertebral nerves.

Difference between epidural and spinal anesthesia

1. The dose of local anesthetic used can produce high concentrations in blood following absorption from the epidural space.
2. The risk of inadvertent intravascular injection is increased in epidural anesthesia, as the epidural space contains a rich venous plexus.
3. There is no sympathetic blockade with epidural anesthesia.

(Ref: Goodman & Gilman-12th edition)

Intravenous Regional Anesthesia (Bier's Block): This technique relies on using the vasculature to bring the local anesthetic solution to the nerve trunks and endings. In this technique, an extremity is exsanguinated with an Esmarch (elastic) bandage, and a proximally located tourniquet is inflated to 100 to 150 mm Hg above the systolic blood pressure. The Esmarch bandage is removed, and the local anesthetic is injected into a previously cannulated vein. Typically, complete anesthesia of the limb ensues within 5 to 10 minutes.

(Ref: Goodman & Gilman-12th edition)Pharmacokinetic profile:

Absorption: Systemic absorption of injected L/A from the site of injection is determined by—

1. Dosages
2. Site of injection
3. Drug-tissue binding
4. Local blood flow
5. Use of vasoconstrictors (Adrenaline)
6. Physiochemical properties of the drug itself.

Metabolism:

- Liver: Amides
- Plasma: Ester

Distribution: The amide L/As is widely distributed after IV bolus administration. There is also sequestration in lipophilic storage sites (e.g. fat).

(Ref: Katzung-13th/441-443)Nice to know

Lipid-soluble (nonionized, uncharged) form of the drug molecule crosses the lipid membrane more rapidly to reach the cytoplasm than does the ionized form. On the other hand, once inside the axon, the ionized (charged) form of the drug is the more effective blocking entity. Thus, both the nonionized and the ionized forms of the drug play important roles—the first in reaching the receptor site and the second in causing the effect.

Q. Mention the mechanism of action of local anesthetics. (DU-13J, 10Ju, CU-13Ju; RU-16J, 15J, 13J, 12J, 11J, SU-15J)

Q. Explain the mechanism of action / anesthetic action of lidocaine. (DU-08J, SU-17J, 14/13/10J, RU-12/09J)

Q. Discuss the mechanism of action of Lignocaine / Xylocaine. (DU-06J, RU-05M, Cu-12Ju)

Q. How local anesthesia reduces / relieves pain? (CU-06S)

Ans.

Mechanism of action of local anesthetics / lidocaine / lignocaine: The primary mechanism of action of local anesthetics is blockade of voltage-gated sodium channels.

Therapeutic Dose

Lidocaine / lignocaine / local anesthetic drugs

↓
Block of voltage-gated Na⁺ channels in the afferent neuron

↓
Reduce the influx of sodium ions

↓
Prevent depolarization

↓
No action potential

↓
No transmission of pain sensation

↓
Local anesthetic action

2) High dose

— K⁺ channel block

(Ref: Katzung-13th/444)

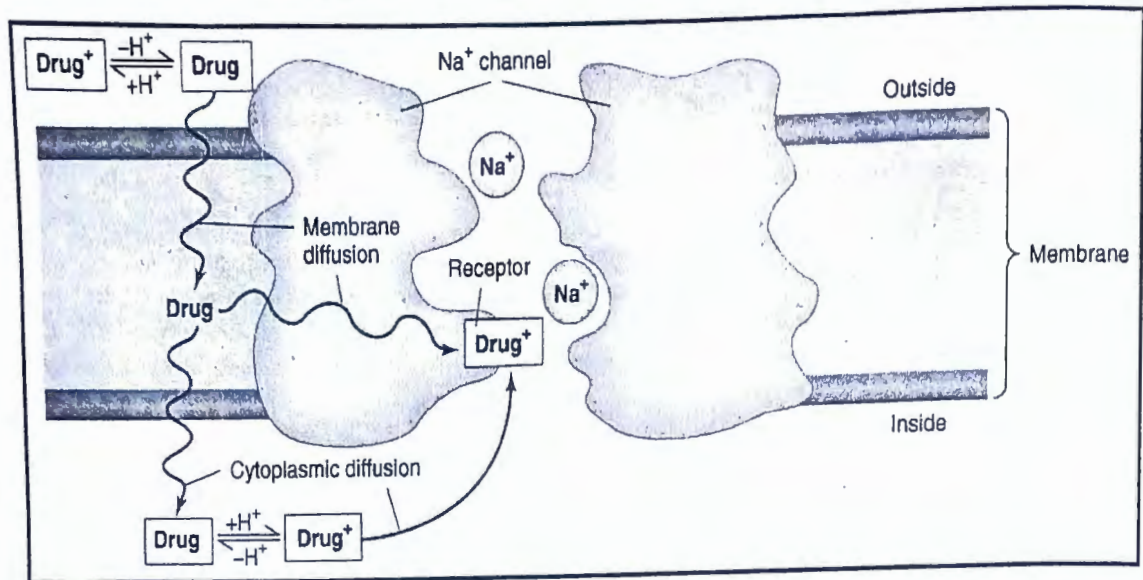


Fig. Mechanism of action of local anesthetics. Sodium ions are not able to pass through the channel when the drug is bound to the receptor.

Q. Why adrenaline is used with local anesthetics? (DU-13J, 10Ju, 07Ju, RU-11J)

Q. How the action of lignocaine could be prolonged? (DU-08J)

Q. Justify the combination of xylocaine & adrenaline. (DU-06Ju, CU-04M, SU-11J)

Q. Explain why adrenaline is premixed with lidocaine. (RU-15J, 13J)

Q. Justify the combined use of lidocaine & adrenaline. (RU-14J, SU-15J, 14Ju, 13Ju)

Q. Mention the justification of using adrenaline with lignocaine. (DU-15J)

Q. Mention the role of using vasoconstrictor along with LA. (RU-16J)

Ans.

Prolongation of action of lignocaine/xylocaine/lidocaine / vasoconstrictor: The duration of action of a local anesthetic is proportional to the time of contact with nerve. Consequently, maneuvers that keep the drug at the nerve prolong the period of anesthesia. Action of a local anesthetic, eg, lignocaine can be prolonged by adding a vasoconstrictor, eg, adrenaline to it.

- 1) Adrenaline
- ↓
 - Local vasoconstriction at the injection site
 - ↓
 - Decreased blood flow to that area
 - ↓
 - Decreased absorption of local anesthetic
 - ↓
 - Local anesthetic can act on the nerve for more time
 - ↓
 - Prolongation of action of a local anesthetic (lignocaine).

- 2) Site change
- 3) Repeated dose
- 2) longer "
- 5) Slowing the injection

(Ref: Goodman & Gilman-12th edition)

Nice to know

Contraindication of adrenaline in local anesthetic

- 1) Adrenaline-containing solutions should not be injected into tissues supplied by end arteries—for example, fingers and toes, ears, the nose, and the penis. The resulting vasoconstriction may cause gangrene.
2. For the same reason, epinephrine should be avoided in solutions injected intracutaneously.
3. Since epinephrine also is absorbed into the circulation, its use should be avoided in those for whom adrenergic stimulation is undesirable.

(Ref: Goodman & Gilman-12th edition)

Q. What are the indications of Lidocaine? (RU-09J)

Ans.

Indications of lidocaine:

1. As a local anesthetic
2. As an anti-arrhythmic drug. → *ventricular tachycardia*
3. As anti-convulsant drug → *Status Epilepticus*

Nice to know

Summary: Drugs Used for Local Anesthesia

Subclass	Clinical Applications	Pharmacokinetics, Toxicities
Amides		
Lidocaine	Short-duration procedures Epidural, spinal anesthesia	• Parenteral • Duration 30–60 min; 2–6 h with epinephrine • Toxicity: CNS excitation
Bupivacaine	Longer-duration procedures	• Parenteral • Duration 2–4 h • Toxicity: CNS excitation cardiovascular collapse
<i>Prilocaine, ropivacaine, mepivacaine, levobupivacaine: Like bupivacaine</i>		
Esters		
Procaine	Very short procedures	• Parenteral • Duration 15–30 min; 30–90 min with epinephrine • Toxicity: Like lidocaine
Cocaine	Procedures requiring high surface activity and vasoconstriction	• Topical or parenteral • Duration 1–2 h • Toxicity: CNS excitation, convulsions, cardiac arrhythmias, hypertension, stroke

(Ref: Katzung-13th/453)

Q. Discuss the dangers of using local anesthetic agents. (DU-08J, CU-08J)

Q. Mention the side effects of lignocaine? (CU-12Ju, RU-10Ju, 06J, 05M)

Q. Mention the side effects of lidocaine? (SU-13J)

Q. Mention the adverse effects of lidocaine? (CU-17J, RU-14J)

Q. Mention the systemic adverse effects of lidocaine? (RU-12J)

Ans.

Adverse effects of local anesthetics (LA): Local anesthetic toxicity derives from two distinct processes:

1. **systemic effects** following inadvertent IV injection or absorption of the LA from the site of administration.
2. **neurotoxicity** resulting from local effects produced by direct contact with neural elements.

CNS toxicity	1. When high plasma concentrations are produced after rapid absorption or inadvertent IV administration, all LA have the ability to produce- • Sleepiness • Light-headedness • Visual and auditory disturbances • Restlessness 2. Circumoral and tongue numbness and a metallic taste. 3. At higher concentrations- • nystagmus • muscular twitching • tonic-clonic convulsions • generalized CNS depression.
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Cardiotoxicity	1. Cardiac arrest 2. Arrhythmia (Ventricular tachycardia and fibrillation)
Neurotoxicity	• Neural toxicity occurs at excessively high concentrations at spinal and epidural administration. • Cauda equina syndrome associated with continuous spinal anesthesia (CSA) (lidocaine). • Transient neurologic symptoms (TNS)—Transient pain or dysesthesia. Occurs in use of lidocaine for spinal anesthesia.
Hematologic	• Methemoglobinemia (large doses (> 10 mg/kg) of prilocaine)
Allergic reactions	• Caused by ester-type local anesthetics.

→ Hb $\xrightarrow{\text{metabolism}}$ Methemoglobin (Ref: Katzung-13th/448-449; Goodman and Gilman's-12th)

Nice to know

✓ **Mechanism of cardiotoxicity of LA:** LA block cardiac sodium channels and thus depress abnormal cardiac pacemaker activity, excitability, conduction and force of contraction. Cardiotoxicity of local anesthetic agents may result from their inadvertent IV administration, especially if epinephrine also is present. Cardiotoxicity is rare, occurs in large doses of bupivacaine, ropivacaine and etidocaine.

Viva Q. How can you prevent local-anesthetic-induced convulsion?

Ans.

Prevention of local-anesthetic-induced convulsion: Convulsions due to excessively high blood levels can be prevented by-

1. Administering the smallest effective dose of the local anesthetic required for adequate surgical analgesia.
2. Avoiding inadvertent IV injection.
3. Avoiding injection into highly perfused tissues.

(Ref: Katzung-13th/448)

Q. Short note: Bupivacaine. (DU-12J)

Ans. Write M/A, indication, adverse effects from above.

Q. List the adverse effects of spinal anesthetic. (CU-08Ju)

Ans.

Adverse effects of spinal anesthetic

1. Bradycardia
2. Hypotension
3. Postural headache
4. Respiratory depression
5. Post-operative urinary retention
6. Irreversible block (High concentrations)
7. Persistent neurological deficits (extremely rare)

(Ref: Goodman & Gilman-12th edition)

Skeletal Muscle Relaxants

Drugs that affect skeletal muscle function include two different therapeutic groups:

1. **Neuromuscular blockers:** These drugs are used during surgical procedures and in the ICU to produce muscle paralysis. Neuromuscular blocking drugs interfere with transmission at the neuromuscular end plate and lack CNS activity. These compounds are used primarily as adjuncts during general anesthesia to facilitate tracheal intubation and optimize surgical conditions while ensuring adequate ventilation.
2. **Centrally acting muscle relaxants / spasmolytics:** These drugs are used to reduce spasticity in a variety of painful conditions, eg, chronic back pain and painful fibromyalgic conditions.

(Ref: Katzung-13th/455)

Centrally acting muscle relaxants

Spasticity: Spasticity may be defined as "disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles." It is characterized by an increase in tonic stretch reflexes and flexor muscle spasms (ie, increased basal muscle tone) together with muscle weakness. It is often associated with spinal injury, cerebral palsy, multiple sclerosis, and stroke. These conditions often involve abnormal function of the bowel and bladder as well as skeletal muscle.

Drugs that modify the reflex arc may modulate excitatory or inhibitory synapses. Thus, to reduce the hyperactive stretch reflex, it is desirable to reduce the activity of the Ia fibers that excite the primary motor neuron or to enhance the activity of the inhibitory interneuronal neurons.

(Ref: Katzung-13th/465)

Q. Define muscle relaxants / spasmolytic. (CU-12J)

Ans.

Muscle relaxants / Spasmolytic: A drug that reduces abnormally elevated muscle tone (spasm) without paralysis is called muscle relaxants / spasmolytic.

(Ref: Katzung & Trevor's-10th edition)

Q. Define centrally acting muscle relaxants / spasmolytic.

Ans.

Centrally acting muscle relaxants / Spasmolytic: They are drugs which reduce skeletal muscle tone by a selective action in the cerebro-spinal axis without altering consciousness. They selectively depress spinal & supraspinal polysynaptic reflexes involved in regulation of muscle tone without significantly affecting monosynaptically mediated stretch reflex.

All centrally acting muscle relaxants have some sedative property & have no effect on NMJ & muscle fibers but reduce decerebrate rigidity, UMN spasticity & hyperreflexia.

(Ref: Tripathi-6th/348)

Q. Classify muscle relaxants / Spasmolytic. (SU-06J)

Q. Name the clinically used skeletal muscle relaxants. (DU-04S, CU-15Ju)

Ans.

Muscle relaxants

A. Centrally acting muscle relaxants:

1. Mephenesin congeners	• Mephenesin • Carisoprodol • Chlorphenesin • Chlorzoxazone • Cyclobenzaprine • Metaxalone • Methocarbamol • Orphenadrine
--------------------------------	--

2. Benzodiazepine	• Diazepam
3. GABA derivatives	• Baclofen • Gabapentin
4. Central α_2 -agonist	• Tizanidine

(Ref: Tripathi-6th/348)**B. Peripherally acting muscle relaxants:** (Described in the ANS chapter.)

1. Non-depolarizing / competitive / reversible group
2. Depolarizing / non-competitive / irreversible group

C. Direct-acting muscle relaxant:

1. Dantrolene
2. Botulinum toxin

(Ref: Katzung-13th/469)

Baclofen

Baclofen (*p*-chlorophenyl-GABA) was designed to be an orally active GABA-mimetic agent and is an agonist at GABA_B receptors.

Mechanism of action of baclofen:**1. Activation of GABA_B receptors**

Baclofen

Binds with GABA_B receptors in the brainIncreases K⁺ conductance (K⁺ efflux)

Hyperpolarization of pre-synaptic membranes

Decreases Ca²⁺ influx

Decreases the release of excitatory transmitters in both the brain and the spinal cord



Muscle relaxation.

2. Baclofen may also reduce pain in patients with spasticity, perhaps by inhibiting the release of substance P (neurokinin-1) in the spinal cord.

(Ref: Katzung-13th/467)

Dose: Dosage is started at 15 mg twice daily, increasing as tolerated to 100 mg daily.

Indication

1. Spasticity associated with spinal injury, cerebral palsy, multiple sclerosis, and stroke.
2. Intractable low back pain
3. Reduction of craving in recovering alcoholics
4. Prevention of migraine headaches in some patients.

(Ref: Katzung-13th/467)**Adverse effects of Baclofen:**

1. **CNS adverse effects:** Weakness, ataxia, drowsiness, mental confusion, raised serum transaminases etc.
2. **Sudden withdrawal after chronic use may cause:** Hallucination, seizure, tachycardia etc.

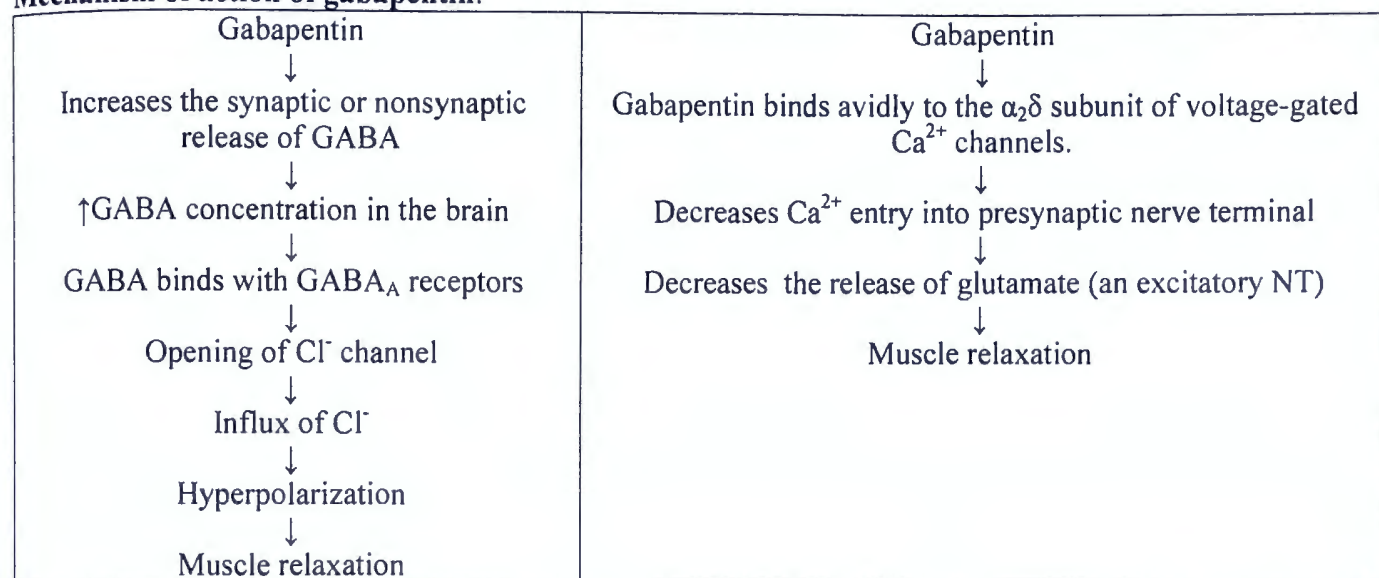
(Ref: Tripathi-6th/349)

Advantages of baclofen:

1. It is as effective as diazepam.
2. Less sedation.
3. Does not reduce overall muscle strength as much as dantrolene.
4. Rapidly & completely absorbed after oral administration & has a plasma half life 3-4 hours.

(Ref: Katzung-13th/467)**Gabapentin**

Gabapentin is an amino acid, an analog of GABA, that is effective against partial seizures. Originally planned as a spasmolytic, it was found to be more effective as an antiseizure drug.

Mechanism of action of gabapentin:(Ref: Katzung-13th/406)**Clinical Use**

1. Gabapentin is effective as an adjunct against partial seizures and generalized tonic-clonic seizures
2. Neuropathic pain (eg, postherpetic neuralgia in adults)

Adverse effects of Gabapentin:

1. Somnolence
2. Dizziness
3. Ataxia
4. Headache
5. Tremor.
6. Weight gain.
7. Diarrhoea.

(Ref: Katzung-13th/406; Lippincott's-5th/186)

Dantrolene

Dantrolene is a hydantoin derivative related to phenytoin that has a unique mechanism of spasmolytic activity. In contrast to the centrally acting drugs, dantrolene reduces skeletal muscle strength by interfering with excitation-contraction coupling in the muscle fibers.

Mechanism of action of dantrolene:

Dantrolene binds with calcium channel, ryanodine receptor1 (RyR1) channel



Blocks the opening of the channel.



Blocks Ca^{2+} release from sarcoplasmic reticulum of skeletal muscle cells



No excitation-contraction coupling



Muscle relaxation

Cardiac muscle and smooth muscle are minimally depressed because the release of calcium from their sarcoplasmic reticulum involves a different RyR channel (RyR2).

(Ref: Katzung-13th/467-468)

Adverse effects of dantrolene:

1. Muscular weakness.
2. CNS: Sedation, malaise, light headedness.
3. Diarrhoea.
4. Hepatotoxicity (long term use 0.1- 0.5 %)

(Ref: Tripathi-6th/347)

Indication

1. **IV:** Malignant hyperthermia
2. **Oral:** Spasm due to cerebral palsy, spinal cord injury, multiple sclerosis

(Ref: Katzung-13th/469)

Q. Write the differences between centrally & peripherally acting muscle relaxants.

Ans.

Differences between centrally & peripherally acting muscle relaxants:

Traits	Centrally acting	Peripherally acting
1. Voluntary power	Decreases muscle tone without reducing voluntary power	Causes muscle paralysis & voluntary movements are also lost
2. Mechanism	Selectively inhibit polysynaptic reflexes in CNS	Block neuromuscular transmission
3. CNS depression	Causes some CNS depression	No effect on CNS
4. Route	Given orally, sometimes parenterally	Practically always given in I/V route
5. Uses	Chronic spastic conditions; acute muscle spasms, tetanus etc.	For short-time purposes, like general anesthesia, ECT.

(Ref: Tripathi-6th/348)

MCQ

Q. Newer anxiolytic drugs are- (DU-17M)

- a) buspirone
 - b) zolpidem
 - c) diazepam
 - d) oxazepam
 - e) phenobarbitone
- a.-F, b.-T, c.-F, d.-F e.-F*

Q. Ketamine- (DU-17M,14Ju)

- a. causes profound analgesia
 - b. usually produce bradycardia & fall of BP
 - c. produces no muscular relaxation
 - d. decreases intracranial & intraocular pressure
 - e. can cause hallucination during recovery
- a. T, b. F, c. T, d. F, e. F*

Q. Drugs used to treat parkinsonism are- (DU-16J)

- a) levodopa
 - b) selegiline
 - c) carbamazepine
 - d) neostigmine
 - e) carbidopa
- a. T, b. T, c. F, d. F, e. T*

Q. Carbamazepine- (DU-15Ju)

- a. is the drug of choice for partial seizure
 - b. is effective in trigeminal neuralgia
 - c. may cause hypoxia
 - d. is available only in oral form
 - e. causes fetal hydantoin syndrome
- a. T, b. T, c. F, d. T, e. F*

Q. Morphine causes- (DU-15Ju)

- a. histamine release
 - b. mydriasis
 - c. cough suppression
 - d. diarrhea
 - e. vomiting
- a. T, b. F, c. T, d. F, e. T*

Q. Morphine causes- (DU-14Ju)

- a. histamine to release
 - b. mydriasis
 - c. cough suppression
 - d. tolerance & dependence
 - e. increase in blood pressure
- a. T, b. F, c. T, d. F, e. F*

Q. Diazepam- (DU-14Ju)

- a. has active metabolite
 - b. can cause retrograde amnesia
 - c. can cause muscle relaxation
 - d. never causes fatal overdose
 - e. metabolized mainly in the liver
- a. T, b. F, c. T, d. F, e. T*

Q. Adverse effects of carbamazepine include- (DU-14Ju)

- a. trigeminal neuralgia
 - b. dizziness
 - c. diplopia
 - d. hyponatremia
 - e. hallucination
- a. F, b. T, c. T, d. T, e. F*

Q. Halogenated anesthetics may produce malignant hyperthermia in: (CU-14Ju)

- a) Patients with poor renal function
 - b) Patients allergic to the anesthetic agents.
 - c) Pregnant women.
 - d) Alcoholics
 - e) Patients with genetic defect in muscle calcium regulation.
- a. F, b. F, c. F, d. F, e. T*

Q. Following statements about pain and its drug therapy are: (CU-14Ju)

- a) Substance P and glutamate are responsible neurotransmitters for pain perception.
 - b) Cyclooxygenase inhibition in the CNS by NSAIDs modifies pain perception.
 - c) Stimulation of pain modulating descending pathway is one mechanism of Morphine-induced analgesia.
 - d) Tramadol is better therapeutically than Meperidine as obstetric analgesic.
 - e) Selective COX-inhibitors are better therapeutically than non-selective ones.
- a. T, b. F, c. T, d. T, e. F*

Q. Tricyclic antidepressant group of drugs: (CU-14Ju)

- a) Inhibit the neuronal uptake of Noradrenalin.
 - b) Have a rapid onset of action.
 - c) May cause constipation and dry mouth.
 - d) Do not produce postural hypotension.
 - e) May produce tachycardia and palpitation.
- a. T, b. F, c. T, d. F, e. T*

Q. The following drugs are used in balanced anesthesia- (DU-14J)

- a. haloperidol
 - b. thiopentone
 - c. halothane
 - d. sodium valproate
 - e. atracurium
- a. F, b. T, c. T, d. F, e. T*

Q. The central excitatory effects of morphine include- (DU-14J)

- a. sedation
 - b. emesis
 - c. miosis
 - d. diarrhea
 - e. euphoria
- a. F, b. T, c. T, d. F, e. F*

Q. Ketamine- (DU-14J)

- a. causes profound analgesia
 - b. usually produces bradycardia & fall of BP
 - c. produces muscle relaxation
 - d. decreases intracranial & intraocular pressure
 - e. causes hallucination.
- a. T, b. F, c. F, d. F, e. T*

Q. The adverse effects of carbamazepine include- (DU-13Ju)

- a. trigeminal neuralgia.
 - b. dizziness.
 - c. diplopia.
 - d. hyponatremia.
 - e. hallucination.
- a. F, b. T, c. T, d. T, e. F*

Q. Benzodiazepines- (DU-13Ju)

- a. act by binding to GABA receptor.
 - b. reduce the activity of central neurotransmitter, GABA.
 - c. can cause anterograde amnesia.
 - d. are potent inducer of hepatic drug metabolizing enzyme.
 - e. suppress REM sleep.
- a. T, b. F, c. T, d. F, e. T*

Q. Preanesthetic medication comprises be following- (DU-13J)

- a. diazepam.
- b. atropine.
- c. metoclopramide.

- d. lignocaine.
 - e. ketamine.
- a. T, b. T, c. T, d. F, e. F*

Q. Benzodiazepines- (DU-13J)

- a. potentiate the action of GABA.
 - b. open the chloride channel.
 - c. cause hyperpolarization of the neuron.
 - d. stimulate dopamine receptor.
 - e. cause retrograde amnesia.
- a. T, b. F, c. F, d. T, e. F*

Q. Morphine is contra-indication in- (DU-13J)

- a. head injury.
 - b. acute MI.
 - c. bronchial asthma.
 - d. biliary colic.
 - e. peptic ulcer.
- a. T, b. F, c. T, d. T, e. F*

Q. Action of local anesthetic can be affected by- (SU-13J)

- a. pH of site of action
 - b. Pseudocholinesterase
 - c. Potassium
 - d. Calcium
 - e. Diameter of nerve fibers
- a. T, b. F, c. T, d. T, e. T*

Q. Sedative-hypnotic drug- (SU-13J)

- a. Triazolam is short-acting
 - b. Diazepam is metabolized to alprazolam
 - c. Clonazepam exert anti-epileptic action
 - d. Zopiclone is a benzodiazepine agonist
 - e. Midazolam is not addicting
- a. T, b. F, c. T, d. F, e. F*

Q. In treatment of parkinsonism- (SU-13J)

- a. Balance between acetylcholine & dopamine is maintained
 - b. Dopamine is given orally
 - c. L-dopa is given with carbidopa
 - d. Carbidopa is dopamine agonist
 - e. Neuroleptic-induced parkinsonism is treated by benztropine
- a. T, b. F, c. T, d. T, e. F*

Q. Thiopental sodium is- (DU-12Ju)

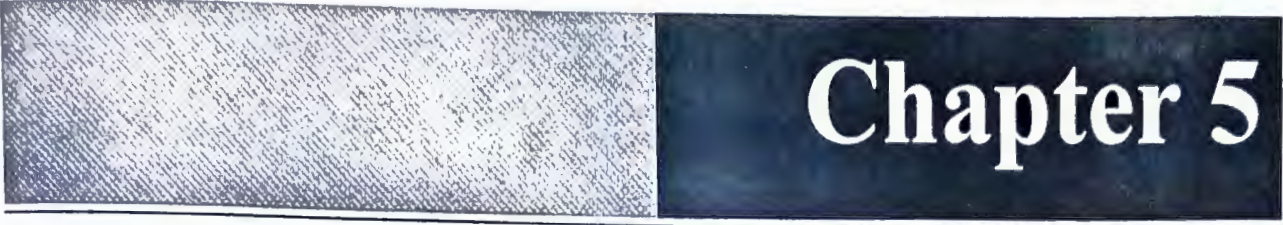
- a. Ultra short acting barbiturate. (T)
- b. Acidic in nature. (?)

- c. Used for maintenance of general anesthesia. (F)
 d. Highly lipid soluble. (T)
 e. Contraindicated in hypertension. (?)
- Q. Morphine- (DU-12Ju)**
 a. Is used to relieve pain in severe head injury. (F)
 b. Withdrawal symptoms can be relieved by methadone.
 c. Causes diarrhea. (F)
 d. Is most effective by oral administration. (?)
 e. Is more potent than pethidine. (T)
- Q. The central excitatory effects of morphine include- (DU-12J)**
 a. Sedation (F)
 b. Emesis (T)
 c. Miosis (T)
 d. Diarrhea (F)
 e. Euphoria (T)
- Q. Following drugs are used in balanced anesthesia- (DU-12J)**
 a. Haloperidol (F)
 b. Thiopental sodium (F)
 c. Halothane (T)
 d. Propranolol (F)
 e. Nitrous oxide (T)
- Q. In status epilepticus, following drugs are used- (DU-11Ju)**
 a. Diazepam (T)
 b. Phenobarbitone (T)
 c. Phenytoin (T)
 d. Adrenaline (F)
 e. Prednisolone (F)
- Q. Ketamine- (DU-11Ju)**
 a. Causes profound analgesia (T)
 b. Usually causes bradycardia & fall of BP (F)
 c. Produces no muscular relaxation (?T)
 d. Decreases intracranial and intraocular pressure (F)
 e. Hallucination. (T)
- Q. Morphine should be avoided in patients with- (DU-11Ju)**
 a. Pancreatitis (F)
 b. Asthma (T)
 c. Respiratory depression (T)
- d. Acute left ventricular failure (F)
 e. Acute MI (F)
- Q. Morphine- (DU-11J)**
 a. Is contraindicated in head injury. (T)
 b. Increases intra-biliary pressure (T)
 c. Is most effective by oral administration (F)
 d. Reduces sensitivity of respiratory center to CO₂ (T)
 e. Causes diarrhea (F)
- Q. Benzodiazepine- (DU-11J)**
 a. Potentiate the action of GABA (T)
 b. Open the Cl⁻ channel (F)
 c. Open K⁺ channel (F)
 d. Causes hyperpolarization of neuron (T)
 e. Stimulate dopamine receptor. (F)
- Q. Pethidine- (DU-10Ju)**
 a. Is a natural drug (F)
 b. Acts on opioid receptor (T)
 c. Causes miosis (F)
 d. Can cause respiratory depression (T)
 e. Produces tolerance (T)
- Q. Nortriptyline- (DU-10Ju)**
 a. blocks uptake I (T)
 b. decreases the level of amines in the brain (F)
 c. can cause sedation (T)
 d. can cause diarrhea (F)
 e. can cause tachycardia (T)
- Q. Benzodiazepines- (DU-10J)**
 a. act by inhibiting GABA receptor (T)
 b. produce hyperpolarization of neuron (T)
 c. produce anterograde amnesia (T)
 d. are used as sedative for endoscopy (T)
 e. are potent hepatic microsomal enzyme inducer (F)
- Q. Antidepressant drugs- (DU-10J)**
 a. increase the level of amines in the brain (T)
 b. can cause diarrhea (F)
 c. can cause bradycardia (F)
 d. provide immediate antidepressive effect (F)
 e. can cause difficulty in micturition (T)
- Q. Chlorpromazine- (DU-10J)**
 a. is an agonist drug (F)
 a. can cause tremor & rigidity (T)

- b. can cause bradycardia (T)
- c. may cause cholestatic jaundice (?)
- d. suppresses lactation (F)

Q. Nitrous oxide- (DU-10J)

- a. is a potent anesthetic agent (F)
 - b. has good analgesic effect (T)
 - c. has got muscle relaxation effect (T)
 - d. can cause diffusion hypoxia (T)
 - e. produces quick onset & slow recovery of anesthesia. (F)
-



Chapter 5

Drugs acting on Cardiovascular System

Antihypertensive drugs

Definition: It is a clinical condition characterized by persistent rise of systemic arterial pressure above the normal range in respect of age and sex.

(Ref: Ganong-24th)

Definition: Persistent rise of blood pressure in respect of age and sex where the systolic pressure is more than 140 mmHg and diastolic pressure is more than 90 mmHg, is called hypertension.

Definition of hypertension:

Category	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Blood pressure		
Optimal	< 120	< 80
Normal	< 130	< 85
High normal	130-139	85-89
Hypertension		
Grade 1 (mild)	140-159	90-99
Grade 2 (moderate)	160-179	100-109
Grade 3 (severe)	≥180	≥110
Isolated systolic hypertension		
Grade 1	140-159	< 90
Grade 2	≥160	< 90

(Ref: Davidson's medicine-22nd)

Types: 2 types:

- Essential hypertension:** When the cause of increased blood pressure is not known, it is called essential hypertension. Over 95% of the hypertensive pt. suffer from essential hypertension. Here, blood pressure persistently exceeds 150/90 or 160/100 mm Hg.
- Secondary hypertension:** In about 5 % of unselected cases, hypertension may be shown to be a consequence of a specific disease or abnormality leading to sodium retention and / or peripheral vasoconstriction. This is called secondary HTN. It occurs mostly due to renal diseases.

Causes of secondary hypertension:

- Alcohol
- Obesity
- Pregnancy (pre-eclampsia)
- Renal disease**
 - Renal vascular disease
 - Polycystic kidney disease
 - Parenchymal renal disease, particularly glomerulonephritis
- Endocrine disease:**
 - Phaeochromocytoma
 - Cushing's syndrome
 - Primary hyperaldosteronism (Conn's syndrome)
 - Hyperparathyroidism
 - Acromegaly
 - ~~Primary hypothyroidism~~
 - Thyrotoxicosis
 - Congenital adrenal hyperplasia due to 11-β-hydroxylase or 17-hydroxylase deficiency
 - Liddle's syndrome
 - 11-β-hydroxysteroid dehydrogenase deficiency

6. **Drugs:** e.g. Oral contraceptives containing oestrogens, anabolic steroids, corticosteroids, non-steroidal anti-inflammatory drugs, carbenoxolone, sympathomimetic agents
7. **Coarctation of the aorta**

(Ref: Davidson's-22nd)

Q. What are the complications of hypertension?

Ans.

Complications of hypertension:

Heart	- Myocardial infarction (MI) - Hypertensive cardiomyopathy - Hypertensive heart failure
Brain	- Stroke - Hypertensive encephalopathy
Eye	Hypertensive retinopathy
Kidney	Hypertensive nephropathy (eg, chronic renal failure)

Q. What are the risk factors of hypertension?

Ans.

Risk factors of hypertension:

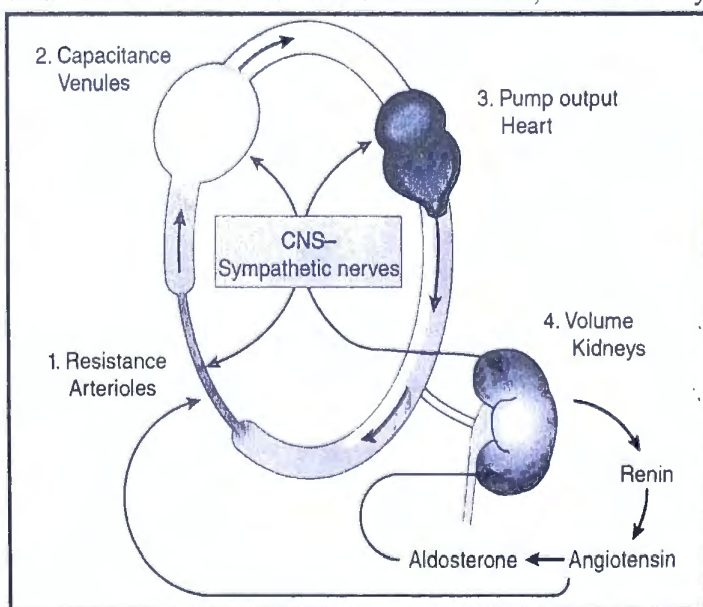
	Non-modifiable	Modifiable
Major risk factors	- Increasing age. - Male gender. - Family history. - Genetic abnormalities.	- Hyperlipidemia. - Cigarette smoking. - Diabetes.
Minor risk factors	- Obesity. - Physical inactivity. - Stress (type-A personality). - Post-menopausal estrogen deficiency. - High carbohydrate intake.	- Alcohol. - Lipoprotein Lp (a). - Hardened (trans) unsaturated fat intake.

Blood pressure regulatory systems

$$\text{Blood pressure (BP)} = \text{Cardiac output (CO)} \times \text{Total peripheral resistance (TPR)}$$

Physiologically, in both normal and hypertensive individuals, blood pressure is maintained by moment-to-moment regulation of cardiac output and peripheral vascular resistance, exerted at three anatomic sites: arterioles, postcapillary venules (capacitance vessels), and heart. A fourth anatomic control site, the kidney, contributes to maintenance of blood pressure by regulating the volume of intravascular fluid. Baroreflexes, mediated by autonomic nerves, act in combination with humoral mechanisms, including the renin-angiotensin-aldosterone system, to coordinate function at these four control sites and to maintain normal blood pressure. Finally, local release of vasoactive substances from vascular endothelium may also be involved in the regulation of vascular resistance. For example, endothelin-1 constricts and nitric oxide dilates blood vessels.

Blood pressure in a hypertensive patient is controlled by the same mechanisms that are operative in normotensive subjects. Regulation of blood pressure in hypertensive patients differs from healthy patients in that the baroreceptors and the renal blood volume-pressure control systems



appear to be "set" at a higher level of blood pressure. All antihypertensive drugs act by interfering with these normal mechanisms.

(Ref: Katzung-13th/170)

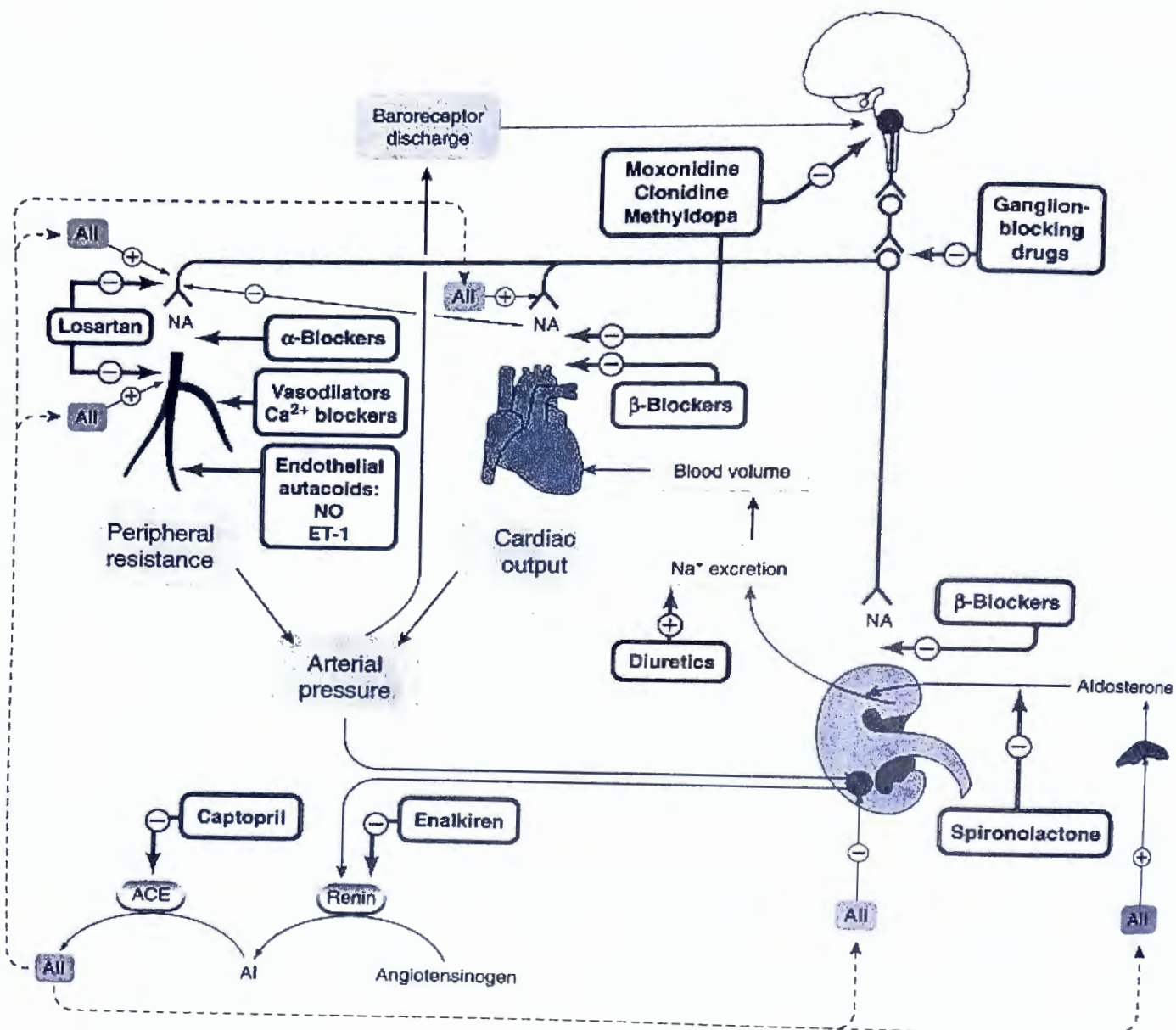


Figure. Diagram showing the main mechanisms involved in arterial blood pressure regulation and the sites of action of antihypertensive drugs. ACE, angiotensin-converting enzyme; AI, angiotensin I; AII, angiotensin II; ET-1, endothelin-1; NA, noradrenaline; NO, nitric oxide.

- Q. Classify antihypertensive drugs. (DU-08Ju, CU-15J, SU-17J, 11J)
 Q. Name the important clinically used antihypertensive drugs. (DU-10Ju, RU-14J)
 Q. Name some commonly used antihypertensive drugs. (DU-15J)
 Q. List the drugs used in the treatment of hypertension. (SU-09J)
 Q. Categorize the anti-hypertensive drugs according to their mechanism of action. (CU-11J, 09J)
 Q. Name the sympatholytic drugs used in hypertension. (SU-07J)
 Q. Name 4 antihypertensive drugs of different group. (DU-07J, 03S; RU-03J)
 Q. Name four common groups of anti-hypertensive drugs. (RU-17J)
 Q. Name the ACE inhibitors. (DU-17M, 11Ju)

Ans.

Classification of anti-hypertensive drugs according to their mechanism of action:

1. **Diuretics:** Lower blood pressure by depleting the body of sodium and reducing blood volume and perhaps by other mechanisms.
 - a. Loop diuretics
 - b. Thiazide diuretics
2. **Sympatholytic drugs:** Lower blood pressure by reducing peripheral vascular resistance, inhibiting cardiac function, and increasing venous pooling in capacitance vessels.
 - a. **Centrally acting:** α -methyl dopa, clonidine, guanabenz, guanfacine.
 - b. **Peripherally acting:**
 - **Adrenergic receptor blocker**
 - ⊗ **β -adrenoceptor blockers:** Atenolol, metoprolol, bisoprolol
 - ⊗ **α -blockers:** Prazosin, terazosin, doxazosin, phenoxybenzamine, phentolamine.
 - ⊗ **Mixed:** Labetalol, carvedilol.
 - **Adrenergic neuron blockers** (α -methyl dopa, guanadrel, guanethidine, reserpine)
3. **Renin-angiotensin-aldosterone system inhibitor:**
 - a. **ACE inhibitors:** Captopril, lisinopril, enalapril, ramipril, quinapril, benazepril, fosinopril, moexipril, perindopril, trandolapril.
 - b. **Angiotensin-II receptor blockers:** Losartan, valsartan, candesartan, irbesartan, telmisartan, eprosartan, olmesartan.
 - c. **Direct renin inhibitors:** Aliskiren
4. **Calcium channel blockers:** Amlodipine, nifedipine, diltiazem, verapamil
5. **Direct vasodilators:** Reduce pressure by relaxing vascular smooth muscle, thus dilating resistance vessels and—to varying degrees—increasing capacitance as well.
 - a. Hydralazine
 - b. Na-nitroprusside.

(Ref: Katzung-13th/171-172)

- Q. Enlist the 1st line antihypertensive drugs. (CU-06J)
 Q. Name commonly used antihypertensive drugs. (RU-06S/J, 05S)

Ans.

1st line anti-hypertensive drugs:

A. In ambulatory patients:

1. **ACE inhibitors (ACEi):** Captopril, lisinopril, enalapril, ramipril
2. **Angiotensin-II receptor blockers (ARB):** Losartan, valsartan
3. **Ca²⁺ channel blockers:** Amlodipine
4. **Thiazide diuretics:** Thiazide

B. In hypertensive emergency / malignant HTN:

1. **Direct vasodilators:** Na-nitroprusside
2. Labetalol

Q. Why the following drugs are first line?

Ans.

1 st line antihypertensive drugs	Why first line
1. ACE inhibitors (ACEi) 2. Angiotensin-II receptor blockers (ARB)	- No postural hypotension. - Additional benefit in DM with proteinuria ✓ Following MI ✓ CCF
3. Ca ²⁺ channel blockers	- Additional benefit in- ✓ Asthma ✓ DM ✓ Angina ✓ Arrhythmia
4. Thiazide diuretics	- No postural hypotension. - No reflex tachycardia. - Inexpensive. - Reduces stroke in clinical trial.

Q. Outline the therapeutic approach to hypertension. (SU-13Ju)

Q. Write down treatment of hypertension?

Q. Justify combination use of drugs in the treatment of hypertension. (SU-06M)

Q. Name the antihypertensive agents of moderate hypertension? (CU-07Ju)

Ans.

Pharmacotherapy / treatment of hypertension:

A. **Non-pharmacological approach:** By life style modification —

1. Dietary restriction: Avoidance of red meat, liver, fast food and high fatty & carbohydrate diet.
2. Salt restriction
3. Weight reduction
4. Smoking cessation
5. Aerobic exercise

If above measures failed to maintain normal BP at 120/80 mm Hg then we go for drug therapy.

B. **Pharmacological approach:**

a. **Monotherapy:** 1st line antihypertensive drugs.

1. **ACE inhibitors (ACEi):** Captopril, lisinopril, enalapril, ramipril
2. **Angiotensin-II receptor blockers (ARB):** Losartan, valsartan
3. **Ca²⁺ channel blockers (CCB):** Amlodipine
4. **Thiazide diuretics:** Thiazide

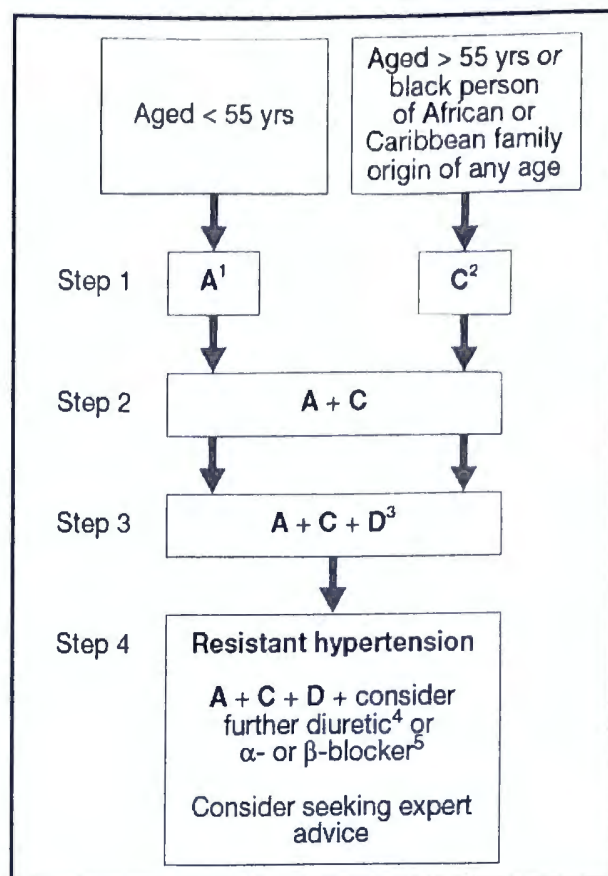
The choice of drug depends on-

1. Patient's age and ethnic background.
2. Cost and convenience.
3. Response to initial therapy and side-effects dictate subsequent treatment.
4. Comorbid conditions: for example-
 - HTN + Angina → β blockers
 - HTN in older people → Thiazide diuretics and CCB.

b. **Polytherapy / polypharmacy:**

1. **Combination of 2 drugs:** Combination of 2 drugs of two different mechanisms. Eg, ACE inhibitors (or ARB) plus CCB or ACE inhibitors (or ARB) plus thiazide diuretics.
2. **Combinations of 3 drugs:** Combination of 3 drugs of three different mechanisms. Eg, ACE inhibitors (or ARB) plus CCB plus thiazide diuretics.

Fig. Antihypertensive drug combinations. ¹A = ACE inhibitor or ARB. ²C = CCB; ³D = thiazide-type diuretic. ⁴Consider a low dose of spironolactone or higher doses of a thiazide-like diuretic. ⁵Consider an α - or β -blocker if further diuretic therapy is not tolerated, or is contraindicated or ineffective.
(Ref: Davidson's medicine-22nd/612)

**Q. What do you mean by polytherapy in hypertension?**

Ans.

Polytherapy in hypertension: In most of the cases, hypertension is controlled by two or more drugs, each acting by a different mechanism. This is called polytherapy.

Objectives / benefits of polytherapy

1. To achieve optimal BP control.
2. Low-dose therapy with two drugs may produce fewer unwanted effects than treatment with the maximum dose of a single drug.
3. Some drug combinations have complementary or synergistic actions; for example, thiazides increase activity of the renin-angiotensin system while ACE inhibitors block it.

(Ref: Davidson's medicine-21st/612)**Q. Define hypertensive emergency?****Q. Mention the policy / principles to treat a patient with hypertensive emergency.****Q. Outline the drug treatment of hypertensive crisis. (RU-08J,07M)****Q. How will you treat a case of hypertension with blood pressure 180/110 mm Hg? (CU-06J; SU-03S)****Q. Categorize the drugs that can be used for Mrs. Lovely who has a mean blood pressure of 180/100. (SU-13J)**

Ans.

Hypertensive emergency / malignant HTN:

Hypertensive emergency is a rare but life-threatening situation characterized by severe elevations in blood pressure (**systolic greater than 180 mm Hg or diastolic greater than 120 mm Hg**) with evidence of impending or progressive **target organ damage** (for example, stroke, myocardial infarction).

(Ref: Lippincott's-6th/237)

Principles of management of hypertensive emergency:

1. Hypertensive emergencies require timely blood pressure reduction with treatment administered intravenously to prevent or limit target organ damage.
2. **Parenteral antihypertensive** medications are used to lower blood pressure rapidly (within a few hours).
3. As soon as reasonable blood pressure control is achieved, **oral antihypertensive** therapy should be substituted, because this allows smoother long-term management of hypertension.
4. The goal of treatment in the first few hours or days is not complete normalization of blood pressure because chronic hypertension is associated with autoregulatory changes in cerebral blood flow. Thus, rapid normalization of blood pressure may lead to cerebral hypoperfusion and brain injury.
5. Rather, blood pressure should be lowered by about **25%**, maintaining **diastolic** blood pressure at no less than **100–110 mm Hg**.
6. **Parenteral drugs used to treat hypertensive emergencies**
 - a. **Nitric oxide vasodilators:** Nitroprusside and nitroglycerin.
 - b. **Adrenergic receptor antagonists:** Phentolamine, esmolol, and labetalol
 - c. **Dopamine agonist:** Fenoldopam
 - d. **Calcium channel blockers:** Nicardipine and clevidipine.
 - e. **Vasodilators:** Diazoxide, Hydralazine

(Ref: Katzung-13th/187; Lippincott's-6th/237)Nice to know

Preferred parenteral drugs for selected hypertensive emergencies: Treatment is directed by the type of target organ damage present and/or comorbidities present.

• Hypertensive encephalopathy	Nitroprusside, Nicardipine, Labetalol
• Malignant hypertension (when IV therapy is indicated)	Labetalol, Nicardipine, Na-nitroprusside, Enalapril
• Stroke	Nicardipine, Labetalol, Na-nitroprusside
• MI or unstable angina	Nitroglycerin, Nicardipine, Labetalol, Esmolol
• Acute left ventricular failure	Nitroglycerin, Enalapril, loop diuretics
• Postoperative hypertension	Nitroglycerin, Na-nitroprusside, Labetalol, Nicardipine
• Pre-eclampsia or eclampsia	Hydralazine, Labetalol, Nicardipine

(Ref: Harrison's medicine-18th edition)

Hypertensive urgency: A severe elevation in blood pressure without evidence of target organ damage is considered a hypertensive urgency.

(Ref: Lippincott's-6th/237)

Resistant hypertension: Resistant hypertension is defined as blood pressure that remains elevated (above goal) despite administration of an optimal three-drug regimen that includes a diuretic. The most common causes of resistant hypertension are poor compliance, excessive ethanol intake, concomitant conditions (diabetes, obesity, sleep apnea, hyperaldosteronism, high salt intake, and/or metabolic syndrome), concomitant medications (sympathomimetics, NSAIDs, or antidepressant medications), insufficient dose and/or drugs, and use of drugs with similar mechanisms of action.

(Ref: Lippincott's-6th/237)

Q. Which drug is to be prescribed in a hypertensive patient with BPH? (CU-05J)

Ans.

Antihypertensive drug for a patient with HTN and BPH: Tamsulosin

It is a α_{1A} receptor blocker present in the neck of the bladder, urethral sphincter and prostate. α_{1A} receptor mediates contraction of smooth muscle. So, Tamsulosin by blocking α_{1A} receptor mediates smooth muscle relaxation to relieve urinary retention of a pt. of BPH.

Q. List the drugs used in the treatment of hypertension associated with asthma. (SU-09J)

Q. Which antihypertensive agent do you prefer in diabetes mellitus? (SU-06M)

Q. Which antihypertensive agent do you prefer in bronchial asthma? (SU-06M)

Ans.

HTN with other co-morbid conditions:

Co-morbid conditions	Antihypertensive therapy
HTN + High coronary disease risk	Diuretics, β -blockers, ACE inhibitors, Ca-channel blockers
HTN + Heart failure	Diuretics, β -blockers, ACE inhibitors, ARBs, Aldosterone receptor antagonist
HTN + Diabetes mellitus	Diuretics, ACE inhibitors, ARBs, Ca-channel blockers
HTN + Bronchial asthma	Ca ²⁺ channel blockers, ARB, Diuretics (ACEi $\rightarrow$ $\uparrow$ Bradykinin $\rightarrow$ Dry cough)
HTN + Recurrent stroke	Diuretics, ACE inhibitors
HTN + Previous myocardial infarction	β -blockers, ACE inhibitors, Aldosterone receptor antagonist
HTN + Chronic renal disease	ACE inhibitors, ARBs
HTN + Pregnancy	α -Methyl dopa, Hydralazine, Ca ²⁺ channel blockers

(Ref: Lippincott's-6th/228)

Q. A male hypertensive patient of 40 years is also suffering from bronchial asthma and angina. Select an antihypertensive drug from him with justification. Mention its adverse effects. (RU-13Ju)

Q. A 40 years old patient suffering from moderate hypertension with bronchial asthma. What are the options of anti-hypertensive to be used with justification in such case? (RU-12Ju)

Ans.

Antihypertensive drug for patient with bronchial asthma and angina

1. Angiotensin-II receptor blockers (ARB)
2. Ca²⁺ channel blockers (CCB)
3. Diuretics

At first, I will start with a ARB. If not controlled, then I will add a CCB and/or a diuretic (preferably thiazide / indapamide) along with ARB. If not still controlled, then I will add a third drug either CCB or a diuretic.

Justification: These drugs are not contraindicated in bronchial asthma and angina.

1. Angiotensin-II receptor blockers (ARB)	• It has no effect on bradykinin level no dry cough. • First choice in a patient below 55 years. • No postural hypotension. • No reflex tachycardia. • Lower incidence of angioedema or skin rashes. • Do not affect male sexual function.
2. Diuretic (thiazide)	• No postural hypotension. • No reflex tachycardia. • Inexpensive. • Reduces stroke in clinical trial. • Diuretics are usually added to combat hyperkalemic effect of ARB.
3. Ca ²⁺ channel blockers	• It has no effect on bradykinin level no dry cough. • Do not impair renal perfusion. • Do not affect male sexual function. • No deleterious effect on serum lipid profile, electrolyte balance & uric acid level. • No / minimal effect on quality of life. • Additional benefit in ✓ Asthma ✓ DM

- ✓ Angina
- ✓ Arrhythmia

- Q. Name the drug of choice that can safely be used to manage HTN in pregnancy. (SU-07J)
- Q. What options are available for gestational hypertension? Explain the mechanism of action and adverse effects of any drug. (RU-16Ju, 14Ju)
- Q. A lady of 27 years is in her 1st trimester of pregnancy. Her BP is 150/100 mmHg. What are the options of antihypertensive drugs to be used with justification? (RU-10Ju)

Ans.

Antihypertensive drugs that can be used safely in pregnancy / Drugs for gestational hypertension:

1. α -methyl dopa: Drug of choice
2. Calcium channel blockers (especially nifedipine) are common second-line drugs
3. Hydralazine → reserved for emergency reduction of blood pressure in late pregnancy.
4. β -blockers (labetalol and atenolol) are often effective and are probably the drugs of choice in the third trimester.

(Ref: Bennet & Brown-11th)

Nice to know

- *Diuretics reduce the chance of developing pre-eclampsia, but are avoided in pre-eclampsia itself because these patients already have a contracted circulatory volume.*
- *ACE inhibitors and angiotensin II receptor blockers (ARBs) are absolutely contraindicated during pregnancy. They cause major malformations after first-trimester exposure and fetal death, typically mid-trimester.*

(Ref: Bennet & Brown-11th)

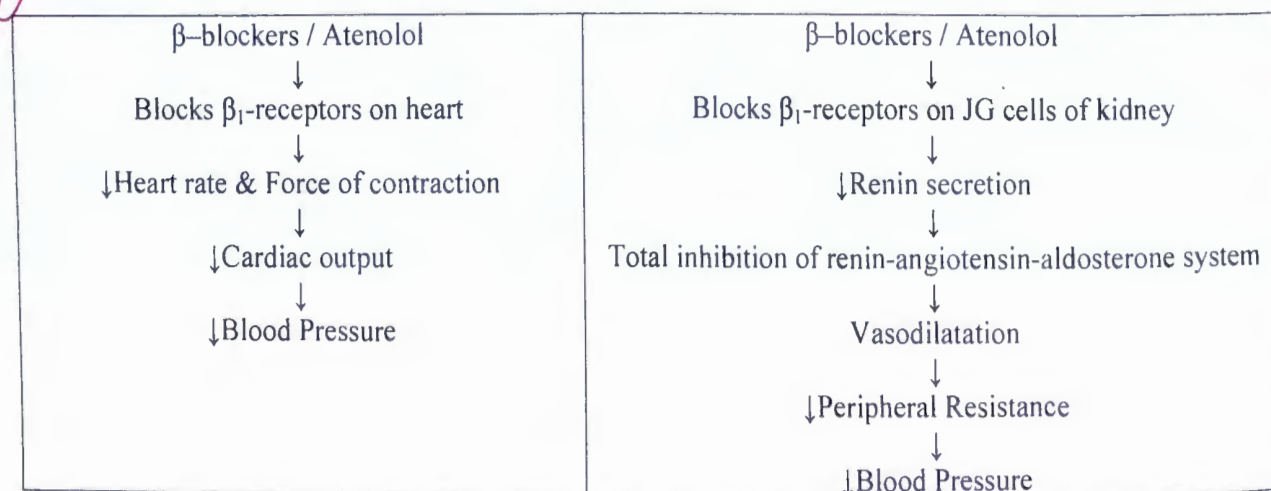
Sympatholytic drugs

β -blockers

- Q. How does β -blockers lower elevated blood pressure? (RU-15J)
- Q. How cardio-selective β blocking drug lowers the BP? (DU-04M, CU-05J)
- Q. How does atenolol lower BP? (DU-14Ju, 11J, RU-09/08Ju)
- Q. Justify the use of atenolol as anti-hypertensive. (SU-15J)

Ans.

Mechanism of action of β -blockers / atenolol as an antihypertensive drug:



Q. Write down the mechanism of action of propranolol. (DU-09Ju)

Q. How a non-selective β blocker lowers the BP? (CU-03S; RU04J)

Ans.

Mechanism of action of propranolol as an antihypertensive drug:

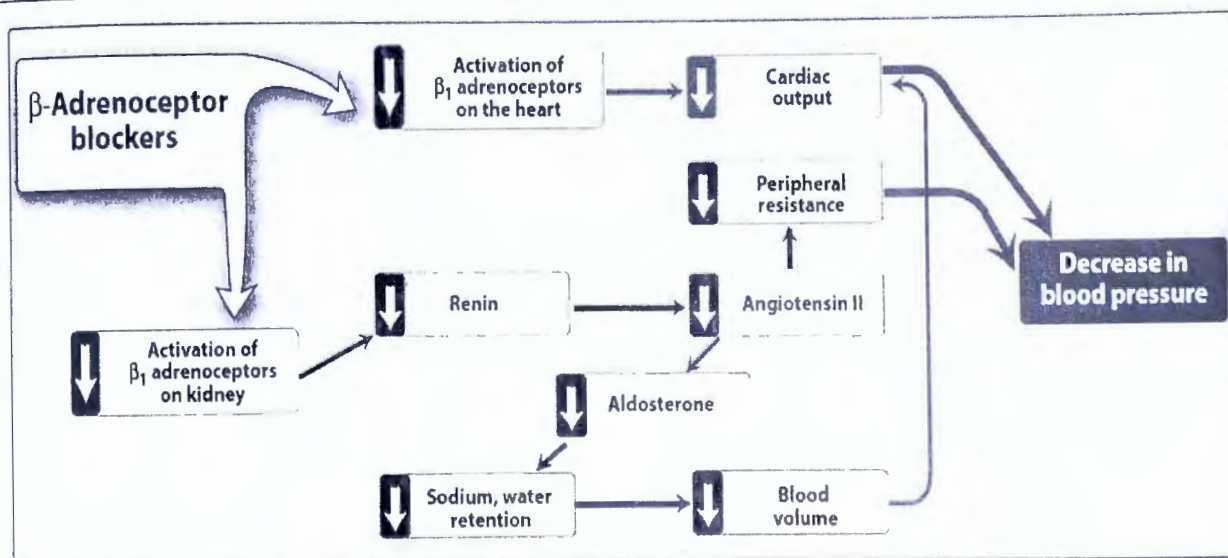
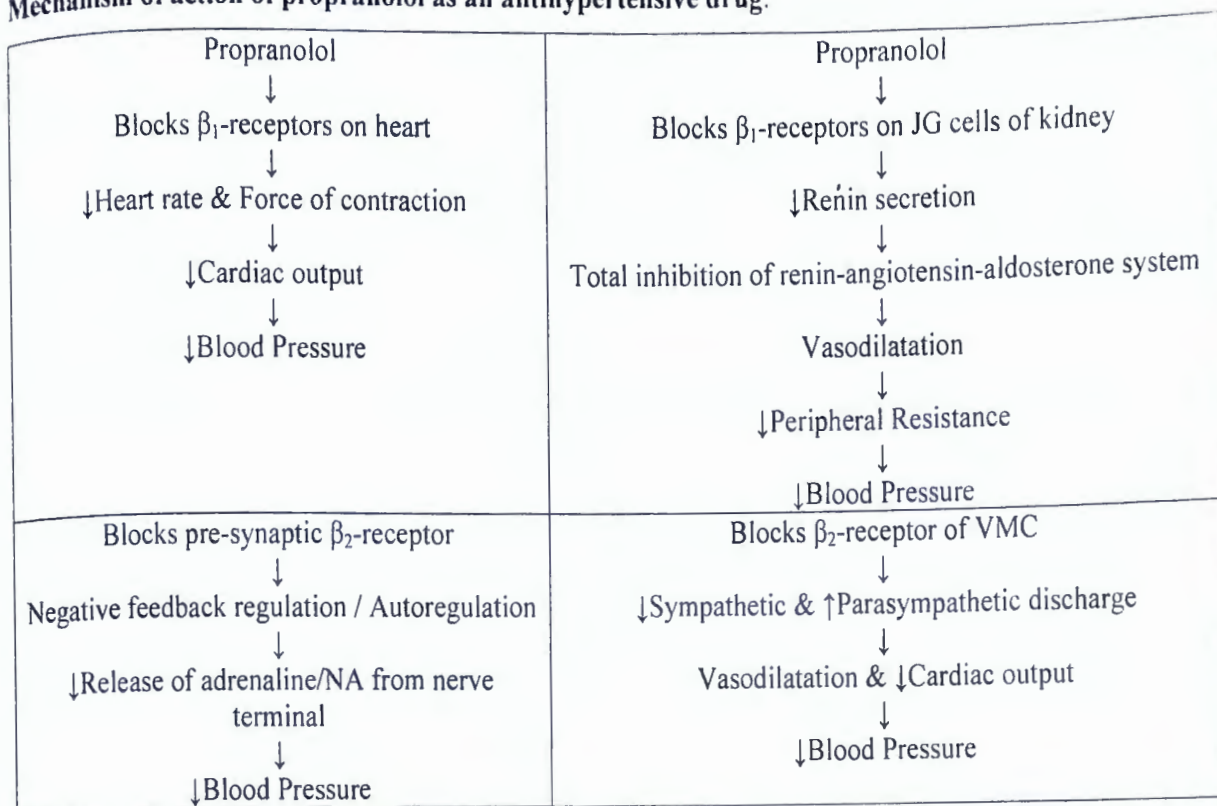


Fig. Actions of β -blockers.

(Ref: Lippincott's-6th/230)

Nice to know: COMMENTS

Therapeutic uses of β -blockers as anti-hypertensives

- These are **no longer** used as **first-line antihypertensive therapy**, except in patients with another indication for the drug (e.g. angina).

(Ref: Davidson's-22nd/612)

- The primary therapeutic benefits of β -blockers are seen in hypertensive patients with concomitant heart disease, such as supraventricular tachyarrhythmia (for example, atrial fibrillation), previous myocardial infarction, angina pectoris, and chronic heart failure.

(Ref: Lippincott's-6th/231)

Q. What is the role of β blockers in angina/MI?

Q. Justify the use of atenolol as anti-anginal. (SU-15J)

Q. Explain the anti-anginal effects of propranolol. (DU-16J)

Ans.

Role of β blockers (propranolol, atenolol) in angina / MI:

1. They reduce the severity and frequency of anginal attack.
2. They improve exercise tolerance in many patients with angina.
3. They are particularly effective in patient with MI. Long-term use of **timolol, propranolol, or metoprolol** in patients who have had a MI prolongs survival.
4. When combined with nitrate, they increase the exercise duration and tolerance.

Mechanism of anti-anginal action of β -blockers

β blockers block β_1 receptors on heart

↓
↓HR and force of contraction

↓
↓Cardiac work

↓
Reduction of cardiac O_2 demand

↓
Relief of anginal pain.

(Ref: Katzung-13th/163)

Q. What are the adverse effects of β -blocking drugs? (CU-08J, RU-10Ju, SU-04M)

Ans.

Adverse effects of β -blocking drugs / propranolol:

CVS adverse effects	▪ Bradycardia ▪ Hypotension ▪ Cardiac conduction abnormalities (cardiac arrhythmias) ▪ Cold extremities due to decreased peripheral circulation. ▪ Exercise intolerance (β_2 blockade impairs vasodilation in skeletal muscles)
CNS adverse effects	▪ Sedation ▪ Sleep disturbance (Insomnia, Nightmares) ▪ Depression ▪ Suicidal tendency (in case of long term use)
Others	▪ Bronchoconstriction ▪ Dyslipidaemia ▪ Prolongation of hypoglycemia ▪ Sexual dysfunction in men

(Ref: Katzung-13th/165; Goodman & Gilman's-11th/283,287-288 (Table 10-6))

Q. When the use of β -blockers in a patient with HTN is contraindicated?

Ans.

Relative contraindications of β -blockers:

1. Bradycardia
2. Heart block
3. Moderate or severe left ventricular failure
4. Hypotension
5. Shock
6. Active airways disease such as asthma.
7. Severe peripheral vascular disease

(Ref: Katzung-13th/163-164; Lippincott's-6th/231)

Q. How to withdraw β blockers?

Ans.

β blocker withdraw phenomenon: β blocker should be withdrawn slowly. Sudden withdrawal of β blockers causes severe **rebound hypertension** which may be dangerous.

Chronic administration of β blockers for hypertension results in **up-regulation of β_1 receptor**.

↓
Sudden withdrawal of β blockers.

↓
Endogenous catecholamine now can act on more β_1 receptor than previous.

↓
Severe hypertension

β blocker withdraw phenomenon is more prominent in β_1 selective and least for drugs having partial agonist property.

How to withdraw β blockers: Reduce the dose **over 10-14 days** and then withdraw it.

Nice to know**Metoprolol & Atenolol**

- ✓ Metoprolol and atenolol, which are cardioselective, are the **most widely used β blockers** in the treatment of hypertension.
- Relative cardioselectivity is advantageous in treating hypertensive patients who also suffer from asthma, diabetes, or peripheral vascular disease.

Bisoprolol

Non-selective $\Rightarrow \beta$
 $\Rightarrow$ vasoconstriction

- Bisoprolol are β_1 -selective blockers that are primarily metabolized in the liver but have long half-lives.
- Because of these relatively long half-lives, these drugs can be administered once daily.
- Bisoprolol is usually begun at a dosage of 5 mg/d.

Labetalol

- Labetalol blocks both α and β adrenoceptors. These drugs have additional vasodilating effects.
- Labetalol has a 3:1 ratio of β : α antagonism after oral dosing.
- Blood pressure is lowered by reduction of systemic vascular resistance (via α blockade) without significant alteration in heart rate or cardiac output.
- Because of its combined α - and β -blocking activity, labetalol is useful in treating the hypertension of pheochromocytoma and **hypertensive emergencies**.
- Oral daily doses of labetalol range from 200 to 2400 mg/d.
- Labetalol is given as repeated intravenous bolus injections of 20–80 mg to treat hypertensive emergencies.

Carvedilol

- Half-life is 7–10 hours.
- The usual starting dosage of carvedilol for ordinary hypertension is 6.25 mg twice daily.
- Carvedilol reduces mortality in patients with heart failure and is therefore particularly useful in patients with both **heart failure and hypertension**.

Esmolol

- Esmolol is a β_1 -selective blocker that is rapidly metabolized via hydrolysis by red blood cell esterases.
- It has a short half-life (9–10 minutes) and is administered by intravenous infusion.
- Esmolol is generally administered as a loading dose (0.5–1 mg/kg), followed by a constant infusion.

- Esmolol is used for management of intraoperative and postoperative hypertension, and sometimes for hypertensive emergencies.

(Ref: Katzung-13th/180)

Prazosin and other α -blockers

Q. Explain the role of prazosin in hypertension. (SU-05J)

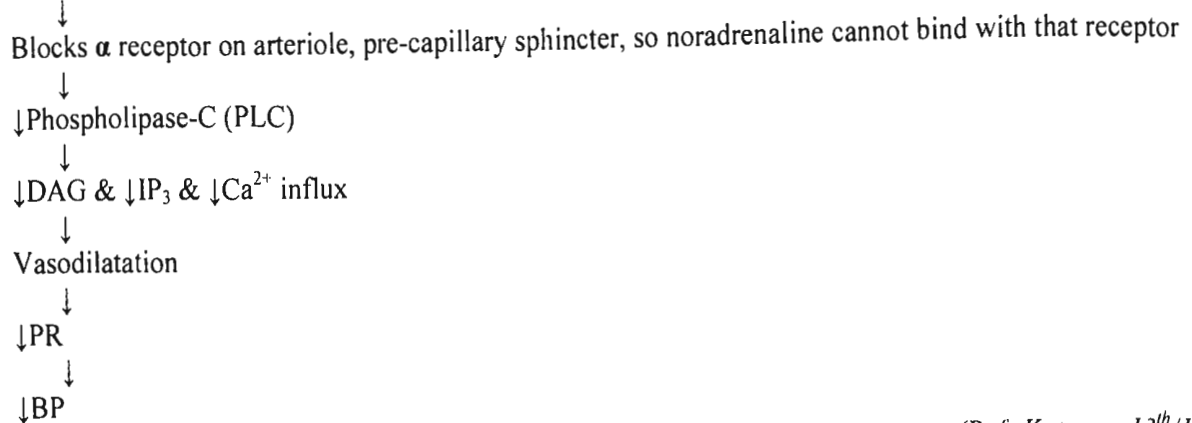
Q. What are the pharmacological actions of α -blockers? (SU-04M)

Ans.

Mechanism of action/ role of Prazosin, Terazosin, and Doxazosin in hypertension:

Prazosin, terazosin, and doxazosin produce most of their antihypertensive effects by selectively blocking α_1 receptors in arterioles and venules. Alpha blockers reduce arterial pressure by dilating both resistance and capacitance vessels.

Prazosin / α -blockers

(Ref: Katzung-13th/180)

Nice to know: Information on α -blockers

- As expected, blood pressure is reduced more in the upright than in the supine position.
- Retention of salt and water occurs when these drugs are administered without a diuretic.
- The drugs are more effective when used in combination with other agents, such as a β blocker and a diuretic, than when used alone.
- These drugs cause only minimal changes in cardiac output, renal blood flow, and glomerular filtration rate. Therefore, long-term tachycardia does not occur.
- Reflex tachycardia and postural hypotension often occur at the onset of treatment and with dose increases, requiring slow titration of the drug in divided doses.
- Due to weaker outcome data and their side effect profile, α -blockers are no longer recommended as initial treatment for hypertension, but may be used for refractory cases.

(Ref: Katzung-13th/180)(Ref: Lippincott's-6th/235)

Q. What are the adverse effects of α receptor blockers? (CU-04J; RU-14Ju, SU-09Ju, 06S)

Q. Mention the adverse effects of prazosin. (DU-13Ju)

Ans.

Adverse effects of α -receptor blockers / Prazosin:

- Cardiac:** Postural hypotension, reflex tachycardia (they are less marked in prazosin)
- Eye:** Miosis
- GIT:** Diarrhea, vomiting.
- Others:** Ejaculatory failure, nasal decongestion, flushing, headache, dizziness.

(Ref: Goodman & Gilman's-12th)

Viva Q. What is first-dose effect?

Ans. First-dose effect: The first dose of the α_1 blocker drugs produces an exaggerated **orthostatic hypotensive response** that can result in syncope (fainting). This action, termed a first-dose effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime.

(Ref: Lippincott's-6th/89)

Pregnancy use α_1 blocker
→ teratogenic

α -methyl dopa

α_2 receptor uterus α_2 receptor
SO, α_2 receptor contraction 20, 21

Q. Short note: α -methyl dopa. (DU-17J, 15Ju, 11Ju)

Q. How methyl dopa reduces blood pressure? Mention its adverse effect. (SU-07J)

Q. Explain antihypertensive action of α -methyl dopa. (SU-17J)

Ans.

α -methyl dopa: Methyl dopa is an α_2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS. α -methyl dopa is an analogue of L-dopa (dopa is the precursor of dopamine /NA /adrenaline).

Pharmacokinetics:

1. Less than 1/3 of oral dose is absorbed.
2. Onset: Within 4-6 hours.
3. Duration: 12-24 hours.

α -methyl DOPA

↓ Brain
 α -methyl NA (false NT)

↓ α_2 agonism (partial) → Decreased adrenergic outflow

Mechanism of action of α -methyl dopa: α -methyl dopa converts into α -methyl NA in the brain, α -methyl NA is a false NT & a potent α_2 -agonist. α -methyl NA then binds with the pre-synaptic α_2 receptor & causes decreased adrenergic outflow from brain. Ultimately this leads to decreased total peripheral resistance & decreased BP. (NA: Nor Adrenaline; NT: Neurotransmitter)

Indication: Hypertension in pregnancy

Adverse effects of α -methyl dopa:

1. **Common:** Hypotension, persistent mental lassitude, impaired mental concentration. → mental retardation
2. **Less common:** Nightmares, depression, vertigo, extra-pyramidal symptoms, lactation (both in male & female), hypersensitivity.
3. Positive Coombs test.
4. **Rare:** Hemolytic anemia, hepatitis and drug fever.

Advantage of using:

1. It can be used in HTN with renal insufficiency, because cardiac output is not decreased & blood flow to the vital organ (e.g. kidney) is not diminished.
2. No Postural hypotension.

(Ref: Katzung-13th/175-176; Rang-Dale-5th/178, 181; Tripathi-6th/547; Lippincott's-6th/236)

Clonidine

Clonidine: It is a partial α_2 -agonist.

Mechanism of action: Clonidine inhibits sympathetic vasomotor center → Decrease adrenergic outflow from brain. Ultimately this leads to decreased total peripheral resistance & decreased BP.

Indications:

1. Occasionally used in combination with diuretics in mild to moderate HTN.
2. **Post-menopausal women:** To reduce vasomotor symptoms.
3. **Migraine.**

Advantage of using: Clonidine does not decrease renal blood flow or glomerular filtration. So, it can be used in HTN complicated with renal insufficiency.

(Ref: Lippincott's-6th)

Adverse effects:

1. Retention of Na^+ & H_2O → May causes **edema** (So, administered along with diuretics).
2. Rebound HTN after abrupt withdrawal (So, should be withdrawn slowly).
3. Postural hypotension
4. Bradycardia
5. Dryness of mouth, eyes & nasal mucosa (Due to ↓central action).
6. Constipation (Due to ↓intestinal secretion)

(Ref: Rang Dale-5th/179; Tripathi-6th/546; Lippincott's-6th)

Vasodilators

Q. Name the vasodilators used to treat hypertension. (RU-09Ju)

Q. Classify vasodilators.

Ans.

Classification of vasodilators:

A. According to route of administration:

Parenteral vasodilators	▪ Na-nitroprusside ▪ Diazoxide ▪ Fenoldopam
Oral vasodilators	▪ Hydralazine ▪ Minoxidil

B. Accord in to site of action:

Arterial	▪ Hydralazine ▪ Minoxidil ▪ Diazoxide ▪ Fenoldopam
Both arterial & venous	▪ Na-nitroprusside

(Ref: Katzung-13th/180-181)

C. According to nature of action:

Direct vasodilators	▪ Na-nitroprusside, Diazoxide, Hydralazine
Indirect vasodilators	▪ Ca channel blockers ▪ ACE inhibitors ▪ Angiotensin-II receptor blockers ▪ Renin release inhibitors: β-blockers

D. According to mechanism of action:

Mechanism	Vasodilators
Release of nitric oxide from drug or endothelium	Nitroprusside, hydralazine, nitrates, histamine, acetylcholine
Reduction of calcium influx	Verapamil, diltiazem, nifedipine
Hyperpolarization of smooth muscle membrane through opening of potassium channels	Minoxidil, diazoxide
Activation of dopamine receptors	Fenoldopam

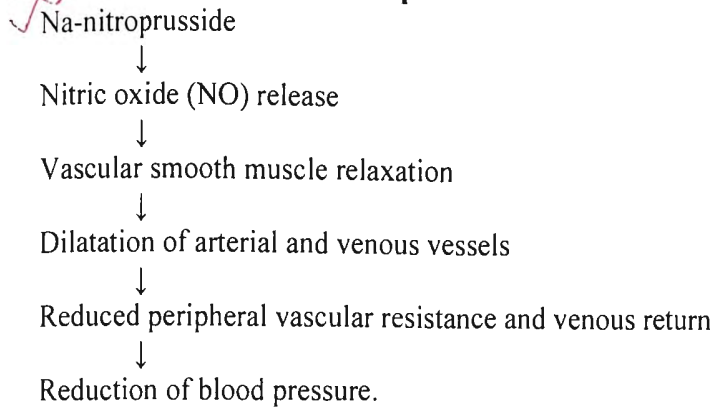
(Ref: Katzung-13th/181)

Direct vasodilators

Na-nitroprusside

Nitroprusside is a complex of iron, cyanide groups, and a nitroso moiety. It is rapidly metabolized by uptake into red blood cells with liberation of cyanide.

Mechanism of action of Na-nitroprusside:



(Ref: Katzung-13th/182)

Route of administration: IV

Indications:

1. Hypertensive emergency
2. Severe / refractory heart failure
3. For controlled hypotension during surgery to reduce bleeding.
4. Aortic dissection (along with β blocker).

Adverse effects:

1. Profound hypotension
2. Due to accumulation of cyanide:
 - a) Severe lactic acidosis
 - b) Arrhythmia
 - c) Excessive hypotension
 - d) Death
3. Thiocyanate toxicity is manifested as —
 - a) Weakness
 - b) Disorientation
 - c) Psychosis
 - d) Muscle spasm
 - e) Convulsion
4. Hypothyroidism (Rare)
5. Methemoglobinemia

(Ref: Katzung-13th/182)

Limitations of Na-nitroprusside in emergency hypertension:

1. Short duration of action. Only 3 minutes. Average 1-10 minutes. (Duration of action of diazoxide 4-12 hours).
2. It requires continuous IV infusion due to its short half-life.
3. Due to its thiocyanate toxicity, it requires close monitoring.
4. Cannot be used in patients with hepatic and renal disease.

Diazoxide

Diazoxide is an effective and relatively long-acting parenterally administered arteriolar dilator.

Mechanism of action: Opening of K^+ channel in smooth muscle membranes of arterioles → Hyperpolarization → stabilization of the membrane potential at the resting level → No depolarization → No vascular smooth muscle contraction → Vasodilation → ↓BP.

Indication: Hypertensive emergency

Adverse effects:

1. Excessive hypotension leading to stroke and myocardial infarction
2. The reflex sympathetic response can provoke angina, cardiac failure in patients with ischemic heart disease. So, should be avoided in such situation.
3. Hyperglycemia by inhibiting insulin release from the pancreas.

(Ref: Katzung-13th/182-183)

Q. Why diazoxide not Na-nitroprusside is the drug of choice in the management of emergency hypertension?

Ans.

Advantages of diazoxide over Na-nitroprusside:

1. Long duration of action (4 – 12 hours)
2. Can be given orally in emergency hypertension.
3. No chance of thiocyanate toxicity.
4. Does not require monitoring.

Disadvantages / limitations of diazoxide

1. Excessive hypotension (*that's why dose should be started with 50-150 mg rather than 300 mg*) → leads to stroke, MI.
2. Causes salt and water retention.

Minoxidil

Mechanism of action: Same as Diazoxide

Indication:

1. Severe to malignant hypertension which don't respond to other drugs. (Minoxidil must be used in combination with a β blockers & a loop diuretic)
2. Alopecia: Topical Minoxidil is now used as a stimulant to hair growth for correction of baldness.

Adverse effects:

1. Headache.
2. Sweating.
3. Hirsutism in women.
4. Tachycardia, palpitations, angina, and edema are observed when doses of β -blockers and diuretics are inadequate.

(Ref: Katzung-13th/181 + Lippincott's-6th/236)

Hydralazine

Mechanism of action: Dilate arterioles. But the mechanism of vasorelaxation is unclear.

Pharmacokinetics:

1. Well absorbed after oral administration
2. 1st pass hepatic metabolism
3. Highly tissue binding

4. Metabolism by acetylation

Indication: Pregnancy induced hypertension.

Adverse effects:

1. Headache
2. Nausea
3. Anorexia
4. Palpitation
5. Sweating
6. Flushing
7. In patients with ischemic heart disease, reflex tachycardia and sympathetic stimulation may provoke angina or ischemic arrhythmias.
8. SLE like syndrome
9. Peripheral neuropathy in slow acetylators.

(Ref: Katzung-13th/181 + Lippincott's-6th/236)

Q. Why the duration of action of hydralazine is 12 hours, though its half-life is 1 hour?

Ans. Due to its active metabolites.

Q. How hydralazine causes tachycardia / tachyphylaxis?

Ans.

Hydralazine



Vasodilation



↓BP → Reflex tachycardia



↓GFR



↑Renin secretion



↑Angiotensin II and aldosterone



↑Salt & water retention



Tachyphylaxis = A decrease in a response of a drug

Treatment of tachycardia:

Hydralazine + β blocker

Hydralazine causes tachycardia, while β blocker decreases tachycardia.

Treatment of tachyphylaxis:

Hydralazine + Diuretics

Hydralazine causes salt & water retention.

Diuretics increases salt & water excretion → Tachyphylaxis overcome.

Q. As a vasodilator, hydralazine does not produce hypotension. Why?

Ans.

Hydralazine does not produce hypotension

1. Due to venous resistance.
2. Reflex tachycardia
3. Hydralazine stimulates epinephrine release.

Fenoldopam

Fenoldopam is a peripheral arteriolar dilator. It acts primarily as an agonist of dopamine D₁ receptors, resulting in dilation of peripheral arteries and natriuresis.

Indications:

1. Hypertensive emergency
2. Postoperative hypertension

Adverse effects:

1. Reflex tachycardia
2. Headache
3. Flushing
4. Increased intraocular pressure

(Ref: Katzung-13th/183)

Q. Justify combination of direct acting vasodilators and diuretics with β blockers?

Ans.

Combination of direct vasodilators & diuretics with β -blockers: Vasodilatation and diuresis will stimulate the rennin-angiotensin system, and turn non-renin dependent hypertension into renin-dependent hypertension. Addition of beta blockers in these conditions can antagonize the release of rennin, and thus blood pressure will be controlled properly.

(Ref: Bennett, Brown-11th)

Nice to know

Vasodilators work best in combination with other antihypertensive drugs that oppose the compensatory cardiovascular responses.

(Ref: Katzung-13th/180)

Q. "Vasodilator therapy does not cause orthostatic hypotension or sexual dysfunction ." - Explain.

Ans.

Vasodilator therapy does not cause orthostatic hypotension or sexual dysfunction: All the vasodilators that are useful in hypertension relax smooth muscle of arterioles, thereby decreasing systemic vascular resistance. Sodium nitroprusside and the nitrates also relax veins. Decreased arterial resistance and decreased mean arterial blood pressure elicit compensatory responses, mediated by **baroreceptors** and the **sympathetic nervous system**, as well as **renin**, **angiotensin**, and **aldosterone**. Because sympathetic reflexes are intact, vasodilator therapy does not cause orthostatic hypotension or sexual dysfunction.

(Ref: Katzung-13th/180)

Ca²⁺ channel blockers

Q. Describe the calcium channels present in the body. (CU-16Ju)

Ans.

Types of Ca²⁺-channels:

A. According to the opening duration of Ca²⁺ channel:

Type	Location	Properties of the Ca ²⁺ Current
L-type (L for long lasting)	Cardiac, skeletal, smooth muscle, neurons, endocrine cells, bone	Long, large, high threshold
T-type (T for transient period)	Cardiac muscle, neuron	Short, small, low threshold
N type	Neurons, sperm	Short, high threshold
P/Q	Neurons	Long, high threshold
R	Neurons, sperm	Pacemaking

- Ca²⁺ channel blockers act mainly by blocking L-type Ca²⁺ channel
- Ca²⁺ channel blockers act on arterial end.

B. According to opening selectivity of Ca²⁺ channel:

- Voltage gated Ca²⁺ channel: Exclusively blocked by Ca²⁺ channel blockers
- Receptor operated Ca²⁺ channel: Blocked by β blockers.

(Ref: Katzung-13th/199)

Q. Classify Ca²⁺ channel blockers.

Q. Enumerate Ca²⁺ channel blockers. (DU-12J, RU-16J)

Q. Enumerate Ca²⁺ channel blockers indicating their selectivity. (SU-17M)

Q. Enumerate five Ca²⁺ channel blockers. (DU-14Ju, 13J)

Q. How Ca²⁺ channel blockers are categorized? (SU-14J)

Q. Name 3 (three) important Ca²⁺ channel blockers. (DU-16J, 14J)

Ans

Classification of Ca²⁺ channel blockers (CCB):

A. According to chemical structure:

1. Diphenylalkylamines	Verapamil
2. Benzothiazepines	Diltiazem
3. Dihydropyridines	First generation
	Nifedipine
	Second generation
	Amlodipine
	Felodipine
	Nicardipine
	Nimodipine
	Isradipine
	Nisoldipine
	Nitrendipine

(Ref: Lippincott's-6th/234)

B. According to degree of selectivity:

1. CCB acting on both cardiac & vascular smooth muscle	Verapamil Diltiazem
2. CCB acting mainly on vascular smooth muscle	Amlodipine Nifedipine Nicardipine Nimodipine

Cardio selective
Vascular selective

(Ref: Lippincott's-6th/234; Katzung-13th)

Nice to know

Role of Ca^{2+} channels in vascular smooth muscles and cardiac muscle: Voltage-sensitive Ca^{2+} channels (L-type or slow channels) mediate the entry of extracellular Ca^{2+} into smooth muscle and cardiac myocytes and SA) and AV nodal cells in response to electrical depolarization. In both smooth muscle and cardiac myocytes, Ca^{2+} is a trigger for contraction, albeit by different mechanisms. Ca^{2+} channel antagonists, also called Ca^{2+} entry blockers, inhibit Ca^{2+} channel function. In vascular smooth muscle, this leads to relaxation, especially in arterial beds. These drugs also may produce negative inotropic and chronotropic effects in the heart.

(Ref: Goodman & Gilman's-12th)

- Q. How Ca^{2+} channel blockers cause antihypertensive action? (DU-03S, RU-03J)
 Q. How Ca^{2+} channel blockers lower elevated blood pressure? (RU-16J)
 Q. Explain antihypertensive action of amlodipine. (DU-13J, 12J, 10/07Ju, CU-05M, RU-11J, 09J, SU-11J, 09J)
 Q. Mention how amlodipine reduces blood pressure. (DU-16J, 14J, RU-15Ju)
 Q. Explain antihypertensive action of diltiazem. (SU-12Ju/J)
 Q. Explain antihypertensive action of nifedipine. (SU-17J, 07Ju, 05J, RU-03J)
 Q. Explain antihypertensive action of diltiazem. (SU-12Ju, 10J, 04J)

Ans.

Mechanism of action / Antihypertensive effect of Ca^{2+} channel blockers (CCB):

1. **Action on cardiac muscle:** CCBs (Verapamil, diltiazem) decreases heart rate and force of contraction of heart muscle.

Binds with the L-type Ca^{2+} channel in cardiac muscle

↓
Decrease the frequency of opening of voltage gated Ca^{2+} channel in response to depolarization.

↓
Decreases Ca^{2+} influx

- ↓
 ▪ Decrease in SA pacemaker rate and AV node conduction velocity → ↓ heart rate
 ▪ Inhibition of interaction between actin and myosin → ↓ force of contraction of heart

↓
↓ Cardiac output

↓
↓ Blood pressure.

2. **Action on vascular smooth muscles:** All the CCBs cause vasodilation of peripheral vessels.

Binds with the L-type Ca^{2+} channel in smooth muscle of blood vessels

↓
Decrease the frequency of opening of voltage gated Ca^{2+} channel in response to depolarization

↓
Decreases Ca^{2+} influx

↓
No Ca^{2+} -calmodulin complex

↓
No actin-myosin coupling

↓
No muscle contraction

↓
Vasodilation of peripheral vessels, mainly arterioles.

↓
↓ Peripheral resistance

↓
↓ Blood pressure.

(Ref: Katzung-13th/201; Lippincott's-6th/234)

Q. Mention the indications of calcium channel blockers. (DU-07Ju, CU-08J; RU-11J, SU-07Ju)

Q. Mention the indications of

- Amlodipine. (DU-14J, 10/07Ju)
- Nifedipine. (DU-07J, CU-08J, SU-09Ju)
- Diltiazem. (CU-08J, SU-09J)

Ans.

Indications of Ca^{2+} channel blockers:

1. **Hypertension:** Amlodipine, isradipine, nicardipine, nifedipine, verapamil
2. **Angina:** Amlodipine, diltiazem, nicardipine, nifedipine, verapamil
3. **Migraine**
4. **Prevention of ischemic neurological damage following subarachnoid hemorrhage:** Nimodipine (60 mg every 4 hours).
5. **Hemorrhagic stroke with ventricular extension:** Nimodipine
6. **Cardiac arrhythmia:** Verapamil
7. **Raynaud's phenomenon:** Nifedipine
8. **Post-MI SVT:** Verapamil, Diltiazem.
9. **Hypertrophic cardiomyopathy**

(Ref: Bennett & Brown-11th)

Ca^{2+} channel blockers	Indication
Amlodipine	▪ Hypertension ▪ Angina ▪ Migraine ▪ Cardiomyopathy ▪ Raynaud's phenomenon
Nifedipine	▪ Angina due to coronary arterial spasm ▪ Hypertension ▪ Raynaud's phenomenon
Nimodipine	▪ Subarachnoid hemorrhage ▪ Hemorrhagic stroke with ventricular extension
Felodipine	▪ Hypertension ▪ Raynaud's phenomenon
Isradipine	▪ Hypertension
Nicardipine	▪ Angina ▪ Hypertension
Nisoldipine	▪ Hypertension
Nitrendipine	▪ Investigational
Verapamil	▪ Angina ▪ Hypertension ▪ Arrhythmias ▪ Migraine
Diltiazem	▪ Angina ▪ Hypertension ▪ Raynaud's phenomenon

(Ref: Katzung-13th, 200)

Q. Mention the adverse effects of Ca^{2+} channel blockers. (DU-00M, RU-02J, SU-05J)

Q. Mention the adverse effects of-

- Amlodipine. (DU-10/07Ju; RU-09J, 03J)
- Nifedipine. (RU-03J, CU-02M, SU-07Ju)
- Diltiazem. (CU-02J)

Ans.

Adverse effects of Ca^{2+} channel blockers/ Amlodipine/ Nifedipine/ Diltiazem:

1. **Excessive inhibition of calcium influx** can cause **serious cardiac depression**, including cardiac arrest, bradycardia, atrioventricular block, and heart failure. These effects are rare in clinical use.
2. Short-acting calcium channel blockers such as prompt-release **nifedipine** increase the risk of **myocardial infarction** in patients with hypertension and should be **avoided**.
3. **Minor toxicity** (troublesome but not usually requiring discontinuance of therapy)-
 - a. Flushing
 - b. Dizziness
 - c. Nausea
 - d. Constipation (common with verapamil)
 - e. Peripheral edema (eg, ankle edema).

(Ref: Katzung-13th/202 + Bennet & Brown)

Viva Q. Why ankle edema occurs in use of calcium channel blockers?

Ans. Ankle edema due to CCB is probably due to a rise in intracapillary pressure as a result of the selective dilatation by calcium blockers of the precapillary arterioles. Thus the edema is not a sign of sodium retention. It is not relieved by a diuretic but disappears after lying flat, e.g. overnight.

(Ref: Bennett & Brown-11th)

Viva Q. What is the limitation of dihydropyridine derivatives?

Ans.

Dihydropyridine derivatives → Vasodilation → Reflex tachycardia → ↑HR → ↑Myocardial O_2 demand → Precipitates angina. So these drugs cannot be used in stable angina. But they can be used in variant angina as they can reduce coronary arterial spasm.

Viva Q. Name the drugs used for Raynaud's phenomenon.

Ans.

Drugs used for Raynaud's phenomenon

1. Nifedipine
2. Reserpine
3. α blocker (sub-hypotensive dose)
4. epoprostenol

Q. Mention the contraindications of calcium channel blockers?

Ans.

Contraindications or cautions of Ca^{2+} -channel blockers / Amlodipine / Nifedipine:

1. Cardiac depression
 - Cardiac arrest
 - Bradycardia
 - Heart failure.
 - 2nd & 3rd degree heart block.
 - Sick sinus syndrome
 - Wolf-Parkinson-white (WPW) syndrome
2. During labor of a pregnant mother
3. Constipation

(Ref: Katzung-13th edition)

Q. Mention advantages and disadvantages of amlodipine as antihypertensive drug. (CU-05M)

Ans.

Advantages of amlodipine:

1. Do not compromise hemodynamic status; no impairment of physical activity.
2. No sedation or other CNS effects.
3. Cerebral perfusion is maintained.

4. Not contraindicated in asthma, angina (especially variant) & peripheral vascular disease (PVD) patient; rather may benefit this condition.
5. No adverse fetal effects. Can be used in pregnancy (but can weaken uterine contraction during labour).
6. Do not impair renal perfusion.
7. Do not affect male sexual function.
8. No deleterious effect on plasma lipid profile, uric acid level & electrolyte balance.
9. Shown to have no / minimal effect on quality of life.

(Ref: Tripathi-6th/543)

Disadvantages of amlodipine: See adverse effects of amlodipine.

Q. Compare Nifedipine, Verapamil and β - blockers. (CU-16Ju)

Q. Compare Dihydropyridine with Verapamil and β -blockers. (CU-16J)

Ans.

Comparison of Propranolol, GTN & Diltiazem as anti-anginal drugs

Traits	β - blockers	Dihydropyridine /Nifedipine	Verapamil / Diltiazem
1. M/A	Blocks β -adrenoceptors	Blocks L-type Ca^{2+} channel in peripheral vessels.	Blocks L-type Ca^{2+} channel in cardiac muscle & peripheral vessels.
2. Important Indications	• IHD • Hypertension. • Arrhythmias • Heart failure	• Angina due to coronary arterial spasm • Hypertension • Raynaud's phenomenon	• Angina • Hypertension • Raynaud's phenomenon
3. Use in Raynaud's phenomenon	No	Yes	Yes
4. Bronchoconstriction (aggravates asthma)	Yes	No	No
5. Risk of hypoglycemia in pt taking insulin	Yes	No	No
6. Peripheral edema (eg, ankle edema).	No	Yes	Yes
7. Cold extremities	Yes	No	No
8. Sexual dysfunction in men	Yes	No	No
9. Flushing, Dizziness	No	Yes	Yes
10. Constipation	No	Less common	Common
11. Dyslipidemia	May occur	No	No
12. CNS disturbances	May occur	No	No
13. Tolerance	No	No	No
14. Postural hypotension	Yes	Yes	Yes

Q. Compare Nifedipine and Amlodipine. (CU-15J)

Ans.

Traits	Nifedipine	Amlodipine
1. Type	Ca ²⁺ -channel blockers	Ca ²⁺ -channel blockers
2. Mechanism of action	Acts on blood vessels more	Acts on blood vessels & heart
3. Half life	2 hours	40 hours
4. Use	Not emergency condition. Used as antihypertensive drugs.	Emergency condition. Safe to use in patient with cardiac failure.
5. Missed dose	Missed dose can activate sympathetic system	Missed dose is of little consequence
6. Adverse effect	Gum hypertrophy	Less adverse effect

Q. Why amlodipine is preferred to nifedipine in hypertension with angina? (SU-14Ju)

Ans. Immediate-acting **nifedipine** increased the risk of **myocardial infarction** in patients with hypertension. This is why amlodipine is preferred to nifedipine in hypertension with angina.

Q. Write short notes on amlodipine. (DU-15J,10/09Ju)

Ans. Write mechanism of action + indications + adverse effects of from above.

Q. Justify the rationale of amlodipine & atenolol drug combination. (RU-14Ju,10, SU-16J)

Q. Should the Ca²⁺ channel blockers and β blockers be used in combination? (SU-14J)

Q. Justify the rationale of nifedipine & atenolol drug combination. (CU-16J)

Ans.

Rationale of drug combination of amlodipine/nifedipine & atenolol:

1. In combination they have synergistic effect. So they can lower the BP more effectively & at a lower dose than single use of each of them.
2. It is a good combination (acting over two different antihypertensive pathways) for those hypertensive patients in which single drug (amlodipine or atenolol) is not enough to control hypertension.
3. Amlodipine is a good drug for isolated **systolic hypertension** & atenolol is very effective in isolated **diastolic hypertension**.
4. Atenolol decreases peripheral circulation (cold extremities); on the other hand amlodipine improves peripheral circulation.
5. Amlodipine causes **reflex tachycardia**, whereas atenolol causes bradycardia.

vas. selective

*CCB → Sys
ATN
β blocker → diast*

Q. Explain the role of nimodipine in subarachnoid hemorrhage.

Ans.

Role of nimodipine in subarachnoid hemorrhage: Cerebral vasospasm and infarction is a complication of subarachnoid hemorrhage. Nimodipine has a high affinity for cerebral blood vessels and **prevents vasospasm** in the cerebral vessels. Thus nimodipine **prevents ischemic stroke** after a subarachnoid hemorrhage.

(Ref: Katzung-13th/202)

Renin angiotensin aldosterone system (RAAS) inhibitors

Q. Enumerate the functions of Angiotensin-II. (CU-16J, SU-06Ju)

Ans.

Functions of angiotensin-II:

1. Increases peripheral resistance.
2. Release of aldosterone from adrenal cortex.
3. Reabsorption of Na^+ from proximal convoluted tubule.
4. Renal vasoconstriction.
5. Hypertrophy and remodeling of vessels and heart.

(Ref: Goodman & Gilman-10th/798)

Q. Enumerate the factors that influence rennin release. (CU-15Ju)

Ans.

Factors that influence rennin release

1. Increased sympathetic activity via renal nerves
2. Increased circulating catecholamines
3. Prostaglandins

ACEi, ARB, Spironolactone → Hypokalemia
(Ref: Ganong-24th edition)

Q. Name the antihypertensive drugs which act through Renin-Angiotensin-Aldosterone System. (DU-13Ju, 10/08J, 06M; CU-08J, 05S, 04S; RU-15Ju, 13Ju, 11Ju, 07J, 06M, 05M; SU-16J, 014Ju, 12Ju/J, 10J)

Q. Categorize the inhibitors of RAAS. (CU-14J, RU-08J)

Q. Enumerate ACE inhibitors. (DU-17M, 15Ju, 11Ju, 09J, SU-09Ju; RU-13J, 12J)

Q. Enlist 3 (three) important ACE inhibitors. (DU-14J)

Q. Enumerate angiotensin-II receptor blockers. (DU-12Ju, CU-11J)

Ans.

Renin angiotensin aldosterone system (RAAS) inhibitors:

A. Angiotensin converting enzyme inhibitors (ACEi)	▪ Captopril ▪ Enalapril ▪ Lisinopril ▪ Ramipril ▪ Benazepril ▪ Fosinopril ▪ Moexipril ▪ Perindopril ▪ Quinapril ▪ Trandolapril ▪ Fosinopril
B. Angiotensin-II receptor blockers (ARB)	▪ Losartan ▪ Valsartan ▪ Candesartan ▪ Eprosartan ▪ Irbesartan ▪ Telmisartan ▪ Olmesartan
C. Direct renin inhibitor	▪ Aliskiren
D. Drugs that block renin secretion	▪ Propranolol ▪ Atenolol ▪ Metoprolol ▪ Clonidine

Q. Draw a diagram showing the site of action of different antihypertensive drugs in Renin-Angiotensin-Aldosterone System (RAAS). (CU-08J)

Ans.

Diagram showing the sites of action of different antihypertensive drugs in RAAS:

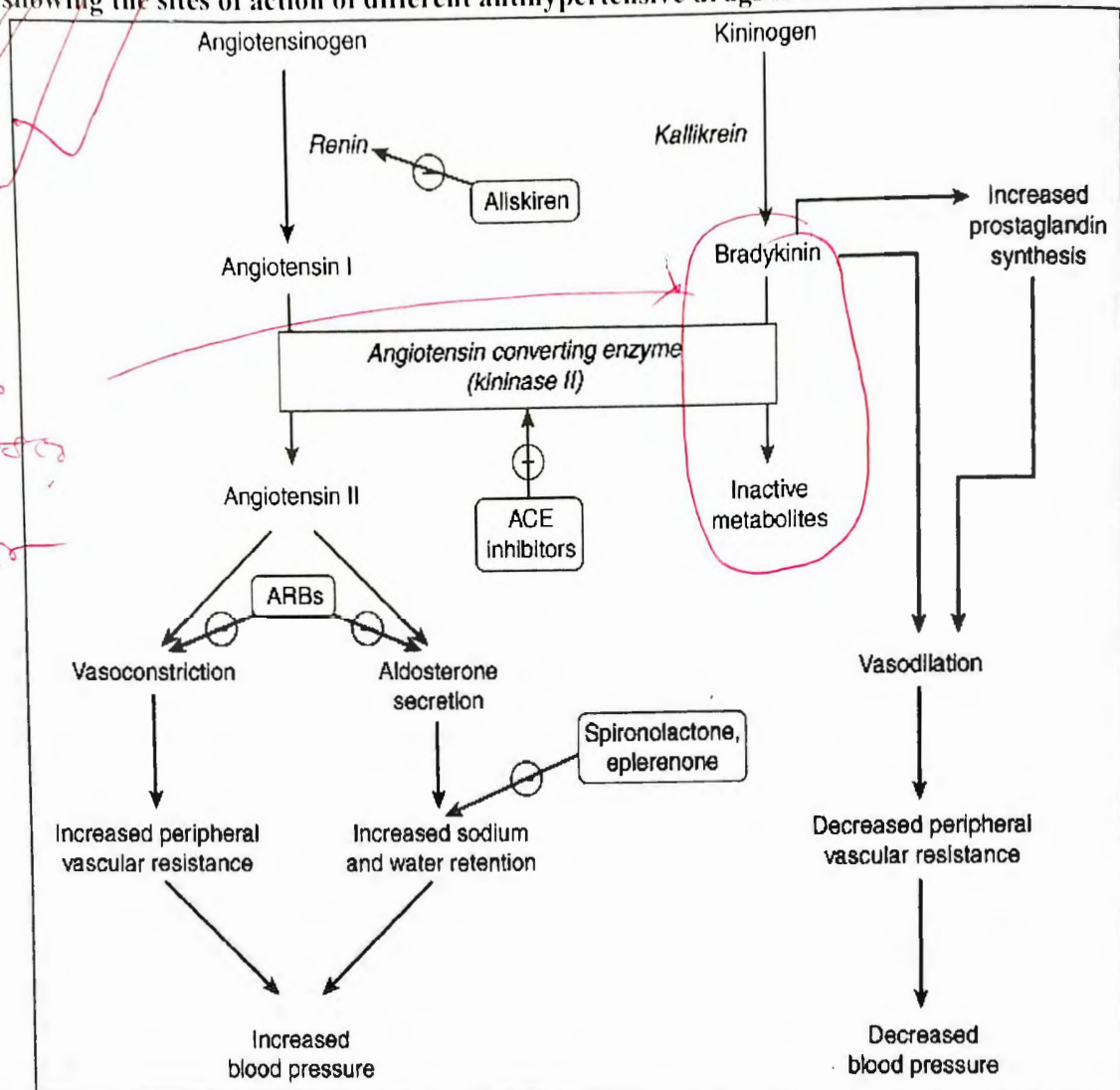


Fig. Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.

(Ref: Katzung-12th edition)

ACE inhibitors

Q. Mention the indications of ACE inhibitors. (DU-17M, RU-13J, SU-15Ju,15J)

Q. Write down the indications of captopril. (CU-02J, RU-05M)

Q. Write down the indications of lisinopril. (RU-02M)

Q. State in short the indications of ramipril. (DU-12Ju)

Ans.

Indications of ACEI / ramipril / captopril / lisinopril:

1. Hypertension (highly effective in renovascular, resistant HTN & diabetic patient with HTN).
2. Myocardial infarction (MI): To prevent remodeling of the heart.
3. Diabetic nephropathy due to vasoconstriction probably caused by angiotensin-II (hypertensive patient with type-I DM).
4. Cardiac hypertrophy
5. Chronic heart failure.

(Ref: Bennett & Brown-10th)

(Reduces PBF without increasing CO, HR, etc)

Q. Discuss the role of ACE inhibitors in hypertension with DM. (SU-17M, 13Ju)

Q. Why ACE inhibitors are drug of choice in HTN with DM?

Q. Justify preference of ramipril to thiazides in diabetes. (SU-15Ju)

Ans.

Role of ACE inhibitors in hypertension with DM:

1. In patients with **type 1 diabetes mellitus** and **diabetic nephropathy**, captopril and lisinopril prevents or delays the progression of renal disease and decrease albuminuria.
2. In addition, ACE inhibitors may decrease retinopathy progression in type 1 diabetics.

(Ref: Goodman & Gilman-12th edition)

Q. Explain the rationality of using ACE inhibitors in diabetic nephropathy. (CU-14Ju)

Ans.

Rationality of using ACE inhibitors in diabetic nephropathy: In patients with type 1 diabetes mellitus and diabetic nephropathy, captopril and lisinopril prevents or delays the progression of renal disease and decrease albuminuria.

Mechanisms of renal protection by ACE inhibitors:

1. Increased glomerular capillary pressure induces glomerular injury, and ACE inhibitors reduce this parameter both by decreasing arterial blood pressure and by dilating renal efferent arterioles.
2. ACE inhibitors inhibit mesangial cell proliferation and matrix production, two processes that contribute to expansion of the mesangium in diabetic nephropathy.

(Ref: Goodman & Gilman-12th edition)

Q. Explain the antihypertensive effect of ACE inhibitors. (DU-04J, CU-14Ju, 11J, RU-12J, SU-03J)

Q. Explain how ACE inhibitors lower BP? (DU-17M, CU-16J, RU-13J, 07J/S, 05M, SU-08Ju, 07Ju, 06S)

Q. Discuss the antihypertensive action of captopril. (DU-15J, RU-05/04M, SU-08/07Ju, 06S)

Q. How does lisinopril lower blood pressure? (DU-11Ju, SU-09Ju, RU-08J, 07J)

Q. Write down the mechanism of action of Lisinopril. (DU-15Ju)

Q. Write down the mechanism of action of Acipril. (SU-16J)

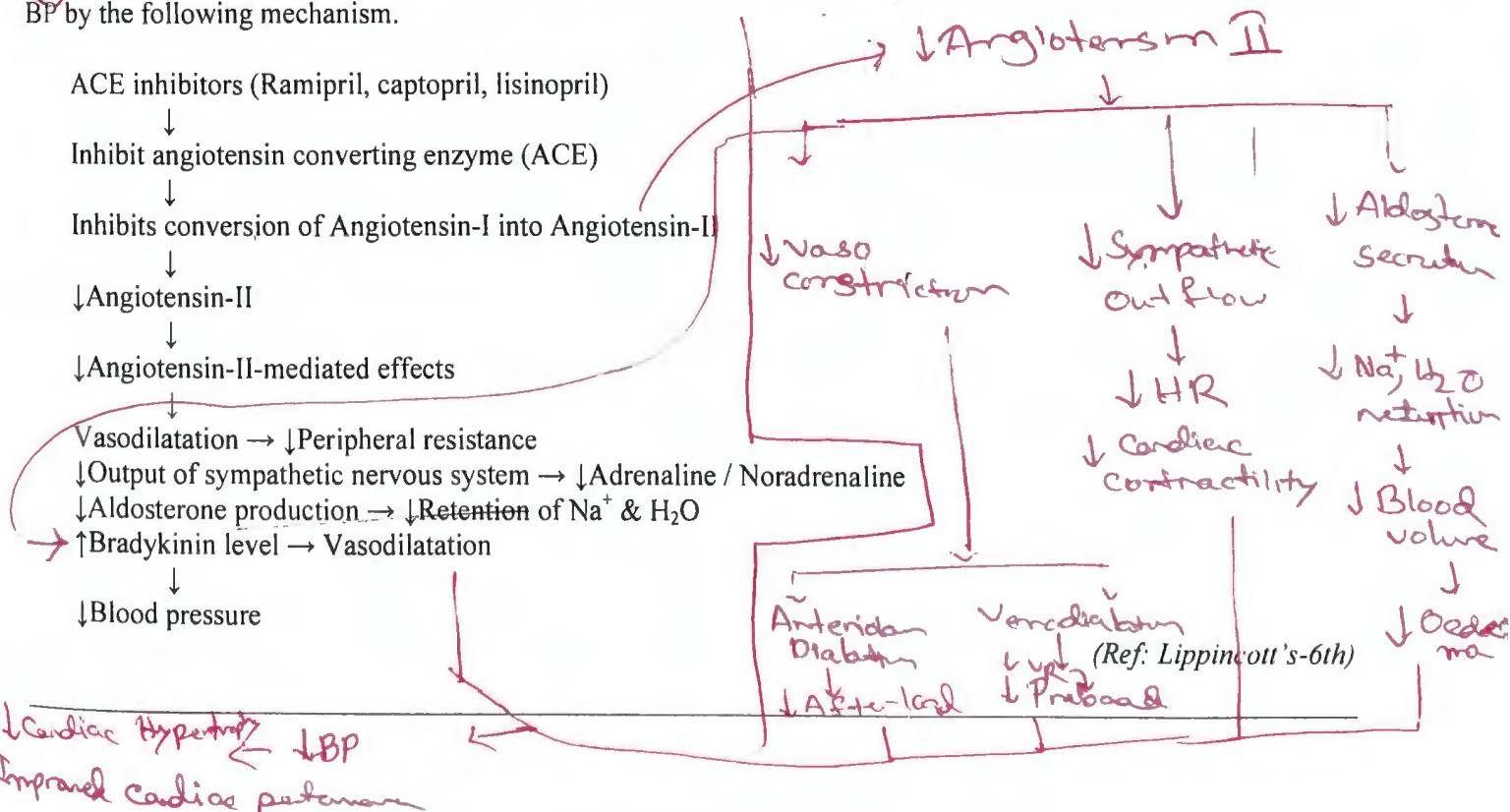
Q. Discuss how enalapril lower blood pressure. (DU-14J, RU-17J)

Q. State in short the M/A of ramipril. (DU-12Ju, SU-13J)

Q. Write short note on: Ramipril. (DU-11J, 09Ju)

Ans.

Mechanism of action of ACE inhibitors / Ramipril / Captopril / Lisinopril / Enalapril: ACE inhibitors lower BP by the following mechanism.



- Q. Mention the adverse effects of ACE inhibitors. (DU-10J; CU-14J, 11Ju, RU-06M/S, SU-15Ju, 15J, 08/07Ju)
 Q. How do ACE inhibitor users develop cough? (DU-09J, RU-12J)
 Q. Mention the adverse effects of captopril. (DU-15J, RU-14Ju)
 Q. Mention the adverse effects of lisinopril. (RU-02M)
 Q. Mention 3 adverse effects of lisinopril. (DU-15Ju)
 Q. Mention the 2 common adverse effects of enalapril. (RU-17J)

Ans.

Adverse effects of ACE inhibitors / Captopril / Lisinopril / enalapril:

1. **Dry cough:** Due to accumulation of bradykinin & substance-P in the lungs.
2. **Angioedema:** Due to elevated bradykinin & prostaglandin level
3. **First dose hypotension**
4. **Hyperkalemia:** Due to decreased aldosterone secretion & more likely in patients with renal impairment & K⁺ sparing diuretics, NSAIDs or β blockers.
5. **Acute renal failure** due to dilation of efferent arteriole in patients with bilateral renal artery stenosis, heart failure or volume depletion owing to diarrhea or diuretics.
6. Skin rash
7. Teratogenesis.
8. **Fetal renal shut down** in case of pregnancy.

(Ref: Lippincott's-5ht/235; Tripathi-6th/484)

Q. Why dry cough occurs with ACE inhibitors? How to reduce it?

Ans.

In 5-20% of patients, ACE inhibitors induce a bothersome, dry cough mediated by the accumulation in the lungs of **bradykinin**, **substance P**, and/or **prostaglandins**. Thromboxane antagonism, aspirin, and iron supplementation reduce cough induced by ACE inhibitors. ACE dose reduction or switching to an ARB is sometimes effective. Once ACE inhibitors are stopped, the cough disappears, usually within 4 days.

(Ref: Goodman & Gilman-12th edition)

Q. What is first dose hypotension?

Q. Short note: First dose phenomenon. (RU-16Ju, 15Ju)

Ans.

First dose hypotension: A steep fall in blood pressure may occur following the first dose of an **ACE inhibitor** in patients with elevated plasma renin activity (PRA). Care should be exercised in patients who are salt depleted, are on multiple antihypertensive drugs, or who have congestive heart failure.

(Ref: Goodman & Gilman-12th edition)

Mechanism of first dose hypotension:

ACE inhibitors



↓Angiotensin-II



Vasodilatation → ↓Peripheral resistance

↓Output of sympathetic nervous system → ↓Adrenaline / Noradrenaline



First dose hypotension

Prevention of first dose hypotension: As there is chance of serious drop of blood pressure, therapy should be initiated at bed time and patient should be warned.

Q. What are the contraindications of ACE inhibitors / captopril / ramipril / acipril? (CU-11Ju, SU-16J)

Q. Enlist the absolute contraindications of ACE inhibitors. (CU-15Ju)

Ans.

Contraindications or cautions of captopril / ramipril / ACE inhibitors:

1. Renal failure.
2. Pregnancy.
3. Hyperkalemia.

4. Bilateral renal artery stenosis.

(Ref: Harrison's medicine-17th edition)

Q. Why ACE inhibitors are contraindicated in pregnancy?

Ans.

ACE inhibitors are contraindicated in 2nd and 3rd trimesters of pregnancy, because it causes-

1. Fetal calvarial hypoplasia
2. Fetal pulmonary hypoplasia
3. Fetal growth retardation
4. Anuria
5. Fetal death

Q. Why ACE inhibitors are contraindicated in bilateral renal artery stenosis?

Ans.

Angiotensin II, by constricting the efferent arteriole, helps to maintain adequate glomerular filtration when renal perfusion pressure is low. Inhibition of ACE by ACE inhibitors can induce acute renal insufficiency in patients with bilateral renal artery stenosis, stenosis of the artery to a single remaining kidney.

(Ref: Goodman & Gilman-12th edition)

Q. Why ACEi is indicated before meal?

Ans.

Orally taken captopril gives 70% bioavailability after fasting, but bioavailability is reduced by 30-40% when drug is taken with food. So it is better to take the drug 1-2 hours before meal.

Nice to know

Important drug interaction

1. ACEi + Frusemide

ACEi causes hyperkalemia.

Frusemide causes hypokalemia.

So, one drug compensates the adverse effects of the other.

2. ACEi + Spironolactone (K⁺ sparing diuretic) → Hyperkalemia develops.

3. ACEi + NSAID: Aspirin blocks bradykinin mediated vasodilation, so hypotensive action of ACEi is impaired.

Advantages of captopril / ramipril / ACE inhibitors:

1. They have no postural hypotension, electrolyte disturbances, feeling of weakness & CNS effects.
2. Safe in patients with DM & PVD.
3. Prevention of secondary hyperaldosteronism & K⁺ loss.
4. Improves renal perfusion.
5. They reverse LVH & decrease the wall-to-lumen ratio of blood vessels that occurs in HTN.
6. No effects on uric acid level & plasma lipid profile.
7. Minimum worsening of quality of life; e.g. work performance, sleep, sexual performance, general well-being.
8. Recent evidence shows that long term use of ACEi potentially decreases the incidence of type-II DM in high risk subjects.

(Ref: Tripathi-6th/486)

Advantages of ACE inhibitors over β blocker, Ca²⁺ channel blocker, diuretic: ACE inhibitors-

1. Do not cause hyperglycemia like diuretics.
2. Do not aggravate asthma and heart block like beta blocker.
3. Do not inhibit VMC like Ca²⁺ channel blocker and can be used in CCF where Ca²⁺ channel blocker cannot be used.

Angiotensin-II Receptor Blockers (ARB)

Q. Explain the mechanism of action of losartan. (SU-09J,06S)

Q. How do you antagonize the action of angiotensin-II? (SU-06J)

Ans.

Mechanism of action of ARB / Losartan / Valsartan:

ARB / Losartan / Valsartan

↓
Blocks angiotensin-II receptor

↓
Angiotensin-II cannot bind with the receptor

↓
↓Angiotensin-II-mediated effects

↓
Vasodilatation → ↓Peripheral resistance

↓Output of sympathetic nervous system → ↓Adrenaline / Noradrenaline

↓Aldosterone production → ↓Retention of Na⁺ & H₂O

↑Bradykinin level → Vasodilatation

↓
↓Blood pressure

(Ref: Lippincott's-5th/235,236)

Q. Mention the indications of angiotensin-II receptor blockers (ARB). (DU-13Ju, CU-11J)

Q. Mention the indications of losartan.

Ans.

Indications of angiotensin-II receptor blockers/ losartan:

1. Hypertension.
2. Hypertensive patient with bronchial asthma or dry cough.
3. Chronic heart failure (valsartan)
4. MI (valsartan) due to absence of reflex tachycardia may be due to downward resetting of the baroreceptor or due to enhanced parasympathetic activity.
5. Diabetic nephropathy (losartan)
6. Prophylaxis of stroke (losartan).

Q. Mention the adverse effects of angiotensin-II receptor blockers (ARB). (DU-13Ju, CU-11J)

Ans.

Adverse effects of angiotensin-II Receptor Blockers:

1. Hypotension
2. Hyperkalemia
3. Acute renal failure (ARF)
4. Teratogenic

Q. What are the contraindications of angiotensin-II receptor blockers?

Ans.

Contraindications or cautions of angiotensin-II receptor blockers / Losartan:

1. Renal failure.
2. Hyperkalemia.
3. Pregnancy.
4. Bilateral renal artery stenosis.

(Ref: Harrison's medicine-17th edition)

Q. Mention the rationale of drug combination of losartan & hydrochlorothiazide. (RU-14Ju, 13Ju, 10J)
Ans.

Rationale of drug combination of losartan & hydrochlorothiazide: Losartan is an antihypertensive drug which causes hyperkalemia. On the other hand hydrochlorothiazide is an antihypertensive drug and causes hypokalemia. So when these two drugs are used in combination, K⁺ homeostasis remains unaltered. That's why it is a popular antihypertensive drug combination & used commonly if they are indicated.

Q. What are the advantages of ARBs / losartan over ACE inhibitors?

Ans.

Advantages of ARBs / losartan over ACE inhibitors:

1. No dry cough.
2. Lower incidence of angioedema.
3. Lower incidence of rashes.

Direct renin inhibitors: Aliskiren

Aliskiren directly inhibits the renin.

Mechanism of action: Directly inhibits enzyme activity of rennin and thus acts earlier in the rennin-angiotensin-aldosterone system than do ACE inhibitors or ARBs.

Effects: Reduces angiotensin I and II and aldosterone.

Indication: Hypertension

Adverse effects:

1. Hyperkalemia
2. Renal impairment
3. Potential teratogen.
4. Cough
5. Angioedema
6. Diarrhea at higher dose

Contraindication

1. Pregnancy

Advantage over ACE inhibitors or ARBs: ACE inhibitors, ARBs and diuretics increase plasma renin activity. Aliskiren not only decreases baseline plasma renin activity in hypertensive subjects but also eliminates the rise produced by ACE inhibitors, ARBs, and diuretics and thereby results in a greater antihypertensive effect. Renin inhibition has thus proved to be an important new approach to the treatment of hypertension.

(Ref: Katzung-13th; Lippincott's-6th)

Q. Compare and contrast of hydrochlorothiazide and propranolol as antihypertensive drugs. (CU-05M)

Ans.

Differences between hydrochlorothiazide & propranolol:

Trait	Hydrochlorothiazide	Propranolol
1. Group	Thiazide group of diuretics	Non-selective β -blocker
2. Mechanism of antihypertensive action	Decreases BP by diuresis and by decreasing responsiveness of blood vessel to catecholamines.	By blockage of β_1 receptors of heart and JG apparatus of kidney
3. Onset of action	Slow	Rapid
4. Duration of action	Prolonged	Short
5. Adverse effects	1. Hypokalemia 2. Ventricular tachycardia 3. Hyperglycemia 4. Dyslipidemia 5. Gout 6. Paresthesia 7. Muscle pain	1. Bradycardia 2. Hypoglycemia 3. Dyslipidemia 4. Peripheral ischemia 5. Bronchospasm 6. Sedation 7. Depression
6. Advantages	- No postural hypotension - Inexpensive	- No postural hypotension - Inexpensive
7. Indications	Mild to moderate HTN	Mild to moderate HTN

Q. Compare β -blockers and ACE inhibitors as antihypertensive agents, possible adverse effects and clinical indications. (CU-06M/S)

Ans.

Comparison between β -blockers & ACE inhibitors:

Traits	β -blockers / Atenolol	ACE inhibitors / Captopril
Mechanism of action	By blockage of β_1 receptors of heart and JG apparatus of kidney	Inhibits conversion of angiotensin-I into angiotensin-II.
Adverse effects	- Bradycardia - Hypotension - Hyperkalemia - Bronchospasm	- Reflex tachycardia & 1st-dose hypotension - Hyperkalemia - Bronchodilation
Effective for	Mild to moderate HTN.	Mild to moderate HTN.

Q. Compare and contrast atenolol and losartan as antihypertensive drugs? (CU-05J)

Ans.

Comparison between atenolol and losartan as antihypertensive drugs:

Traits	Atenolol	Losartan
1. Group	Selective β_1 blockers	Angiotensin II receptor blocker
2. M/A	By blockage of β_1 receptors of heart and JG apparatus of kidney.	Blocks angiotensin II receptor → Blocks the action of angiotensin-II
3. Oral bioavailability	60%	35%
4. Plasma half life	6 hours	1-2 hours
5. Solubility	Water soluble	Lipid soluble
6. Hypotension	Yes	Yes
7. Hyperkalemia	Yes	Yes
8. Advantages	Can be used in patients with asthma, COPD, MI, DM, PVD	Same
9. Effective for	Mild to moderate HTN	Mild to moderate HTN

- Q. Write down the differences between captopril & losartan. (DU-10Ju)
- Q. Compare and contrast amlodipine & losartan as antihypertensive agents? (CU-07J)
- Q. Compare & contrast enalapril, amlodipine & losartan as antihypertensive drugs. (CU-09/08Ju)
- Q. Compare & contrast ACE inhibitor & ARBs. (CU-15Ju)
- Q. Compare & contrast ACE inhibitor & ARBs in respect to mechanism of action and adverse effect profile. (RU-15J)

Ans.

Comparison among enalapril, amlodipine & losartan as antihypertensive drugs

Traits	ACEI (Enalapril/ Captopril)	Amlodipine	ARB (Losartan)
1. Group	ACE inhibitor	Ca ²⁺ channel blocker	Angiotensin II receptor blocker
2. Mechanism of action	Inhibits ACE	Decreases BP by vasodilation	Blocks angiotensin II receptor → Blocks the action of angiotensin-II
3. Oral bioavailability	50%	65-90%	35%
4. Plasma half life	11 hours	Prolonged	Short (1-2 hours)
5. First pass metabolism	-	High	Low
6. Plasma protein binding	-	High (>90%)	Low
7. Metabolism	-	Extensive metabolism	No
8. Excretion	Kidney	Kidney	Kidney
9. Adverse effect profile			
• Ankle edema	No	Yes	No
• Flushing	No	Yes	No
• Reflex tachycardia	No	No	No
• Dry cough	Occurs	No	No
• Hyperkalemia	Yes	No	Yes
• Acute renal failure	Yes	No	Yes
• First dose hypotension	More severe	No	Less severe
10. Use in pregnancy	Contraindicated	Safe	Contraindicated
11. Indication	All grades of HTN	Mild to moderate HTN	Mild to moderate HTN

Antianginal drugs

Coronary heart disease (CHD)/Ischemic heart disease (IHD) is the most common form of heart disease and the single most important cause of premature death. Disease of the coronary arteries is almost always due to **atherosclerosis** and its complications, particularly **thrombosis** in the **coronary arteries**.

Table: Coronary heart disease: clinical manifestations and pathology

Clinical problem	Pathology
Stable angina	Ischemia due to fixed atheromatous stenosis of one or more coronary arteries
Unstable angina	Ischemia caused by dynamic obstruction of a coronary artery due to plaque rupture with superimposed thrombosis and spasm
Myocardial infarction	Myocardial necrosis caused by acute occlusion of a coronary artery due to plaque rupture and thrombosis
Heart failure	Myocardial dysfunction due to infarction or ischemia
Arrhythmia	Altered conduction due to ischemia or infarction
Sudden death	Ventricular arrhythmia, asystole or massive myocardial infarction

Acute coronary syndrome: Acute coronary syndrome is a term that encompasses both **unstable angina** and **MI**.

Angina pectoris: Angina pectoris is a characteristic sudden, severe, pressing chest pain radiating to the neck, jaw, back, and arms. It is caused by coronary blood flow that is insufficient to meet the oxygen demands of the myocardium, leading to ischemia. The imbalance between oxygen delivery and utilization may result during exertion, from a spasm of the vascular smooth muscle, or from obstruction of blood vessels caused by atherosclerotic lesions. These transient episodes (15 seconds to 15 minutes) of myocardial ischemia do not cause cellular death, such as occurs in myocardial infarction.

(Ref: Lippincott's-6th)

Types of angina:

- Stable angina:** Stable angina is the most common form of angina and, therefore, is called **typical or classical angina pectoris**. It is characterized by a burning, heavy, or squeezing feeling in the chest. It is caused by the reduction of coronary perfusion due to a **fixed obstruction** produced by **coronary atherosclerosis**. The heart becomes vulnerable to ischemia whenever there is increased demand, such as that produced by physical activity, emotional excitement, or any other cause of increased cardiac workload. Typical angina pectoris is promptly relieved by rest or nitroglycerin (a vasodilator).
- Unstable angina:** Unstable angina lies between stable angina on the one hand and myocardial infarction on the other. In unstable angina, chest pains occur with **increased frequency** and are **precipitated by progressively less effort**. The symptoms are not relieved by **rest or nitroglycerin**. Unstable angina **requires hospital admission** and more aggressive therapy to prevent death and progression to myocardial infarction.
- Prinzmetal's or variant or vasospastic angina:** Prinzmetal's angina is an uncommon pattern of episodic angina that occurs **at rest** and is due to **coronary artery spasm**. Symptoms are caused by decreased blood flow to the heart muscle due to spasm of the coronary artery. Prinzmetal's angina generally responds promptly to coronary vasodilators, such as nitroglycerin and calcium-channel blockers.

(Ref: Lippincott's-6th)

Determinants of Myocardial Oxygen Demand: Myocardial O₂ consumption depends on-

- Heart rate:**
 - ↑ Heart rate → ↑ Myocardial O₂ demand → ↑ Angina.
- Force of contraction:**
 - ↑ Force of contraction → ↑ Myocardial O₂ demand → ↑ Angina.

Rest Angina:
 Rupture of ~~atherosclerotic~~ atherosclerotic plaque & partial/comple thrombosis of coronary artery

3. **Preload:** The preload is the degree to which the myocardium is stretched before it contracts. Preload is usually considered to be the end-diastolic pressure when the ventricle has become filled.
 - $\uparrow$ Preload $\rightarrow \uparrow$ Myocardial O_2 demand $\rightarrow \uparrow$ Angina.
4. **After load:** The afterload is the resistance against which heart pumps the blood.
 - $\uparrow$ Afterload $\rightarrow \uparrow$ Myocardial O_2 demand $\rightarrow \uparrow$ Angina.

Q. Describe the goal of anti-anginal therapy. (CU-16Ju)

Ans.

Treatment objective of angina or myocardial infarction (MI):

A. To decrease myocardial O_2 demand by-

1. Stopping of provocative exercises (physical/emotional)
2. Decreasing preload $\rightarrow \downarrow$ end diastolic volume
3. Decreasing after load
4. Decreasing heart rate.
5. Decreasing force of contraction.
6. Dilating the coronary arteries.

B. To increase myocardial blood flow by-

1. Revascularization by thrombolytic therapy or coronary artery angioplasty.
2. Coronary artery bypass surgery.

Q. Describe peculiarities of coronary circulation. (CU-14Ju)

Ans.

Peculiarities of coronary circulation:

1. Sometimes **left coronary artery** arises from the **pulmonary trunk** producing cyanotic symptoms followed by the left ventricular failure.
2. On occasions **left coronary artery** arises from the **anterior aortic sinus** and undergoes a longer course behind the pulmonary trunk before dividing. In this anomaly the trunk of the artery may be compressed between the aorta and pulmonary trunk after severe exercise, and culminates in *sudden cardiac death (SCD)*.
3. **Parasympathetic** stimulation has negligible direct effect on coronary vessels. **Sympathetic** alpha receptors (constrictor receptors) are predominant in epicardial coronary vessels; beta receptors (dilator receptors) are predominant in intramuscular arteries. Therefore sympathetic stimulation constricts the epicardial arteries, and dilates the intra-muscular arteries.
4. Coronary arteries are the only vessels where the **blood flows in diastole**.
5. Coronary artery is a **functional end artery**.

(Ref: A.K. Datta-9th)

Q. Classify anti-anginal drugs. (DU-15Ju, 14Ju, CU-08J, 06M; RU-16Ju, 15Ju, 13J, 07Ju; SU-09/08Ju, 06S/J).

Q. Categorize anti-anginal drugs according to their mechanism of action. (CU-12Ju)

Q. What are the drugs used in IHD/angina pectoris? (DU-17J, 13J, 12J, 06J, RU-14J, 06J)

Q. Name some important anti-anginal drugs. (DU-09Ju)

Q. Name the drugs for angina of effort (classical angina). (CU-04S)

Q. Name the nitrates and nitrites used in angina? (RU-05S)

Ans.

Classification of anti-anginal drugs:

A. Organic nitrates / nitroglycerin:

Short acting	▪ Sublingual: Glyceryl-tri-nitrate (GTN), isosorbide dinitrate ▪ Inhalant: Amyl nitrite
Long acting	▪ GTN: Slow release tablets, 2% ointment, oral sustained action preparation ▪ Isosorbide mononitrate: Oral sustained action preparation. ▪ Isosorbide dinitrate: Chewable oral, oral.

(Anti hypertensive $\rightarrow$ 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th, 12th, 13th, 14th, 15th, 16th, 17th, 18th, 19th, 20th, 21st, 22nd, 23rd, 24th, 25th, 26th, 27th, 28th, 29th, 30th, 31st, 32nd, 33rd, 34th, 35th, 36th, 37th, 38th, 39th, 40th, 41st, 42nd, 43rd, 44th, 45th, 46th, 47th, 48th, 49th, 50th, 51st, 52nd, 53rd, 54th, 55th, 56th, 57th, 58th, 59th, 60th, 61st, 62nd, 63rd, 64th, 65th, 66th, 67th, 68th, 69th, 70th, 71st, 72nd, 73rd, 74th, 75th, 76th, 77th, 78th, 79th, 80th, 81st, 82nd, 83rd, 84th, 85th, 86th, 87th, 88th, 89th, 90th, 91st, 92nd, 93rd, 94th, 95th, 96th, 97th, 98th, 99th, 100th)

B. Ca^{2+} channel blockers:

- Verapamil
- Diltiazem
- Nifedipine
- Nicardipine
- Amlodipine

C. β -blockers

- Propranolol
- Atenolol
- Metoprolol

D. **Newer Antianginal Drugs:** Because of the high prevalence of angina, new drugs are actively sought for its treatment.

Drugs or Drug Groups under Investigation for Use in Angina
● Metabolic modulators, eg, trimetazidine, ranolazine ● Direct bradycardic agents, eg, ivabradine ● Potassium channel activators, eg, nicorandil ● Capsaicin ● Amiloride

↑ Not channel blocker

E. Antiplatelet:

- Low dose aspirin (75-150 mg)
- Clopidogrel (75 mg)

F. Anticoagulant:

- Heparin
- Low-molecular-weight heparin

Q. How will manage a case of acute anginal attack? (SU-07Ju)

Q. Outline therapeutic approach in angina. (SU-17J)

Q. Outline the management of IHD. (SU-16Ju)

Q. Outline therapeutic approach in the treatment of ischemic heart disease. (SU-12J,10J)

Q. "A man aged 46 years old had severe chest pain after climbing several stairs" — what kind of anti-anginal drugs will prescribe to relieve chest pain? Explain its molecular action & mention adverse effects of the drugs. (SU-09J) (Dx- Stable angina)

Ans.

Management of angina pectoris / ischemic heart disease / IHD

A. Bed rest

B. Oxygen inhalation

C. Antiplatelet therapy

1. Low-dose aspirin (75-150 mg)
2. Clopidogrel (75 mg daily)

Antiplatelet drugs reduce the risk of adverse events such as MI and should be prescribed for all patients with coronary artery disease indefinitely.

D. Anti-anginal drug treatment: Four groups of drugs are used to help relieve or prevent the symptoms of angina: nitrates, β -blockers, calcium antagonists and potassium channel activators.

1. **Nitrates:** Sublingual **glyceryl trinitrate (GTN)** will usually relieve an attack of angina in 2-3 minutes. When blood pressure of the patient is low, oral '**trimetazidine**' can be used instead of nitroglycerine.
2. **Beta-blockers:** e.g. Atenolol, metoprolol, bisoprolol.
3. **Calcium channel blocker (CCB):** Nifedipine, amlodipine, nicardipine, verapamil, diltiazem

4. **Potassium channel activators:** Nicorandil is the only drug in this class currently available for clinical use.

E. **Revascularization** should be considered if an appropriate combination of two drugs fails to achieve a symptomatic response.

(Ref: Davidson's-22nd)

Nice to know

Angina with concomitant diseases:

Concomitant diseases	Drugs commonly used in treating angina
None	Long acting nitrates, β -blockers & Ca^{2+} -channel blockers
Recent MI	Long acting nitrates & β -blockers.
COPD, Asthma	Long acting nitrates & Ca^{2+} -channel blockers
Diabetes	Long acting nitrates & Ca^{2+} -channel blockers
Chronic renal disease	Long acting nitrates & Ca^{2+} -channel blockers (β -blockers are less effective)
Hypertension	β -blockers & Ca^{2+} -channel blockers (long acting nitrates are less effective)

(Ref: Lippincott's-6th)

Organic nitrates / GTN

- Q. Discuss briefly the mechanism of action of nitroglycerine/GTN. (DU-11J,09Ju, RU-12/11J, SU-16Ju)
 Q. How does glyceryl trinitrate (GTN) produce its antianginal action? (DU-13J,12J, SU-12Ju)
 Q. Mention the beneficial role of nitroglycerine in angina. (DU-17J, RU-16Ju,14J)
 Q. Discuss the role glyceryl trinitrate in IHD. (SU-13J,11J,10J,08Ju)
 Q. Explain the anti anginal effect of isosorbide mononitrate. (SU-08J,07J/Ju,06M)
 Q. How do nitrates relieve acute anginal pain? (DU-06S; CU-16Ju, RU-13J,07Ju,04M; SU-11Ju,06S)
 Q. Explain the anti-anginal effects of nitroglycerine/GTN. (DU-15Ju, CU-05M; RU-15Ju; SU-17M/1,16J,14J,09Ju)
 Q. Explain the rationale/role of nitroglycerine in ischemic heart disease (IHD). (RU-07J, SU-14Ju,08Ju)

Ans.

Mechanism of action of nitroglycerine / role of GTN in IHD / angina / MI:

Nitroglycerine (GTN)

↓
Release of nitric oxide (NO), which is a vasodilator

↓
Vascular smooth muscle relaxation

- ↓
- Venodilatation → Decrease venous return → Decrease preload → Decrease intraventricular pressure → Decrease cardiac work → Decrease O_2 ~~consumption~~ ^{demand} → Relief of angina.
 - Arterial dilatation → Decrease peripheral resistance → Decrease afterload → Decrease cardiac work → Decrease O_2 ~~consumption~~ ^{demand} → Relief of angina.

GTN → Nitrites → NO
 → c GMP → Dephosphorylation
 of myosin light chain
 → Vascular smooth
 muscle relaxation

Coronary Artery Vasodilatation → ↑ O_2 supply

(Ref: Katzung-12th/197)

- Q. Give various formulations of glyceryl-tri-nitrate. (DU-08J)

Ans.

Formulations of glyceryl-tri-nitrate / GTN:

1. Oral

- Sublingual tablet
- Buccal tablet
- Slow release tablet (both sublingual & buccal)

238 - Ingredient

d. GTN sustained release capsule (in inflammatory bowel disease)

2. Parenteral

- a. Slow release transdermal patch
- b. IV

3. **Inhalation:** Sublingual spray

4. **GTN suppository** (in anal fissure)

5. **GTN ointment** (in anal fissure)

Q. Mention various routes of GTN administration. (RU-12J)

Ans.

Various routes of GTN administration

1. Sublingual
2. Inhalant
3. Oral
4. Transdermal
5. Rectal (in case of GTN suppository and ointment in anal fissure)

Q. Enumerate the indications of GTN.

Ans.

Indication of GTN:

1. Stable angina
2. Unstable angina.
3. Prinzmetal's angina.
4. MI
5. CCF

Q. Write down the beneficial and deleterious effects of nitrates in the treatment of angina. (CU-13Ju)

Q. Mention the beneficial and adverse effects of GTN. (DU-14Ju)

Q. Mention the beneficial effects of nitroglycerin. (CU-13Ju, RU-05S)

Ans.

Beneficial effects of nitroglycerin	Result
1. Decreased ventricular volume	Decreased myocardial oxygen requirement
2. Decreased arterial pressure	
3. Decreased ejection time	
4. Vasodilation of epicardial coronary arteries	Relief of coronary artery spasm
5. Increased collateral flow	Improved perfusion to ischemic myocardium
6. Decreased left ventricular diastolic pressure	Improved subendocardial perfusion

(Ref: Katzung-12th/200)

Potential deleterious effects of nitroglycerin	Result
1. Reflex tachycardia	Increased myocardial oxygen requirement
2. Reflex increase in contractility	
3. Decreased diastolic perfusion time due to tachycardia	Decreased coronary perfusion

(Ref: Katzung-12th/200)

Q. Mention the adverse effects of nitroglycerin / GTN. (DU-17J, 11J, 09Ju, 08J; RU-11J, SU-06S; CU-12Ju)

Q. Write down the side effects of nitroglycerine. (DU-07J, 06S; CU-06M/J; 04S)

Q. Mention 2 adverse effects of nitroglycerin / GTN. (DU-15Ju)

Ans.

Adverse effects of nitroglycerine / GTN:

1. Throbbing type of headache
2. Postural hypotension
3. Tachycardia.

4. **Nitrate tolerance:**

- *True tolerance:* This is due to functional deficiency of glutathione 'S' transferase. It is mitigated by taking nitroglycerine at night in case of classical angina.
- *Pseudo tolerance:* This is due to reflex tachycardia. It is overcome by taking β -blockers and Ca^{2+} channel blockers.

5. **Carcinogenic** (there is a strong epidemiologic correlation between the incidence of **esophageal & gastric carcinoma** & the nitrate contents of the food)

(Ref: Katzung-12th/198-200)

Q. Short note: Nitroglycerine. (DU-14J)

Ans. Write in short from above discussion.

Q. State and explain throbbing headache after sublingual administration of glyceryl trinitrate? (CU-15J)

Ans.

Throbbing headache after GTN administration: Throbbing headache is probably due to the stretching of pain-sensitive tissues around the meningeal arteries resulting from the increased pulsation that accompanies the local vasodilatation.

(Ref: Bennett & Brown-11th)

Q. Explain the term nitrate tolerance. (CU-17J)

Ans.

Nitrate tolerance: During long-term treatment, continuous administration of organic nitrate results in complete / partial loss of its beneficial effects. It is called nitrate tolerance.**Cause of tolerance:** It is due to-

1. $\downarrow$ cGMP activation
2. $\uparrow$ volume expansion
3. Neurohormonal activation
4. Depletion of -SH group.

Prevention of nitrate tolerance: Tolerance to the actions of nitrates develops rapidly (tachyphylaxis). The blood vessels become desensitized to vasodilation. Tolerance can be overcome by providing a daily "nitrate-free interval" to restore sensitivity to the drug. This interval is typically 10 to 12 hours, usually at night, because demand on the heart is decreased at that time. Nitroglycerin patches are worn for 12 hours then removed for 12 hours.(Ref: Lippincott's-5th/222)**Nice to know****Procedure of taking GTN:** To avoid postural hypotension, GTN should be taken in lying position. Legs should be raised above head to restore venous return.**Advice to the patient:** Patient should be warned of the sign of overdose like **headache**. So that an excess dose can be spitted out.**Monday disease:** It is the headache and transient dizziness that occurs to the workers in the factory of nitrates on each Monday. Continuous exposure to high levels of nitrates can occur in the chemical industry, especially where explosives are manufactured. When contamination of the workplace with volatile organic nitrate compounds is severe, workers find that upon starting their work week (Monday), they suffer headache and transient dizziness ("Monday disease"). After a day or so, these symptoms disappear owing to the development of tolerance. Over the weekend, when exposure to the chemicals is reduced, tolerance disappears, so symptoms recur each Monday.(Ref: Katzung-12th/200)**Q. Mention the contraindications of nitroglycerin / GTN.**

Ans.

Contraindications of nitroglycerin / GTN

1. Angina due to severe anemia

2. Glaucoma
3. Intracranial pressure
4. Migraine headache
5. A known case of methemoglobinemia / tolerance

Q. Enumerate clinical importance of sublingual administration of nitroglycerin in angina pectoris.

Ans.

Nitroglycerin is given sublingually, (not orally), because-

1. Rapid onset of action (within 4 min)
2. Directly go to systemic circulation.
3. Avoid 1st pass metabolism
4. Dose requirement is minimum.
5. Short duration of action (20 min)
6. Highly lipid soluble and rapidly absorbed.
7. Less chance of adverse effect due to short duration of action

Q. Mention the metabolism of GTN.

Ans.

Metabolism of GTN: In liver- Glyceryl dinitrate is converted into Glyceryl mononitrate → Converted into G.M glucuronide which is excreted through kidney.

Q. What is nitrovasodilator?

Ans.

Nitrovasodilator: The organic nitrate and nitrite and several other compounds are capable of denitration to release NO (nitric oxide). They are collectively called nitrovasodilators.

Types:

1. Organic nitrate: GTN
2. Nitroprusside

Q. Why organic nitrate is given rather than inorganic nitrate?

Ans.

Inorganic nitrate	Organic nitrate
Less lipid soluble	More lipid soluble
Less tissue selective	More tissue selective

Q. Justify glyceryl trinitrate not propranolol is the drug of choice in the treatment of stable angina / acute anginal pain. (DU-09J; RU-10J)

Ans.

GTN

1. has rapid onset of action (within 4 mins) after giving sublingually and relieves anginal pain effectively.
2. Decreases coronary artery spasm and thus increases myocardial O₂ supply.
3. Redistribution of blood to ischemic region, thus preserve the viable tissue and decreases size of infarct.
4. ↓Cardiac load (↓preload + ↓ afterload) → ↓myocardial O₂ demand.

Propranolol

1. ↓Cardiac load.
2. But it has no effect on coronary artery dilation. Rather it causes coronary arterial spasm.
5. Causes bronchoconstriction which decreases ventilation.

This is why, glyceryl trinitrate, not propranolol, is the drug of choice in the treatment of stable angina / acute anginal pain.

Q. Give advantages & disadvantages of glyceryl-trinitrate as anti-anginal drug. (CU-01J)

Ans.

Advantages & disadvantages of glyceryl-trinitrate as anti-anginal drug:

Advantages

1. Rapid onset of action. So, can be given in acute attack.
2. Potency is higher than long acting nitrate i.e. isosorbide di/mono nitrate.

Disadvantages

1. Short duration (10 - 30 min) of action, so cannot be given for prophylaxis & more sustained effect.
2. Undergoes significant first pass metabolism. So, it should be given sublingually or in the form of patch.
3. Adverse effects: Headache, hypotension, tachycardia.
4. Tolerance develops rapidly.

Q. Compare & contrast Isosorbide dinitrate with Isosorbide mononitrate. (CU-17J,14Ju)

Ans.

Comparison between Isosorbide dinitrate and Isosorbide mononitrate

Traits	Isosorbide dinitrate	Isosorbide mononitrate
1. First pass hepatic metabolism	Extensive	Littler
2. Oral bioavailability	10 – 20%	100%
3. Onset of action	Rapid	Slow
4. Duration of action	Shorter	Longer
5. Dosage frequency	More	Less

Q. Name the drugs used in acute MI. (RU-06J)

Q. A 60 years old man experienced severe chest pain. Physician administered morphine injection, nitroglycerine under tongue and 150 mg aspirin orally. Briefly discuss the role of the mentioned drugs. (SU-12J) (Hint: diagnosis: MI)

Q. The physician prescribed morphine and 75 mg aspirin on arrival of a patient with suspected MI. mention role and mechanism of action of the mentioned drugs. (SU-15Ju)

Ans.

Drugs used in acute MI:

1. **Streptokinase:** In acute ST segment elevated MI, within 12 hours of onset of pain.
2. **Heparin (Enoxaparin):** If ST depression & T-inversion or ST-elevation but onset of pain >12 hrs.
3. **Nitrovasodilators:** GTN.
4. **Aspirin / Clopidogrel:** As anti-platelet.
5. **Morphine / Pethidine:** To relieve severe pain.
6. **β -blockers:** Atenolol, Metoprolol.

Q. Explain the pharmacological basis of using morphine the management of MI. (CU-06M)

Ans.

Role of morphine in myocardial infarction: Morphine provides analgesia in MI. Adequate analgesia is essential not only to relieve distress, but also to lower adrenergic drive and thereby reduce vascular resistance, BP, infarct size and susceptibility to ventricular arrhythmias. IV opiates (initially morphine sulphate 5-10 mg or diamorphine 2.5-5 mg) and antiemetics (initially metoclopramide 10 mg) should be administered and titrated by giving repeated small aliquots until the patient is comfortable.

(IM injections should be avoided because the clinical effect may be delayed by poor skeletal muscle perfusion, and a painful haematoma may form following thrombolytic or anti-thrombotic therapy.)

(Ref: Davidson's-21st/592)

Q. Briefly discuss the drugs mentioning their role in minimizing the imbalance between supply and demand of O₂ to heart. (SU-13Ju)

Ans.

Role of drugs used in IHD:

Drugs	Actions
Glyceryl trinitrate (GTN)	↓ Preload ↓ Afterload ↑ Coronary vasodilatation
Ca Channel blockers - Verapamil - Diltiazem - Nifedipine	↓ Myocardial contractility ↓ Afterload (Nifedipine) ↓ Preload (Verapamil, Diltiazem) - Coronary vasodilatation
β-blockers - Atenolol - Propranolol	↓ Myocardial contractility ↓ HR ↓ O₂ demand
Antiplatelet drugs - Aspirin - Clopidogrel	To prevent thrombus formation

↑ contractility

↓ HR

↑ coronary vasospasm

Q. What is the role of low dose Aspirin on IHD? (SU-06M)

Q. Explain rationale of low dose aspirin in the management of unstable angina? (CU-05J)

Ans.

Rationale of using low dose Aspirin in the management of unstable angina: Activation of platelets is an essential process for arterial thrombosis. Low dose aspirin (75-150 mg/day) acts as an antiplatelet drug. Unstable angina is associated with a high risk of myocardial infarction and death. Low-dose aspirin prevents platelet activation and thus prevents development of coronary artery thrombosis and myocardial infarction and death and should be prescribed for all patients with coronary artery disease indefinitely.

(Ref: Davidson's medicine-22nd)

Q. What are the roles of Ca²⁺-channel blockers in angina?

Q. Explain the anti-anginal effects of verapamil. (SU-17J)

Ans.

Roles of Ca²⁺-channel blockers in angina: Ca²⁺-channel blockers cause the following effects:

1. Coronary vasodilation → Improves O₂ supply to the myocardium → Relief of anginal pain.
2. Vasodilation other than coronary arteries → ↓ Total peripheral resistance → ↓ Afterload → ↓ Cardiac workload → Relief of anginal pain.
3. No actin-myosin coupling → ↓ Force of contraction of contraction → ↓ O₂ requirement of cardiac muscle → Relief of anginal pain.
4. Decreases heart rate and slows the cardiac conduction → ↓ myocardial O₂ demand → Relief of anginal pain.

CCB → Binds to Ca²⁺ channel → Reduces the frequency of opening of Ca²⁺ channel due to depolarization → Long lasting relaxation in smooth

Cardiac muscle
↓ PACE MAKING
↓ AV node conduction velocity

Vasodilation

Vessel-selective Ca²⁺-channel blockers (Amlodipine / Nifedipine) has limited or minimal effect on cardiac conduction or heart rate.

Cardio-selective Ca²⁺-channel blockers (Diltiazem / Verapamil) has less peripheral effects. So they hardly decrease afterload & thereby cardiac workload is uncommonly decreased in case of cardio-selective Ca²⁺-channel blockers.

Q. Justify the combination of nitrates and β-blockers.

Ans.

Nitrates + β-blockers

1. Combined action of the two drugs is additive.
2. One drug minimizes the adverse effects of the other.
3. β-blockers can block the reflex tachycardia produced by nitrates.
4. Nitrates can attenuate the increase in left ventricular EDV associated with β-blocker by increasing venous capacitance.
5. The combination is very useful in exertional angina.

Q. Justify the combination of nitrates and Ca^{2+} channel blocker.

Ans.

Nitrates + Ca^{2+} channel blocker: Combined action of the two drugs is additive.

- **Nitrates:** Decrease preload and afterload.
- **Ca^{2+} channel blocker:** Decrease afterload.
- **Net effect:** Reduction of myocardial O_2 demand.

So, this combination is effective in vasospastic or exertional angina with cardiac failure.

Q. Justify the combination of nitrates, Ca^{2+} channel blocker and β -blockers.

Ans.

Nitrates + Ca^{2+} channel blocker + β -blockers

- **Nitrates:** Decrease preload and afterload.
- **Ca^{2+} channel blocker:** Decrease afterload.
- **β -blockers:** Decrease heart rate and force of contraction.

So, this combination is effective in exertional angina not controlled with two types of anti-anginal drugs.

Q. Compare Propranolol, GTN & Diltiazem as anti-anginal drugs. (CU-17M,12J,09J)

Ans.

Comparison of Propranolol, GTN & Diltiazem as anti-anginal drugs

Traits	Propranolol	GTN	Diltiazem
1. Group	Non-selective β -blocker	Organic nitrate	Cardio-selective Ca^{2+} channel blocker
2. M/A	Acts by decreasing heart rate & force of contraction	Acts by venodilation & arterial dilation	Acts by vasodilation & decreasing force of contraction of heart
3. Use in acute attack	Not suitable	GTN sublingual spray & tablets are used for acute attack	Not suitable
4. Bronchospasm	Occurs; so can't be used in asthma	No	No
5. Dyslipidemia	Occurs	No	No
6. CNS disturbances	Occurs	No	Less
7. Throbbing headache	No	Occurs	Headache may occur but less severe
8. Tolerance	No	Occurs	No
9. Postural hypotension	No	Occurs	No
10. Ankle edema	No	No	Occurs

Q. Compare β blocker, verapamil and diltiazem as anti-anginal drugs. (CU-13J)

Ans.

Comparison of β blocker, verapamil and diltiazem as anti-anginal drugs

Traits	β blocker	Verapamil	Diltiazem
1. ↓ Afterload	No	No	No
2. ↓ Preload	No	Yes	Yes
3. ↓ Myocardial contractility	Yes	Yes	Yes
4. ↓ HR	Yes	Yes	Yes
5. ↓ O_2 demand	Yes	Yes	Yes
6. Relief of angina	Yes	Yes	Yes
7. Use in acute attack	Not suitable	Not suitable	Not suitable
8. Ankle edema	No	Yes	Yes

Drugs for Heart Failure

when heart is unable to pump sufficient blood to meet the needs of the body

Heart failure: Heart failure occurs when cardiac output is inadequate to provide the oxygen needed by the body. It is a highly lethal condition, with a 5-year mortality rate conventionally said to be about 50%. The most common cause of heart failure is coronary artery disease. Two major types of failure may be distinguished. In systolic failure, the mechanical pumping action (contractility) and the ejection fraction of the heart are reduced. In diastolic failure stiffening and loss of adequate relaxation plays a major role in reducing cardiac output and ejection fraction may be normal.

(Ref: Katzung-13th)

Types of heart failure: The left side of the heart is a term for the functional unit of the left atrium and left ventricle, together with the mitral and aortic valves; the right heart comprises the right atrium, right ventricle, tricuspid and pulmonary valves.

1. **Left-sided heart failure (left ventricular failure (LVF)).** There is a reduction in the left ventricular output and/or an increase in the left atrial or pulmonary venous pressure. An acute increase in left atrial pressure may cause pulmonary congestion or pulmonary edema. Patients present with respiratory distress.
2. **Right-sided heart failure.** There is a reduction in right ventricular output for any given right atrial pressure. Causes of isolated right heart failure include chronic lung disease (cor pulmonale), multiple pulmonary emboli and pulmonary valvular stenosis. Patients present with leg edema, ascites etc.
3. **Biventricular heart failure.** Failure of the left and right heart may develop because the disease process (e.g. dilated cardiomyopathy or ischemic heart disease) affects both ventricles, or because disease of the left heart leads to chronic elevation of the left atrial pressure, pulmonary hypertension and right heart failure.

(Ref: Davidson's medicine-22nd)

Cardio-vascular consequences of heart failure:

- Heart failure → Increased venous pressure → Increased capillary filtration → Edema.
- Heart failure → Decreased cardiac output → ↓Blood pressure & ↑sympathetic → (Both of them) decreases renal blood flow → ↑Renin & Angiotensin-II → ↑Aldosterone → ↑Sodium & water retention → Edema.

(Ref: Lippincott's-6th)

Pathophysiology of Cardiac Performance: Cardiac performance is a function of four primary factors:

1. **Preload:** Preload represents the venous return to the ventricles. It is equal to the end diastolic volume. Preload is usually increased in heart failure because of increased blood volume and venous tone. Venodilator drugs (eg, nitroglycerin) reduce preload by redistributing blood away from the chest into peripheral veins.
2. **Afterload:** Afterload is the resistance against which the heart must pump blood and is represented by aortic impedance and systemic vascular resistance. As cardiac output falls in chronic failure, there is a reflex increase in systemic vascular resistance.
3. **Contractility.**
4. **Heart rate.**

(Ref: Katzung-13th)

Q. Outline the pathophysiology of heart failure. (CU-13Ju)

Ans.

Pathophysiology of heart failure

Almost all forms of **heart disease** can lead to **heart failure**. Eg, MI, myocarditis, cardiomyopathy, hypertension, valvular heart disease, ventricular septal defect, arrhythmia.

The primary **signs and symptoms** of all types of heart failure include tachycardia, decreased exercise tolerance, shortness of breath, and cardiomegaly. Peripheral and pulmonary edema (the congestion of congestive heart failure) are often but not always present.

(Ref: Katzung-13th)

↑ Preload
↑ Afterload
↑ HR
⇒ ↑ Heart size
Oedema
Dyspnoea

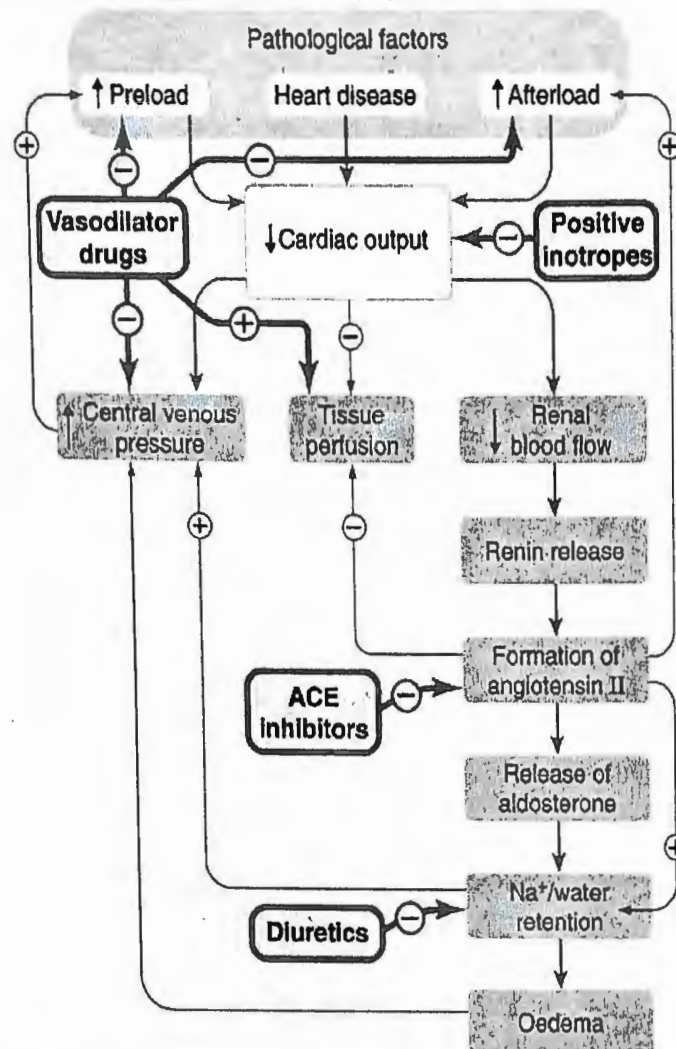


Figure. Pathogenesis of heart failure, and the sites of action of some of the drugs used to treat it.

Q. Describe the compensatory mechanisms that operate following congestive cardiac failure. (CU-16Ju/J,14Ju)

Ans.

Compensatory mechanisms following congestive cardiac failure

1. **Myocardial hypertrophy:** This increase in muscle mass helps maintain cardiac performance. However, after an initial beneficial effect, hypertrophy can lead to ischemic changes, impairment of diastolic filling, and alterations in ventricular geometry.
2. **Remodeling** is the term applied to dilation and other slow structural changes that occur in the stressed myocardium.
3. **Apoptosis:** Ultimately, myocytes in the failing heart die at an accelerated rate through **apoptosis**, leaving the remaining myocytes subject to even greater stress.

(Ref: Katzung-13th)

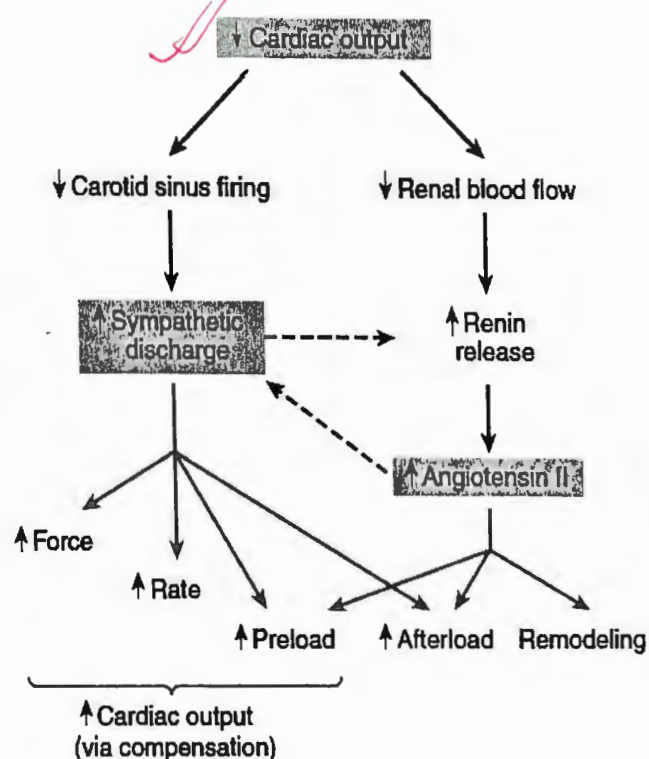


Fig. Some compensatory responses that occur during congestive heart failure.

- Q. List the drugs used in the treatment of heart failure. (DU-10Ju,07J)
 Q. Name the group of drugs that are used for the treatment of cardiac failure. (RU-08Ju)
 Q. Enlist the drugs used in CCF/congestive cardiac failure. (DU-16Ju, CU-06J, RU-04M/J; SU-17J,09/08Ju)
 Q. Name the drug other than digitalis used in CCF. (RU-03J)

Ans.

Classification of drugs for heart failure / Congestive cardiac failure (CCF):

A. According to the effect of the drug:

1. Reduction of preload	- Diuretics - Nitrates
2. Reduction of afterload	Direct acting vasodilators (hydralazine, minoxidil, Na-nitroprusside, diazoxide)
3. Reduction of both preload and afterload	- ACE inhibitors (ramipril, captopril, enalapril, lisinopril) - Angiotensin-II receptor blockers (losartan, valsartan, olmesartan, candesartan, telmisartan) - Beta blockers (Metoprolol, bisoprolol, carvedilol) - Spironolactone
4. Stimulation of myocardium	- Digoxin - Digitoxin - Phosphodiesterase inhibitors (enoximone and milrinone)

(Ref: Bennett & Brown-11th)

B. According to mechanism of action:

(Anti hypertensive to 2022 exam)
CCF, Glycoside, Bagonist, PDE inhibitors

1. Drugs with positive inotropic effects.	
Cardiac glycosides	- Digoxin - Digitoxin - Ouabain
β-agonist	- Dobutamine - Dopamine
PDE inhibitors: Bipyridine <i>phosphodiesterase</i>	- Inamrinone - Milrinone
2. Drugs without positive inotropic effects	
Diuretics	Furosemide
ACE inhibitors	Captopril, Enalapril, Lisinopril, Ramipril
Angiotensin-II receptor blockers	Losartan, Valsartan, Telmisartan
Aldosterone antagonists	Spironolactone
β-blockers	Bisoprolol, Carvedilol, Metoprolol
Vasodilators	Hydralazine and isosorbide dinitrate

(Ref: Katzung-13th edition)

Digoxin + CCB = Cardiotonic

- Q. Describe management of heart failure at different stages. (CU-15Ju)
 Q. Outline the treatment of CCF. (RU-05S,04M)
 Q. Outline the therapeutic approach to congestive heart/cardiac failure/ CCF. (SU-17M,16Ju,11Ju)

Ans.

Treatment of acute left ventricular failure (ALVF): This is a common medical emergency. There are signs of low cardiac output and pulmonary edema (severe respiratory distress).

- Oxygen inhalation.
- IV Furosemide 40-80 mg, is the mainstay of therapy and provides benefit both by a rapid and powerful venodilator effect reducing preload, and by the subsequent diuresis.
- IV morphine or diamorphine, which relieve anxiety and pain and have a valuable venodilator effect.

(Ref: Bennett & Brown-11th)

Management of chronic cardiac failure: Experts have classified HF into four stages, from least severe to most severe.

Stage of heart failure	Treatment options
STAGE A High risk with no symptoms	Risk factor reduction, patient education Treat hypertension, diabetes, dyslipidemia; <u>ACE inhibitors or ARBs in some patients</u>
STAGE B Structural heart disease, no symptoms	<u>ACE inhibitors or ARBs in all patients</u> ; <u>β-blocker in selected patients</u>
STAGE C Structural heart disease, previous or current symptoms	<u>ACE inhibitors and β-blockers in all patients</u> ; <u>aldosterone antagonists and FDC HYD/ISDN in select patients</u> Dietary sodium restriction; diuretics and digoxin

(Ref: Lippincott's-6th/267)

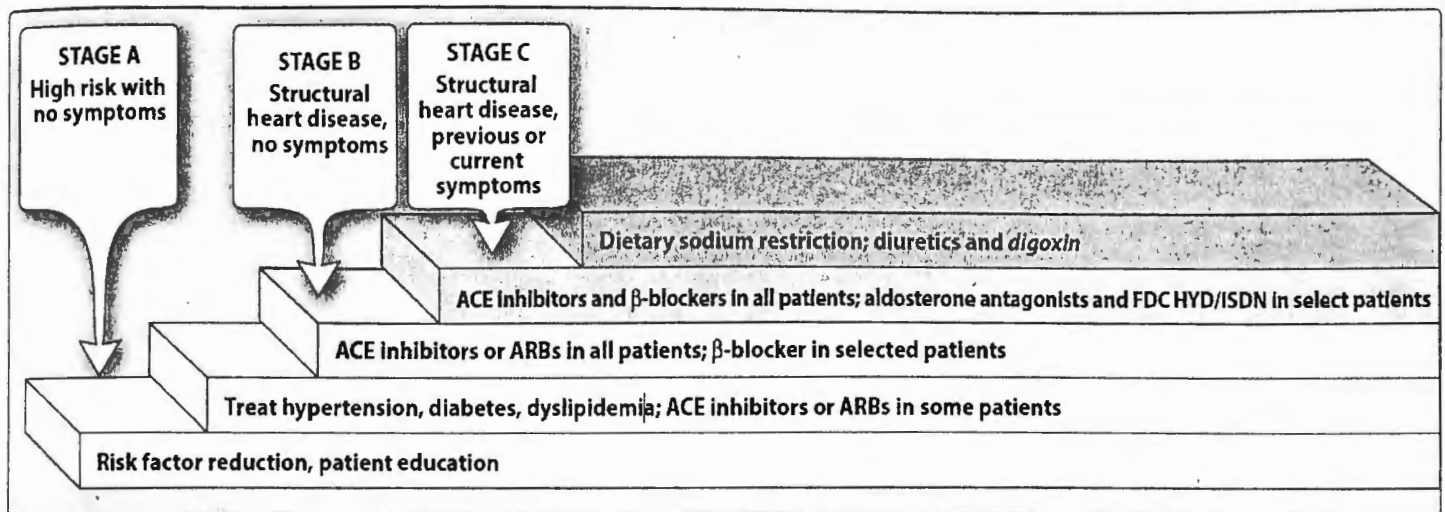


Fig. Treatment options for various stages of HF. FDC = fixed dose combination; HYD = hydralazine; ISDN = isosorbide dinitrate. Stage D (refractory symptoms requiring special interventions) is not shown.

Q. Explain the role of frusemide in heart failure/CCF. (SU-17M,12Ju,09/08Ju,07J,06S)

Ans.

Role of frusemide in heart failure/CCF: Frusemide reduces the accumulation of edema, particularly in the lungs. Reduction of pulmonary vascular congestion with diuretics may actually improve oxygenation and thereby improve myocardial function. Reduction of preload can reduce the size of the heart, allowing it to work at a more efficient fiber length.

(Ref: Katzung-13th)

Q. Explain pharmacological basis of using frusemide in ALVF with pulmonary edema?

Ans.

Pharmacological basis of using frusemide in ALVF with pulmonary edema:

Frusemide
 ↓
 Inhibition of luminal $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ transporter in the thick ascending limb of loop of Henle
 ↓
 Causes increased NaCl, KCl and water excretion through kidney.
 ↓
 Decreases volume of body fluid.
 ↓
 Decreases blood volume
 ↓
 Edema fluid in the alveolar space returns to the blood vessels

↓
Reduction of pulmonary edema.

↓
Relief from respiratory distress.

Cardiac glycosides

Q. Define cardiac glycosides. (RU-50S,03S/J)

Q. Classify cardiac glycosides according to source. (RU-05S,03S/J;SU-06J)

Ans.

Cardiac glycosides: Cardiac glycosides are those glycosides which have the specific action on the failing heart, ie, increase force of contraction and decrease heart rate in a failing heart.

Classification: 3 types of cardiac glycosides-

1. Plant origin: from the leaves or seeds of plant.	▪ Digoxin ▪ Digitoxin ▪ Ouabain ▪ Gitoxin
2. Animal origin: Skin glands of toad.	▪ Bufotoxin
3. Synthetic	▪ Digoxigenin

Nice to know

Chemical structure of cardiac glycoside: Cardiac glycosides consist of –

1. **Sugar part (Glycone portion):** Connected to carbon 3 of the steroid nucleus.
2. **Non-sugar part (Aglycone portion):**
 - A steroid nucleus
 - A lactone ring at the 17 position of steroid nucleus.

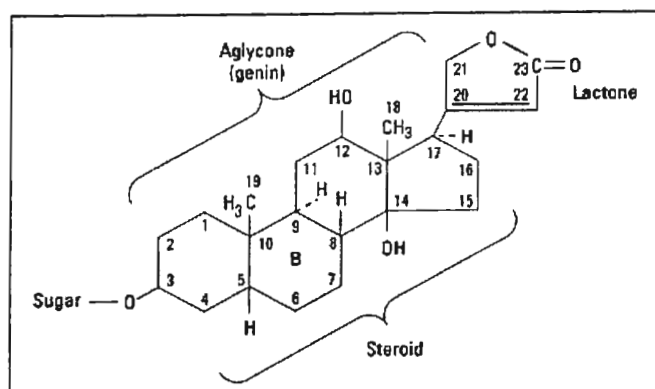


Fig. Structure of cardiac glycoside

Q. Write down pharmacological properties of digoxin. What factors potentiate its action? (SU-02J)

Ans.

Pharmacological properties of digoxin:

A. **Sugar / glycone part:** This portion is responsible for pharmacokinetic properties.

1. Lipid soluble
2. Helps in absorption
3. Increase potency and duration of action of cardiac glycosides
4. Facilitates the attachment of drug to the cardiac muscles
5. Protects the other part from enzymatic destruction

B. **Non sugar / aglycone part:** This portion is responsible for pharmacodynamic properties.

1. **Steroid nucleus:** Mineralocorticoid effects (hypokalemia & gynecomastia).

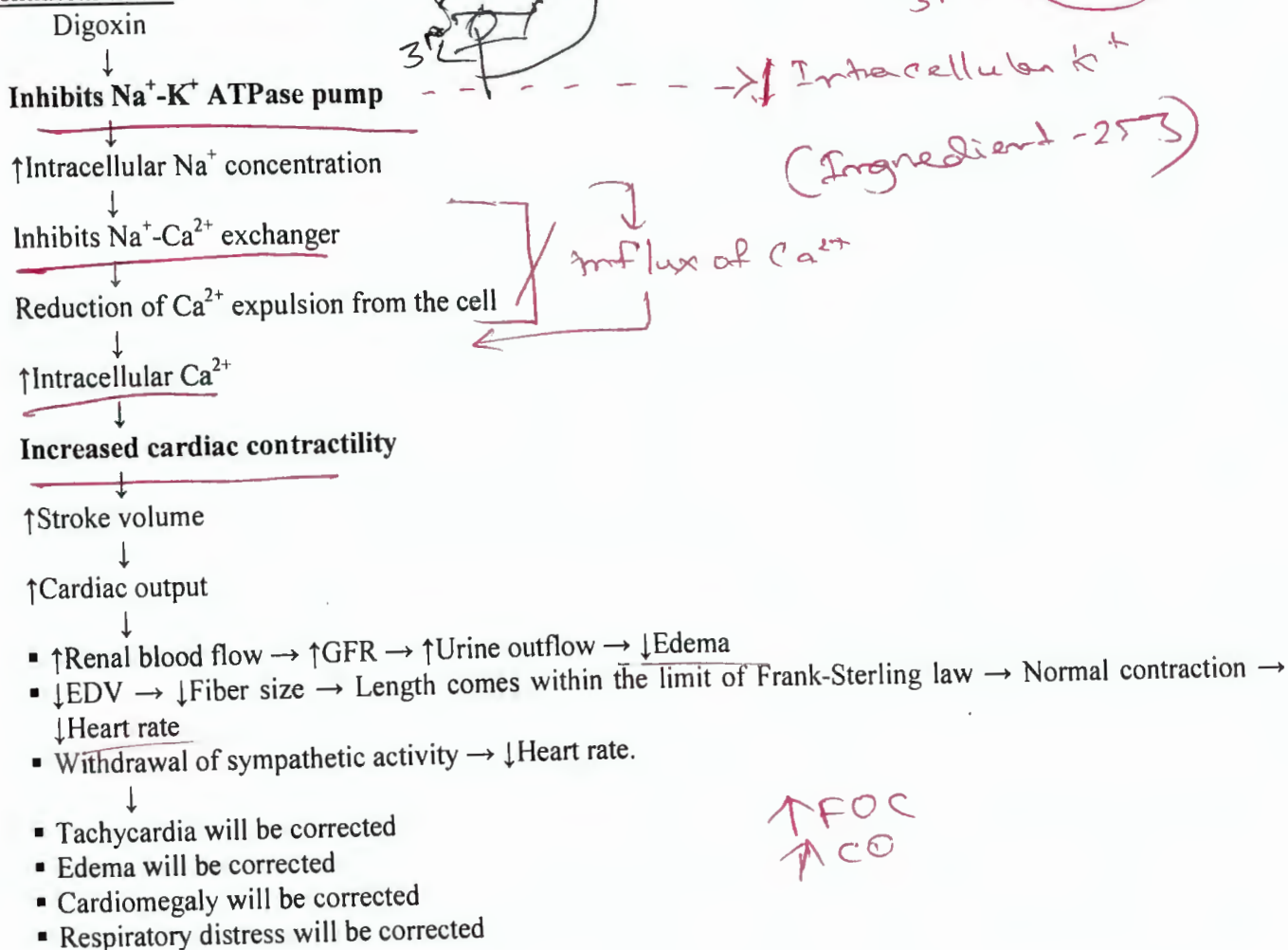
2. Lactone ring: Essential for cardiotonic action.
3. OH group: Responsible for prolong cardiotonic action & absorption.

- Q. Describe briefly the mechanism of action of digoxin in failing heart. (DU-10Ju, CU-17J, SU-15J)
 Q. How does digitalis act in failing heart? (DU-03M, RU-16J, 13J, SU-04M)
 Q. How does digoxin help in failing heart? (RU-15J)
 Q. How digoxin helps in heart failure? (RU-13J, 11J, 10J, SU-13Ju)
 Q. Discuss the role of digoxin in the treatment of CCF. (SU-17J, 16Ju, 12J, 11Ju, 10Ju, 09Ju, 08J)
 Q. How does digoxin act in CCF? (SU-06S)
 Q. How does digoxin produce negative chronotropic effect in a patient with CCF? (SU-08Ju, CU-00M)
 Q. What are the beneficial roles of digoxin in heart failure? (CU-06S; RU-17J; SU-08Ju)
 Q. Outline the role/benefits of digoxin in the management of heart failure. (CU-15J, 09J)
 Q. Narrate the pharmacological effects of digoxin on failing heart. (RU-03S; SU-07Ju)
 Q. Write the M/A of digitalis. (SU-16J)
 Q. How K and Ca modify the action of digitalis? (SU-06M)

Ans.

Roles of digoxin in heart failure:

Mechanical effect:



Electrical effect:

1. **SA node** → Decrease rate.
2. **Atrial muscle** → Decrease refractory period.
3. **AV node** → Decrease conduction velocity, increase refractory period.
4. **Purkinje system** → Slight decrease refractory period.
5. **Ventricular muscles** → Decrease refractory period.
6. **Electrocardiogram** → Increase PR interval, decrease QT interval.

(Ref: Katzung-13th)

Q. Write the pharmacological properties of cardiac glycosides.

Q. Write the pharmacological effects of digoxin. (DU-12Ju)

Q. Write the effects of cardiac glycosides on heart.

Ans.

Pharmacodynamic properties/effects of cardiac glycosides / digoxin:

1. Inhibits of $\text{Na}^+ - \text{K}^+$ ATPase pump
 2. Cardio-selective parasympathomimetic activity
 3. Cardio-selective sympathomimetic activity
 4. Amine neurotransmitter reuptake inhibitors (only for ouabain)
1. **Inhibitors of $\text{Na}^+ - \text{K}^+$ ATPase pump:** By this action, cardiac glycosides play role in heart failure.
 2. **Cardio-selective parasympathomimetic activity:** Occurs in normal therapeutic dose.
 - $\downarrow$ H.R
 - $\downarrow$ Contractility
 - $\downarrow$ Automaticity
 - Delayed AV conductivity: Delayed AV conductivity seems to be interruption or cut up the connection between atria and ventricle. That is, all atrial impulse cannot reach to the ventricle even atria is generating impulse in high rate. For this property, cardiac glycosides can be used in atrial fibrillation or atrial flutter (atrial beat: 240-300/mm).
 3. **Cardio-selective sympathomimetic activity:** Occurs in overdose of cardiac glycosides.
 - $\uparrow$ H.R
 - $\uparrow$ Contractility
 - $\uparrow$ Rhythmicity ($\uparrow$ Atrial depolarization in regular interval)
 - $\uparrow$ Automaticity
 - Atrium is controlled by dual nerve supply both sympathetic & parasympathetic. But ventricle is controlled almost solely by sympathetic nerve. As a result toxic effect of cardiac glycosides (e.g. ectopic focus) occurs mainly over ventricle which leads to ventricular fibrillation. In ventricular fibrillation, ventricle will not be able to fill sufficiently & it will contract as an empty cavity
 4. **Amine neurotransmitter reuptake inhibitors:**
 - In autonomic nervous system: Indirectly acting adrenergic drug; e.g. TCA
 - In cardiovascular system: Ouabain

Q. Explain the interaction of digoxin with common electrolytes. (DU-07J)

Q. How does Ca^{2+} & K^+ modify the effects of digoxin? (SU-06S, RU-06J)

Ans.

Interaction of digoxin with common electrolytes

1. **Interaction of digoxin with K^+ :** Potassium and digitalis interact in two ways. First, they inhibit each other's binding to $\text{Na}^+ - \text{K}^+$ ATPase; therefore, hyperkalemia reduces the enzyme-inhibiting actions of cardiac glycosides, whereas hypokalemia facilitates these actions. Second, abnormal cardiac automaticity is inhibited by hyperkalemia. Moderately increased extracellular K^+ therefore reduces the effects of digitalis, especially the toxic effects.

Hypokalemia ($\downarrow \text{K}^+$) $\rightarrow$ $\uparrow$ Cardiac glycoside activity $\rightarrow$ $\uparrow$ Frequency & intensity of adverse effects. To neutralize / decrease the adverse effects, potassium supplementation is needed.

Co-administration of Frusemide & Digoxin: Frusemide causes hypokalemia & potentiate the toxicity of digoxin.

2. **Interaction of digoxin with Ca^{2+} :** Calcium ion facilitates the toxic actions of cardiac glycosides by accelerating the overloading of intracellular calcium stores that appears to be responsible for digitalis-induced abnormal automaticity. **Hypercalcemia therefore increases the risk of a digitalis-induced arrhythmia.**

$\downarrow \text{K}^+, \uparrow \text{Ca}^{2+}, \downarrow \text{Mg}^{2+} \rightarrow \uparrow \text{Digoxin activity}$

3. **Interaction of digoxin with Mg^{2+} :** The effects of magnesium ion appear to be opposite to those of calcium.

These interactions mandate careful evaluation of serum electrolytes in patients with digitalis-induced arrhythmias.

(Ref: Katzung-13th)

Q. Which factors may precipitate digoxin toxicity? (SU-14Ju)

Ans.

Factors that may precipitate digoxin toxicity

1. Hypokalemia
2. Hypomagnesemia
3. Hypercalcemia

Diuretics to 2015
Digoxin from frusemide
with K⁺ supplement
from
(massive edema?)

Q. Which diuretic can be used in the combination with digoxin? (CU-00S)

Q. Discuss the role of digoxin & frusemide in the management of CCF. (SU-12Ju)

Ans.

Digoxin + Diuretic:

- K^+ losing diuretics (eg, frusemide, hydrochlorothiazide) will cause hypokalemia which will lead to digoxin toxicity.
- But K^+ sparing diuretic, eg, spironolactone will cause hyperkalemia which will reduce toxic effects of digoxin. So **spironolactone** can be used in the combination with digoxin.

Q. Justify the combination- Hydrochlorothiazide & triamterene in a CCF case treated with digoxin

Ans.

When hydrochlorothiazide and triamterene are used together, there is no hypokalemia, because triamterene is a potassium sparing drug. So, there is no digitalis toxicity.

Q. Justify the combination of using Digoxin & Lisinopril in the Rx of congestive cardiac failure (CCF). (SU-14J,09J,07J,06M)

Ans.

Combination of Digoxin & Lisinopril in CCF: Lisinopril is an ACE inhibitor and it causes hyperkalemia. Hyperkalemia reduces the toxic effects of digoxin. Both drugs help to improve heart failure.

Q. Discuss the role of Digoxin & Losartan in the management of CCF. (SU-12Ju,08J)

Ans.

Role of digoxin & losartan in the management of CCF: Losartan cause hyperkalaemia & hyperkalaemia reduces the toxic effects of digoxin. Both drugs help to improve heart failure.

Q. Mention the consequences when digoxin is used along with propranolol. (RU-16J)

Ans. Digitalis + β -blocker / propranolol $\rightarrow$ More bradycardia $\rightarrow$ Heart block.

Nice to know

Other drug interaction:

1. **Digitalis + Steroids:** Steroids cause hypokalemia which potentiates digoxin toxicity.
2. **Digitalis + Thiazide diuretics:** Thiazide diuretics cause hypokalemia which potentiates digoxin toxicity.
3. **Digitalis + β -blocker** $\rightarrow$ More bradycardia $\rightarrow$ Heart block.
4. **Digitalis + Ca^{2+} channel blocker** $\rightarrow$ Verapamil & nifedipine increases free digitalis in the blood by competing for the same binding site of plasma protein $\rightarrow$ Digitalis toxicity.
5. **Digitalis + IV infusion of Ca^{2+} :** Death of pt. immediately.
6. **Digitalis + Quinidine** $\rightarrow$ $\uparrow$ conc. of free digitalis in the blood due to replacement from tissue binding and impairment in renal excretion of digitalis $\rightarrow$ Digitalis toxicity.

Q. What are the indications of Digoxin? (SU-11J,06J, RU-15J,13J,06J)

Ans.

Indication of Digoxin:

1. Heart failure / CCF
2. Cardiac arrhythmia:
 - Atrial fibrillation
 - Atrial flutter
 - Paroxysmal Supraventricular Tachycardia (SVT)

Q. Mention the adverse effects of cardiac glycosides. (SU-07/06J, CU-02S)
Q. Write down the adverse effects of digoxin/digitalis. (DU-12/10Ju, RU-04M, SU-16J,13J)
Q. Write down the cardiac adverse effects of digoxin. (CU-15J)
Q. Outline the risks of digoxin in the management of heart failure. (CU-13Ju,09J)
Q. What are the signs of Digoxin toxicity? (CU-17J,16J)
Q. Categorize cardio-toxicity of digitalis according to serum digitalis concentration. (CU-15Ju)
Q. Mention two adverse effects of digoxin. (RU-17J)

Ans.

Adverse effects of Digoxin:**A. GIT adverse effects: (Most frequent)**

1. Anorexia
2. Nausea
3. Vomiting
4. Diarrhea

B. Cardiac adverse effects:

1. Bradycardia (earliest adverse effect.)
5. Bigeminy
6. Trigeminy
7. Ectopic focus leading to ventricular fibrillation (in toxic dose)

C. CNS adverse effects:

1. Insomnia
2. Disorientation
3. Visual hallucination leading to color blindness (due to increased depolarization in rods and cones)
4. Agitation
5. Convulsion
6. Steroid psychosis for chronic use: Hallucination, Delusion
7. Vomiting: By stimulating vomiting centre at chemoreceptor trigger zone (CTZ)

D. Miscellaneous:

1. Hypokalemia
2. Gynecomastia in male (due to steroid nucleus)
3. Galactorrhea in female

Q. What are the early adverse effects of digoxin. (RU-13J,11J, SU-11J)

Q. What are the early toxicities of digoxin. (RU-15J)

Ans.

Early adverse effects of digoxin

1. Bradycardia (earliest adverse effect.)
2. GIT adverse effects (Most frequent)
3. Ectopic focus
4. Hypokalemia

Q. Mention the contraindications of cardiac glycosides / digoxin. (DU-98M, RU-04M,03J)

Ans.

Contraindications of cardiac glycosides / digoxin:

1. Ventricular fibrillation

2. Ventricular flutter
3. A-V heart block
4. Hypokalemia
5. Hypercalcemia
6. Liver failure
7. Renal failure
8. Constrictive pericarditis
9. Sinus tachycardia
10. Pericardial effusion
11. Hypothyroidism

Q. Compare digoxin and digitoxin. (SU-11J)

Ans.

Comparison between digoxin & digitoxin

Traits	Digoxin	Digitoxin
1. Lipid solubility	Medium	High
2. Route of administration	Oral / IV	Oral
3. Oral bioavailability	60 - 80 %	> 90 %
4. Onset of action	15 - 30 minutes	½ hour - 2 hours
5. Duration of action	2 - 6 days	2 - 3 weeks
6. Plasma $t_{1/2}$	40 hours	5 - 7 days
7. Plasma protein binding	25%	95%
8. Metabolism	Medium	High
9. Distribution	Widely distributed including CNS	Widely distributed including CNS
10. Therapeutic index (TI)	Narrow	Narrow
11. Excretion	Kidney	Liver
12. Enterohepatic recycling	Absent	Present

(Ref: Tripathi-6th/497)

Role of ACEI / ARB in heart failure

Q. Discuss the role of ACEI in chronic heart failure / CCF. (DU-16Ju, CU-16Ju, RU-15Ju, SU-16Ju)

Q. How does captopril correct CCF? (DU-08Ju; CU-04M, RU-14Ju, 12Ju, 11J)

Q. Explain the rationale of using captopril in CCF. (CU-13J, 07Ju; RU-08J, 06M)

Q. Explain the benefits of captopril in the treatment of CCF. (CU-17M, 12J, 09/08Ju; RU-13Ju)

Q. Explain the role of lisinopril in heart failure. (SU-17J, 10Ju)

Q. Outline the role of ramipril in congestive heart failure. (SU-14Ju)

Q. Justify preference of olmesartan to verapamil in CCF. (SU-15Ju)

Ans.

Role of ACEI and ARB in the management of CCF / heart failure: ACEI reduces both preload & afterload in CCF. Moreover only ACEI & Angiotensin-II receptor blockers alter the course of pathological changes in CCF. They afford symptomatic benefits as well as disease modifying benefits by retarding / reversing **ventricular hypertrophy, myocardial cell apoptosis & remodeling**. There are prognostic benefits of ACEI & ARBs have established in mild to severe CCF as well as in patients with asymptomatic systolic dysfunction.

ACE inhibitors retard the progression of LV systolic dysfunction & prolong survival of chronic HF patient. So, ACE inhibitors are the 1st line drugs in all patients with symptomatic or asymptomatic LV dysfunction unless they are contraindicated. A diuretic, β -blocker with or without digitalis may be added according to need.

(Ref: Tripathi-6th/504, 505)

Q. Outline the risks of captopril in the treatment of CCF. (CU-17M)

Ans. Write adverse effects of captopril from above.

Q. Describe the mechanism of action of captopril/ ACE inhibitors in CCF.

Ans.

Mechanism of action of captopril/ ACE inhibitors in CCF:

ACE inhibitors / Captopril / Lisinopril / Ramipril

↓
Inhibits angiotensin converting enzyme (ACE)

↓
Inhibition of conversion of angiotensin-I into angiotensin-II

↓
↓Angiotensin-II level

↓
↓Angiotensin-II-mediated effects

- No direct vasoconstriction → Vasodilation → ↓Preload
- ↓Sympathetic outflow → ↓Heart rate → ↓Cardiac work
- ↓Aldosterone production → No retention of Na & H₂O → ↓Blood volume → ↓Edema and ↓Peripheral resistance → ↓Afterload
- ↑Bradykinin level → Vasodilatation → ↓Preload

↓
When preload and afterload decrease, cardiac workload also decreases and **REMODELLING & hypertrophy of the heart** is prevented.

(Ref: Lippincott's-6th)

Q. Rationalize the combination use of losartan & frusemide in CCF. (SU-13J)

Ans.

Rationale of drug combination of losartan & frusemide in CCF:

- Losartan is an ARB drug which causes hyperkalemia. On the other hand, frusemide causes hypokalemia. So when these two drugs are used in combination, K⁺ homeostasis remains unaltered.
- Both drugs have beneficial role in CCF. Losartan reduces both preload & afterload in CCF. Frusemide reduced preload. Thus, combination use of these two drugs has synergistic effect in CCF.

Q. Compare digoxin and captopril as drugs for congestive cardiac failure. (CU-11J)

Ans.

Comparison between digoxin and captopril as drugs for congestive cardiac failure

Traits	Digoxin	Captopril
1. Mechanism	Inhibits Na ⁺ -K ⁺ ATPase pump	Inhibits angiotensin converting enzyme
2. Effects on perfusion	Increases perfusion of other organs.	No effect.
3. Cardiac remodeling	No effect	Prevents remodelling & hypertrophy of the heart.
4. Cardiac arrhythmia	Can occur which may be fatal.	Uncommon
5. Effects on K ⁺ level	Hypokalemia	Hyperkalemia
6. Gynecomastia	Occurs	Does not occur
7. Nausea & vomiting	Common	Uncommon
8. Dry cough	Does not occur	Occurs

β -blockers in CCF

Q. Discuss the role of β -blockers in heart failure. (SU-13Ju)

Q. Outline the role of carvedilol in congestive heart failure. (SU-17M, 14Ju)

Ans.

Role of β -blockers in heart failure: When initiated in standard doses, β -blockers may precipitate acute-on-chronic heart failure, but when given in small incremental doses under carefully monitored conditions, they can-

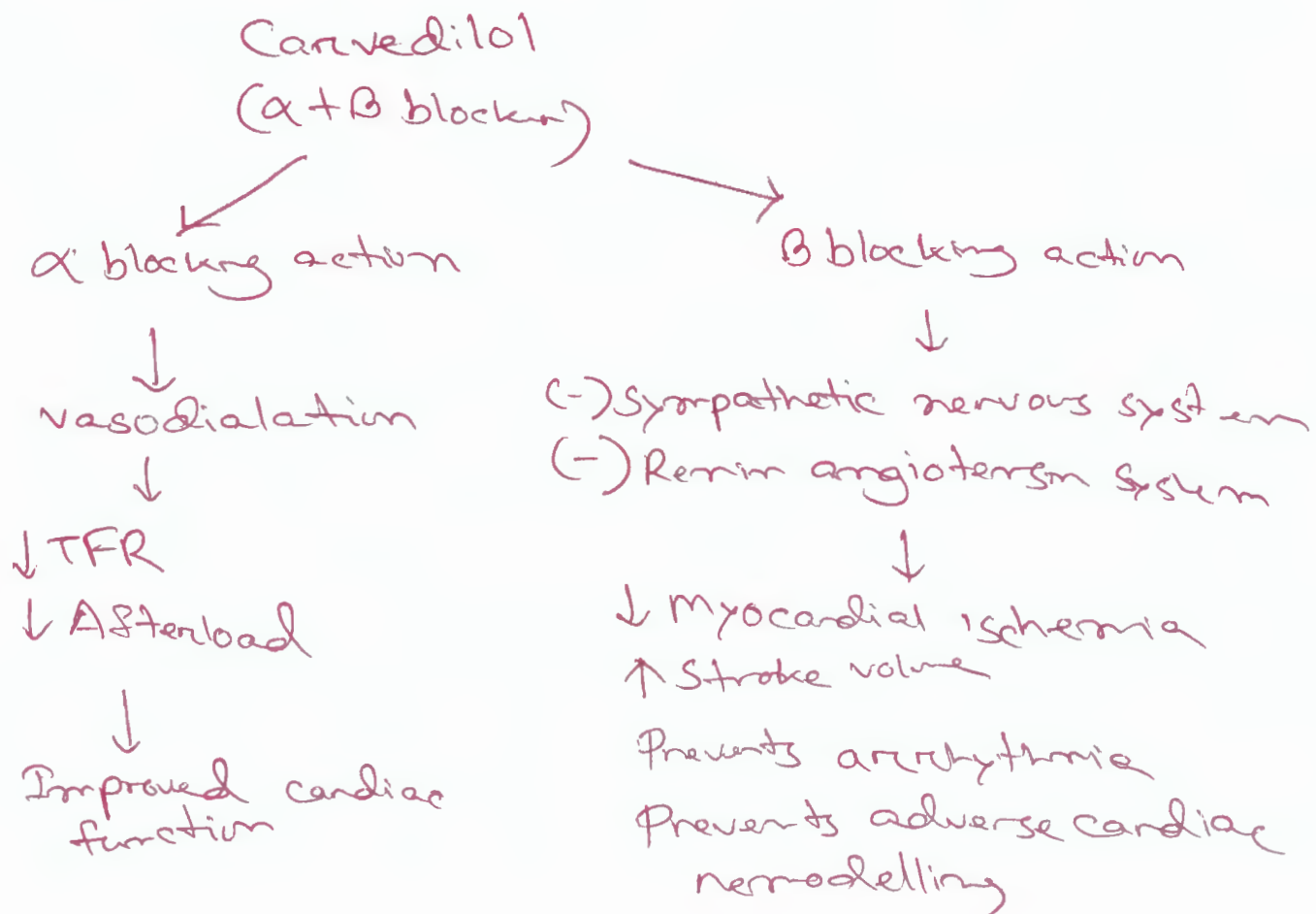
1. Reduce the risk of arrhythmias and sudden death.
2. Increase ejection fraction, improve symptoms, reduce the frequency of hospitalization and reduce mortality in patients with chronic heart failure.

(Ref: Davidson's medicine-22nd)

Studies with **bisoprolol**, **carvedilol**, and **metoprolol** showed a reduction in mortality in patients with stable severe heart failure. The probable mechanism of the beneficial action of β blockade include-

1. Reduce the adverse effects of high concentrations of catecholamines (including apoptosis).
2. Up-regulation of β -receptors.
3. Decreased heart rate.
4. Reduced remodeling through inhibition of the mitogenic activity of catecholamines.

(Ref: Katzung-13th)



Anti-arrhythmic drugs

Types of cardiac tissue: There are broadly two types of cardiac tissue.

1. **Ordinary myocardial (atrial and ventricular) muscle**, responsible for the pumping action of the heart.
2. **Specialized conducting tissue** that initiates the cardiac electrical impulse and determines the order in which the muscle cells contract.

The important property of being able to form impulses spontaneously is called *automaticity* and is a feature of certain parts of the conducting tissue, e.g. the sinoatrial (SA) and atrioventricular (AV) nodes.

(Ref: Bennet & Brown-11th)

Action potential of cardiac muscle and conducting tissues:

Phases	Stages of action potential	Causes
Phase 0	Depolarization	Fast influx of Na^+ by Na^+ channels
Phase 1	Initial rapid repolarization	Closure of Na^+ channels and outflow of K^+ ions by K^+ channels.
Phase 2	Plateau (delay in repolarization)	Caused mainly by a slow influx of Ca^{2+} through voltage-gated Ca^{2+} channels ('long-opening' or L-channels).
Phase 3	Late rapid repolarization	Closure of the Ca^{2+} channels and K^+ efflux through various types of K^+ channels
Phase 4	Resting membrane potential (For cardiac muscle cell)	
	Pacemaker potential (For conducting tissues)	Influx of K^+ and efflux of Na^+ and Ca^{2+}

(Ref: Bennett & Brown-11th+Ganong-24th)

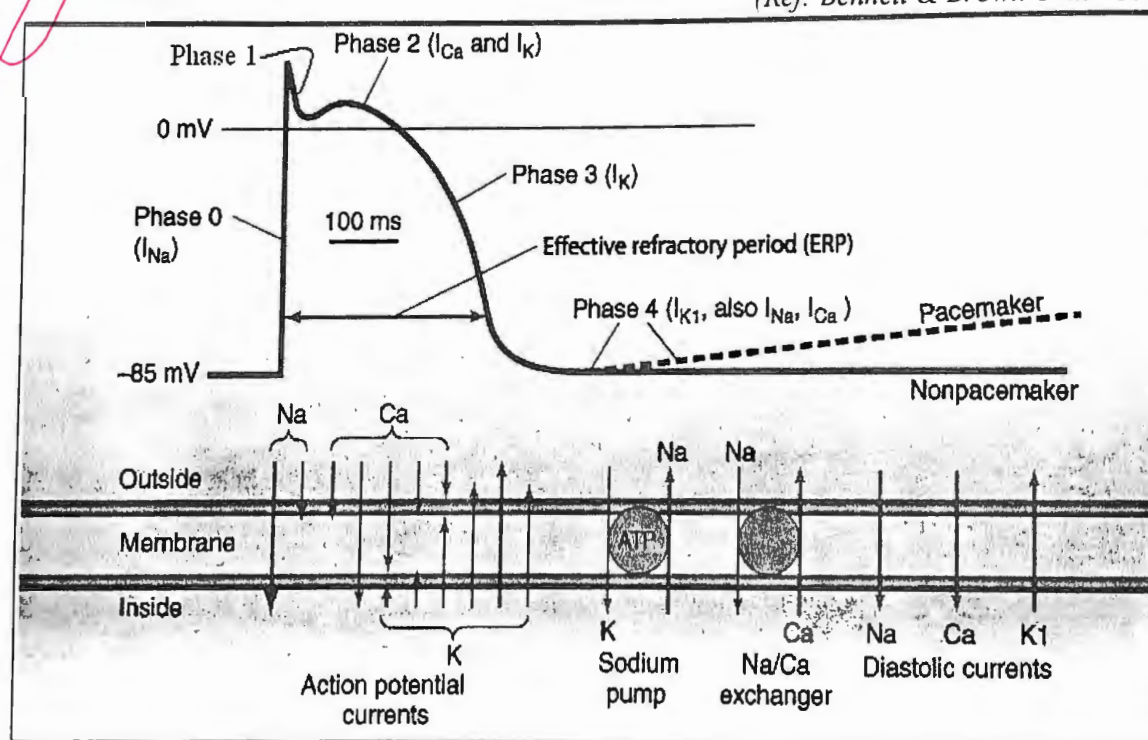


Fig. Action potential (AP) in a typical Purkinje or ventricular cardiac cell. In non-pacemaker cells, the outward potassium current during phase 4 is sufficient to maintain a stable negative resting potential as shown by the solid line at the right end of the tracing. In pacemaker cells, however, the potassium current is smaller and the depolarizing currents (sodium, calcium, or both) during phase 4 are large enough to gradually depolarize the cell during diastole (dashed line).

Refractory period: In phases 1 and 2 the cell is in an **absolutely refractory** state and is incapable of responding further to any stimulus but during phase 3, the **relative refractory period**, the cell will depolarize again if a stimulus is sufficiently strong.

(Ref: Bennett & Brown-11th)

Cardiac arrhythmia: Arrhythmia means abnormalities in impulse generation or conduction or both in the conducting tissue of heart.

Mechanism of arrhythmias: Most cardiac arrhythmias are probably due either to:

1. **Impaired conduction** in part of the system leading to the formation of **re-entry circuits** (> 90% of tachycardia) or
2. **Altered rate of spontaneous discharge** in conducting tissue. Some ectopic pacemakers appear to depend on adrenergic drive.

(Ref: Bennett & Brown-11th)

Types of arrhythmia:

1. **Sinus arrhythmia:** Sinus bradycardia, Sinus tachycardia
2. **Atrial fibrillation:** Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. Atria beat rapidly, but in an uncoordinated and ineffective manner. The ventricles are activated irregularly at a rate determined by conduction through the AV node. This produces the characteristic 'irregularly irregular' pulse. The ECG shows normal but irregular QRS complexes; there are no P waves but the baseline may show irregular fibrillation waves.
3. **Atrial flutter:** The atrial rate is approximately 300/min. It is usually associated with 2:1, 3:1, or 4:1 atrioventricular block (with corresponding heart rates of 150, 100, 75).
4. **Supraventricular tachycardia (SVT):** Tachycardia with narrow QRS complex.
5. **Ventricular ectopic beats**
6. **Ventricular tachycardia (VT):** Tachycardia with very broad QRS complexes.
7. **Ventricular fibrillation**
8. **Torsades De pointes:** This form of polymorphic ventricular tachycardia occurs due to prolonged QT interval.

(Ref: Davidson's-22nd edition)

Q. Classify anti-arrhythmic drugs. (CU-08J,06S, RU-08J, SU-13Ju,11J)

Ans.

Classification of anti-arrhythmic drugs:

1. **Class-I drugs:** They are voltage sensitive Na^+ -channel blockers.

Class IA	▪ Prolong the action potential duration (APD) by slowing phase 0 depolarization. ▪ Increase ventricular effective refractory period. ▪ Dissociate from the channel with intermediate kinetics.	• Quinidine • Procainamide • Disopyramide
Class IB	▪ Shorten the APD in some tissues of the heart by shortening phase 3 repolarization. ▪ Dissociate from the channel with rapid kinetics.	• Lidocaine • Mexiletine
Class IC	▪ Markedly slow phase 0 depolarization. ▪ Cause marked conduction slowing. ▪ Have minimal effects on the APD and ventricular effective refractory period. ▪ Dissociate from the channel with slow kinetics.	• Flecainide • Encainide • Moricizine • Propafenone

2. **Class-II drugs:** They are β -adrenoceptor blocker. They suppress phase 4 depolarization, thus depressing automaticity, prolonging AV conduction, and decreasing heart rate and contractility.

1. Esmolol
2. Metoprolol
3. Propranolol
4. Pindolol
5. Sotalol
6. Atenolol

3. **Class-III drugs:** They are voltage sensitive K^+ channel blocker and thus diminish efflux of K^+ during repolarization of cardiac cells. They prolong phase-3 repolarization in ventricular muscle fiber.

1. Amiodarone
 2. Dronedarone
 3. Sotalol
 4. Dofetilide
 5. Ibutilide
4. **Class-IV drugs:** They are voltage sensitive **Ca²⁺ channel blocker**. They decrease Ca²⁺ influx, resulting in decreased rate of phase 4 spontaneous depolarization. They slow conduction in tissues that are dependent on calcium currents, eg, SA node, AV node.
- Verapamil
 - Diltiazem
5. **Miscellaneous Antiarrhythmic Agents:**
- Digoxin
 - Adenosine
 - Magnesium
 - Potassium

(Ref: Lippincott's-5th/207-217, Katzung-12th edition)

Q. Justify the use of atenolol as anti-arrhythmic. (SU-15J)

Ans.

Use of atenolol as anti-arrhythmic: Atenolol suppress phase 4 depolarization, thus depressing automaticity, prolonging AV conduction, and decreasing heart rate and contractility.

Q. Name the commonly used anti-arrhythmic drugs. (RU-08J)

Ans.

Commonly used anti-arrhythmic drugs:

1. Amiodarone
2. Adenosine
3. Metoprolol
4. Lidocaine
5. Propafenone
6. Carvedilol
7. Diltiazem
8. Verapamil

Quinidine

Q. Discuss the mechanism of action of quinidine. (CU-08J)

Ans.

Mechanism of action of quinidine:

1. Quinidine → Voltage sensitive Na⁺ channel blocker → Block rapid inflow of Na⁺, thus slowing the rapid upstroke during phase-0 depolarization → Prolong the action potential duration (APD) and increase ventricular effective refractory period → Antiarrhythmic effect.
2. Quinidine → Membrane stabilizing activity → ↑Threshold level → Limits the responsiveness to excitation of cardiac cells → Antiarrhythmic effect.
3. Quinidine also decreases the slope of phase 4 spontaneous depolarization.

(Ref: Lippincott's-5th/211)

Q. Discuss the adverse effects of quinidine. (CU-08J)

Ans.

Adverse effects of quinidine:

A. Cardiac Effects

1. Exacerbation of arrhythmia

2. Ventricular tachycardia
3. SA or AV block or asystole
4. Excessive QT interval prolongation
5. Induction of Torsades de pointes arrhythmia.

B. Extracardiac Effects

1. GIT side effects of diarrhea, nausea, and vomiting are observed commonly.
2. A syndrome of headache, dizziness, disorientation, psychosis, and tinnitus (**cinchonism**) is observed at toxic drug concentrations.
3. Idiosyncratic or immunologic reactions, including thrombocytopenia, hepatitis, angioneurotic edema, and fever, are observed rarely.

(Ref: Lippincott's-5th/212; Katzung-12th/238-239)

Lidocaine

Q. Briefly explain the anti-arrhythmic action of lidocaine. (SU-02J)

Ans.

Anti-arrhythmic action of lidocaine:

1. Lidocaine shortens the duration of action potential in some tissues of the heart by shortening phase 3 repolarization.
2. Lidocaine suppresses arrhythmias caused by abnormal automaticity.
3. It abolishes ventricular re-entry.
4. Lidocaine blocks activated and inactivated sodium channels with rapid kinetics which result in the selective depression of conduction in depolarized cells.

(Ref: Lippincott's-5th/213, Katzung-12th/240)

Q. Write down the adverse effects of lidocaine. (RU-08J)

Ans.

Adverse effects of lidocaine:

A. **Cardiac:** Lidocaine is one of the least cardiotoxic of the currently used sodium channel blockers.

1. Proarrhythmic effects and ventricular arrhythmias are uncommon with lidocaine use.
2. In large doses, it may cause hypotension.

B. **Extracardiac:** Lidocaine's most common adverse effects—like those of other local anesthetics—are **neurologic:**

1. Paresthesias
2. Tremor
3. Nausea of central origin
4. Lightheadedness
5. Hearing disturbances
6. Slurred speech, and
7. Convulsions.

These occur most commonly in elderly or otherwise vulnerable patients or when a bolus of the drug is given too rapidly. The effects are dose-related and usually short-lived; seizures respond to intravenous diazepam. In general, if plasma levels above 9 mcg/mL are avoided, lidocaine is well tolerated.

(Ref: Katzung-12th/240)

Q. Write down mechanism of action of propranolol. (CU-06S)

Ans.

Mechanism of action of propranolol as an anti-arrhythmic drug: Propranolol is a non-selective β -blocker. It suppresses phase 4 depolarization, thus depressing automaticity, prolonging AV conduction, and decreasing heart rate and contractility.

Amiodarone

Q. Write down mechanism of action and adverse effects of amiodarone.

Ans.

Mechanism of action of amiodarone:

1. Amiodarone is a voltage sensitive K^+ channel blocker

↓
Diminish efflux of K^+ during repolarization of cardiac cells

↓
Prolong phase-3 repolarization in ventricular muscle fiber

↓
Prolongation of refractoriness

↓
Prevent reentry circuit

↓
Anti-arrhythmic effect.

2. Amiodarone also significantly blocks inactivated sodium channels.
It also has weak adrenergic and calcium channel blocking actions.

↓
Slowing of the heart rate and AV node conduction.

The broad spectrum of actions may account for its relatively high efficacy.

(Ref: Lippincott's-6th; Katzung-13th)

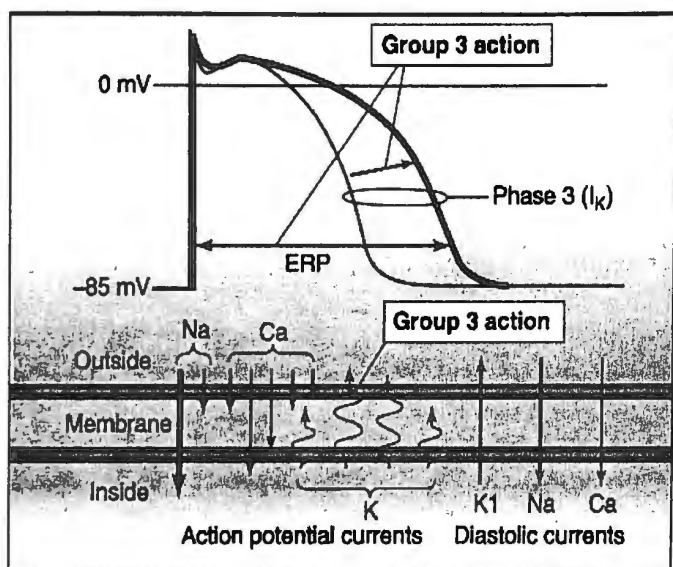


Fig. Schematic diagram of the effects of group 3 agents (eg, amiodarone). All group 3 drugs prolong the AP duration in susceptible cardiac cells by reducing the outward (repolarizing) phase 3 potassium current (I_K , wavy lines). The main effect is to prolong the effective refractory period (ERP).

Adverse effects of Amiodarone:

Cardiac: Symptomatic bradycardia and heart block in patients with preexisting sinus or AV nodal disease.

Extracardiac: Amiodarone accumulates in many tissues, including the heart, lung, liver, and skin, and is concentrated in tears.

1. Interstitial pulmonary fibrosis (*most important adverse effect*)
2. Hepatitis
3. Photodermatitis
4. Gray-blue skin discoloration in sun-exposed areas, eg, the malar regions.
5. Asymptomatic corneal microdeposits
6. Halos develop in the peripheral visual fields of some patients.
7. Optic neuritis → blindness.
8. Hypothyroidism
9. Hyperthyroidism.

10. Tremor
11. Ataxia
12. Neuropathy
13. Muscle weakness.

(Ref: Lippincott's-6th; Katzung-13th)

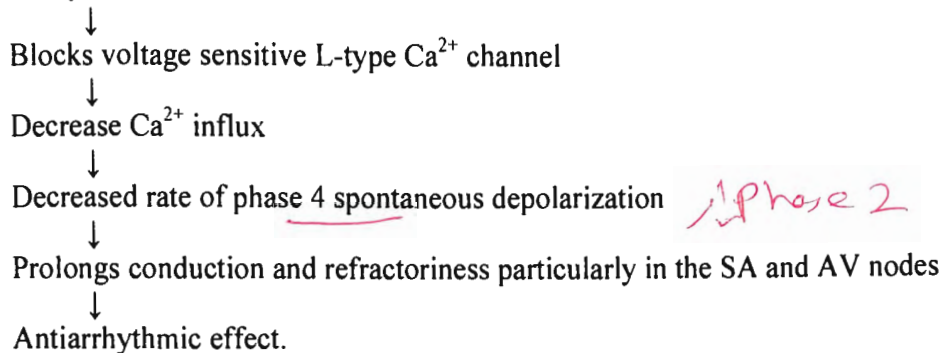
Verapamil

Q. Mention the mechanism of action and adverse effects of verapamil.

Ans.

Mechanism of action of verapamil:

Verapamil



(Ref: Lippincott's-6th; Katzung-13th)

Adverse effects of verapamil:

Cardiac: Verapamil's cardiotoxic effects are dose-related and usually avoidable.

1. Hypotension
2. Bradycardia
3. Ventricular fibrillation
4. AV block- in large doses or in patients with AV nodal disease.
5. Sinus arrest, in patients with sinus node disease.

Extracardiac:

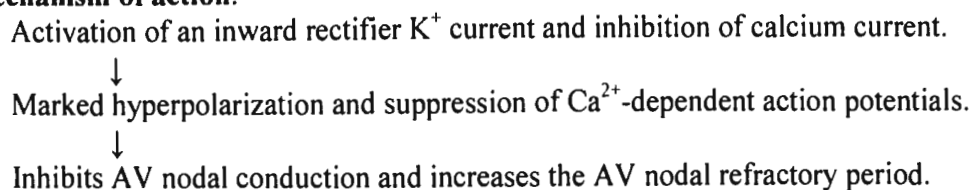
1. Constipation
2. Lassitude
3. Nervousness, and
4. Peripheral edema.

(Ref: Katzung-13th)

Adenosine

Adenosine is a nucleoside that occurs naturally throughout the body.

Mechanism of action:



Indication: Paroxysmal supraventricular tachycardia.

Toxicity:

1. Flushing (20% of patients)
2. Shortness of breath or chest burning (perhaps related to bronchospasm) in over 10%.
3. Induction of high-grade AV block
4. Atrial fibrillation
5. Less common toxicities : Headache, hypotension, nausea, and paresthesias.

(Ref: Katzung-12th/245)

MCQ

Q. Drugs used in angina pectoris are- (DU-17J)

- a. adrenaline
 - b. atropine
 - c. propranolol
 - d. morphine
 - e. nitroglycerine
- a.-F, b.-F, c.-F, d.-T, e.-T*

Q. ACE inhibitors are- (DU-17J)

- a. nifedipine
 - b. ramipril
 - c. captopril
 - d. amlodipine
 - e. enalapril
- a.-F, b.-T, c.-T, d.-F, e.-T*

Q. ACE inhibitors- (DU-15Ju)

- a. are drug of choice in chronic congestive heart failure
 - b. can be given in COPD patient
 - c. reduce preload of heart
 - d. are safe in pregnancy
 - e. reduce afterload of heart
- a. T, b. F, c. T, d. F, e. T*

Q. Anti-hypertensives safe in pregnancy are- (DU-14Ju)

- a. hydrochlorothiazide
 - b. α -methyl dopa
 - c. labetalol
 - d. captopril
 - e. amlodipin
- a. F, b. T, c. T, d. F, e. T*

Q. Following drugs produce peripheral ischemia: (CU-14Ju)

- a) Metoprolol.
 - b) Propranolol.
 - c) Lidocaine
 - d) Minoxidil
 - e) Phenylephrine
- a. T, b. T, c. T, d. F, e. T*

Q. Following would be the initial treatment of choice to manage the hypertension in a black woman with a past medical history of gout and sever hypokalaemia: (CU-14Ju)

- a) Hydrochlorothiazide
- b) Spironolactone

- c) Atenolol
 - d) Triamterene
 - e) Enalapril
- a. F, b. T, c. T, d. ?F, e. F*

Q. Nifedipine in comparison to Verapamil is more likely to: (CU-14Ju)

- a) Have negative inotropic effects.
 - b) Cause flushing and headache.
 - c) Cause diarrhea
 - d) Worsen angina
 - e) Cause ankle swelling unresponsive to diuretics.
- a. F, b. T, c. T, d. T, e. T*

Q. Indications of ramipril include- (DU-13Ju)

- a. hypertension.
 - b. diabetic nephropathy.
 - c. heart failure.
 - d. angina pectoris.
 - e. ventricular fibrillation.
- a. T, b. T, c. T, d. F, e. F*

Q. The following drugs are appropriate for hypertension during pregnancy- (DU-13Ju)

- a. hydralazine.
 - b. atenolol.
 - c. labetalol.
 - d. ACR inhibitor.
 - e. alpha methyl dopa.
- a. T, b. T, c. F, d. F, e. T*

Q. Nifedipine- (DU-13J)

- a. is indicated in prophylaxis of angina.
 - b. is used to treat hypertension.
 - c. is a long acting calcium channel blocker.
 - d. can cause bradycardia.
 - e. can cause ankle edema.
- a. T, b. T, c. F, d. F, e. T*

Q. Anti-hypertensive role of drugs involve- (SU-13J)

- a) Lisinopril is Angiotensin II blocker
 - b) Labetalol blocks alpha & beta receptor
 - c) Diltiazem decreases action of atenolol
 - d) Olmesartan inhibits Ang II synthesis
 - e) Diazoxide is safe in pregnancy
- a. F, b. T, c. F, d. F, e. F*

Q. Nitroglycerine produces action by- (SU-13J)

- a) Decrease platelet aggregations

- b) Decrease cardiac contractility
 - c) Activating adenylyl cyclase
 - d) Forming nitric oxide
 - e) By increasing cGMP
- a. F, b. F, c. F, d. T, e. F*

Q. Drug(s) exerting both anti-anginal & anti-arrhythmic action- (SU-13J)

- a. Propranolol
 - b. Clonidine
 - c. Nifedipine
 - d. Verapamil
 - e. Prazosin
- a. T, b. F, c. F, d. T, e. F*

Q. Indications of ACEI are- (DU-12Ju)

- a. Hypertension (T)
- b. Cardiac failure (T)
- c. Diabetic neuropathy. (T)
- d. Bronchial asthma. (F)
- e. Acute renal failure. (F)

Q. Ramipril- (DU-12J)

- a. Is an ACE inhibitor. (T)
- b. Is an AT1 receptor blocker. (F)
- c. Is contraindicated in heart failure. (F)
- d. Is indicated in pregnancy with hypertension. (F)
- e. Commonly causes dry cough. (T)

Q. The effects of nitroglycerine to relieve angina pectoris are- (DU-12J)

- a. Decreased preload. (T)
- b. Decreased afterload. (T)
- c. Decreased heart rate. (T)
- d. Increased myocardial contractility. (F)
- e. Increased coronary collateral circulation. (T)

Q Nifedipine- (DU-11Ju)

- a. Is indicated in prophylaxis of angina (F)
- b. Is used to treat hypertension (T)
- c. Is a long-acting calcium channel blocker (F)
- d. Can cause bradycardia (T)
- e. Can cause ankle edema. (T)

Q. The followings are the adverse effects of nifedipine- (DU-10Ju)

- a. Cold extremities (F)
- b. Ankle edema (T)
- c. Rebound anginal pain on sudden withdrawal (?)
- d. Tachycardia (T)
- e. Bronchospasm (F)

Q. Regarding Digoxin- (DU-10Ju)

- a. It inhibits K^+/H^+ ATPase pump in myocardium
 - b. It increases the refractory period of AV node
 - c. Its toxicity is aggravated due to hypokalemia
 - d. It causes tachycardia
 - e. It is indicated in supraventricular tachycardia
- a. F, b. T, c. T, d. F, e. T*

Q. ACE inhibitors- (DU-10J)

- a. inhibit angiotensin I synthesis (F)
- b. reduce pre-load (T)
- c. reduce after-load (T)
- d. may cause dry cough (T)
- e. safe in pregnancy (F)

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Chapter 6

Drugs affecting Renal function: Diuretics

Diuretics

Q. Define diuretics. (DU-00S)

Ans.

Diuretics: Diuretics are the drugs which can increase urinary excretion of salt and water by acting over different part of nephron.

(Note: Alcohol, caffeine, digoxin, theophylline and water intake increase urine output. But these are not classical diuretics. They are called physiological diuretics.)

Q. Classify diuretics according to their site of action. (DU-12J, CU-16Ju, 15J, RU-06/04M, SU-17J, 16Ju, 08Ju)

Q. Categorize diuretics incorporating their mechanism of action. (CU-12Ju, 11J, 08Ju)

Q. Classify diuretics incorporating K^+ homeostasis, efficacy and their mechanism of action. (CU-11Ju, 08Ju)

Q. Classify diuretics according to their efficacy. (DU-16J, 15J, 13J, 11J, CU-10/07J, 06S; RU-14J, 10Ju)

Q. Classify diuretics according to their efficacy and electrolyte action. (SU-15Ju)

Q. Classify diuretics according to their potency. (SU-15J)

Q. Enumerate clinically useful diuretics according to their efficacy. (DU-14J, CU-06M)

Q. Classify diuretics according to cortical diluting segment of renal tubule. (RU-12Ju)

Q. Name the loop diuretics. (DU-08J; RU-08Ju, 05M, 03M; SU-07J, 06S)

Q. Name the high-ceiling diuretics. (DU-07J, SU-11J)

Q. Name the high-efficacy diuretics. (DU-10Ju, RU-17J, 15J, 11J)

Q. Classify / Name the low-efficacy diuretics. (RU-11Ju, SU-16J)

Q. Name a long acting thiazide diuretic. (CU-07Ju)

Q. Enlist thiazide & thiazide-like diuretics. (RU-16Ju, 15Ju)

Q. Lists the K^+ losing diuretics. (DU-08Ju, CU-12J, 09Ju, RU-06J, 03S; SU-07J)

Q. Enumerate potassium sparing diuretics. (DU-12Ju, CU-12J, RU-14Ju)

Ans.

Classification of diuretics

A. According to their site of action and mechanism of action:

1. **Thiazide & thiazide-like diuretics:** Inhibit $NaCl$ reabsorption from the early part of distal convoluted tubule by blocking the Na^+/Cl^- transporter-

- Chlorothiazide
- Hydrochlorothiazide
- Chlorthalidone
- Indapamide — Non thiazide / Thiazide like
- Metolazone
- Bendroflumethiazide
- Hydroflumethiazide
- Polythiazide
- Trichlormethiazide

2. **Loop diuretics:** Inhibits $Na^+-K^+-2Cl^-$ transporter at the thick ascending limb of loop of Henle-

- Furosemide / Frusemide
- Torsemide
- Bumetanide
- Ethacrynic acid

3. **K^+ sparing diuretics:** Diuretics acting over collecting tubule-

a. Aldosterone receptor antagonist	■ Spironolactone ■ Eplerenone
b. Na^+ channel blockers	■ Amiloride ■ Triamterene

4. **Carbonic anhydrase inhibitors** (*rarely used*): Inhibit carbonic anhydrase located in the **proximal tubular epithelium**-
- Acetazolamide
 - Dorzolamide
 - Methazolamide
 - Brinzolamide
 - Dichlorophenamide
5. **Osmotic diuretics**: Diuretics acting over **proximal convoluted tubule**-
- Mannitol
 - Inulin
 - Urea
 - Glucose.

Pregnancy to sale

(Ref: Katzung-13th; Lippincott's-6th)

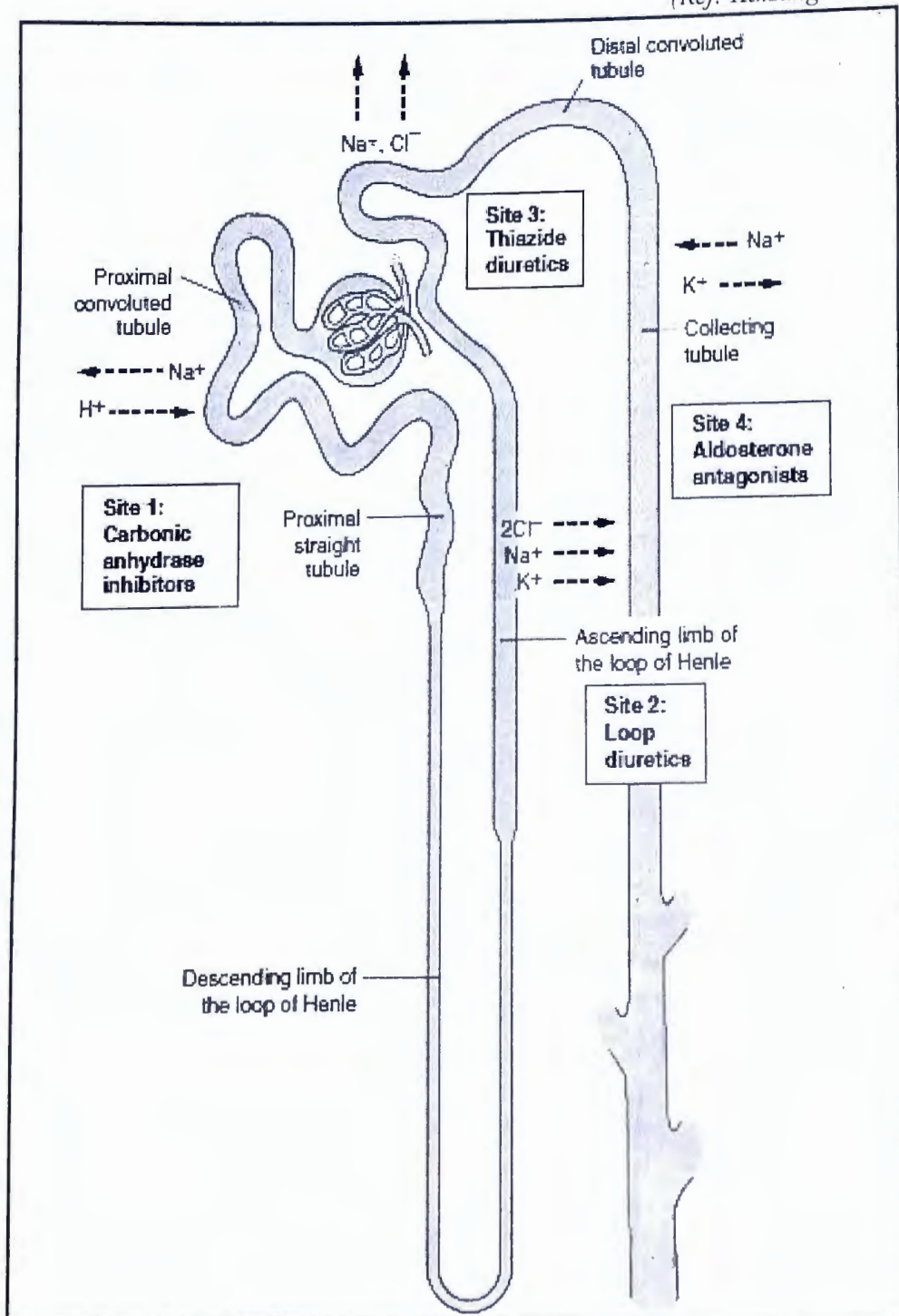


Figure. Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

B. According to efficacy / potency:

1. **High efficacy diuretics/ high ceiling diuretic:** Can cause up to 25% of filtered sodium to be excreted.
 - Loop diuretics
2. **Moderate efficacy diuretics:** Can cause 5-10% of filtered sodium load to be excreted.
 - Thiazide diuretics
 - Non-thiazide
3. **Low efficacy diuretics:** Can cause 5% of the filtered sodium to be excreted.
 - Carbonic anhydrase inhibitors
 - K^+ sparing diuretics
 - Osmotic diuretics

(Ref: Bennet & Brown & Brown-11th)

C. According to K^+ sparing capacity:

1. **K^+ losing diuretic:**
 - a. Loop diuretics
 - b. Thiazide diuretics
 - c. Carbonic anhydrase inhibitors
 - d. Osmotic diuretics

2. **K^+ sparing diuretic:**

a. Aldosterone receptor antagonist	▪ Spironolactone ▪ Eplerenone
b. Na^+ channel blockers	▪ Amiloride ▪ Triamterene

Q. Classify the drugs used in edematous state. (DU-03M)

Ans.

Drugs used in edematous state:

1. **Diuretics for pulmonary edema caused by LVF:** Loop diuretics
2. **Diuretics used in edema caused by cirrhosis of liver, renal diseases:** Spironolactone / loop diuretics
3. **Diuretics for cerebral edema:** Carbonic anhydrase inhibitors, osmotic diuretics.

Q. Name the commonly used diuretics with their indications. (RU-09J)

Ans.

Commonly used diuretics:

1. Frusemide.
2. Hydrochlorothiazide.
3. Spironolactone.
4. Indapamide

Indications of commonly used diuretics:

Edematous conditions	1. Heart failure 2. Pulmonary edema 3. AGN 4. Nephrotic syndrome 5. Liver cirrhosis 6. Pre-menstrual edema
Non-edematous conditions	1. Hypertension (HTN) 2. Nephrolithiasis 3. Hypercalcaemia 4. Diabetes insipidus

(Ref: Lippincott's-6th)

Q. Discuss diuretic braking / compensatory reactions of diuretic therapy. (CU-13Ju,09J)

Ans.

Diuretic breaking: Diuretic braking is a process by which the body slowly adapts to and resists the diuretic effects of thiazide diuretics. After several weeks of thiazide therapy, a noticeable decline in diuresis occurs. The loss of thiazide-induced diuresis is the defining event in the subacute phase of treatment, and it is most likely due to the phenomenon known as diuretic braking.

Mechanism of diuretic braking: It occurs by-

1. increasing the activity of the sympathetic nervous system
2. increasing the activity of the renin-angiotensin system, and
3. increasing the release of antidiuretic hormone.

Despite the reduction in diuresis during the subacute phase of treatment, the BP-lowering effects of these agents remain. Although this fact may seem counterintuitive, the decline in BP is most likely due to a developing reduction in peripheral vascular resistance.

Loop diuretics / Furosemide

Furosemide (INN) or frusemide (former BAN)

Hypertensive emergency

Q. Name the loop diuretics. (DU-08J)

Q. Name the high ceiling diuretics. (DU-10/09Ju,07J; RU-11J,09/07Ju,04J, SU-11J)

Q. Name 4 high ceiling diuretics. (RU-12J)

Q. Why are they called high ceiling? (DU-16Ju,10Ju, RU-045J, SU-11J,02J, CU-99J)

Q. Explain why frusemide is called high ceiling diuretics. (DU-17J)

Q. Mention the high efficacy diuretics with justification of naming. (RU-16J)

Q. Why frusemide is high efficacious? (RU-11J,04J)

Q. Name the forced diuretics. (RU-05M)

Q. Mention the characteristics/criteria of high ceiling diuretics. (DU-17M,13Ju, RU-17J)

Ans.

Loop diuretics / high ceiling diuretics: High ceiling diuretics are those where progressive increase in dose is matched by increasing diuresis, i.e. they have a *high* 'ceiling' of effect. Loop diuretics are called high ceiling diuretics.

1. Frusemide / Furosemide
2. Torsemide
3. Bumetanide
4. Ethacrynic acid

Loop diuretics are called high ceiling diuretics, because-

1. Progressive increase in dose of these drugs is matched by increasing diuresis, i.e. they have a *high* 'ceiling' of effect.
2. They are very potent and can cause up to 25% of filtered sodium to be excreted.
3. Their action impairs the powerful urine concentrating mechanism ($\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ transporter) of the loop of Henle and confers higher efficacy compared to other diuretics.

(Ref: Bennet & Brown-11th)

Q. Explain the mechanism of action of frusemide. (DU-12J,09Ju,08J; RU-15J,13J,09/08Ju, SU-08Ju,06J)

Q. Explain the diuretic action of frusemide. (SU-14J,08Ju)

Q. Name the mechanism of action of high ceiling/ high efficacy diuretics. (RU-16J, SU-11J)

Ans.

Mechanism of action of frusemide / loop diuretics:

1. Frusemide inhibits $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ transporter (NKCC2) at the **thick ascending limb of loop of Henle** → Reduce reabsorption of Na^+ , K^+ , Cl^- ions → ↑Loss of these ions along with iso-osmotic volume of water leads to diuresis.

- By inhibiting $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ transporter, frusemide also diminish the **lumen-positive potential** that comes from K^+ recycling. This positive potential normally drives divalent cation reabsorption in the loop and by reducing this potential, loop diuretics cause an increase in Mg^{2+} and Ca^{2+} excretion.
- Loop diuretics induce synthesis of renal **prostaglandins**, which participate in the renal actions of these diuretics.
- Furosemide increases **renal blood flow** $\rightarrow \uparrow \text{GFR} \rightarrow \uparrow \text{Urine formation} \rightarrow \text{Diuresis}$.

(Ref: Katzung-13th)

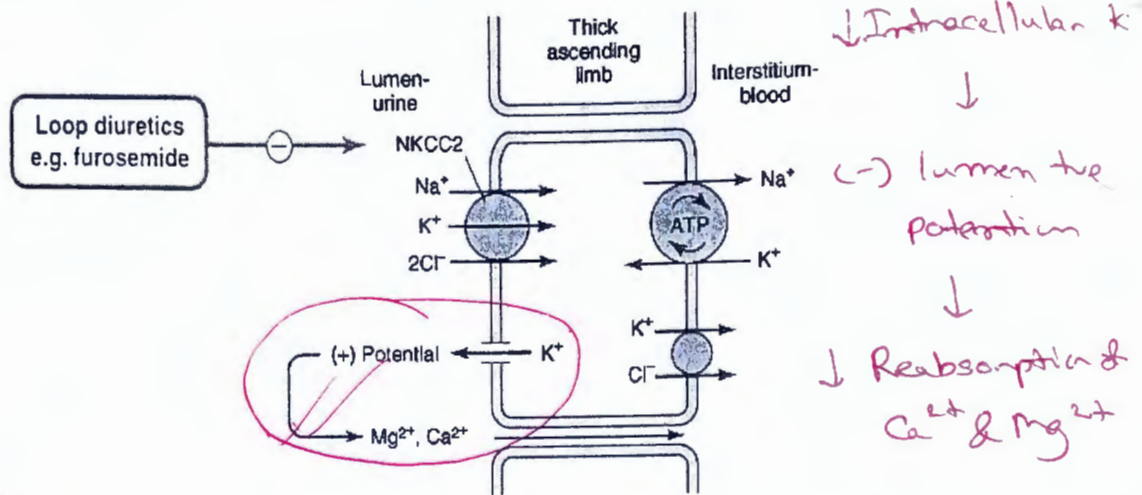


Figure: Frusemide inhibits $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ transporter (NKCC2) at the thick ascending limb of loop of Henle

- Q. Describe the clinical uses of frusemide. (DU-15J; CU-07Ju; SU-06J)
 Q. Write down the indications of frusemide. (DU-17J, CU-06M, RU-14J, 13J, 07Ju, SU-15Ju, 15J)
 Q. Write down the indications of high ceiling diuretics. (DU-10Ju)
 Q. Enlist three clinical uses of frusemide with their specific role in each class. (DU-17M)

Ans.

Indications of frusemide:

- Heart failure leading to acute pulmonary edema and other edematous conditions:** Frusemide reduces the accumulation of edema, particularly in the lungs. Reduction of pulmonary vascular congestion with diuretics may actually improve oxygenation and thereby improve myocardial function. Reduction of preload can reduce the size of the heart, allowing it to work at a more efficient fiber length.
- Acute hypercalcaemia:** Hypercalcemia can be a medical emergency. Because loop diuretics reduce Ca^{2+} reabsorption significantly, they can be quite effective in promoting Ca^{2+} diuresis. Saline must be administered simultaneously with loop diuretics if an effective Ca^{2+} diuresis is to be maintained.
- Hyperkalaemia:** Loop diuretics can significantly enhance urinary excretion of K^+ .
- Acute renal failure:** Loop agents can increase the rate of urine flow and enhance K^+ excretion in acute renal failure. However, they cannot prevent or shorten the duration of renal failure.
- Anion overdose:** Loop diuretics are useful in treating toxic ingestions of bromide, fluoride, and iodide, which are reabsorbed in the thick ascending limb.

The most important indications for the use of the loop diuretics include acute pulmonary edema, other edematous conditions, and acute hypercalcemia.

(Ref: Katzung-13th)

Q. Explain the role of frusemide in CCF. (SU-12Ju, 08Ju, 07J, 06S)

Q. Explain the role of frusemide in heart failure. (DU-13Ju)

Q. Explain the role of frusemide in pulmonary edema. (DU-16Ju)

Q. Describe the role of intravenous Frusemide in left ventricular failure. (CU-16Ju)

Q. Explain pharmacological basis of using frusemide in ALVF with pulmonary edema?

Ans.

Pharmacological basis of using frusemide in ALVF with pulmonary edema: In acute left ventricular failure (LVF) and congestive cardiac failure (CCF), there is pulmonary congestion & edema which impairs oxygenation of blood in the lungs and results in severe respiratory distress. At this point, diuretic use becomes necessary to reduce the accumulation of edema, particularly in the lungs. Reduction of pulmonary vascular congestion with diuretics may actually improve oxygenation and thereby improve myocardial function. Reduction of preload can reduce the size of the heart, allowing it to work at a more efficient fiber length. Edema associated with heart failure is generally managed with **loop diuretics (frusemide)**. In some instances, salt and water retention may become so severe that a combination of thiazides and loop diuretics is necessary.

(Ref: Katzung-13th)

Q. Mention the adverse effects of frusemide. (DU-15J, 12J, 09Ju, 05J, RU-14J, 09Ju, 08Ju, 07Ju, SU-16J/Ju, 15Ju, 15J, 07Ju)

Q. Mention the adverse effects of high ceiling diuretics. (SU-11J)

Q. List the metabolic adverse effects of frusemide. (SU-14J)

Ans.

Adverse effects of frusemide:

1. Hypovolemia (in case of massive IV administration)
2. Hypokalaemia
3. Hypokalemic metabolic alkalosis.
4. Reversible ototoxicity (due to inhibition of symport mechanism in the endolymph)
5. Hypomagnesaemia
6. Hypocalcaemia
7. Hyperuricemia (leading to gouty attack)
8. Allergic & other reactions: Except for ethacrynic acid, the loop diuretics are sulfonamides. Therefore skin rash, eosinophilia and, less often, interstitial nephritis are occasional side effects of these drugs.

(Ref: Katzung-13th)



Q. How do you manage hypokalaemia induced by frusemide? (SU-07J)

Ans.

Management of frusemide induced hypokalaemia:

1. Stop the drug.
2. K^+ sparing diuretics should be given.
3. Correct hypovolemia and reduce Na^+ intake.
4. K^+ containing foods: Banana, guava, green coconut.
5. I/V KCl or K-containing syrup (after meal)
6. Regular monitoring:
 - Vital signs: Pulse, blood pressure, respiratory rate, urine output, temperature etc.
 - 12 lead ECG for hypokalemic change in ECG.

Q. What are the contraindications of loop diuretics?

Ans.

Contraindications of loop diuretics:

1. Hypersensitivity to loop diuretics (very rare).
2. Overzealous use of any diuretic is dangerous in hepatic cirrhosis, borderline renal failure, or heart failure

(Ref: Katzung-13th)

Q. Enumerate advantages and disadvantages of frusemide as diuretics. (CU-04S)

Ans.

Advantages of frusemide:

1. Highly efficacious diuretic.
2. Increase of dose is able to increase diuresis.
3. Not self limiting.
4. Remain effective even at GFR of below 10 ml/min (as in severe renal and cardiac failure).
5. Rapid onset of action (Emergency diuresis): 2-3 min.
6. More potent.

Disadvantages of frusemide:

1. Reversible ototoxicity
2. Intravenous massive dose causes hypovolemic shock
3. Hypomagnesaemia
4. Hypokalaemia
5. Hypokalemic metabolic alkalosis
6. Hyperuricemia leading to gout
7. Hyperglycemia
8. Hypersensitivity

Q. Write down the cautions of during use of frusemide. (CU-05M)

Ans.

Cautions of during use of frusemide:

1. Close monitoring during frusemide therapy.
2. Assess state of dehydration
3. Serum electrolytes estimation (especially K)
4. Frusemide administration with combination of K sparing diuretics
5. Frusemide should administer at lower doses.
6. Avoidance of simultaneous administration of other ototoxic agents
7. Correction of hypovolemia by saline infusion
8. Monitoring of uric acid level at one week interval

Q. Explain gout after frusemide administration.

Ans.

Gout after frusemide administration: Loop diuretics can cause hyperuricemia and precipitate attacks of gout. This is caused by **hypovolemia-associated increase of uric acid reabsorption in the proximal tubule**. It may be prevented by using lower doses to avoid development of hypovolemia.

(Ref: Katzung-13th)

Q. Explain hypokalaemia after frusemide administration.

Ans.

Hypokalemia and Hypokalemic Metabolic Alkalosis after frusemide administration: By inhibiting salt reabsorption in the TAL, loop diuretics increase delivery to the collecting duct. Increased delivery leads to aldosterone-induced increased secretion of K^+ and H^+ by the duct, causing hypokalemia and hypokalemic metabolic alkalosis. This toxicity is a function of the magnitude of the diuresis and can be reversed by K^+ replacement and correction of hypovolemia.

(Ref: Katzung-13th)

Thiazide diuretics / hydrochlorothiazide

Q. Explain the antihypertensive effect of thiazide. (DU-16J,15/11Ju,10/09J, CU-13J; RU-07J; SU-17J,13J,12Ju)

Q. How does thiazide diuretic lower elevated BP? (DU-12Ju, CU-17J)

Q. Enumerate the mechanism of action of thiazide? (DU-06S; CU-11Ju, RU-13Ju,06S; SU-09J)

Q. Explain diuretics effect of hydrochlorothiazide. (RU-11J, SU-17M,14J,11Ju,08J)

Ans.

Mechanism of action of thiazide:

1. Thiazides inhibit NaCl reabsorption from the luminal side of epithelial cells in the DCT by blocking the **Na⁺/Cl⁻ transporter (C₁)** → ↑Loss of Na⁺, Cl⁻ ions along with iso-osmotic volume of water leads to diuresis → ↓Blood volume → ↓BP. (10-15 days)
2. In case of long standing therapy, thiazide decreases responsiveness of blood vessels to circulatory catecholamines → vasodilation → ↓peripheral resistance → ↓BP.

(Ref: Katzung-13th)

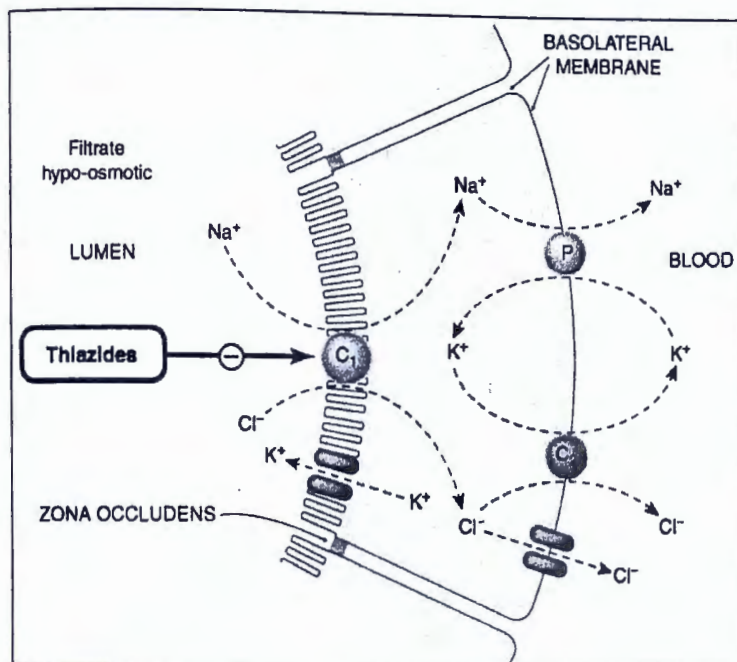


Figure. Salt transport in the distal convoluted tubule, showing the site of action of thiazide diuretics. Sodium and chloride ions enter by an electroneutral cotransport carrier (C₁).

Q. Enumerate the indications of thiazide diuretics. (DU-13J, 11J/Ju, CU-11Ju, RU-16Ju, SU-15J)

Q. Enumerate the indications of hydrochlorothiazide. (DU-06S; RU-06J, SU-17M)

Ans.

Indications of thiazide diuretics / hydrochlorothiazide: The major indications for thiazide diuretics are

1. hypertension
2. heart failure
3. nephrolithiasis due to idiopathic hypercalciuria, and
4. nephrogenic diabetes insipidus.

(Ref: Katzung-13th)

Q. Explain the role of diuretics in hypertension. (SU-07Ju)

Q. Why Thiazides not Frusemides are used as anti-hypertensive? (SU-16Ju)

Q. Which diuretics are used in the treatment of hypertension & why?

Ans.

Role of diuretics in hypertension:

1. Initially, diuretics reduce blood pressure by reducing blood volume and cardiac output. Later diuretics lower blood pressure primarily by depleting body sodium stores.
2. Diuretics are effective in lowering blood pressure by 10-15 mm Hg in most patients, and diuretics alone often provide adequate treatment for mild or moderate essential hypertension.
3. In more severe hypertension, diuretics are used in combination with sympathoplegic and vasodilator drugs to control the tendency toward sodium retention caused by these agents.
4. **Thiazide** diuretics are appropriate for most patients with mild or moderate hypertension and normal renal and cardiac function.

5. More powerful diuretics such as **furosemide** are necessary in severe hypertension.

(Ref: Katzung-13th)

Q. Enumerate the adverse effects / toxicities of **hydrochlorothiazide / thiazide**? (DU-14J, 13J, 10/09J, 07Ju; CU-07J; RU-16Ju, 10/06J)

Q. What are the adverse effects of **thiazide therapy**? (CU-11Ju, RU-09J)

Q. List the metabolic adverse effects of **hydrochlorothiazide / thiazide**. (RU-15Ju, SU-14J, 09J)

Q. List 3 adverse effects of **hydrochlorothiazide**. (DU-15Ju)

Ans.

Adverse effects / toxicities of hydrochlorothiazide / thiazide: Most of the adverse effects involve problems in fluid and electrolyte balance.

1. **Hypokalemia:** Hypokalemia is the most frequent problem encountered with the thiazide diuretics.
2. **Hyponatremia**
3. **Hypercalcemia**
4. **Metabolic alkalosis.**
5. **Hyperuricemia** (precipitation of gout).
6. **Hyperglycemia.**
7. **Hyperlipidemia** (5-15% increase in serum cholesterol as well as increased LDL).
8. **Hypersensitivity**
9. **Others:** Weakness, fatigability, and paresthesia.

(Ref: Lippincott's-6th; Katzung-13th)

Nice to know

Contraindications of thiazide:

1. Excessive use of any diuretic is dangerous in hepatic cirrhosis, borderline renal failure, or heart failure.

(Ref: Katzung-13th)

Viva Q. Why does hyponatremia occur in thiazide therapy?

Ans.

It is due to a combination of hypovolemia-induced elevation of ADH, reduction in the diluting capacity of the kidney, and increased thirst. It can be prevented by reducing the dose of the drug or limiting water intake.

(Ref: Katzung-13th)

Q. What is the rationale for combination use of diuretics? (SU-11Ju)

Q. State why **spironolactone** is used in combination with **loop diuretic**. (RU-11Ju)

Ans.

Rationale for combination use of diuretics

1. **To prevent adverse effect:**

Furosemide & thiazide: Produce hypokalemia.

Spironolactone: Prevents K^+ loss.

So, simultaneous administration of **furosemide & spironolactone** or **thiazide & spironolactone** maintain K^+ concentration within normal limit.

2. **To potentiate the action of each other:**

Organic mercurial diuretic + CA inhibitor →

Mercurial diuretic is active in acidic environment. Acetazolamide causes metabolic acidosis, thus enhances the action of mercurial diuretic.

Acetazolamide is active in alkaline environment. Mercurial diuretic causes metabolic alkalosis, thus enhances the action of acetazolamide.

3. **To increase the duration of diuretic therapy:**

Primarily acting (thiazide) + secondarily acting (digitalis alkaloid).

4. **To obtain pharmacological synergism:** Pharmacological synergism can be obtained by sequentially blocking more than one site in the nephron by two diuretics. For example, **furosemide and thiazide** acting at different nephron sites exhibit synergy and produce more than an additive diuretic response.
5. **To avoid refractory to single drug:** The combination of **loop diuretics and thiazide** can mobilize large amount of fluid, even in patients who have been refractory to single drug.

Q. Discuss the rationale of using thiazide diuretics along with angiotensin II receptor blockers. (CU-08L05S)

Q. Rationalize the combination of losartan with hydrochlorothiazide. (RU-13Ju)

Ans.

Rationale of using thiazide along with angiotensin II receptor blockers (losartan): Angiotensin-II receptor blockers (ARB) cause hyperkalaemia. On the other hand thiazide causes hypokalaemia & thus antagonizes the hyperkalemic effect of ARB. Moreover both of them produce antihypertensive effects in different mechanisms. So in combination use there is minimization of adverse effect & pharmacological potentiation occurs.

Q. Discuss the rationale of using thiazide diuretics along with Ca^{2+} channel blockers. (CU-08J,05S)

Ans.

Rationale of using thiazide along with Ca^{2+} channel blockers (CCB): Both thiazide diuretics and CCB reduce blood pressure and are widely used as antihypertensive drugs. When used in combination, these two drugs can reduce more BP by **additive effects**. Therefore, when monotherapy with one drug fails to control BP properly, combination of these two drugs can be used for good control of BP.

(Ref: Adverse drug interactions-page 93)

Q. Why hypokalaemia occurs after thiazide diuretics? (CU-16J, RU-07J)

Ans.

Mechanism of hypokalaemia after thiazide diuretics:

Thiazide diuretics inhibit Na^+ reabsorption in the early part of DCT

↓

Increased Na^+ delivery to the collecting duct

↓

This stimulates **aldosterone** secretion (for the purpose of Na^+ reabsorption)

↓

Increased Na^+ reabsorption at the collecting duct in exchange of increased K^+ excretion by Na^+-K^+ ATPase pump by the action of aldosterone

↓

Hypokalemia

(Ref: Katzung-13th)

Q. Outline the management of thiazide induced hypokalaemia. (CU-06S)

Q. Which adverse effect of thiazide requires special attention?

Ans.

Adverse effects of thiazide diuretics requiring special attention: Hypokalaemia.

Management of thiazide induced hypokalemia: Same as furosemide induced hypokalaemia.

Viva Q. Explain gout after thiazide administration.

Ans.

Mechanism of gout after thiazide administration: Thiazide diuretics are actively secreted by acidic transport protein at proximal convoluted tubule and so, inhibit uric acid secretion at proximal convoluted tubule, which leads to hyperuricemia and gout.

Viva Q. How thiazide produces hyperglycemia?

Ans.

Hyperglycemia by thiazide:

1. Thiazides administration $\rightarrow$ Hypokalaemia $\rightarrow$ $\downarrow$ K^+ concentration into β cell of pancreas $\rightarrow$ Block depolarization $\rightarrow$ $\downarrow$ Ca^{2+} transport into β cell through voltage-gated Ca^{2+} channel $\rightarrow$ $\downarrow$ Insulin release $\rightarrow$ Hyperglycaemia.
2. Thiazide administration $\rightarrow$ Diminished tissue utilization of glucose $\rightarrow$ Hyperglycaemia.

Q. Explain the use of thiazides in diabetes insipidus.

Ans.

Use of thiazides in diabetes insipidus:

Diabetes insipidus is due either to deficient production of ADH (neurogenic or central diabetes insipidus) or inadequate responsiveness to ADH (nephrogenic diabetes insipidus). Administration of supplementary ADH or one of its analogs is only effective in central diabetes insipidus.

Thiazide diuretics can reduce polyuria and polydipsia in both types of diabetes insipidus. This seemingly paradoxical beneficial effect is mediated through plasma volume reduction, with an associated fall in glomerular filtration rate, enhanced proximal reabsorption of NaCl and water, and decreased delivery of fluid to the downstream diluting segments. Thus, the maximum volume of dilute urine that can be produced is lowered and thiazides can significantly reduce urine flow in the polyuric patient.

(Ref: Katzung-13th)

Q. Explain the use of thiazide diuretics as first line antihypertensive?

Q. Explain antihypertensive action of hydrochlorothiazide. (SU-12Ju)

Q. Short note: Thiazide in the treatment of hypertension. (CU-14J)

Ans.

Use of thiazide diuretics as first line antihypertensive, because—

1. Prolonged duration of action (10-12 hours)
2. Onset of action is slow; so not need of close monitoring.
3. Low dose required
4. Long-standing thiazide therapy decreases responsiveness of blood vessel to circulatory catecholamines.
5. Thiazide causes diuresis without changing acid base balance.
6. No postural hypotension
7. No reflex tachycardia

Viva Q. Justify use of thiazides in nephrolithiasis (renal stone).

Ans.

Approximately two thirds of kidney stones contain Ca^{2+} phosphate or Ca^{2+} oxalate. Many patients with such stones exhibit a defect in proximal tubular Ca^{2+} reabsorption that causes hypercalciuria. This can be treated with thiazide diuretics, which enhance Ca^{2+} reabsorption in the distal convoluted tubule and thus reduce the urinary Ca^{2+} concentration. Salt intake must be reduced in this setting, as excess dietary NaCl will overwhelm the hypocalciuric effect of thiazides. Calcium stones may also be caused by increased intestinal absorption of Ca^{2+} . In these situations, thiazides are also effective, but should be used as adjunctive therapy with decreased Ca^{2+} intake and other measures.

(Ref: Katzung-13th)

Q. Name some thiazide like diuretics. (CU-17J)

Q. What are the thiazide-like analogs?

Ans.

Thiazide-like analogues: These compounds lack the thiazide structure, but like the thiazides, they have the unsubstituted sulfonamide group and share their mechanism of action.

1. **Chlorthalidone:** Chlorthalidone behaves pharmacologically like hydrochlorothiazide. It has a very long duration of action and, therefore, is often used to treat hypertension. It is given once per day for this indication.
2. **Metolazone:** Metolazone is more potent than the thiazides and, unlike the thiazides, causes Na^+ excretion in advanced renal failure.
3. **Indapamide.**

(Ref: Lippincott's-6th)

Q. Explain the antihypertensive action of indapamide. (SU-12J)

Q. Short note: Indapamide. (DU-17J)

Ans.

Indapamide: Indapamide is a lipid-soluble, nonthiazide diuretic that has a long duration of action. At low doses, it shows significant antihypertensive action with minimal diuretic effects. Indapamide is metabolized and excreted by the gastrointestinal tract and the kidneys. It is therefore less likely to accumulate in patients with renal failure and may be useful in their treatment.

(Ref: Lippincott's-6th)

Q. Compare frusemide & hydrochlorothiazide as antihypertensive drug. (CU-09Ju)

Q. Compare and contrast frusemide & thiazide diuretics? (DU-06S; CU-15J,12J,07J,06J; SU-15J,06S)

Q. Compare thiazide & loop diuretics with respect to their efficacy, pattern of electrolyte loss, effectiveness in presence of renal failure & adverse effects. (CU-13Ju,04M)

Q. Compare diuretic effect of frusemide and indapamide mentioning site, mechanism of action and adverse effects. (SU-14Ju)

Ans.

Differences between frusemide (loop) & thiazide diuretics:

Trait	Frusemide	Thiazide
1. Site of action	Thick ascending limb of loop of Henle	Proximal part of DCT
2. Efficacy	High (Can cause up to 25% of filtered sodium to be excreted.)	Moderate (Can cause up to 5-10% of filtered sodium to be excreted.)
3. Mechanism of action	Block luminal $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ transporter	Block luminal $\text{Na}^+ - \text{Cl}^-$ co-transporter
4. Onset of action	Rapid onset in IV route (2-3 min)	Slow onset (30 min)
5. Duration of action	Short (4 hrs)	Long (12-14 hrs)
6. Plasma protein binding	Extensive plasma albumin binding	Not so
7. Effectiveness	Effective even when GFR falls below 10 ml/min	Ineffective when GFR falls below 30 ml/min
8. Use	In emergency	In long-term therapy
	In hypertensive emergency	Mild to moderate hypertension
	Not used	Nephrogenic diabetes insipidus
9. Adverse effects	Ototoxicity	No
	Electrolyte change • Hypokalaemia • Hyponatremia • Hypocalcaemia • Hypomagnesaemia	Electrolyte change • Hypokalemia • Hyponatremia • Hypercalcemia

K⁺ sparing diuretics / spironolactone

Q. Write down the mechanism of action of spironolactone. (DU-14Ju, CU-16J, RU-14Ju, 11Ju, 06J, SU-17J)

Q. Shortly discuss the mechanism of action of spironolactone. (SU-09J)

Q. Explain diuretic effect of spironolactone. (SU-08J)

Ans.

Mechanism of action / diuretic action of spironolactone:

1. Normally aldosterone binds with cytoplasmic receptor. The receptor-hormone complex then stimulates specific gene of the DNA to produce specific protein. These mediator proteins normally stimulate the Na⁺-K⁺ exchange sites of the collecting tubules and this leads to Na⁺ reabsorption and K⁺ and H⁺ secretion.
2. Spironolactone antagonizes aldosterone at the receptor level. Spironolactone binds with the receptor and the spironolactone-receptor complex is inactive and does not stimulate specific gene of the DNA to produce specific protein. Thus, lack of mediator proteins prevents Na⁺ reabsorption and, therefore, K⁺ and H⁺ secretion. Spironolactone is weak diuretic because most of the filtered Na⁺ is reabsorbed before reaching the CT.

(Ref: Lippincott's-6th)

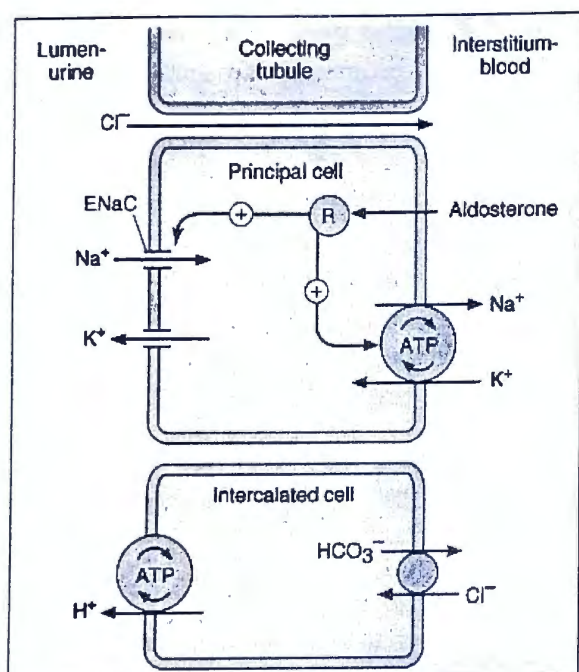


Fig. Ion transport pathways in the collecting tubule and collecting duct cells. Inward diffusion of Na⁺ via the epithelial sodium channel (ENaC) leaves a lumen-negative potential, which drives reabsorption of Cl⁻ and efflux of K⁺. (R, aldosterone receptor)

Q. Mention the indications of spironolactone. (DU-14Ju, RU-14Ju, SU-16J, 08Ju)

Ans.

Indications of spironolactone:

1. **Hyperaldosteronism:** It is the most useful in states of mineralocorticoid excess or hyperaldosteronism, due either to-
 - a. Primary aldosteronism (Conn's syndrome)
 - b. Secondary aldosteronism, evoked by cirrhosis of liver, heart failure, nephrotic syndrome.
2. **Diuretic:**
 - a. Used in combination with K⁺ losing diuretics (loop & thiazide diuretics) to prevent hypokalemia.
 - b. Diuretic of choice in cirrhosis of liver.
3. **Heart failure:** Spironolactone prevents the remodeling that occurs as compensation for the progressive failure of the heart.

(Ref: Katzung-13th; Lippincott's-6th)

Q. Mention the adverse effects of spironolactone. (SU-17J)

Q. Mention the adverse effects of K^+ sparing diuretics. (SU-07J)

Ans.

Adverse effects of K^+ sparing diuretics/ spironolactone:

1. **Hyperkalemia:** Unlike other diuretics, K^+ -sparing diuretics can cause mild, moderate, or even life-threatening hyperkalemia.
2. **Metabolic acidosis** (only diuretic that can cause metabolic acidosis): By inhibiting H^+ secretion in parallel with K^+ secretion.
3. **Gastric upset & PUD** (due to its steroid nucleus).
4. **Estrogenic effect** of spironolactone:
 - Gynecomastia, impotence & BPH in male.
 - Menstrual irregularity in female.
 - Increases the risk of breast carcinoma for chronic use.
5. **Acute renal failure:** Occurs in combined use of triamterene and indomethacin.
6. **Kidney stones:** Triamterene is only slightly soluble and may precipitate in the urine, causing kidney stones.

(K^+ / H^+ antiparity)

Q. Enumerate advantages and disadvantages of spironolactone as a diuretic drug. (CU-05J)

Ans.

Advantages of spironolactone:

1. Antagonizes aldosterone receptor. That's why it is used in primary aldosteronism or secondary aldosteronism (in CLD).
2. Low efficacious diuretic; less chance of volume deletion.
3. Compromise hypokalaemia when used combined with K^+ loosing diuretics.

Disadvantages of spironolactone:

1. Less efficacious. So can not be used in moderate-severe edematous condition.
2. Due to its steroid nucleus & estrogenic effects it cannot be used in chronic case.
3. It can cause hyperkalaemia. So can not be used in renal failure.
4. It also can cause metabolic acidosis.

Q. Write down the difference between thiazide & spironolactone. (DU-10J)

Ans.

Differences between thiazide & spironolactone:

Trait	Thiazide	Spironolactone
1. Chemistry	Sulfonamide derivative	Synthetic steroid
2. Site of action	Early part of DCT	Collecting tubule
3. Mechanism of action	Block luminal Na^+-Cl^- transporter at early part of DCT.	Antagonizes aldosterone receptor at collecting tubule
4. Onset of action	Relatively faster (30 min)	Very slow (several days)
5. Efficacy	Moderate (Can cause 5-10% of filtered sodium load to be excreted.)	Low (Can cause 5% of filtered sodium load to be excreted.)
6. Effect on K^+ level	Hypokalemia	Hyperkalemia
7. Effect on body pH	Metabolic alkalosis	Metabolic acidosis
8. Role in CLD	No role (even cause / exacerbate secondary aldosteronism)	Diuretic of choice in CLD.
9. Gynecomastia	No	May occur
10. Hyperglycemia	May occur	No
11. Dyslipidaemia	May occur	No
12. Paresthesia	May occur	No
13. Muscle pain	May occur	No

Q. Rationalize the combination of spironolactone with loop diuretics / frusemide / thiazides. (RU-14J)

Q. Justify the combination of hydrochlorothiazide and amiloride. (CU-04M, SU-01J)

Ans.

Combination of spironolactone & frusemide / thiazides: Frusemide & thiazides are K^+ -losing diuretics (i.e. cause hypokalaemia). On the other hand spironolactone is a K^+ -sparing diuretic (i.e. cause hyperkalaemia). So, if spironolactone is used in combination with frusemide / thiazides, it can oppose the hypokalemic imbalance & there is less or no chance of hypokalaemia.

Carbonic anhydrase inhibitors / acetazolamide

Functions of carbonic anhydrase enzyme:

1. Aqueous humor formation
2. CSF formation
3. HCl formation in gastric cell
4. Relation with RBC

Mechanism of action carbonic anhydrase inhibitors / acetazolamide:



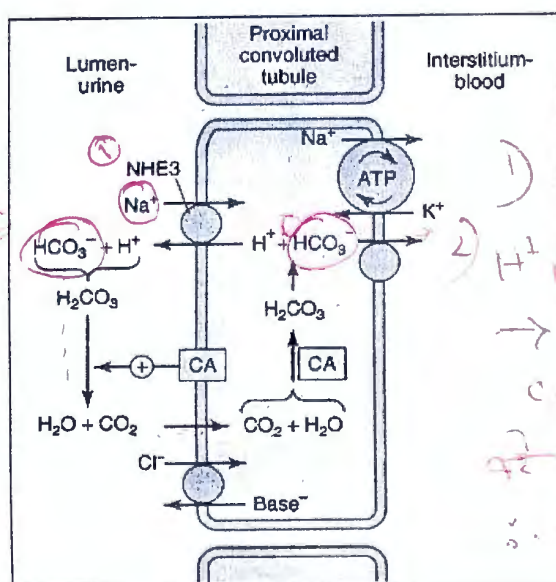
Sodium bicarbonate reabsorption by the PCT is initiated by the action of a Na^+/H^+ exchanger (NHE3) located in the luminal membrane of the proximal tubule epithelial cell

↓
Carbonic anhydrase inhibitors **inhibit carbonic anhydrase in the luminal membrane** and so there is less breakdown of carbonic acid into H_2O & CO_2 .

↓
Accumulation of H^+ in the lumen which impairs the transport action of Na^+/H^+ exchanger

↓
Decreased reabsorption of Na^+ and bicarbonate (HCO_3^-)

↓
Diuresis.



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(Ref: Katzung-13th)

1) exchange (Na^+/H^+) off
∴ Na^+ reabs
off
2) H^+ recycle in lumen HCO_3^-
→ $H_2CO_3 \rightarrow H_2O + CO_2 \rightarrow$
cell reabs.
∴ recycle stop
∴ HCO_3^- reabsorption stop

Figure: Apical membrane Na^+/H^+ exchange (via NHE3) and bicarbonate reabsorption in the proximal convoluted tubule cell. Carbonic anhydrase (CA) is found in other locations in addition to the brush border of the luminal membrane.

(Ref: Katzung-13th)

Q. Write the clinical uses of acetazolamide.

Ans.

Clinical uses acetazolamide / carbonic anhydrase inhibitors:

1. **Glaucoma:** The reduction of aqueous humor formation by carbonic anhydrase inhibitors decreases the intraocular pressure. It is the most common indication for use of carbonic anhydrase inhibitors.
2. **Urinary alkalization:** By increasing urinary pH, carbonic anhydrase inhibitors can increase renal excretion of cystine (in cystinuria) and other weak acids.
3. **Metabolic alkalosis:** Due to excessive use of diuretics in patients with severe heart failure.
4. **Acute mountain sickness:** In more serious cases of mountain sickness, rapidly progressing pulmonary or cerebral edema can be life-threatening. By decreasing CSF formation and by decreasing the pH of the CSF and brain, acetazolamide can increase ventilation and diminish symptoms of mountain sickness.
5. **Other uses:**
 - a. As adjuvants in the treatment of epilepsy.
 - b. In some forms of hypokalemic periodic paralysis.
 - c. To increase urinary phosphate excretion during severe hyperphosphatemia.

(Ref: Katzung-13th)

Q. Write the adverse effects of acetazolamide.

Ans.

Adverse effects of acetazolamide / carbonic anhydrase inhibitors:

1. **Hyperchloremic metabolic acidosis:** Results from chronic reduction of body HCO_3^- stores
2. **Renal potassium wasting** → Hypokalemia
3. **Renal stone:** Calcium salts are relatively insoluble at alkaline pH → renal stone formation.
4. **Other toxicities:**
 - a. Drowsiness and paresthesias (in large doses)
 - b. Nervous system toxicity (in renal failure)
 - c. Hypersensitivity reactions (fever, rashes, bone marrow suppression, and interstitial nephritis)

(Ref: Katzung-13th)

Contraindication of acetazolamide

1. Liver cirrhosis

(Ref: Katzung-13th)

Q. Why carbonic anhydrase inhibitors are self limiting diuretics?

Ans.

Carbonic anhydrase inhibition causes significant HCO_3^- losses and hyperchloremic metabolic acidosis. Because of reduced HCO_3^- in the glomerular filtrate and the fact that HCO_3^- depletion leads to enhanced NaCl reabsorption by the remainder of the nephron, the diuretic efficacy of acetazolamide decreases significantly with use over several days. This is why, carbonic anhydrase enzyme inhibitors are called "self-limiting diuretics":

(Ref: Katzung-13th)

Osmotic diuretics

Q. Write down the mechanism of action of mannitol. (SU-11Ju, RU-05M)

Q. Write down the diuretic action of mannitol. (SU-17M)

Ans.

Mechanism of action of mannitol:

- Osmotic diuretics have their major effect in the proximal tubule and the descending limb of Henle's loop. Through osmotic effects, they also oppose the action of ADH in the collecting tubule.

- The presence of a nonreabsorbable solute such as mannitol prevents the normal absorption of water by interposing a countervailing osmotic force. As a result, urine volume increases.
- The increase in urine flow rate decreases the contact time between fluid and the tubular epithelium, thus reducing Na^+ as well as water reabsorption.
- The resulting natriuresis is of lesser magnitude than the water diuresis, leading eventually to excessive water loss and hypernatremia.

(Ref: Katzung-13th)

Q. Mention the uses of mannitol in special situations. (SU-17M)

Ans.

Clinical uses of mannitol:

1. **To increase urine volume:** In acute renal failure due to shock, drug toxicities, and trauma.
2. **Reduction of intracranial pressure** in cerebral edema
3. **Reduction of intraocular pressure** before ophthalmologic procedures.

(Ref: Katzung-13th; Lippincott's-6th)

Adverse effects of mannitol:

1. **Extracellular volume expansion:** Mannitol is rapidly distributed in the extracellular compartment and extracts water from cells. Prior to the diuresis, this leads to expansion of the extracellular volume and hyponatremia. This effect can complicate heart failure and may produce florid pulmonary edema. Headache, nausea, and vomiting are commonly observed in patients treated with osmotic diuretics.
2. **Dehydration, Hyperkalemia, and Hypernatremia:** Excessive use of mannitol without adequate water replacement can ultimately lead to severe dehydration, free water losses, and hypernatremia. As water is extracted from cells, intracellular K^+ concentration rises, leading to cellular losses and hyperkalemia.
3. **Hyponatremia:** When used in patients with diminished renal function, parenterally administered mannitol is retained intravenously and causes osmotic extraction of water from cells, leading to hyponatremia.

(Ref: Katzung-13th)

Q. What is the role of osmotic diuretics in acute renal failure?

Ans.

Role of osmotic diuretics in acute renal failure: In acute renal failure, there is decreased GFR & increased total fluid reabsorption in PCT. This causes dryness of DCT & CT which leads to acute tubular necrosis. Diuretics catch up H_2O and maintain urine flow through the whole part of nephron & make them wet. Thus osmotic diuretics preserve long-term kidney function and may save the patient from dialysis.

(Ref: Katzung-13th; Lippincott's-6th)

Q. Write down the indications of low-efficacy diuretics. (SU-16J)

Ans. Write down the indications of Carbonic anhydrase inhibitors, K^+ sparing diuretics and Osmotic diuretics from above.

Q. What are the precautions to be taken during prolonged diuretics therapy?

Ans.

Precautions to be taken during prolonged diuretic therapy:

1. Assess state of dehydration
2. Serum electrolytes estimation
3. Monitoring of uric acid level at one week interval.
4. Correction of hypovolemia by saline infusion
5. Combination use of K^+ sparing diuretics with K^+ losing diuretics.
6. Close monitoring during furosemide therapy
7. Avoidance of simultaneous administration of other ototoxic agents with loop diuretics.

MCQ

Q. The adverse effects of thiazide includes- (DU-17M)

- a) hyperglycaemia
 - b) hyper-uricaemia
 - c) ototoxicity
 - d) hypokalaemia
 - e) hypo-magnesaemia
- a. T, b. T, c. F, d. T, e. T*

Q. Adverse effects of thiazide are- (DU-17J)

- a. hyperglycaemia
 - b. hypercalcaemia
 - c. hyperuricaemia
 - d. hypovolemia
 - e. hyperkalaemia
- a. T, b. T, c. T, d. T, e. F*

Q. Thiazide diuretics are associated with- (DU-16J)

- a) hypoglycaemia
 - b) hyponatraemia
 - c) hypocalcaemia
 - d) hyperuricaemia
 - e) hyperglycaemia
- a. F, b. T, c. F, d. T, e. T*

Q. The adverse effect of thiazide when used as antihypertensive include- (DU-15Ju)

- a. hyperglycemia
 - b. hyperuricemia
 - c. ototoxicity
 - d. hypokalemia
 - e. hypomagnesemia
- a. T, b. T, c. F, d. T, e. T*

Q. Frusemide- (DU-14J)

- a. acts on distal convoluted tubule
 - b. accelerates calcium loss from the body
 - c. can cause hyperuricemia
 - d. can cause hypermagnesemia
 - e. is effective in acute renal failure.
- a. F, b. T, c. T, d. F, e. T*

Q. Thiazide diuretic- (DU-13Ju)

- a. acts by blocking $\text{Na}^+/\text{K}^+ 2\text{Cl}^-$ transporter.
 - b. enhances Ca^{2+} reabsorption.
 - c. relieves acute pulmonary edema.
 - d. causes impaired carbohydrate tolerance.
 - e. causes hyperuricemia.
- a. F, b. T, c. F, d. T, e. T*

Q. Diuretics:- (SU-13J)

- a) Acetazolamide is used in the treatment of glaucoma
 - b) Frusemide is indicated in pulmonary edema
 - c) Thiazides can cause hyperglycemia
 - d) Amiloride block aldosterone receptors
 - e) Frusemide can cause ototoxicity
- a. T, b. T, c. T, d. F, e. T*

Q. Spironolactone- (DU-12Ju)

- a. Is an agonist drug. (F)
- b. Act at loop of Henle. (F)
- c. Causes hyperkalemia. (T)
- d. Inhibits Na^+/K^+ -co-transport. (F)
- e. Is a weak diuretic. (T)

Q. Adverse effects of thiazide diuretics are- (DU-12J)

- a. Ototoxicity (F)
- b. Hyperglycemia (T)
- c. Hyperuricemia (T)
- d. Hypermagnesemia (F)
- e. Hypokalemia (T)

Q. Frusemide- (DU-11Ju)

- a. Is the drug of choice in acute renal failure.
 - b. Induces hypercalcemia.
 - c. Is contraindicated when there is pulmonary edema.
 - d. Acts on PCT.
 - e. Is ototoxic.
- a. T, b. F, c. F, d. F, e. T*

Q. Spironolactone- (DU-11J)

- a. Is a high efficacy diuretic (F)
- b. Causes hyperkalemia (T)
- c. Is a steroid (T)
- d. Acts on PCT (F)
- e. Is drug of choice in acute renal failure (F)

Q. Spironolactone- (DU-10J)

- a. Is an agonist drug. (F)
- b. Acts at loop of Henle (F)
- c. Causes hyperkalemia (T)
- d. Inhibits Na^+/Cl^- co-transport (F)
- e. Is a weak diuretic. (T)

Q. Thiazide- (DU-10Ju)

- a. is a high-ceiling diuretic (F)
- b. acts on DCT (T)

- c. causes hyperkalaemia (F)
- d. causes hypercalcaemia (T)
- e. causes hyperuricemia(T)

Chapter 7

Antimicrobial Drugs

Amino quore cell wall
→ cidal

Basic principles of chemotherapy Amino → Name

- Q. Define antimicrobial agents.
- Q. Classify antimicrobial drugs. (SU-12Ju)
- Q. What do you mean by antibiotics & chemotherapeutic agents? (SU-08J)
- Q. Enumerate different categories of antimicrobial drugs. (CU-05J)
- Q. Define antibiotics. (DU-04J; RU-05S,03M, SU-13Ju,08J)

NA Syn. Inh.
→ narrow spectrum
Narrowly cidal
growth - Inh

Ans. **Antimicrobial agents:** Drugs that are used to kill or inhibit the growth and multiplication of microorganisms are called antimicrobial agents / drugs.

Classification of antimicrobial drugs:

- A. On the basis of source:
- 1. **Antibiotics:** Antibiotics are antibacterial substances produced by various species of microorganisms (bacteria, fungi, and actinomycetes) that suppress the growth of other microorganisms.
(Ref- Goodman & Gilman-12th edition)
 - 2. **Chemotherapeutics:** Chemotherapeutic agents then, are chemicals that are intended to be toxic for the pathogenic organism (or cancer cells) but innocuous to the host.
(Ref: Rang & Dale's-8th)
- B. According to the type of organism against which they are active:
- 1. Antibacterial drugs
 - 2. Antiprotozoal drugs
 - 3. Anthelmintic drugs
 - 4. Antifungal drugs
 - 5. Antiviral drugs
- C. According to spectrum of activity:
- 1. Broad spectrum antimicrobial drugs
 - 2. Narrow spectrum antimicrobial drugs

(Ref. Bennett & Brown-11th)

(Note: Common usage often extends the term antibiotics to include synthetic antimicrobial agents, such as sulfonamides and quinolones.)

(Ref- Goodman & Gilman-12th edition)

Q. Mention the sources of antibiotics.

Ans. Sources of antibiotics:

Organisms	Antibiotics
1. Actinomycetes (58%)	1. Actinomycin 2. Chloramphenicol 3. Macrolides 4. Aminoglycosides 5. Tetracycline
2. Fungi (18%)	1. Penicillin 2. Cephalosporins 3. Griseofulvin
3. Higher plants and bacteria (9%)	1. Bacitracin 2. Polymyxin
4. Algae, animal, lichens (3%)	

Q. What do you mean by chemotherapy?

Ans.

Chemotherapy: Chemotherapy means use of chemotherapeutic drugs to treat microbial infections or cancer cells without toxic effect on the host tissue.

(Ref: Rang & Dale's-8th)

Q. Differentiate between antibiotic and chemotherapeutics.

Ans.

Difference between antibiotic and chemotherapeutics:

Antibiotic	Chemotherapeutics
1. Natural	1. Synthetic
2. All antibiotics are chemotherapeutics.	2. All chemotherapeutics are not antibiotics
3. Antibiotics are active against microorganisms except virus & cancer cells	3. Chemotherapeutics are active against all microorganisms and cancer cells.

Q. Mention types of antimicrobial therapy.

Ans.

Types of antimicrobial therapy: 2 types —

1. **Empirical / presumptive / best guess therapy:** It is defined as the use of antimicrobial agents before the pathogen responsible for a particular illness or the susceptibility of the pathogen to a particular antimicrobial agent is known. *before C/S*
2. **Specific / definitive therapy:** Administration of an antimicrobial drug after confirming the sensitivity of the pathogen to that drug by culture and sensitivity (C/S) test is called specific therapy. *after C/S*

(Ref: Katzung-13th)

Q. What do you mean by empiric antimicrobial therapy? (RU-13Ju)

Q. Write short note on: Empirical or best guess therapy.

Ans.

Empirical / best guess therapy: Antimicrobial agents are frequently used before the pathogen responsible for a particular illness or the susceptibility to a particular antimicrobial agent is known. This use of antimicrobial agents is called empirical (or presumptive) therapy.

(Ref: Katzung-13th)

Approach to empiric therapy

1. **Formulate a clinical diagnosis of microbial infection:** (eg, pneumonia, cellulitis, sinusitis).
2. **Obtain specimens for laboratory examination**
3. **Formulate a microbiologic diagnosis**
4. **Determine the necessity for empiric therapy**
5. **Institute treatment:** selection of empiric therapy may be based on the microbiologic diagnosis or a clinical diagnosis without available microbiologic clues. if no microbiologic information is available, the antimicrobial spectrum of the agent or agents chosen must necessarily be broader, taking into account the most likely pathogens responsible for the patient's illness.

(Ref: Katzung-13th)

Indication of empirical / best guess therapy:

1. Community acquired pneumonia, in which it is difficult to identify a specific pathogen.
2. Treatment of febrile episodes in neutropenic cancer patients.
3. Bacteremia.
4. Critically ill patient.

(Ref: Katzung-13th + Bennett & Brown-11th)

Q. Classify antimicrobial agents on the basis of mechanism / mode of action. (DU-14J, CU-14J, RU-04M, SU-17M/J, 12Ju, 11J, 09Ju)

Q. Classify antibiotics according to their site of action on bacteria. (DU-11J)

Q. List the bacterial/microbial cell wall synthesis inhibitors. (DU-17M, 16Ju, 15J, CU-09Ju)

- Q. List the antimicrobials that inhibit protein synthesis. (DU-17J, CU-15J, SU-10J)
 Q. List the bacterial nucleic acid synthesis inhibitors. (CU-09J, SU-09J)
 Q. Classify antibacterial drugs. (CU-05S, RU-04J, SU-16Ju)
 Q. Classify antibiotics. (SU-01J)
 Q. How antimicrobials are grouped? (SU-12Ju)

Ans.

Classification of anti-bacterial drugs:

A. According to mechanism / mode of action / site of action: (This classification usually comes in the written exams)

Mechanism of Action	Drugs
1. Inhibition of cell wall synthesis	
a. Antibacterial activity	
▪ Inhibition of cross-linking (transpeptidation) of peptidoglycan	Penicillins, cephalosporins, imipenem, aztreonam, vancomycin
▪ Inhibition of others steps in peptidoglycan synthesis	Cycloserine, bacitracin
b. Antifungal activity	
▪ Inhibition of β -glucan synthesis	Caspofungin
2. Inhibition of protein synthesis	
▪ Action on 50S ribosomal subunit	Chloramphenicol, erythromycin, clindamycin, linezolid
▪ Action on 30S ribosomal subunit	Tetracyclines and aminoglycosides
3. Inhibition of nucleic acid synthesis	
▪ Inhibition of nucleotide synthesis	Sulfonamide, trimethoprim
▪ Inhibition of DNA synthesis	Quinolones
▪ Inhibition of mRNA synthesis	Rifampicin
4. Alteration of cell membrane function	
▪ Antibacterial activity	Polymyxin, daptomycin
▪ Antifungal activity	Amphotericin B, nystatin, ketokonazole
5. Other mechanisms of action	
▪ Antibacterial activity	Isoniazid, metronidazole, ethambutal, pyrazinamide
▪ Antifungal activity	Griseofulvin, pentamidine

(Ref: Review-Medical microbiology-12th)

B. According to effect on bacteria:

- Bacteriostatic:** Bacteriostatic drugs arrest the growth and replication of bacteria at serum levels achievable in the patient, thus limiting the spread of infection while the body's immune system attacks, immobilizes, and eliminates the pathogens. For example, sulphonamides, tetracyclines and chloramphenicol. If the drug is removed before the immune system has scavenged the organisms, enough viable organisms may remain to begin a second cycle of infection.
- Bactericidal:** Bactericidal drugs kill bacteria at drug serum levels achievable in the patient. Because of their more aggressive antimicrobial action, these agents are often the drugs of choice in seriously ill patients. For example, penicillins, cephalosporins, aminoglycosides, isoniazid and rifampicin.

(Ref: Lippincott's-6th)

C. According to spectrum of activity:

- Broad-spectrum:** An antibiotic that is effective against a wide range of microorganisms which includes both Gram positive and Gram negative bacteria is called as a broad spectrum antibiotic. Eg, fluroquinolone, cephalosporin, tetracycline, chloramphenicol etc.
- Narrow spectrum:** Chemotherapeutic agents acting only on single or a limited group of microorganisms are said to have a narrow spectrum. Eg, isoniazid is active only against mycobacteria. Narrow spectrum antibiotics are active against either Gram positive or Gram negative bacteria.

3. **Extended spectrum:** Extended spectrum is a term applied to antibiotics that are effective against Gram positive organisms and also against a significant number of Gram-negative bacteria. Extended spectrum antibiotics are effective against *Pseudomonas aeruginosa*. Eg, anti-pseudomonal penicillin, ceftazidime.
(Ref: Lippincott's-6th)

Q. Enlist the bactericidal antibiotics. (CU-16J)

Ans. Write from the table below.

* Reverse spectrum
→ penicillins
→ Pregnancy induced diarrhoea (Silexam)

Nice to know

It is possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another. For example, chloramphenicol is bacteriostatic against gram-negative rods and is bactericidal against other organisms, such as *S. pneumoniae*.

(Ref: Lippincott's-6th)

Bacteriostatic drugs: Antimicrobials that inhibit microbial growth are called bacteriostatic drugs. In general protein synthesis inhibitors are bacteriostatic. 1. Macrolides 2. Clindamycin 3. Ethambutol 4. Tetracyclines 5. Sulfonamides 6. Trimethoprim 7. Nitrofurantoin 8. Chloramphenicol 9. Novobiocin 10. Oxazolidinones	Bactericidal drugs: Antimicrobials that kill microbials are called bactericidal drugs. In general cell wall active agents are bactericidal. 1. Beta-lactam antibiotics. 2. Quinolones 3. Aminoglycosides 4. Metronidazole 5. Isoniazid 6. Rifampicin 7. Pyrazinamide 8. Vancomycin 9. Ketolides 10. Bacitracin
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(Ref: Katzung-13th)

Q. What do you mean by broad spectrum antibiotics? Why they are called so? (SU-08Jan)

Q. Define broad spectrum antibiotics with example. (CU-03S, RU-04S, 03S, SU-03M)

Q. Shortly discuss the adverse effects associated with the use of broad spectrum antibiotics. (SU-13Ju, 09J)

Q. Give the advantages and disadvantages of broad spectrum antibiotics.

Ans.

Broad spectrum antibiotics: An antibiotic that is effective against a wide range of microorganisms which includes both Gram positive and Gram negative bacteria is called as a broad spectrum antibiotic. Eg,

1. Penicillin: Ampicillin, amoxicillin
2. Fluoroquinolone
3. Cephalosporin
4. Tetracycline
5. Chloramphenicol etc.

Advantages of broad spectrum antibiotics:

1. Coverage of wide range of microorganisms
2. No need to apply combination therapy.

Disadvantages / adverse effects of broad spectrum antibiotics:

1. Risk of development of drug resistance
2. Superinfection
3. Chance of treatment failure
4. Masking of infection
5. Hypersensitivity to antimicrobial or their metabolic product

6. Recurrence of infection
7. Chance of cross resistance.

Q. Classify bactericidal antibiotics.

Q. Define time-dependent and concentration-dependent killing of bacteria. (CU-15Ju)

Ans.

Bactericidal antibiotics: Bactericidal agents can be divided into two groups:

1. **Agents that exhibit concentration-dependent killing:** For drugs whose killing action is concentration-dependent, the rate and extent of killing increase with increasing drug concentrations.

Drugs showing concentration-dependent killing:

- a. Aminoglycosides
- b. Fluoroquinolones
- c. Carbapenems

Importance: Concentration-dependent killing is responsible for the efficacy of **once-daily dosing** of aminoglycosides.

2. **Agents that exhibit time-dependent killing:** For drugs whose killing action is time-dependent, bactericidal activity continues as long as serum concentrations are greater than the MBC.

Drugs showing time-dependent killing:

- a. β -lactams
- b. Vancomycin
- c. Glycopeptides
- d. Macrolides
- e. Clindamycin
- f. Linezolid

(Ref: Katzung-13th; Lippincott's-6th)

Q. Define MIC and MBC? (CU-05M)

Ans.

Minimum inhibitory concentration (MIC): It is the lowest concentration of drug that inhibits the growth of the microorganisms.

Importance: To guide the physician to choose both the drug and dose.

Minimum bactericidal concentration (MBC): It is the lowest concentration of drug that kills bacteria or inhibits at least 99.9% of bacterial colonies.

(Ref: LANGE Microbiology-12th edition)

Relation between MIC and MBC:

- In case of bactericidal drugs: MBC is equal or very similar to MIC.
- In case of bacteriostatic drugs: MBC is 2 to 8 times higher than MIC.

Q. Define post-antibiotic effect? (RU-10Ju, CU-15J,07J)

Q. Discuss the concept of post antibiotic effect with examples? (CU-06M, SU-11J)

Q. Short note: Post-antibiotic effect. (DU-15J, RU-16Ju)

Ans.

Post-antibiotic effect or PAE: Persistent suppression of bacterial growth after limited exposure to an antimicrobial agent is known as the postantibiotic effect (PAE). The PAE reflects the time required for bacteria to return to logarithmic growth.

Calculation: The PAE can be expressed mathematically as follows:

$$PAE = T - C$$

$T \rightarrow$ time required for the viable count to increase tenfold after drug removal.

$C \rightarrow$ time required for the count in an untreated culture to increase tenfold.

Proposed mechanisms include

1. slow recovery after reversible nonlethal damage to cell structures;
2. persistence of the drug at a binding site or within the periplasmic space; and
3. the need to synthesize new enzymes before growth can resume.

Example:

PAE against gram '+ve' cocci	PAE against gram '-ve' bacilli
Aminoglycosides	Aminoglycosides
Cephalosporins	Carbapenems
Penicillin	Tetracycline
Fluoroquinolones	Rifampicin
Macrolides	
Carbapenems	

(Ref: Katzung-13th)

Q. Write down the principles of anti-microbial drug therapy. (DU-16J, CU-17J, RU-17J, SU-14J, 13Ju/J, 11J, 09J)

Q. Enumerate general principles of antimicrobial prescribing? (CU-14Ju, 04S)

Ans.

General principles of antimicrobials prescribing: The following principles are a guide to good practice with antimicrobial agents.

1. **Making a diagnosis:** Make a diagnosis as precisely as is possible and define the site of infection, the organism(s) responsible and their sensitivity to drugs.
2. **Removal of barrier to cure**, e.g. drainage of abscess, removal of obstruction in urinary or respiratory tract.
3. **Decide whether chemotherapy is really necessary or not.** As a general rule, acute infections require chemotherapy whilst other measures may be more important for resolution of chronic infections, eg, surgery for chronic abscess or empyema under antibiotic coverage.
4. **Selection of the best drug**, depending on specificity, pharmacokinetic factor and the patient.
5. Administration of the drug in **optimal dose and frequency**.
6. **Continue therapy** until apparent cure has been achieved; most acute infections are treated for **5-10 days**. There are many exceptions to this, such as typhoid fever, tuberculosis and infective endocarditis, in which relapse is possible long after apparent clinical cure and so the drugs are continued for a longer time.
7. **Test for cure.** In some infections (eg, UTI in pregnancy), microbiological proof of cure is desirable because disappearance of symptoms and signs occurs before the organisms are eradicated. Microbiological culture must be done, of course, after withdrawal of chemotherapy.
8. **Prophylactic chemotherapy** for surgical and dental procedures should be of very limited duration, often only a single large dose being given.
9. **Carriers of pathogenic or resistant organisms**, in general, should not routinely be treated to remove the organisms for it may be better to allow natural re-establishment of a normal flora.

(Ref- Bennett & Brown-11th)

Q. What do you mean by rational use of antibiotics? (RU-04S)

Q. Discuss rational use of antibiotics? (CU-11Ju)

Q. Describe principles of rational use of antibiotics. (CU-16J)

Q. How can you use antimicrobials rationally? (DU-11Ju)

Q. Write a short note on: Rational use of antibiotics. (CU-06S)

Ans.

Rational use of antibiotics: Rational use of antibiotics means prescribing the drugs by considering their therapeutic efficacy & suitability.

Criteria / factors of rational use of antibiotic:

1. Appropriate diagnosis
2. Appropriate antibiotic with adequate bacteriological information
3. Adequate dosage, frequency and route of administration
4. Adequate duration
5. No indiscriminate use of broad spectrum antibiotics
6. Consideration of patient's condition during antibiotic selection
7. Restriction of antimicrobial combination to appropriate circumstances e.g. tuberculosis.
8. Constant monitoring of resistance pattern.
9. Limit the use of new drug.

Q. Enumerate the important criteria for selecting right antimicrobial drug for a patient or diseases. (DU-09Ju, CU-08J, SU-14Ju)

Q. Discuss the factors governing the choice of antimicrobials in the treatment of specific infections. Give examples to illustrate your points. (CU-11J,09J,08Ju)

Ans.

Important criteria for selecting right antimicrobial drug:

A. Host factors:

1. Concomitant disease status e.g. AIDS, severe chronic liver disease, chronic renal failure (CRF)
2. Prior adverse drug reactions
3. Impaired elimination or detoxification of the drug
4. Age of the patient
5. Pregnancy status
6. Epidemiologic exposure.

B. Pharmacologic factors:

1. Pharmacokinetics factors: Absorption, distribution & elimination.
2. Drug interactions: Both pharmacodynamic & pharmacokinetic interactions.
3. The ability of the drug to be delivered at the site of action
4. The potential toxicity of the drug

C. Other factors:

1. Susceptibility of an organism
2. Spectrum of activity
3. Dosing interval of drug
4. Cost-effective ratio of the drug
5. Benefit risk ratio

(Ref: Katzung-13th)

Q. Describe the factors on which dose frequency of antibiotics depends. (CU-15Ju)

Ans.

Factors affecting dose frequency of antibiotics

1. **Half life of drugs**
 - ↑Half life → ↓ dose frequency.
 - ↓Half life → ↑ dose frequency.
2. **Severity of clinical illness:** ↑Severity → ↑ dose frequency.
3. **Post-antibiotic effect (PAE):** Presence of PAE → ↓ dose frequency.

Q. Explain the general hazards of antimicrobial therapy.

Q. Describe the hazards of indiscriminate use of antibiotic? (DU-06/05M, CU-08J)

Q. Mention the limitations of using of antimicrobials. (DU-14Ju)

Ans.

Hazards of indiscriminate use of antibiotics:

1. Risk of development of drug resistance
2. Super infection
3. Failure of antibiotic therapy
4. Chance of cross resistance
5. Recurrence of infection
6. Severe toxic effects

Q. What factors may be responsible for the failure of antimicrobial drug therapy (DU-13Ju,11/10Ju, CU-07Ju,05M, SU-12Ju,11Ju,10Ju)

Q. Write the reasons of treatment failure. (SU-16J)

Q. Outline antimicrobial treatment failure in brief. (SU-17M)

Ans.

Causes of failure of antimicrobial drug therapy:

1. Development of drug resistance
2. Failure of selection of right antimicrobial drug
3. Suboptimal use of antibiotic:
 - Inadequate dose
 - Prolong dosing interval
 - Short duration of therapy
 - Unsuitable route
4. Presence of abscesses or foreign bodies
5. Low immune status of patient: Malnutrition, malignancy, HIV infection.
6. Inadequate culture and sensitivity test
7. Super infection by other pathogens

(Ref: Katzung-13th)

Q. Name the antimicrobial agents which can be prescribed in pregnancy safely. (DU-08J)

Q. List the antimicrobials that are safe in pregnancy. (CU-15J,07Ja, SU-12Ju)

Q. Outline rational use antimicrobials in pregnancy and lactation. (SU-14Ju)

Ans.

Safe antimicrobials in pregnancy:

1. Penicillins
2. Cephalosporins
3. Monobactam
4. Carbapenems
5. Vancomycin
6. Fosfomycin
7. Macrolides
8. Clindamycin
9. Quinolone (Not the fluoroquinolones)
10. Proguanil

(Ref: Katzung-13th)

Q. Short note: Chemoprophylaxis. (DU-14Ju,10J)

Q. What is chemoprophylaxis? Give example. (CU-03S; RU-11J,06S)

Q. Define chemoprophylaxis with examples where this phenomenon is exploited. (RU-16J)

Ans.

Chemoprophylaxis: Chemoprophylaxis means administration of drugs to prevent infection or to prevent development of clinical attacks.

(Ref: Rang & Dale's-8th)

Example:

1. Benzathine penicillin G is used for prophylaxis of rheumatic fever:

2. Ampicillin is used for prophylaxis of neonatal sepsis and meningitis in children born of mothers carrying *Streptococcus pyogenes*.
3. Cefazolin is used for prophylaxis of staphylococcal surgical wound infections.
4. Ceftriaxone is used for prophylaxis of gonorrhoea in those exposed to *Neisseria gonorrhoeae*.
5. Ciprofloxacin is used for prophylaxis of meningitis in those exposed to *Neisseria meningitidis* and prevention infection in neutropenic patients.

(Ref: LANGE Microbiology-12th edition)

Antimicrobial combination & synergism

- Q. What do you mean by combination of chemotherapeutics? Give the advantages & disadvantages of it. (RU-03S, SU-14Ju)
- Q. Justify antimicrobial combination with examples. (DU-17M, 14Ju, 12Ju, 10J, RU-13Ju, 12Ju, 10Ju)
- Q. Mention the objectives of antimicrobial combination with examples. (RU-14J, SU-15J)
- Q. Outline the principles of combined use of antimicrobials. (RU-15Ju)
- Q. What are the advantages of combination of chemotherapy? (DU-10Ju, RU-03S)
- Q. Explain with example: Chemotherapeutic potentiation. (RU-04M)
- Q. Short note: Antimicrobial combination. (DU-11Ju)
- Q. Short note: Aims and objectives of antimicrobial combination. (SU-16J, 15Ju)

Ans.

Combination of chemotherapeutics: It means administration of two or more chemotherapeutics at the same time for a particular infectious disease.

Advantages / justification / Aims and objectives of combination of chemotherapeutics:

1. To provide broad-spectrum empiric therapy in seriously ill patients.
2. To treat polymicrobial infections such as intra-abdominal abscesses.
3. To decrease the emergence of resistant strains, eg, treatment of tuberculosis.
4. To decrease dose-related toxicity by using reduced doses of one or more components of the drug regimen.
5. To obtain enhanced inhibition or killing.
6. To obtain potentiation or synergism.

(Ref: Katzung-13th)

Disadvantages of combination of chemotherapeutics:

1. Increased risk of super infections.
2. Wide range of adverse effects. Toxicity of one agent may be enhanced by another; e.g. Vancomycin + Tobramycin & Gentamicin + Cephalothin produces exaggerated kidney failure.
3. Antibiotic antagonism.
4. Increased cost burden to the patient.
5. Risk of development of cross-resistance.

(Ref: Tripathi- 6th/678)

Q. What is chemotherapeutic synergism? (RU-10J)

Q. What is chemotherapeutic synergism & how it can be exploited in therapeutics? (RU-05M)

Q. What do you mean by chemotherapeutic potentiation? How does it help in therapeutics? (RU-04S)

Ans.

Chemotherapeutic synergism: When the inhibiting or killing effects of two or more antimicrobials used together are significantly greater than expected from their effects when used individually, then it is called chemotherapeutic synergism.

(Ref: Katzung-13th)

Mechanisms of Synergistic Action: There are 3 major mechanisms:

1. **Blockade of sequential steps in a metabolic sequence:** Trimethoprim-sulfamethoxazole is the best-known example of this mechanism of synergy. Blockade of the two sequential steps in the folic acid pathway by trimethoprim-sulfamethoxazole results in a much more complete inhibition of growth than achieved by either component alone.

2. **Inhibition of enzymatic inactivation:** Enzymatic inactivation of β -lactam antibiotics is a major mechanism of antibiotic resistance. Inhibition of β -lactamase by β -lactamase inhibitor drugs (eg, sulbactam) results in synergism.
3. **Enhancement of antimicrobial agent uptake:** Penicillins and other cell wall-active agents can increase the uptake of aminoglycosides by a number of bacteria, including staphylococci, enterococci, streptococci, and *P. aeruginosa*. Enterococci are thought to be intrinsically resistant to aminoglycosides because of permeability barriers. Similarly, amphotericin B is thought to enhance the uptake of flucytosine by fungi.

(Ref: Katzung-13th)

Advantages of chemotherapeutic synergism

1. Broaden the spectrum of antimicrobial activity.
2. Decrease the emergence of resistance.
3. Decrease dose related toxicity.
4. To obtain enhanced inhibition or killing.

(Ref: Katzung-13th + Bennett & Brown-11th)

Q. Give with example some disease condition where chemotherapeutic synergism is helpful. (RU-10J)

Q. What are the indications of combination of chemotherapeutics?

Ans.

Indications / examples of combination of chemotherapeutics:

1. **Treatment of mixed bacterial infections (e.g. peritonitis):**
 - Metronidazole + 2nd / 3rd generation cephalosporins (cefoxitin / cefmetazole / cefotetan / ceftizoxime / moxalactam)
2. **Treatment of highly resistant strains of microorganism (e.g. meningitis caused by highly penicillin resistant strains of pneumococci):**
 - 3rd generation cephalosporins (ceftriaxone or cefotaxime) + gentamicin / vancomycin
3. **Therapy of severe infections (e.a. hospital acquired pneumonia):**
 - Cefuroxime + flucloxacillin
4. **Extended coverage of antibacterial activity (e.g. Staphylococcal endocarditis):**
 - Gentamicin + nafcillin
5. **Prevention of emergency of resistant strains of microorganisms (e.g. pulmonary tuberculosis):**
 - Isoniazid
 - Rifampicin
 - Pyrazinamide
 - Ethambutol
 - Streptomycin
6. **For pseudomonas infected orthopedic prosthesis:**
 - 3rd generation cephalosporin (ceftazidime / Cefoperazone) + ciprofloxacin

Q. Explain with example: Antibiotic antagonism. (RU-04M)

Ans.

Antibiotic antagonism: Combination of bacteriostatic and bactericidal drugs may protect the microorganism from bactericidal effect of bactericidal drug. This is known as antibiotic antagonism.

Examples: In **pneumococcal meningitis**, patients who were treated with the combination of penicillin and chlortetracycline had a mortality rate of 79% compared with a mortality rate of 21% in patients who received penicillin monotherapy.

Mechanism of antibiotic antagonism: There are 2 major mechanisms of antimicrobial antagonism:

1. **Inhibition of cidal activity by static agents:** Bacteriostatic agents such as tetracyclines and chloramphenicol can antagonize the action of bactericidal cell wall-active agents because cell wall-active agents require that the bacteria be actively growing and dividing.

2. **Induction of enzymatic inactivation:** Beta-lactam antibiotics such as imipenem, ceftioxin, and ampicillin are potent inducers of β -lactamase production. If an inducing agent is combined with an intrinsically active but hydrolyzable β -lactam such as piperacillin, antagonism may result.

(Ref: Katzung-13th)

Bacterial resistance to antibiotics

- Q. What is meant by bacterial resistance to antibiotics? (RU-04M)
 Q. Outline the mechanism of microbial resistance development against antimicrobials. (CU-11J, 09/08Ju, SU-15J)
 Q. How does microorganism develop resistance against antibiotics? (DU-11J, 07M)
 Q. How microbes develop resistance to antimicrobials? (DU-04J, CU-07J, 06S, SU-17J, 16Ju, 13Ju, 11J)
 Q. Short note: Mechanism of non-genetic drug resistance. (SU-15Ju)

Ans.

Bacterial resistance: When an inhibitory or killing effect of antibiotics cannot be achieved without toxic effects to host cell, it is called bacterial resistance.

MIC is 10 times more

Mechanism of drug resistance:

Genetic $\rightarrow$ Chromosomal (mutation), Plasmid (Resistance Transposon)

Mechanism	Example	Drugs commonly affected
1. Production of enzymes which inactivate drug	β -lactamase produced by Gram-negative bacteria	β -lactam drugs such as penicillins, cephalosporins etc.
2. Modification of target site of drug action	a. Mutation in penicillin-binding proteins.	Penicillins
	b. Mutation in protein in 30S ribosomal subunit.	Aminoglycosides
	c. Replace alanine with lactate in peptidoglycan.	Vancomycin
	d. Mutation in DNA gyrase.	Quinolones
	e. Mutation in RNA polymerase.	Rifampicin
	f. Mutation in catalase-peroxidase.	Isoniazid
3. Reduction of permeability of drug	Mutation in porin proteins	Penicillins, aminoglycosides etc.
4. Pumping out of drug from bacterial cell	Multidrug resistance pump	Tetracyclines, sulfonamides etc.

(Ref: Review-Medical microbiology-12th)

- Q. Short note: Bacterial beta lactamase. (SU-12Ju)

Ans.

Bacterial beta lactamase: β -lactamase is an enzyme produced by staphylococci, gram-negative bacteria, haemophili, gonococci, and others. More than 50 different β -lactamases are known, most of them produced under the control of bacterial plasmids. Some β -lactamases are inducible by the newer cephalosporins.

Function: β -lactamase produces resistance against β -lactam drugs by hydrolyzing the β -lactam ring.

β -lactamase inhibitors: Clavulanic acid and sulbactam bind strongly to β -lactamases and inactivate them. Combinations of these inhibitors and penicillins, e.g., clavulanic acid and amoxicillin, can overcome resistance.

(Ref: Review-12th; Jawetz's-25th)

Q. Write down about transfer of resistance genes among bacteria.

Ans.

Transfer of resistance genes: Antibiotic resistance in bacteria spreads at three levels:

- A. **By transfer of bacteria between people**
- B. **Transmission of resistance genes between genetic elements within the bacterium** by transposons.
- C. **Transmission of resistance genes between bacteria of same or different species:** It is of fundamental importance in the spread of resistance to antibiotics. There are three mechanisms for gene transfer:
 1. Conjugation
 2. Transduction
 3. Transformation

Transposons: Segments of DNA containing resistance genes are called transposons. Transposons can be fairly readily transferred (transposed) from one plasmid to another and also from plasmid to chromosome or vice versa in the same bacteria.

Conjugation: Conjugation involves cell-to-cell contact during which chromosomal or extrachromosomal DNA is transferred from one bacterium to another. It is the main mechanism for the spread of resistance. Many Gram-negative and some Gram-positive bacteria can conjugate.

Transduction: Transduction is a process by which plasmid DNA is enclosed in a bacterial virus (or phage) and transferred to another bacterium of the same species. It is a relatively ineffective means of transfer of genetic material.

Transformation: In a few species, a bacterium can, under natural conditions, undergo transformation by taking up naked DNA from its environment and incorporating it into its genome through the normal cross-over mechanism. Transformation is probably not of importance in the clinical problem of drug resistance.

(Ref: Rang & Dale's-8th)

Q. What do you mean by selection pressure?

Ans.

Selection pressure / natural selection: When antibiotic is administered, susceptible strains are killed but resistant strains caused by mutation, still survive and multiply. This process of emergence of resistant strains is referred to as selection pressure; e.g. *Staphylococcus aureus* possesses selection pressure by producing penicillinase through resistant strains.

Q. How can you limit antimicrobial resistance? (DU-17M, 12Ju, 10J, RU-16J, 12Ju, 11Ju)

Q. Short note: Prevention of non-genetic drug resistance. (SU-15Ju)

Q. How drug resistance is overcome? (SU-17J)

Ans.

How to limit drug resistance:

1. Avoidance of indiscriminate use of antibiotic.
2. Use of combination of antimicrobials, eg, in the treatment of tuberculosis.
3. Avoidance of unnecessary use of combination therapy to prevent cross resistance.
4. Constant monitoring of resistance pattern in hospital or community.
5. Restriction of use of the newest member of antimicrobials.

(Ref- Bennett & Brown-11th)

Superinfection

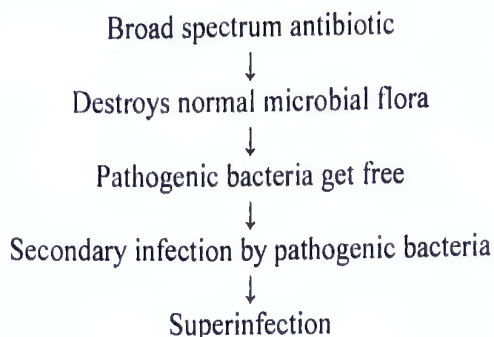
Q. What is superinfection? How does it occur? How could you limit it? (DU-03J/S, RU-14J, SU-11J)

Q. Outline the management of superinfection? (CU-07J)

Q. Short note: Superinfection. (DU-15J, 13J, 12J, 07M, SU-15J)

Ans.

Superinfection: Clinical evidence of new infection during antimicrobial therapy for one infection is called superinfection.

Mechanism of superinfection:**Drugs causing superinfection:**

1. Broad spectrum penicillin: Ampicillin & Amoxicillin
2. Cephalosporins
3. Chloramphenicol
4. Aminoglycosides
5. Tetracycline

Conditions predisposing to superinfection:

1. Corticosteroid therapy
2. Leukemia & other malignancies
3. Anticancer drugs.
4. AIDS
5. Agranulocytosis
6. Diabetes mellitus
7. SLE etc.

Sites of superinfection:

1. Oropharynx
2. Intestine
3. Respiratory tract
4. Genitourinary tract
5. Skin

Management of superinfection:**A. General management:**

1. Immediate discontinuation of drug
2. Culture and sensitivity test
3. Vitamin-B complex can be given if there is stomatitis, cheilosis

B. Specific management:

Organism	Clinical sign	Treatment
<i>Candida albicans</i>	Monilial diarrhea, thrush, <i>(oral thrush)</i> vulvovaginitis	• Nystatin or clotrimazole
Resistant <i>S. aureus</i>	Gastroenteritis <i>(Abdominal cramps, diarrhoea)</i>	• Cloxacillin, flucloxacillin
<i>Clostridium difficile</i>	Pseudomembranous colitis	Metronidazole & vancomycin
<i>Proteus</i>	UTI, enteritis	Cephalosporins or gentamicin
<i>Pseudomonas</i>	UTI, enteritis	Carbenicillin, ticarcillin or gentamicin.

(Ref: Tripathi-6th/672, 673)

Miscellaneous

Q. Write short note on: Opportunistic infection.

Ans.

Opportunistic infection: The infection that arises in patients with compromised immune system or reduced phagocytic cellular defenses caused by disease (AIDS, leukemia, hypogammaglobulinemia) or drugs (cytotoxics, adrenal steroids).

Some opportunistic organisms and diseases:

<i>Pneumocystis carinii</i>	Pneumonia
<i>E. coli</i> and <i>Klebsiella</i>	Primary septicemia
<i>Staphylococcus epidermidis</i>	Infection of intravenous catheters

(Ref: Bennett & Brown-11th)

Q. Mention the drugs used in anaerobic infection. (CU-17M, SU-07Ju)

Q. Explain the action of drugs used in anaerobic infection. (SU-07Ju)

Q. Enumerate the drugs that are effective against anaerobic microbes. (CU-13Ju)

Ans.

Drugs used in anaerobic infection

Anaerobic bacteria	1 st choice	2 nd choice
Gram +ve (<i>Clostridia</i> , <i>Peptococcus</i> , <i>Actinomyces</i> , <i>Peptostreptococcus</i>)	Penicillin Clindamycin	Vancomycin, Carbapenems.
<i>Clostridium difficile</i>	Metronidazole	Vancomycin, Bacitracin
<i>Bacteroides fragilis</i>	Metronidazole	Carbapenems, Clindamycin, Co-amoxiclav

(Ref: Katzung-13th)

Q. Enlist the anti-pseudomonal antibiotics. (CU-15Ju, SU-17M)

Q. Categorize antimicrobials that are effective against *pseudomonas aeruginosa*. (CU-04S)

Q. Name the drugs used in the treatment of pseudomonas infection. (DU-07M)

Ans.

Anti-pseudomonal drugs:

1. **Extended spectrum penicillins:** Ticarcillin, Piperacillin, Mezlocillin, Azlocillin
2. **3rd generation cephalosporins:** Cefoperazone, Ceftazidime (Other members don't act against pseudomonas)
3. **4th generation cephalosporin:** Cefepime
4. **Monobactam:** Aztreonam
5. **Carbapenem:** Imipenem, Meropenem
6. **Aminoglycosides:** Tobramycin, Gentamicin, Amikacin, Netilmicin
7. Azithromycin
8. **Fluoroquinolones** except Norfloxacin: Ciprofloxacin, Lomefloxacin, Levofloxacin

(Ref: Katzung-13th)

Q. Name the drugs used in rickettsial infection. (RU-10J)

Ans.

Anti-rickettsial drugs:

1. Tetracyclines.
2. Chloramphenicol.
3. In tetracycline & chloramphenicol resistance strains (in Thailand): Rifampicin.

(Ref: Davidson's medicine-22nd edition)

Q. Enumerate the anti-staphylococcal antimicrobials. (SU-17M)

Ans.

Anti-staphylococcal drugs:

1. **Penicillins:** Nafcillin, Methicillin, Oxacillin, Cloxacillin, Flucloxacillin.
2. **Combined Penicillin:** Co-amoxiclav
3. **Cephalosporins:** 1st generation cephalosporins (cephradine, cefazolin)
4. **Vancomycin** (Methicillin Resistant Staphylococcus aureus, MRSA)
5. **Others:** Co-trimoxazole, Minocycline (MRSA).

Q. Name the drugs that can be used for treating Gram -ve infections.

Ans.

Antimicrobial drugs effective against Gram -ve bacteria:

1. **Broad spectrum penicillins:** Ampicillin, Amoxicillin
2. **Extended spectrum penicillins:** Ticarcillin, Piperacillin, Mezlocillin, Azlocillin
3. **3rd & 4th generation cephalosporins:** Ceftazidime, Cefoperazone, Cefepime.
4. **Monobactam:** Aztreonam
5. **Carbapenems:** Ertapenem, Imipenem, Meropenem
6. **Aminoglycosides:** Clindamycin
7. Tetracycline
8. **Folate antagonists:** Co-trimoxazole, Sulfonamides, Trimethoprim
9. **Fluoroquinolones:** Ciprofloxacin, Levofloxacin, Lomefloxacin.

(Ref: Katzung-13th)

Q. Name the antimicrobial drugs that are effective against Gram +ve microorganisms.

Ans.

Antimicrobial drugs effective against Gram +ve bacteria:

1. **Penicillins:** Benzylpenicillin, Phenoxymethylpenicillin, Ticarcillin, Flucloxacillin, Dicloxacillin.
2. **1st & 2nd generation cephalosporins:** Cephadrine, Cephalexin, Cephazolin, Cefuroxime.
3. **Macrolides:** Erythromycin, Azithromycin, Clarithromycin
4. Carbapenem
5. Vancomycin
6. Chloramphenicol
7. **Aminoglycosides:** Clindamycin, Gentamycin
8. **Folate antagonist:** Co-trimoxazole, Sulfonamides, Trimethoprim
9. **Fluoroquinolones:** Moxifloxacin, Trovafloxacin.

(Ref: Katzung-13th)

Q. Name four chemotherapeutic agents which should not be used in children. (DU-13Ju)

Ans.

Four chemotherapeutic agents which should not be used in children

1. **Tetracycline:** In children below 10 years of age- Chance of dental caries.
2. **Fluroquinolones / ciprofloxacin:** Arthropathy
3. **Chloramphenicol:** Gray baby syndrome in newborn infants.
4. **Pyrantel pamoate:** Children under age of 2 years.
5. **Praziquantel:** Children under age of 4 years.
6. **Sulfonamides:** Newborn baby → Kernicterus.

Q. Enlist five antibiotics which cannot cross blood-brain barrier? (CU-15Ju)

Ans.

Antibiotics which cannot cross blood-brain barrier

1. Gentamicin
2. Amikacin
3. Streptomycin
4. Erythromycin
5. Fusidic acid

Nice to know:Anti-microbial dose adjustment in disease condition:**A. Dose adjustment in liver diseases:**

Require dose reduction	1. Metronidazole 2. Clindamycin 3. Isoniazid 4. Rifampicin 5. Chloramphenicol
Should be avoided in any liver disease	1. Erythromycin estolate 2. Pyrazinamide 3. Talampicillin 4. Tetracyclines 5. Nalidixic acid 6. Pefloxacin

B. Dose adjustment in renal diseases:

Require dose reduction (even in mild renal impairment)	1. Aminoglycosides 2. Cephalosporins 3. Vancomycin 4. Amphotericin B 5. Ethambutol 6. Flucytosine
Should reduce dose (only in moderate to severe renal failure)	1. Metronidazole 2. Cotrimoxazole 3. Aztreonam 4. Meropenem 5. Imipenem 6. Clarithromycin 7. Carbenicillin 8. Fluoroquinolones
Antimicrobials should be avoided	1. Cephalothin 2. Nalidixic acid 3. Talampicillin 4. Tetracyclines (except Doxycycline) 5. Nitrofurantoin

(Ref: Tripathi-6th/673 & 674)

Cell wall synthesis inhibitors

overall
classification
I-301

Q. List β -lactam antibiotics. (DU-15Ju,06S; CU-11J,08Ju; SU-13J,10J,08J, RU-17J,13J)

Q. Why β -lactam drugs are called so? (RU-17J,13J)

Ans.

β -lactam antibiotics: These antibiotics have a **β -lactam ring** structure and exert a bactericidal action by disrupting cell wall synthesis in rapidly dividing organisms. They are classified into eight groups:

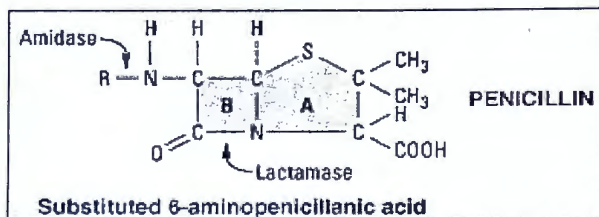
1. **natural penicillins:** benzylpenicillin, phenoxymethylpenicillin
2. **penicillinase-resistant penicillins:** meticillin, flucloxacillin
3. **aminopenicillins:** ampicillin, amoxicillin
4. **carboxy- and ureidopenicillins:** ticarcillin, piperacillin → *Antipseudomonal*
5. **cephalosporins:** first-fourth-generation compounds
6. **monobactams:** aztreonam
7. **carbapenems:** imipenem, meropenem
8. **β -lactamase inhibitors,** e.g. clavulanic acid.

(Ref: Davidson's medicine-22nd)

Penicillins

Structure of penicillin: All penicillins have the basic structure shown in Figure below. A **thiazolidine ring (A)** is attached to a **β -lactam ring (B)** that carries a secondary amino group (RNH-). Structural integrity of the 6-aminopenicillanic acid nucleus is essential for the biologic activity of these compounds. Hydrolysis of the β -lactam ring by **bacterial β -lactamases** yields penicilloic acid, which lacks antibacterial activity.

(Ref: Katzung-13th)



Q. Classify penicillins. (CU-05J, SU-06S)

Q. Classify penicillins according to their spectrum of activity. (DU-15J)

Q. Name broad spectrum penicillins. (SU-03M, RU-02J)

Q. Enlist the extended spectrum. (RU-15J)

Ans.

Classification of penicillins:

1. According to source	Natural penicillins	Benzylpenicillin / penicillin G, Phenoxymethylpenicillin / penicillin V
	Semisynthetic penicillin	Ampicillin, amoxicillin, cloxacillin
2. According to spectrum coverage	Narrow spectrum	Penicillin G, Penicillin V
	Broad spectrum	Ampicillin, amoxicillin, pivampicillin, talampicillin, bacampicillin
	Extended spectrum	Ticarcillin, piperacillin, mezlocillin, azlocillin
3. According to β -lactamase sensitivity	β -lactamase sensitive	Benzylpenicillin
		Amoxicillin
		Ampicillin
		Ticarcillin

Reverse
penicillin
name

	β-lactamase resistant	Nafcillin Cloxacillin Methicillin Dicloxacillin Oxacillin Flucloxacillin
4. According to duration of action	Long-acting	Benzathine penicillin (7-30 days) Procaine penicillin (12-24 hours)
	Short-acting	Ampicillin, amoxicillin, penicillin V
5. According to gastric acid sensitivity	Acid labile (Can't be given orally, always in <u>parenteral route</u>)	Penicillin G Procaine penicillin Benzathine penicillin
	Acid stable (Can be given orally)	Penicillin V <u>Ampicillin</u> , amoxicillin, cloxacillin

(Ref: Katzung-13th + Bennett & Brown-11th)

Q. Name some important penicillin. (DU-09Ju)

Q. Name the penicillin preparations. (SU-06J, RU-01J)

Q. Name the parenteral penicillin preparations. (Du-00S)

Ans.

	Parenteral	Oral
Natural	Penicillin G	Penicillin V
Semi-synthetic	Procaine penicillin	Ampicillin
	Methicillin	Amoxicillin
	Nafcillin	Cloxacillin
	Ticarcillin	Flucloxacillin
	Piperacillin	
	Flucloxacillin	

(Ref: Katzung-13th + Bennett & Brown-11th)

Q. Mention the mechanism of action of penicillin. (DU-09Ju, 06S, RU-12J, SU-12/09Ju, 05J)

Q. Write down the mechanism of action of amoxicillin. (DU-17M, 16Ju, 14J)

Q. How β -lactam antibiotics act? (CU-06S, RU-07J)Q. Explain antimicrobial action of β -lactam. (SU-14J)

Q. Give the mechanism of action of cloxacillin? (CU-07S, SU-07J)

Ans.

Mechanism of action of amoxicillin / cloxacillin / penicillin / β -lactam antibiotics: Penicillins and cephalosporins kill bacterial cells by **inhibiting cell wall synthesis** in **actively growing bacteria**.

1. **Inhibition of the transpeptidase enzyme:**Penicillin / cloxacillin / β -lactam antibiotics inhibit transpeptidase enzyme↓
Inhibition of cross-linking (transpeptidation) of peptidoglycan↓
Cell wall becomes porous due to absence or lack of peptidoglycan↓
Water enters the porous cell wall bacteria due to high osmotic pressure inside the bacteria↓
Bacteria swell & burst out↓
Bacteria are killed

(Ref: Katzung-13th + Lippincott's-6th)

2. **Binding with penicillin-binding proteins (PBP):** Penicillin binds with and inactivates some PBPs present on the bacterial cell membrane and thus alters the morphology of bacteria & also kill them. (Ref: Lippincott's-6th)
3. **Production of autolysins:** Many bacteria produce degradative enzymes (autolysins) that participate in the normal remodeling of the bacterial cell wall. In the presence of penicillins, the degradative action of the autolysins proceeds in the absence of cell wall synthesis.

Thus, the anti-bacterial effect of penicillin is the result of both inhibition of cell wall synthesis and destruction of existing cell wall by autolysins.

(Ref: Lippincott's-6th)

Q. Mention the limitations of penicillin-G / benzylpenicillin. (DU-06M, RU-08/07J)

Q. How can you overcome these limitations? (CU-04M, SU-04M)

Ans.

Limitation of penicillin G:

1. Narrow spectrum penicillin- only acts on Gram +ve bacteria.
2. Acid labile- so, cannot be given orally. Should be given parenterally.
3. Short duration of action (4-6 hours)
4. High degree of drug resistance
5. Hypersensitivity reaction
6. Parenteral administration is painful
7. Destroyed by β -lactamase
8. Cannot act on pseudomonas.

Processes to overcome the limitation of penicillin G:

1. Administration of broad spectrum penicillins
2. Administration of acid stable (orally active) penicillins
3. Prolongation of duration of action of penicillins
 - Intermediate acting penicillin: Procaine penicillin
 - Long acting penicillin: Benzathine penicillin
4. Administration of penicillinase resistant penicillins
5. Administration of extended spectrum penicillins
6. Administration of combined penicillins

Q. Mention the indications of penicillinase resistant penicillin. (RU-06S)

Q. Mention the indications of anti-staphylococcal penicillins. (RU-12J)

Q. Mention the absolute indications of penicillins. (CU-14J)

Q. Give the indications of amoxicillin. (RU-03M)

Q. Write down the indication of amoxicillin & clavulanic acid combination. (SU-13J)

Q. What are the prophylactic uses of benzathine penicillin? (RU-08J)

Q. Write a short note on: Penicillin. (CU-06J)

Ans.

Indications of different penicillins:

Benzyl penicillin / penicillin G: It is always given in parenteral route.

1. **Prophylactic use:** Rheumatic fever, bacterial endocarditis & in patient with agranulocytosis.
2. **Streptococcal infections:** Pharyngitis, otitis media, scarlet fever, rheumatic fever.
3. **Tetanus**
4. **Gas gangrene**
5. **Sub-acute bacterial endocarditis (SABE)** caused by *Streptococcus viridans* or *faecalis*.
6. **Primary & secondary syphilis** (not in neurosyphilis as penicillin cannot enter CNS)
7. **Gonorrhoea**
8. **Pneumococcal infection**
9. **Meningococcal infection:** Meningococcal meningitis.
10. **Drug of choice in some rare diseases:** Anthrax, actinomycosis, trench mouth, rat bite fever,

Phenoxymethylpenicillin / penicillin V:

1. **Streptococcal infections:** Acute & chronic tonsillitis, pharyngitis, sinusitis, otitis media & prevention of rheumatic fever.
2. Less serious pneumococcal infection.
3. Trench mouth

Ampicillin:

1. **Respiratory tract infections:** Bronchiolitis, pneumonia, sinusitis, otitis media.
2. **Neonatal infections** (≤ 28 days baby): RTI, septicemia, meningitis, septicemia & mixed infections (high dose & often along with gentamicin & 3rd generation cephalosporins).
3. **In SABE** with gentamicin.
4. **Acute cholecystitis** (it is a good drug because high concentrations are attained in bile)
5. Shigellosis.
6. Gonorrhea.

OC PN

Amoxicillin:

1. **Child infections** (≥ 28 days baby): Bronchitis, bronchiolitis, pneumonia (usual dose) & septicemia, meningitis & other mixed infections (high dose with gentamicin or cephalosporins).
2. **Streptococcal infections:** Acute & chronic tonsillitis, pharyngitis, sinusitis, otitis media & prevention of rheumatic fever.
3. **Urinary tract infection**
4. **Gonorrhoea** (in combination with probenecid)

Co-amoxiclav $\rightarrow$ MRSAExtended spectrum penicillins:

- UTI, Pneumonia (caused by *Pseudomonas*)

Anti-staphylococcal penicillins / penicillinase resistant penicillins / Flucloxacillin:

1. Skin and soft tissue infections
2. Burn to prevent secondary infection.
3. Respiratory tract infection
4. Urinary tract infection
5. Meningitis

Q. What are the adverse effects of penicillins? (DU-15J, 09Ju, CU-03J, RU-03M)

Q. What are the limitations of benzathine penicillin? (RU-08J)

Ans.

Adverse effects of penicillins:

1. **Hypersensitivity reaction:** $\rightarrow$ *More Sensitiv = more macrophages*
 - Anaphylactic shock
 - Stevens-Johnson syndrome (SJS)
2. Superinfection
3. **GIT upset:** Nausea, vomiting, diarrhea
4. Hemolytic anemia
5. Eosinophilia
6. Vasculitis
7. Thrombocytopenia
8. **Methicillin:** Causes interstitial nephritis
9. **Nafcillin:** Causes neutropenia
10. **Oxacillin, flucloxacillin, co-amoxiclav:** Causes hepatitis
11. **Ampicillin:** Associated with pseudomembranous colitis.

Neurotoxicity

(Ref: Katzung-13th)

Q. Give the Management of penicillin induced anaphylactic shock. (RU-15J)

Q. Outline the drug therapy of penicillin induced hypersensitivity reaction. (CU-07Jan)

Ans. Management of penicillin induced anaphylactic shock: See ANS chapter.

Q. Name the antimicrobials that can be used in penicillin hypersensitive individuals.

Ans.

Antimicrobials used in penicillin hypersensitive individuals:

1. Macrolides
2. Metronidazole
3. Vancomycin
4. Aztreonam

Q. Name the drugs that are effective against staphylococcal infections. (DU-07Ju, RU-07J)

Q. Lists the β -lactamase / penicillinase resistant penicillins. (DU-14J,07J; CU-04S; RU-06S)

Q. List the penicillins that can be used in infections caused by β -lactamase producing *S. aureus*. (CU-06M,05S)

Q. List the anti-staphylococcal penicillins with their indications. (RU-14J,12J)

Ans.

Anti-staphylococcal penicillins / Drugs effective in β -lactamase producing *S. aureus* infection:

1. Methicillin
2. Cloxacillin
3. Nafcillin
4. Dicloxacillin
5. Oxacillin
6. Flucloxacillin

Q. Mention the β -lactamase inhibitors. (DU-17M)

Q. Write short note on: β -lactamase inhibitors. (CU-06J, SU-15Ju,15J)

Ans.

β -lactamase inhibitors:

1. Clavulanic acid
2. Sulbactam
3. Tazobactam

Combination of β -lactamase inhibitors & penicillins: β -lactamase inhibitors are used in combination with β -lactamase sensitive penicillin to provide chemotherapeutic synergisms.

1. Amoxicillin & clavulanic acid (Co-amoxiclav)
2. Ampicillin & sulbactam
3. Piperacillin & Tazobactam

Q. Justify the combination of amoxicillin & clavulanic acid. (DU-16J, CU-16J,13Ju, SU-03S, RU-15Ju,11J)

Q. Write down the mechanism of action of amoxicillin & clavulanic acid. (SU-13J)

Ans.

Combination of amoxicillin & clavulanic acid: Amoxicillin is a broad spectrum penicillin & is destroyed by β lactamase /penicillinase. On the other hand, clavulanic acid is a penicillinase enzyme inhibitor. So, there is chemotherapeutic potentiation of action occurs. When both are given together, clavulanic acid inhibits the enzyme β lactamase. So, amoxicillin is not destroyed by the enzyme β lactamase and the action of amoxicillin is prolonged.

Q. What may be the drawbacks of using β -lactam antibiotic? (RU-05M)

Ans.

Drawbacks of using β -lactam antibiotics:

1. Hypersensitivity reaction
2. Super infection
3. Nephrotoxicity
4. Neutropenia in case of nafcillin

5. Hepatitis in case of cloxacillin
6. Pseudomembranous colitis in case of ampicillin.

Q. Discuss the resistance to penicillin & other β -lactam antibiotics. (SU-13J,07Ju)

Q. Discuss the microbial resistance to penicillin. (SU-03M)

Ans.

Mechanisms of bacterial resistance to penicillin: Resistance to penicillins and other β -lactams is due to one of four general mechanisms:

1. Inactivation of antibiotic by β -lactamase
 2. Modification of target penicillin-binding-proteins (PBPs)
 3. Impaired penetration of drug to target PBPs
 4. Efflux of drug.
1. **Inactivation of antibiotic by β -lactamase:** β -Lactamase production is the most common mechanism of resistance. Bacteria producing β -lactamase include- *Staphylococcus aureus*, *Haemophilus* sp, *E. coli*, *Pseudomonas aeruginosa* and *Enterobacter* sp.
 2. **Modification of target PBPs:** Altered target PBPs are the basis of methicillin resistance in staphylococci and of penicillin resistance in pneumococci and enterococci. These resistant organisms produce PBPs that have low affinity for binding β -lactam antibiotics, and consequently they are not inhibited.
 3. **Impaired penetration of drug to target PBPs:** It occurs only in **gram-negative** species. β -Lactam antibiotics cross the outer membrane and enter gram-negative organisms via **outer membrane protein channels (porins)**. Absence of the proper channel or down-regulation of its production can greatly impair drug entry into the cell.
 4. **Efflux of drug:** Gram-negative organisms also may produce an **efflux pump** that efficiently transports some β -lactam antibiotics from the periplasm back across the outer membrane.

(Ref: Katzung-13th)

Q. How the duration of action of penicillin can be prolonged? (DU-11J)

Q. Discuss the probable outcome of using penicillin with probenecid concomitantly. (DU-15Ju)

Q. Justify combination of penicillin and probenecid.

Ans.

Prolongation of duration of action of penicillin:

1. **By decreasing excretion of penicillin by adding probenecid:** Penicillin is rapidly excreted by the kidneys; small amounts are excreted by other routes. About 10% of renal excretion is by glomerular filtration and 90% by tubular secretion.
 - Penicillin is a weakly acidic drug. It needs a carrier for active tubular secretion.
 - Probenecid is also a weakly acidic drug which competes with penicillin for the same carrier protein for active tubular secretion.
 - Probenecid has got better affinity for the carrier protein than penicillin.
 - When penicillin and probenecid are given in combination, probenecid will be secreted into the tubular lumen and penicillin remains in the circulation and increase the duration of action.
 - Eg, in dental surgery, 3 gm ampicillin + 1 gm probenecid is used for prophylactic purpose.
2. **By decreasing absorption of penicillin by adding less soluble substances:**
 - Penicillin G + Benzathine $\rightarrow$ Benzathine Penicillin (1 month action)
 - Penicillin G + Procaine $\rightarrow$ Procaine penicillin (10 days action)
 - When penicillin is used for prophylaxis of rheumatic fever $\rightarrow$ 1 benzathine penicillin/month (1.2 million unit IM)

Q. Mention the advantages of semi-synthetic penicillin over penicillin-G. (DU-98M)

Ans.

Advantages of semi-synthetic penicillin over penicillin-G:

1. Broad spectrum penicillin
2. More plasma half life
3. Acid resistant, so suitable for oral administration
4. Less potent against gram (+ve) cocci
5. Less allergic reactions

Q. Compare and contrast ampicillin & amoxicillin. (DU-12Ju, CU-15J, RU-08Jan, SU-16J,15Ju,15J,12Ju)

Ans.

Differences between ampicillin & amoxicillin:

Traits	Ampicillin	Amoxicillin
1. Oral bioavailability	75 %	85%
2. Risk of drug induced diarrhea	More	Less
3. Frequency of administration	4 times/day	3 times/day
4. Interference of absorption by food	Yes	No
5. Chance of superinfection	More	Less
6. Use in shigellosis	More effective; as more drug (25%) remains unabsorbed	Less effective.

Q. Compare and contrast ampicillin & cloxacillin. (SU-17J,14Ju)

Ans.

Comparison between ampicillin & cloxacillin:

Traits	Ampicillin	Cloxacillin
1. Route of administration	Oral/IV	Oral/IV
2. Risk of drug induced diarrhea	More	Less
3. Frequency of administration	4 times/day	4 times/day
4. Interference of absorption by food	Yes	Yes
5. Chance of superinfection	More	Less
6. Anti-staphylococcal activity	No	Yes
7. Pseudomembranous colitis	Yes	No

Q. Compare & contrast Flucloxacillin, Co-amoxiclav & Ceftriaxone with respect to their spectrum of activity. (CU-11J,08Ju)

Ans.

Traits	Flucloxacillin	Co-amoxiclav	Ceftriaxone
1. Group	Anti-staphylococcal penicillin	Amoxicillin + clavulanic acid	3 rd generation cephalosporins
2. Route of administration	Oral / IV	Oral / IV	Only Parenteral
3. Absorption	Interfered by food	Not interfered by food	Not interfered by food
4. Dosing	6 hourly	8 hourly	Single daily
5. Anti-staphylococcal activity	Yes	Yes	Less / No
6. Gram -ve activity	Much inferior to ceftriaxone	Much inferior to ceftriaxone	Much superior to any penicillin
7. Gram +ve activity	Superior to any cephalosporins	Superior to any cephalosporins	Inferior to any penicillin
8. Bactericidal activity	Time dependent	Time dependent	Time dependent
9. Adverse effects	▪ Hypersensitivity ▪ GIT upset ▪ Superinfection	▪ Hypersensitivity ▪ GIT upset ▪ Superinfection	▪ Hypersensitivity ▪ Nephrotoxicity ▪ Superinfection

Q. Compare Cloxacillin, Co-amoxiclav & Ciprofloxacin with respect to their spectrum of activity. (CU-09Ju)

Ans.

Comparison among Cloxacillin, Co-amoxiclav & Ciprofloxacin:

Traits	Cloxacillin	Co-amoxiclav	Ciprofloxacin
1. Group	Anti-staphylococcal penicillin	Amoxicillin + clavulanic acid	2 nd generation fluoroquinolones
2. Route of administration	Oral/IV	Oral/IV	Oral/IV
3. Anti staphylococcal activity	High	High	Moderate
4. Gram +ve activity	Excellent	Excellent	Good
5. Gram -ve activity	Poor	Poor	Excellent
6. Bactericidal activity	Time dependent	Time dependent	Conc. dependent
7. Clinical uses	Mostly Gram +ve infection.	Mostly Gram +ve infection.	Mostly Gram -ve infections & some Gram +ve infection.
8. Arthropathy in children	No	No	Occurs; so contraindicated in <18 years
9. Hypersensitivity	More common	More common	Less common
10. CNS toxicity	Less	Less	Can occur

Cephalosporins

General consideration

- Cephalosporins are similar to penicillins, but more stable to many bacterial β -lactamases and therefore have a **broader spectrum** of activity.
- However, strains of *E coli* and *Klebsiella* species expressing extended-spectrum β -lactamases that can hydrolyze most cephalosporins are becoming a problem.
- The nucleus of the cephalosporins is **7-aminocephalosporanic acid**.
- **Bactericidal** in action.
- Relatively acid stable, so can be given **orally**.
- Source: Cephalosporium (fungus)

Q. Classify cephalosporins. (DU-17J, CU-05J, RU-06M)

Q. Name the different cephalosporins according to their generations. Discuss how different generations differ from one another. (DU-16J, 14Ju, 13Ju, SU-17J)

Q. List the 3rd generation cephalosporins with preferred routes of administration. (CU-14Ju)

Q. Classify cephalosporins according to their antimicrobial spectrum. (SU-10Ju, 08/07Ju)

Q. Categorize cephalosporins in accordance to their properties. (DU-12Ju)

Q. Discuss the criteria on which cephalosporins are categorized in generations. (CU-07Ju)

Q. Explain antimicrobial spectrum of cephalosporin. (SU-14J, 13J)

Q. Mention the characteristics/properties of 3rd generation cephalosporins. (DU-17J, CU-15Ju, 14Ju, 12Ju)

Ans.

Classification of cephalosporins: Cephalosporins can be classified into four major groups or generations, depending mainly on the spectrum of antimicrobial activity.

	Drugs	Criteria / antibacterial spectrum
1 st generation	Oral: Cephadrine Cefadroxil Cephalexin Parenteral: Cephalothin Cephadrine Cefazolin Cephapirin	- Resistant to β-lactamase enzyme. - Very active against Gram +ve cocci: Pneumococci, streptococci, staphylococci (except enterococci & MRSA) - Moderately active against Gram -ve rods, eg, <u>PEcK</u>: <i>Proteus mirabilis</i>, <i>E. coli</i>, <i>Klebsiella pneumoniae</i>. Anaerobic cocci (eg, peptococcus, peptostreptococcus) are usually sensitive. - Activity against <i>P aeruginosa</i>, enterobacter, citrobacter, and acinetobacter is poor.
2 nd generation	Oral: Cefaclor Cefuroxime axetil Cefprozil Loracarbef Parenteral: Cefuroxime Cefamandole Cefotetan Cefoxitin Cefmetazole Cefonicid	- More resistant to β-lactamase enzyme. - More active against Gram -ve rods and less active against Gram +ve bacteria. - They have extended gram-negative coverage. Spectrum of Gram -ve bacteria: <u>PEcK + HEN</u> (<i>H. influenzae</i>, <i>Enterobacter aerogenes</i>, and some <i>Neisseria</i>). - As with first-generation agents, none is active against enterococci or <i>P aeruginosa</i>.
3 rd generation	Oral: Cefixime Cefdinir Ceftibuten Cefpodoxime proxetil Parenteral: Ceftriaxone Ceftazidime Cefoperazone Cefotaxime Moxalactam Ceftizoxime	- Less active against Gram +ve bacteria - They have expanded gram-negative coverage. Spectrum of Gram -ve bacteria: <u>HENPEcK + PSC</u> → <i>Providencia</i>, <i>Serratia marcescens</i>, citrobacter. - Ceftazidime and cefoperazone are the only two drugs active against <i>P aeruginosa</i>. - Ceftizoxime and moxalactam are active against <i>B fragilis</i>. - Cefixime and ceftibuten are much less active against pneumococci and <i>S aureus</i>.
4 th generation	Only parenteral: Cefepime Cefpirome	- More resistant to β-lactamases. - Cefepime has good activity against <i>P aeruginosa</i>, Enterobacteriaceae, <i>S aureus</i>, and <i>S pneumoniae</i>. - Unlike ceftazidime, cefepime has good activity against most penicillin-resistant strains of streptococci. - It is highly active against haemophilus and neisseria. - It <u>penetrates well into CSF</u>.

(Ref: Katzung-12th/797-800; Lippincott's-5th/387)Nice to know5th generation cephalosporin

- Ceftobiprole* has been described as "fifth-generation" cephalosporin, though acceptance for this terminology is not universal. It has powerful antipseudomonal activity and is less susceptible to development of resistance.
- Ceftaroline* has also been described as "fifth-generation" cephalosporin, but does not have the anti-pseudomonal coverage.

(Ref: Internet)

Nice to know

- **Cefazolin** is the only first-generation parenteral cephalosporin still in general use.
- All cephalosporins are **safe in pregnancy** & well tolerated by children & neonates & hence are used commonly in neonatal & children infection invariably.

(Ref- Katzung-13th)

Q. Name some important cephalosporins. (DU-10J)

Q. Enumerate commonly used cephalosporins.

Ans.

Important / Commonly used cephalosporins

Oral cephalosporins	Parenteral cephalosporins
1. Cephadrine .	1. Ceftriaxone .
2. Cefixime	2. Cefuroxime
3. Cefuroxime axetil	3. Ceftazidime
4. Cefpodoxime proxetil	4. Cephadrine .
5. Cefaclor	5. Cefepime
6. Cefdinir	6. Cefotaxime
7. Cephalexin	7. Cefazolin
8. Cefadroxil	8. Cefoxitin

Bolded cephalosporins are used more commonly in Bangladesh.

(Ref- Katzung-13th)

Q. Briefly discuss the antibacterial mechanism of action of cephalosporins. (DU-16J, 15Ju, 10J, SU-14Ju, 13J)

Q. Write down the mechanism of action of 3rd generation cephalosporins. (DU-08J)

Q. Explain the mechanism of action of ceftriaxone in enteric fever. (RU-09J)

Q. Explain the mechanism of action of cephradine. (RU-13J)

Q. Give the mechanism of action of ceftriaxone. (RU-06M, SU-12Ju)

Ans. *Same as penicillin*

Mechanism of action of cephalosporins / ceftriaxone / 3rd generation cephalosporins: Cephalosporins kill bacterial cells by inhibiting cell wall synthesis in actively growing bacteria.

1. **Inhibition of the transpeptidase enzyme:**

Cephalosporins/ ceftriaxone inhibit transpeptidase enzyme



Inhibition of cross-linking (transpeptidation) of peptidoglycan



Cell wall becomes porous due to absence or lack of peptidoglycan



Water enters the porous cell wall bacteria due to high osmotic pressure inside the bacteria



Bacteria swell & burst out



Bacteria are killed

(Ref: Katzung-13th + Lippincott's-6th)

2. **Binding with penicillin-binding proteins (PBP):** Cephalosporins binds with and inactivates some PBPs present on the bacterial cell membrane and thus alters the morphology of bacteria & also kill them.

(Ref: Lippincott's-5th/3382)

3. **Production of autolysins:** Many bacteria produce degradative enzymes (autolysins) that participate in the normal remodeling of the bacterial cell wall. In the presence of cephalosporins, the degradative action of the autolysins proceeds in the absence of cell wall synthesis.

(Ref: Lippincott's-6th)

Q. List the indications of 1st generation cephalosporins.

Q. List the indications of cephradine.

Ans.

Indications/ Clinical uses of 1st generation cephalosporins/cephradine:

1. Cellulitis
2. Soft tissue infection.
3. Any skin infection.
4. Sinusitis.
5. Urinary tract infection
6. Cefazolin is an alternative to anti-staphylococcal penicillin in case of penicillin hypersensitivity.
7. Surgical chemoprophylaxis of lower abdominal use.
8. Can be used in the place where ampicillin & amoxicillin are used.

Strepto
Staphylo
Bacteremia
URT (Resistant UTI)

(Ref- Katzung-13th)

Q. List the indications of 2nd generation cephalosporins.

Ans.

Indications/ Clinical uses of 2nd generation cephalosporins:

1. Sinusitis
2. Otitis media
3. Lower respiratory tract infection
4. Mixed anaerobic infection: Peritonitis, diverticulitis (Cefoxitin, Cefmetazole & Cefotetan).
5. Community acquired pneumoniae (Cefuroxime) caused by β lactamase producing *H. influenza* or *Klebsiella pneumoniae*.
6. Pyelonephritis (Cefuroxime)
7. Septicemia (Cefuroxime)
8. Urinary tract infection.
9. Cellulitis, Soft tissue infection.
10. Surgical chemoprophylaxis of lower abdominal use (especially in gynecological & obstetrical use).
11. Can be used in the place where ampicillin & amoxicillin are used.

→ eg. rectal surgery

(Ref- Katzung-13th)

Q. List the indications of ceftriaxone. (DU-14Ju,12Ju,07J, RU-10Ju,06M)**Q. List the clinical uses of 3rd and 4th generation cephalosporins.** (RU-06J,05S,04M)

Ans.

Clinical uses of 3rd /4th generation cephalosporins / ceftriaxone/ceftazidime/cefepime:

1. Enteric fever
2. Meningitis
3. Osteomyelitis
4. Respiratory tract infections (pneumonia, lung abscess, secondary infection in COPD patients etc.)
5. Septicemia
6. Aspiration pneumonia
7. Pyelonephritis (ceftriaxone)
8. Urinary tract infection (UTI) - Resistant UTI
9. Complicated acute suppurative otitis media (ASOM) & chronic suppurative otitis media (CSOM).
10. Biliary tract infection
11. Intra-abdominal infections
12. Pelvic infections (especially in pregnancy & postpartum period)
13. Surgical chemoprophylaxis during intra-abdominal & pelvic surgeries.
14. Prostatitis
15. Synovitis
16. Gonorrhoea - Resistant gonorrhoea
17. In pregnancy, childhood infections it is safe & well tolerated.
18. Ceftazidime is effective against hospital acquired infections usually caused by *Pseudomonas aeruginosa*.
19. Cefepime has good activity against most penicillin resistant strains of streptococci and in the treatment of enterobacter infections.

(Ref- Katzung-13th)

Q. Will the 3rd generation cephalosporins be useful in infections caused by β -lactamase producing *S. aureus*? (CU-06M,05S)

Ans.

3rd generation cephalosporins in β -lactamase producing *S. aureus*: Effective.

Q. What are the toxic / adverse effects of cephalosporins? (CU-03M, SU-14J)

Q. Mention the adverse effects of ceftriaxone. (DU-14Ju,10/06J, RU-09J)

Q. Mention the adverse effects of 3rd & 4th generation cephalosporins? (RU-05S)

Q. Write down the 2 important adverse effects of cephalosporins? (DU-16J)

Ans.

Adverse effects of cephalosporins:

1. **Allergy:** Cephalosporins may cause hypersensitivity reactions that are identical to those of penicillins, including anaphylaxis, fever, skin rashes, nephritis, granulocytopenia, and hemolytic anemia. Patients with a history of anaphylaxis to penicillins should not receive cephalosporins due to the presence of cross-allergenicity.
2. **Renal toxicity:** Interstitial nephritis and tubular necrosis.
3. **Bleeding:** Cefamandole, cefmetazole, cefotetan, cefoperazone frequently cause hypoprothrombinemia and bleeding disorders. Administration of vitamin K₁, 10 mg twice weekly, can prevent this.
4. **Hemolytic anemia.**
5. **Granulocytopenia.**
6. **Super infection:** With methicillin resistant staphylococci & Enterococci
7. **GIT upset:** Nausea, vomiting, diarrhea, abdominal pain.
8. **Thrombo-phlebitis:** In case of IV injection.
9. **Local pain:** In case of IM injection
10. **Disulfiram like action:** When cefamandole, cefotetan or cefoperazone is ingested with alcohol or alcohol-containing medications, a disulfiram-like effect is seen.

(Ref: Katzung-13th + Bennett & Brown-11th ed + Lippincott's-6th)

Q. Short note: Ceftriaxone. (DU-12J)

Ans. Write M/A, indication, adverse effects from above.

Nice to know:

- *Meningitis* caused by pneumococci, meningococci, *H. influenzae* should treat with 3rd generation cephalosporins.
- *Meningitis* caused by *P. aeruginosa* should be treated with ceftazidime.
- *Meningitis* caused by highly penicillin-resistant strains of pneumococci should be treated with 3rd generation cephalosporins (ceftriaxone or cefotaxime) + Aminoglycosides + Vancomycin.
- *Gonorrhoea* should be treated with ceftriaxone or cefixime.
- *Biliary tract infection* should be treated with ceftriaxone or cefoperazone.

(Ref- Katzung-13th)

Q. Write down the advantages of 3rd generation cephalosporins over 1st & 2nd generation cephalosporins. (DU-08J, CU-06M)

Ans.

Advantages of 3rd generation cephalosporins over 1st & 2nd generation cephalosporins:

1. Gram -ve activity is more than 1st & 2nd generation cephalosporins.
2. Can produce therapeutic concentration in pharmacological sanctuary (in CNS, bone, prostate, joint cavity)
3. Much resistant to β -lactamase enzyme.
4. Cefoperazone & Ceftazidime are effective against *P. aeruginosa*.
5. Ceftriaxone and Cefixime are effective against *Neisseria gonorrhoea*.
6. Meningitis caused by highly penicillin resistant strains of pneumococci should be treated with 3rd generation cephalosporins + Aminoglycosides + Vancomycin.

Q. Mention the advantages of cephalosporins over natural penicillin. (DU-00M)

Ans.

Advantages of cephalosporins over natural penicillin:

1. Broad spectrum of activity
2. Much stable to β -lactamase enzyme than natural penicillin.
3. 3rd & 4th generation cephalosporins can reach to pharmacological sanctuary
4. Less hypersensitivity reaction.
5. Relatively stable to temperature and pH changes.

Q. Compare Cephalexin and Ceftriaxone. (SU-13Ju)

Ans.

Comparison between Cephalexin and Ceftriaxone

Traits	Cephalexin	Ceftriaxone
1. Generation	First	Third
2. Route of administration	Oral	Parenteral
3. Resistance to β -lactamase enzyme.	Present	More
4. Activity against Gram +ve bacteria.	Very active	Less active
5. Spectrum of Gram -ve bacteria	Moderately active against Gram -ve rods.	They have expanded gram-negative coverage.
	PEcK: <i>Proteus mirabilis</i> , <i>E. coli</i> , <i>Klebsiella pneumoniae</i>	▪ PEcK ▪ HEN $\rightarrow$ <i>H. influenzae</i>, <i>Enterobacter aerogenes</i>, and some <i>Neisseria</i>. ▪ PSC $\rightarrow$ <i>Providencia</i>, <i>Serratia marcescens</i>, <i>Citrobacter</i>.

Monobactams

Drug: Aztreonam is the only currently available monobactam & structurally similar to ceftazidime.

Group: Monobactams are drugs with a monocyclic β -lactam ring. They are relatively resistant to β -lactamases.

Mechanism of action: Same as penicillin

Antibacterial activity:

1. Aztreonam is active against gram-negative rods (including *pseudomonas* and *serratia*).
2. No activity against Gram +ve bacteria or anaerobes.
3. It resembles aminoglycosides in its spectrum of activity.
4. It penetrates well into CSF.
5. Penicillin allergic patient tolerate aztreonam without reaction.

Indications: Penicillin hypersensitive patients with serious Gram -ve bacterial infections; such as pneumonia, meningitis, septicemia etc.

Adverse effects:

1. Skin rashes
2. Elevation of serum aminotransferase.

(Ref- Katzung-13th)

Carbapenems

Group: β -lactam antibiotics

Drugs of the carbapenem group:

1. Meropenem
2. Imipenem
3. Doripenem
4. Ertapenem

Mechanism of action of carbapenems: Same as penicillin

Antibacterial activities of individual carbapenems:

Imipenem:

1. **Susceptible microorganisms:** Imipenem has a wide spectrum with good activity against many **gram-negative rods**, including *P aeruginosa*, **gram-positive** organisms, and **anaerobes**. It is resistant to most β -lactamases but not metallo- β -lactamases. MRSA, *Clostridium difficile* are resistant.
2. **Inactivation of imipenem:** Imipenem is inactivated by dehydropeptidases in renal tubules, resulting in low urinary concentrations. Consequently, it is administered together with an inhibitor of renal dehydropeptidase, **cilastatin**, for clinical use.

Meropenem:

1. Meropenem is not destroyed by dehydropeptidase & thus does not require an inhibitor.
2. It is similar to imipenem but has slightly greater activity against Gram -ve aerobes & slightly less activity against Gram +ve organisms.

Ertapenem:

1. Ertapenem is less active than imipenem or meropenem in *P. aeruginosa* & *acinetobacter* species.
2. It is not degraded by renal dehydropeptidase.
3. It has the longest half-life (4 hours) & is administered as a once-daily dose. Intramuscular Ertapenem is irritating so formulated with 1% Lidocaine

Indications of carbapenems:

1. Pseudomonas infection.
2. Mixed aerobic & anaerobic infection (septicemia)
3. Penicillin resistant pneumococcal infection (pneumonia).
4. Enterobacter infections which are resistant to other β -lactam antibiotics due to production of β -lactamase.
5. In febrile neutropenic patient carbapenems are used along with aminoglycosides.

Adverse effects:

1. GIT upset: Nausea, vomiting, diarrhea (most common adverse effects)
2. Skin rashes
3. Reactions at the infusion sites
4. Allergic reactions.
5. In case of renal failure high dose carbapenem can cause seizures.

(Ref- Katzung-13th)

Non β-lactam cell wall synthesis inhibitors

Non β-lactam bacterial cell wall synthesis inhibitors:

Glycopeptide Antibiotics	Vancomycin Teicoplanin Dalbavancin Telavancin
Other cell wall or membrane active agents	Daptomycin Bacitracin Cycloserine Fosfomycin

(Ref- Katzung-13th)

Q: Write short note on: Vancomycin.

Ans.

Vancomycin

Mechanism of action: Vancomycin inhibits cell wall synthesis by-

- 1. Binding firmly to the D-Ala-D-Ala side chain of nascent peptidoglycan pentapeptide.
- 2. Inhibiting the transglycosylase and preventing further elongation of peptidoglycan and cross-linking.
- 3. Cell membrane is also damaged, which contributes to the antibacterial effect.

(Ref- Katzung-13th)

Clinical uses:

Parenteral vancomycin:

- 1. Sepsis or endocarditis caused by MRSA.
- 2. Enterococcal endocarditis in a patient with serious penicillin allergy (in combination with gentamicin).
- 3. Meningitis caused by a highly penicillin-resistant pneumococcus (in combination with cefotaxime, ceftriaxone, or rifampin).

Oral vancomycin:

- 1. Antibiotic-associated enterocolitis caused by C difficile. (metronidazole is preferred as initial therapy.)

Adverse effects: Adverse reactions are encountered in about 10% of cases. Most reactions are minor.

- 1. Phlebitis at the site of injection.
- 2. Chills and fever
- 3. Ototoxicity and nephrotoxicity are uncommon with current preparations. (However, administration with another ototoxic or nephrotoxic drug, such as an aminoglycoside, increases the risk of these toxicities.)
- 4. "Red man" or "red neck" syndrome: This infusion-related flushing is caused by release of histamine. It can be largely prevented by prolonging the infusion period to 1–2 hours.

(Ref- Katzung-13th)

Protein synthesis inhibitors

Q. Classify bacterial Protein synthesis inhibitors. (DU-17J, CU-12J, 11Ju, RU-14J, 12J, SU-10Ju/J)

Ans.

Protein synthesis inhibitors:

- **Action on 30S ribosomal subunit:** Aminoglycosides & Tetracyclines.
- **Action on 50S ribosomal subunit:** Chloramphenicol & Macrolides.

(Ref- Katzung-13th)

Aminoglycosides — Narrow

Q. What is aminoglycosides? (RU-03S)

Q. What do you mean by aminoglycosides? (CU-03S)

Q. Outline the antimicrobial spectrum of aminoglycosides? (SU-14Ju, 10J)

Ans.

Aminoglycosides: Aminoglycosides are a group of drugs that have a **hexose ring**, either streptidine (in streptomycin) or 2-deoxystreptamine (other aminoglycosides), to which various **amino sugars** are attached by **glycosidic linkages**. The drugs are **bactericidal** inhibitors of protein synthesis. These agents are useful mainly against **aerobic gram-negative** microorganisms.

(Ref- Katzung-13th)

Q. Enlist aminoglycosides. (DU-14Ju, 13J, 12J, CU-14J, 08Ju; RU-09J; SU-16J, 08J)

Q. Classify aminoglycosides.

Ans.

Classification of aminoglycosides

A. According to source:

Source	Drugs
Natural	Derived from Streptomyces: (having 'mycin' suffix) - Streptomycin - Neomycin - Kanamycin - Tobramycin Derived from Micromonospora: (having 'micin' suffix) - Gentamicin - Sisomicin - Netilmicin
Semisynthetic	- Amikacin - Netilmicin

(Ref: Lippincott's-6th)

B. According to route of administration:

Route of administration	Drugs
Systemic <i>Parenteral</i>	Gentamicin Amikacin Streptomycin Tobramycin Sisomicin Netilmicin Kanamycin
Topical	Neomycin Framycetin
Oral	Neomycin Paromomycin

→ Highly polar
Orally abs. 20-25%

→ Due to severe nephrotoxicity

(Ref- Katzung-13th)

Q. Name the Aminoglycosides derived from micromonospora. (CU-17J)

Ans.

Aminoglycosides derived from micromonospora: Various species of micromonospora are sources of aminoglycoside antibiotics, which spellings often ends with -micin. They include-

1. Gentamicin
2. Sisomicin
3. Mutamicin
4. Netilmicin

Q. What are the common properties / characteristics of aminoglycosides? (DU-17M/J, 14Ju, 13J, 12J, CU-14J, 07J, 06J, RU-17J, m10Ju, 07Ju, SU-16J, 15Ju, 15J, 13Ju, 08Ju)

Q. Write down the pharmacokinetic properties of aminoglycosides. (RU-15J)

Q. Write down six common properties of aminoglycosides. (RU-13J)

Q. Short note: Pharmacokinetic properties of gentamicin. (RU-16J)

Ans.

Common properties of aminoglycosides:

A. Physical and Chemical Properties

1. They have a **hexose ring**, to which various **amino sugars** are attached by **glycosidic linkages**.
2. They are water-soluble, and more active at alkaline pH.

B. Mechanism of Action: Irreversible inhibition of protein synthesis.

C. Pharmacokinetics:

1. **Not absorbed from the gut** due to the highly polar, polycationic structure. They must be given parenterally. *→ water soluble* *Gut sterile*
2. A single daily dose is effective. *metabolism 20-30%*
3. **Excretion:** By kidney.
4. They can **cross blood-placental barrier** (so teratogenic), but **cannot pass blood-brain barrier** (except inflamed meninges). *placenta → rifampin*
5. **They do not reach to pharmacological sanctuary:** CNS, prostate, testes, joint cavity, and ovary.
6. **Dosage adjustments** must be made to prevent accumulation of drug and toxicity in patients with renal insufficiency.

D. Pharmacodynamics:

1. Adverse effects from aminoglycoside are both time- and concentration-dependent.
2. All show common toxicities (nephrotoxicity, ototoxicity).
3. Narrow therapeutic index.

(Ref- Katzung-13th; Lippincott's-6th)

Q. Justify- once-daily dosing of gentamicin. (DU-17M)

Q. Justify- once-daily dosing of aminoglycoside.

Q. Outline the advantage & disadvantage of single dose daily gentamicin administration compared to multiple dose daily administration. (CU-10Ju)

Q. Ans.

Once-daily dosing of aminoglycoside / gentamicin: Traditionally, aminoglycosides have been administered in two or three equally divided daily doses for patients with normal renal function. However, once-daily aminoglycoside dosing may be preferred in certain clinical situations.

1. **More efficacy:** Aminoglycosides have **concentration-dependent killing** and significant **postantibiotic effect**. Because of these properties, a given total amount of aminoglycoside may have better efficacy when administered as a single large dose than when administered as multiple smaller doses.
2. **Less adverse effects:** Numerous clinical studies demonstrate that a single daily dose of aminoglycoside is just as effective—and no more (and often less) toxic—than multiple smaller doses.
3. Once-daily dosing is less expensive to administer.
4. Less nursing time is required.

5. Once-a-day dosing lends itself to outpatient therapy.
6. Repeated determinations of serum concentrations are probably unnecessary unless aminoglycoside is given for more than 3 days.

The exceptions of once-daily dosing are pregnancy, neonatal infections, and bacterial endocarditis, in which these agents are administered in divided doses every 8 hours.

(Ref- Katzung-13th; Lippincott's-6th)

Q. Mention how aminoglycosides produce antimicrobial/bactericidal effect. (RU-09Ju, SU-17M)

Q. How gentamicin acts as antibacterial agents? (DU-16Ju, CU-07J,06M; SU-08J; RU-07J)

Q. Write down the anti-tubercular action of kanamycin. (SU-12Ju)

Ans.

Mechanism of action of aminoglycosides / gentamicin: Aminoglycosides are irreversible inhibitors of protein synthesis.

Steps:

1. Passive diffusion of the drug via porin channels across the outer membrane.
2. Drug is then actively transported across the cell membrane into the cytoplasm by an **oxygen-dependent** process.
3. Binding to specific 30S-subunit ribosomal proteins (S12 in the case of streptomycin).
4. Protein synthesis is inhibited by aminoglycosides in at least three ways:
 - Prevents binding of mRNA with 30S ribosomal subunit.
 - Misreading of mRNA, resulting in formation of nonfunctional or toxic protein.
 - Breakup of polysomes into nonfunctional monosomes.

These activities occur more or less simultaneously, and the overall effect is irreversible and lethal for the cell (**bactericidal**).

(Ref- Katzung-13th)

Q. Name the factors that inhibit transport of aminoglycosides into bacterial cell.

Ans.

1. Low extracellular pH
2. Anaerobic conditions.

Q. Name the factors that inhibit transport of aminoglycosides into bacterial cell.

Ans.

Transport of aminoglycosides into bacterial cell may be **enhanced** by cell wall-active drugs such as penicillin or vancomycin; this enhancement may be the basis of the synergism of these antibiotics with aminoglycosides.

Q. How aminoglycosides develop resistance?

Ans.

Mechanism of resistance against aminoglycosides / gentamicin: Three principal mechanisms have been established:

1. **Production of a transferase enzyme** which inactivates the aminoglycoside by adenylation, acetylation, or phosphorylation.
2. **Impaired entry of aminoglycoside into the cell.** This may be-
 - a. **genotypic**, ie, mutation or deletion of a porin protein.
 - b. **phenotypic**, eg, where oxygen-dependent transport process is not functional.
3. **Receptor protein** on the 30S ribosomal subunit may be **deleted or altered** as a result of a mutation.

(Ref- Katzung-13th)

Q. What are the indications of aminoglycosides? (SU-08Ju)

Q. Mention the clinical uses of gentamicin. (DU-07Ju; RU-03S)

Q. What are the indications of gentamicin? (DU-14Ju,13J,12J, CU-03S; RU-17J,15J,13J)

Q. Mention the specific uses of aminoglycosides. (SU-15Ju)

Ans.

Indications of aminoglycosides / gentamicin/ amikacin: *Bacteremia, Septicemia Endocarditis* Aminoglycosides are mostly used against gram-negative enteric bacteria.

A. Parenteral (IM, IV):

1. Gentamicin is used mainly in severe infections (eg, sepsis and pneumonia) caused by gram-negative bacteria (in combination with a second agent, eg, cephalosporins or penicillin).
2. Endocarditis caused by *Viridans streptococci & Enterococcus faecalis* (In combination with penicillin G).
3. Staphylococcal endocarditis (In combination with Nafcillin)
4. Meningitis caused by Gram -ve bacilli (in combination with 3rd generation cephalosporins.)
5. TB (Streptomycin)
6. In plague, tularemia, and brucellosis, streptomycin is given IM with an oral tetracycline.

B. Topical: Topical gentamicin is used in infected burns, wounds, or skin lesions and the prevention of intravenous catheter infections. 10 mg can be injected subconjunctivally for ocular infections.

C. Intrathecal administration: Meningitis caused by gram-negative bacteria.

(Ref- Katzung-13th)

Q. What are the indications of neomycin?

Ans.

Indications of neomycin: Neomycin (and kanamycin) is now limited to topical and oral use. Neomycin is too toxic for parenteral use, so it is not given parenterally.

1. Topical: Treatment (during dressing) of burn, skin lesion, wound, IV catheter induced infection where *pseudomonas* is suspected or where there is greenish pus present.
2. Oral: Neomycin is used orally in-
 - Preparation of the bowel prior to surgery: 1 g neomycin every 6–8 hours for 1–2 days, plus 1 g erythromycin base. This reduces the aerobic bowel flora with little effect on anaerobes.
 - Hepatic failure: Neomycin suppresses coliform flora and reduces ammonia intoxication. (Use of neomycin for hepatic coma has been almost entirely supplanted by lactulose, which is much less toxic.)

(Ref- Katzung-13th)

Q. Write down the adverse effects of aminoglycosides. (SU-17M)

Q. Write down the adverse effects of gentamicin. (DU-07M; RU-15J,13J)

Ans.

Adverse effects of aminoglycosides / gentamicin:

1. Ototoxicity: Largely irreversible.
 - Vestibular dysfunction: Caused by streptomycin, gentamicin. Manifested by vertigo, ataxia, and loss of balance.
 - Cochlear dysfunction: Caused by amikacin, kanamycin, neomycin. Manifested by tinnitus and high-frequency hearing loss.
2. Nephrotoxicity: Neomycin, tobramycin and gentamicin are most nephrotoxic.
3. Neuromuscular blockade: Occurs in very high doses and results in respiratory paralysis. (This paralysis is usually reversible by calcium gluconate (given promptly) or neostigmine.)
4. Hypersensitivity occurs infrequently.

(Ref- Katzung-13th)

Q. What precautions are to be taken during gentamicin therapy? (DU-03M)

Q. What are the precautions of using aminoglycosides?

Ans.

Precautions of using aminoglycosides / gentamicin:

1. Should avoid with frusemide (both of them cause ototoxicity)

2. Should avoid in pregnancy, because there is risk of fetal ototoxicity.
3. Should avoid concurrent use of other nephrotoxic drugs (e.g. NSAIDs, vancomycin, ACE inhibitors, cyclosporine, cisplatin etc.)
4. Should avoid / use cautiously in patient with compromised renal function or chronic kidney diseases.
5. Cautious use of muscle relaxants in patient with aminoglycoside therapy.
6. Should not mix aminoglycosides with any drug in the same syringe / infusion set.

(Ref: Tripathi-6th/722)

Q. Write down the limitations of aminoglycosides. (CU-17J)

Ans.

Limitations of aminoglycosides:

1. Always parenteral administration.
2. Toxic effect on both kidney and 8th cranial nerve (ototoxicity & nephrotoxicity)
3. Selective activity against aerobic microorganisms as they are transported by O₂-dependent active transport process.
4. Poorly penetrate spinal fluid so must be given intrathecally in meningitis.
5. Reduced activity at acid pH & hyperosmolar urine.

Q. Explain drug interaction with aminoglycosides—

- **Aminoglycosides with loop diuretics**
- **Aminoglycosides with cephalosporins**
- **Aminoglycosides with neuromuscular blockade.**

Ans.

Drug interaction with aminoglycosides

▪ **Aminoglycosides + Loop diuretics:**

Result: Pharmacological potentiation (↑ototoxicity).

Explanation: Aminoglycosides cause irreversible ototoxicity. Loop diuretics (frusemide) also cause reversible ototoxicity. So both drugs are ototoxic leading to pharmacological potentiation.

▪ **Aminoglycosides + Cephalosporins:**

Results: Pharmacological potentiation (↑nephrotoxicity)

Explanation: Aminoglycosides cause reversible nephrotoxicity. Cephalosporins cause reversible nephrotoxicity. So, both drugs are nephrotoxic leading to pharmacological potentiation.

▪ **Aminoglycosides + Neuromuscular blocker:**

Results: Pharmacological potentiation

Explanation: Aminoglycosides cause neuromuscular blockade, so simultaneous administration of neuromuscular blocker will enhance paralysis.

Q. Justify combination of penicillin & gentamicin. What are the advantages of it?

Ans.

Combination of penicillin & gentamicin: Combination provides chemotherapeutic potentiation.

1. **To increase anti-bacterial spectrum:**

- **Penicillin:** Extend antibacterial coverage against Gram +ve pathogens.
- **Gentamicin:** Gram -ve coverage by gentamicin.

In combination their spectrum of activity increase & microbial coverage is excellent.

2. **To increase uptake of gentamicin:** Penicillin inhibits cell wall synthesis which enhances uptake of gentamicin into the cell.

3. **To achieve bactericidal activity.**

4. **To reduce duration of therapy.**

(NB: Combination of penicillin & gentamicin is very effective & safe & thus widely used in pediatric including neonates.)

Kiva Q. Why aminoglycosides are responsible for organ toxicity?

Ans. Aminoglycosides are poly-cationic substances. So they bind with anionic membrane phospholipid leading to organ toxicity.

Q. Why aminoglycosides are ineffective against anaerobic bacteria? (CU-07J)

Q. Explain selective activity of aminoglycosides against aerobic microorganisms.

Ans.

Selective activity of aminoglycosides / gentamicin against aerobic bacteria: Aminoglycosides are actively transported across the cell membrane into the cytoplasm by an **oxygen-dependent process**. So in case of anaerobic microorganisms, aminoglycosides cannot enter into bacteria due to deficiency of O_2 . For this reason aminoglycosides are ineffective against anaerobic bacteria / selectively active against **aerobic microorganisms**.

Nice to know

Gentamicin

Gentamicin is an aminoglycoside isolated from *Micromonospora purpurea*.

Antimicrobial Activity: It is effective against both **aerobic gram-positive** and **gram-negative** organisms.

Resistance: Streptococci and enterococci are relatively resistant to gentamicin owing to failure of the drug to penetrate into the cell.

Tobramycin

1. 2 - 4 times more active against *P. aeruginosa* & *proteus* than gentamicin.
2. More expensive than gentamicin
3. Less ototoxicity & nephrotoxicity than gentamicin.
4. Almost always used in combination with β lactam antibiotics to extend coverage and to take advantage of synergism
5. **Clinical use:** Reserve alternative to gentamicin for serious pseudomonal & proteus infection.

Streptomycin

1. Mainly used as a second-line agent for treatment of **tuberculosis**.
2. It is used to treat **brucellosis** in combination with an oral tetracycline.
3. Active against **enterococcal infections** as enterococcal enzyme doesn't modify streptomycin.
4. **Contraindication:** Pregnant women because of deafness in the newborn

Amikacin

1. Amikacin is a semisynthetic derivative of kanamycin; it is **less toxic** than the parent molecule.
2. Resistant to many enzymes that inactivate gentamicin and tobramycin.
3. Active against many gram-negative enteric bacteria, including *proteus*, *pseudomonas*, *enterobacter*, and *serratia*.
4. Multidrug-resistant *Mycobacterium tuberculosis* (MDR TB) including streptomycin-resistant strains, are usually susceptible to amikacin.
5. Kanamycin-resistant strains may be cross-resistant to amikacin.
6. It is **nephrotoxic** and **ototoxic**. Serum concentrations should be monitored.

Netilmicin

1. Netilmicin may not be inactivated by many gentamicin and tobramycin resistant bacteria.
2. Completely therapeutically interchangeable with gentamicin or tobramycin and has similar toxicities.

(Ref- Katzung-13th)

Tetracyclines

Q. What are tetracyclines? (DU-07J, CU-99J, SU-99J)

Q. What are the antimicrobial spectrums of tetracyclines?

Ans.

Tetracyclines are **broad-spectrum bacteriostatic** antibiotics that **inhibit protein synthesis**. They are active against many **gram-positive** and **gram-negative bacteria**, including anaerobes, rickettsiae, chlamydiae, mycoplasmas, and L forms; and against some protozoa (eg, amebas). The antibacterial activities of most tetracyclines are similar except that tetracycline-resistant strains may be susceptible to doxycycline, minocycline, and tigecycline.

(Ref- Katzung-13th)

Q. Classify tetracyclines. (RU-04J, SU-03J)

Ans.

Classification of tetracyclines:

A. According to source:

Natural tetracyclines	▪ Chlortetracycline ▪ Oxytetracycline ▪ Tetracycline ▪ Demeclocycline
Semisynthetic tetracyclines	▪ Doxycycline ▪ Minocycline ▪ Demeclocycline <i>Methacycline</i>

B. According to plasma half life:

Short acting ($t_{1/2}$ 6-8 hours)	Chlortetracycline, Oxytetracycline & Tetracycline.
Intermediate acting ($t_{1/2}$ 12 hours)	Demeclocycline, Methacycline.
Long acting ($t_{1/2}$ 16-18 hours)	Doxycycline, Minocycline & Tigecycline (36 hrs)

C. According to bioavailability:

Low bioavailability (30%)	Chlortetracycline
Intermediate bioavailability (60-70%)	Oxytetracycline, Tetracycline, Demeclocycline & Methacycline
High bioavailability (95-100%)	Doxycycline, Minocycline.

(Ref- Katzung-13th)

Q. Mention the antibacterial mechanism of tetracycline. (DU-07J, RU-02J)

Q. Explain the mechanism of action of tetracyclines. (RU-14J, 09J)

Q. Explain the antimicrobial action of tetracyclines. (SU-08Ju; RU-06S)

Ans.

Mechanism of action of tetracyclines:

Tetracyclines enter microorganisms in part by passive diffusion and in part by an energy-dependent process of active transport.

↓
Susceptible cells concentrate the drug intracellularly.

↓
Once inside the cell, tetracyclines **bind reversibly to the 30S subunit** of the bacterial ribosome, blocking the binding of aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex.

↓
This prevents addition of amino acids to the growing peptide.

↓
Protein synthesis is inhibited.

↓
No growth & multiplication of bacteria (bacteriostatic).

(Ref- Katzung-13th)

Q. Discuss the mechanism of bacterial resistance against tetracycline. (SU-07Ju)

Ans.

Mechanisms of resistance to tetracycline: Three mechanisms of resistance to tetracycline analogs have been described:

1. Impaired influx or increased efflux by an active transport protein pump;
2. Ribosome protection due to production of proteins that interfere with tetracycline binding to the ribosome.
3. Enzymatic inactivation of the drug.

The most important of these are production of an efflux pump and ribosomal protection. Efflux pumps rapidly remove the drug from the cell and the drug cannot accumulate in the bacteria in sufficient concentration.

(Ref- Katzung-13th)

Importance of tetracycline resistance: Tetracycline resistance is a marker of multidrug resistance to aminoglycosides, sulfonamides & chloramphenicol as efflux pump encoded on a plasmid encodes resistance genes for other drugs which is transmissible by transduction or by conjugation.

Nice to know

- **Tet(AE) efflux pump**-expressing gram-negative species are resistant to the older tetracyclines, doxycycline, and minocycline but not tigecycline
- **Tet(K) efflux pump** of staphylococci confers resistance to tetracyclines, but not to doxycycline, minocycline, or tigecycline.
- **Tet(M) ribosomal protection protein** expressed by gram-positives produces resistance to the tetracyclines, doxycycline, and minocycline, but not to tigecycline.

(Ref- Katzung-13th)

Q. What are the indications of tetracyclines? (RU-04J, SU-06M)

Q. Mention the important uses of tetracyclines? (SU-12J)

Q. Mention the uses of doxycyclines? (SU-16J)

Ans.

Indications of tetracyclines:

1. A tetracycline is the drug of choice in- (1st choice)

- Rickettsial infection (typhus, Rocky mountain fever, Q fever etc.)
- Mycoplasma pneumoniae infection (atypical pneumoniae)
- V cholera infection (cholera), STD
- Chlamydial infections, including sexually transmitted diseases
- Some spirochetes.

2. Plague, tularemia, and brucellosis—usually in combination with an aminoglycoside.

3. Other uses include treatment of-

- Acne
- exacerbations of bronchitis
- Lyme disease, relapsing fever - Borrelia
- Leptospirosis, and
- Some nontuberculous mycobacterial infections (eg, Mycobacterium marinum).

4. **Peptic ulcer disease (PUD):** Used in combination regimen to treat PUD caused by H. pylori.

5. **As antimalarial drug:** Doxycycline & Minocycline (As they are slowly acting blood schizonticide).

6. **As anti-amoebic:** It is effective against Entamoeba histolytica.

7. **Topically in the ophthalmic infection:** Chlortetracycline, Oxytetracycline, Demeclocycline.

8. **Atypical / uncommon use:** UTI, community acquired pneumonia etc. in selective cases after culture & sensitivity.

9. **Eradication of meningococcal carrier state:** Minocycline.

Streptococcus
macrolides

O → madam
one

10. **Demeclocycline** inhibits the action of ADH in the renal tubule and has been used in the treatment of inappropriate secretion of ADH. *SIADH*
11. **Tigecycline**: Its spectrum is very broad. MRSA, vancomycin-resistant staphylococci; penicillin-resistant streptococci; vancomycin-resistant enterococci; gram-positive rods; Enterobacteriaceae; anaerobes, both gram-positive and gram-negative; atypical agents, rickettsiae, chlamydia, and legionella; and rapidly growing mycobacteria all are susceptible. *Proteus* and *P. aeruginosa* are intrinsically resistant.

(Ref- Katzung-13th)

Q. Mention the adverse effects of tetracyclines. (SU-09J, RU-14J, 09J)

Q. Mention the adverse effects of long-acting tetracyclines. (SU-11J)

Q. Mention the side effects of doxycyclines? (SU-16J)

Ans.

Adverse effects of tetracyclines: Hypersensitivity reactions (drug fever, skin rashes) to tetracyclines are uncommon. Most adverse effects are due to direct toxicity of the drug or to alteration of microbial flora.

1. **GIT upset:** Nausea, vomiting, and diarrhea.
2. **In bony structures & teeth:** Tetracyclines are readily bound to calcium deposited in newly formed bone or teeth in young children. When a tetracycline is given during pregnancy, it can be deposited in the fetal teeth, leading to **fluorescence, discoloration, and enamel dysplasia**; it can also be deposited in bone, where it may cause **deformity or growth inhibition**. *Chelating agent to over bind zinc*
Discoloration & hypoplasia of teeth
3. **Hepatotoxicity:** especially in pregnancy, in patients with pre-existing hepatic insufficiency and in high dose.
4. **Nephrotoxicity:** Renal tubular acidosis and other renal injury resulting in nitrogen retention.
5. **Local tissue toxicity:** IV injection can lead to **venous thrombosis**. IM injection produces painful local irritation and should be avoided.
6. **Photosensitization:** Induce sensitivity to sunlight or UV light, particularly in fair-skinned persons (especially demeclocycline).
7. **Vestibular reaction:** Dizziness, vertigo, nausea, vomiting etc., particularly with doxycycline. *primarily cln*
8. **Super infection:** Tetracyclines modify the normal flora, with suppression of susceptible coliform and overgrowth of *pseudomonas*, *proteus*, staphylococci, resistant coliforms, clostridia, and *candida*. This can result in intestinal functional disturbances, anal pruritus, vaginal or oral candidiasis, or enterocolitis with shock and death.

• *Hypersensitivity*

(Ref- Katzung-13th)

Q. Mention the contraindication of tetracyclines. (RU-06S; SU-03J)

Ans.

Contraindications of tetracyclines:

1. **Children below 10 years of age-** Chance of dental caries.
2. **Pregnant women:** Chance of live damage of mother due to fat deposition. Fetal growth retardation.
3. **Nursing mothers:** Growth retardation of children, chance of dental caries.
4. **Renal failure**

Q. Discuss the probable outcome of using tetracycline below eight years of age. (DU-17M, 16Ju, 15Ju)

Ans.

Probable outcome of using tetracycline below eight years of age: Tetracyclines are readily bound to calcium deposited in newly formed bone or teeth in young children. If the drug is given for long periods to children younger than 8 years, it can be deposited in the teeth, leading to fluorescence, discoloration, and enamel dysplasia. It can also be deposited in bone, where it may cause deformity or growth inhibition.

(Ref- Katzung-13th/791)

Nice to know:Pharmacological properties of tetracyclines:

- Absorption:** Absorption is impaired by --
 - Food (Except Doxycycline & Minocycline)
 - Divalent cations (Ca^{2+} , Mg^{2+} , Fe^{2+}) or Al^{3+}
 - Dairy products
 - Antacids which contains multivalent cations.
 - Alkaline pH.
- Bioavailability:** Low, intermediate & high bioavailability.
- Plasma protein binding:** 40 - 80% bound to plasma proteins.
- Distribution:** Distributed widely to tissues & body fluids except CSF. Minocycline remains high conc. in tears & saliva.
- Excretion:** Mainly through bile & urine. There is entero-hepatic circulation.

Q. Compare & contrast oxytetracycline & doxycycline. (CU-12J, RU-12J,08J)

Q. Mention the difference between oxytetracycline & doxycycline. (RU-06M)

Q. Compare & contrast tetracycline with doxycycline. (RU-10J, SU-17J,16Ju,15Ju,15J,14Ju/J,13Ju/J,12Ju)

Ans.

Comparison between oxytetracycline / tetracycline & doxycycline:

Traits	Oxytetracycline/Tetracycline	Doxycycline/Minocycline
1. Source	Natural	Semi-synthetic
2. Potency	Low	High
3. Bioavailability	Moderate (60-70%)	High (95-100%)
4. $T_{1/2}$	6-8 hours	16-18 hours
5. Plasma protein binding	Low	High
6. Excretion	Rapid renal excretion	Primarily excreted in faeces as conjugate
7. Enterohepatic recycling	No	Yes
8. Alteration of intestinal flora	Marked	Less
9. Incidence of diarrhea	High	Low
10. Phototoxicity	Low	High
11. Doses	250-500 mg tds / qds	100-200 mg daily

(Ref: Tripathi-6th/713)

Q. Compare azithromycin with tetracycline. (RU-10J)

Q. Compare azithromycin, doxycycline and gentamycin. (CU-12J)

Ans.

Comparison between azithromycin & tetracycline:

Traits	Azithromycin	Tetracycline
1. Group	Macrolides	Tetracyclines
2. Mechanism of action	Inhibit protein synthesis by binding with 50S ribosomal subunit	Inhibit protein synthesis by binding with 30S ribosomal subunit
3. Absorption	Good & not impaired by food	Less & impaired by food, divalent cations, dairy products, antacid etc.
4. Volume of distribution	More	Less
5. Tissue penetration	More	Less
6. Dosing interval	Once daily	3 times /4 times daily
7. Use in community acquired pneumonia	Excellent	Not a good choice
8. Use in STDs	Good choice	It is a good alternative choice

9. In case of penicillin hypersensitivity cases	Good alternative & used commonly in penicillin hypersensitive cases	Not used.
10. <i>M. pneumoniae</i> infection	Not a good choice	1 st choice
11. Use in rickettsial fever	Not used	1 st choice
12. Use in pregnancy	Unsafe	Contraindicated (deposits in fetal teeth & bone)
13. GIT adverse effects	Less marked	Intense nausea & vomiting
14. Superinfection	Not occur	Occurs

Q. What are the precautions of tetracycline therapy?

Ans.

Precautions of tetracycline therapy:

1. Contraindication in: Pregnancy, lactation & children (≤ 10 years)
2. Should be avoided in patients with diuretic therapy (chance of raised blood urea).
3. Should be used cautiously in patient with renal & hepatic insufficiency.
4. Should not mix tetracycline & penicillin in same syringe (inactivation occurs).
5. Should not inject intrathecally.

(Ref: Tripathi-6th/714)

Chloramphenicol

Chloramphenicol is a **bacteriostatic broad-spectrum** antibiotic that is active against both **aerobic** and **anaerobic gram-positive** and **gram-negative organisms**. It is active also against rickettsiae but not chlamydiae. *H. influenzae*, *N. meningitidis*, and some strains of bacteroides are highly susceptible, and for them chloramphenicol may be bactericidal.

(Ref: Katzung-13th)

Q. Write the mechanism of action of chloramphenicol.

Ans.

Mechanism of action of chloramphenicol: Chloramphenicol is a potent inhibitor of microbial protein synthesis. It binds reversibly to the 50S subunit of the bacterial ribosome and inhibits the peptidyl transferase step of protein synthesis.

(Ref: Katzung-13th)

Q. Mention the indications/clinical uses of chloramphenicol. (SU-16Ju)

Ans.

Indications of chloramphenicol: Because of potential toxicity, bacterial resistance, and the availability of many other effective alternatives, chloramphenicol is **rarely used**.

1. **Topical use:** Used topically in eye infections because of its broad spectrum and its penetration of ocular tissues and the aqueous humor.
2. **Rickettsial infections:** Typhus and Rocky Mountain spotted fever.
3. **Bacterial meningitis:** It is an alternative to a β -lactam antibiotic for-
 - Meningococcal meningitis in patients with penicillin-hypersensitivity.
 - Bacterial meningitis caused by penicillin-resistant pneumococci.

(Ref: Katzung-13th)

Q. Write down the adverse effects of chloramphenicol. (DU-09J, SU-16Ju)

Q. Which drug can produce gray baby syndrome? (CU-03S)

Ans.

Adverse effects of chloramphenicol:

1. **Gastrointestinal disturbance:** Nausea, vomiting, and diarrhea. Oral or vaginal candidiasis may occur as a result of alteration of normal microbial flora.
2. **Bone marrow disturbance:** *a minor Normally use 20-25 mg/kg/d*
 - **Dose dependent:** Dose-related reversible suppression of red cell production at dosages exceeding 50 mg/kg/d after 1–2 weeks.
 - **Dose independent:** Aplastic anemia by idiosyncratic reaction. It is irreversible and fatal.
3. **Interaction with other drugs:**
 - Chloramphenicol inhibits hepatic microsomal enzymes and prolongs the action of phenytoin, tolbutamide, chlorpropamide, and warfarin.
 - As it is bacteriostatic, chloramphenicol can antagonize bactericidal drugs such as penicillins or aminoglycosides.
4. **Gray baby syndrome:** Occurs in newborn infants which is characterized by gray color of the baby, vomiting, diarrhea, shock, flaccidity, collapse, hypothermia.

(Ref: Katzung-13th)

Q. Write the contraindications of chloramphenicol.

Ans.

Contraindications of chloramphenicol:

1. Newborn infants
2. Pregnant women
3. Impaired liver function
4. Haemopoietic disorders

Q. Narrate the mechanism of gray baby syndrome. (CU-03S, RU-03S/01M)**Q. Discuss the probable outcome of chloramphenicol used in premature baby. (DU-16Ju)**

Ans.

Mechanism of grey baby syndrome: Chloramphenicol causes gray baby syndrome in newborn infants as they lack an effective glucuronic acid conjugation mechanism for the degradation and detoxification of chloramphenicol.

Newborn infants lack an effective glucuronic acid conjugation mechanism for the degradation and detoxification of chloramphenicol.

↓

Consequently, when infants are given dosages above 50 mg/kg/d

↓

No degradation & detoxification of chloramphenicol

↓

The drug may accumulate in the body

↓

The drug goes to the CNS through premature and relatively permeable blood-brain barrier

↓

The drug acts on cardio-respiratory center of the brain

↓

Cardio-respiratory collapse leading to vomiting, flaccidity, hypothermia, gray color, shock, and collapse

↓

Gray baby syndrome

To avoid this toxic effect, chloramphenicol should be used with caution in infants and the dosage limited to 50 mg/kg/d or less (during the first week of life) in full-term infants more than 1 week old and 25 mg/kg/d in premature infants.

(Ref: Katzung-13th)

Macrolides

*is Penicillin 2nd Alternative
first used*

The macrolides are a group of closely related compounds characterized by a macrocyclic lactone ring (usually containing 14 or 16 atoms) to which deoxy sugars are attached.

(Ref: Katzung-13th)

Q. Name the macrolides. (DU-15J, 13Ju, 11Ju, 09J, 08J; CU-15J, RU-15J, SU-16Ju)

Ans.

Macrolides:

1. Erythromycin
2. Clarithromycin
3. Azithromycin
4. Roxithromycin
5. Ketolides (Telithromycin)

(Ref: Katzung-13th)

Q. Explain the antibacterial mechanism of macrolides. (DU-13Ju, RU-15J, 11J)

Q. Write the mechanism of action of erythromycin. (DU-10Ju, RU-16Ju, SU-09Ju)

Q. Write the mechanism of action of azithromycin. (RU-07Ju, 05M, 04M)

Ans.

Mechanism of action of macrolides / azithromycin / clarithromycin / erythromycin:

Macrolides / Azithromycin / Clarithromycin / Erythromycin

↓

Bind with the 50S-ribosomal subunit

↓

Block aminoacyl translocation reaction & formation of initiation complex

↓

Inhibition of protein synthesis

The antibacterial action of erythromycin may be inhibitory or bactericidal, particularly at higher concentrations, for susceptible organisms. Activity is enhanced at alkaline pH.

(Ref: Katzung-13th)

Q. Write the antimicrobial spectrum of erythromycin.

Ans.

Antimicrobial spectrum of activity of erythromycin:

1. **Gram +ve organisms:** Erythromycin is effective against gram-positive organisms, especially pneumococci, streptococci, staphylococci, and corynebacteria.
2. **Gram -ve organisms:** Gram-negative organisms such as *Neisseria*, *Bordetella pertussis*, *Bartonella henselae*, and *B. quintana* (etiologic agents of cat-scratch disease and bacillary angiomatosis), some *Rickettsia* species, *Treponema pallidum*, and *Campylobacter* species are susceptible. *Haemophilus influenzae* is somewhat less susceptible.
3. Mycoplasma, legionella, *Chlamydia trachomatis*, *C. psittaci*, *C. pneumoniae*, helicobacter, listeria, and certain mycobacteria (*Mycobacterium kansasii*, *M. scrofulaceum*) are also susceptible.

(Ref: Katzung-13th)

Q. Write down the clinical uses of macrolides. (DU-13Ju, 09J)

Q. Give the indications of erythromycin. (DU-15J, 11Ju, RU-11J, 05M, 04M)

Q. Give the indications azithromycin. (DU-15J, 11Ju, RU-07J, SU-16Ju)

Q. Write down the clinical uses of erythromycin. (DU-08J; CU-07J)

Ans.

Indications of macrolides / azithromycin / erythromycin / clarithromycin:

1. Upper respiratory tract infections: Pharyngitis, tonsillitis, laryngitis, sinusitis, otitis media etc.
2. Community acquired pneumoniae
3. Atypical pneumoniae (*Mycoplasma pneumoniae*)
4. Acute exacerbation of chronic bronchitis.
5. In triple therapy to eradicate *H. pylori* infection in PUD.
6. As an alternative to penicillins in rheumatic fever & SABA.
7. Penicillin allergic individuals as penicillin substitute.
8. Acne
9. Cholera (1 gm single dose as per guideline of ICDDRDB)
10. Chlamydial & rickettsial infections.
11. Pelvic inflammatory diseases.
12. Skin & soft tissue infections
13. Diphtheria.
14. Whooping cough.
15. Clarithromycin and Azithromycin are highly active against STDs / STIs (syphilis, chancroid)

erythromycin 250mg Drug of choice
(Lungs + Triple therapy)

Drug of choice in
chlamydial
cervicitis
- azithromycin

(Ref: Katzung-13th)

Q. Write down the adverse effects of azithromycin? (RU-16Ju, SU-00M)

Q. Write down the adverse effects of erythromycin? (RU-16Ju, SU-00M)

Ans.

Adverse effects of erythromycin / azithromycin:

1. **GIT upset:** Anorexia, nausea, vomiting, and diarrhea.
2. **Liver toxicity:** Acute cholestatic hepatitis (fever, jaundice, impaired liver function), probably as a hypersensitivity reaction. Most patients recover from this.
3. **Allergic reactions** include fever, eosinophilia, and rashes.
4. **Drug interactions:** Erythromycin metabolites can inhibit cytochrome P450 enzymes and thus increase the serum concentrations of numerous drugs, including theophylline, oral anticoagulants, cyclosporine, and methylprednisolone. Erythromycin increases serum concentrations of oral digoxin by increasing its bioavailability.

(Ref: Katzung-13th)

Q. Enumerate the mechanisms of developing resistance to macrolides / erythromycin.

Ans.

Mechanisms of resistance to erythromycin / macrolides: Resistance to erythromycin is usually plasmid-encoded. Three mechanisms have been identified:

1. Reduced permeability of the cell membrane or active efflux;
2. Production (by Enterobacteriaceae) of esterases that hydrolyze macrolides;
3. Modification of the ribosomal binding site (so-called ribosomal protection) by chromosomal mutation or by a macrolide-inducible or constitutive methylase.

Efflux and methylase production are by far the most important resistance mechanisms in gram-positive organisms. Cross-resistance is complete between erythromycin and the other macrolides.

(Ref: Katzung-13th)

Q. Short note: Azithromycin. (RU-17J)

Ans. Write from above discussion.

Q. What are the advantages of azithromycin over erythromycin? (CU-07J/Ju,06J, RU-15J)

Ans.

Advantages of azithromycin over erythromycin:

1. Azithromycin is rapidly absorbed and well-tolerated orally.
2. Aluminum and magnesium antacids do not alter bioavailability.
3. Azithromycin penetrates into most tissues (except CSF) & phagocytic cells extremely well.
4. Prolong duration of action.

5. Azithromycin has **once daily dosing** rather 4 times/day dose of erythromycin.
6. Short duration of therapy.
7. Because azithromycin has a 15-member (not 14-member) lactone ring, azithromycin does not inactivate cytochrome P450 enzymes and therefore is **free of the drug interactions** that occur with erythromycin and clarithromycin.
8. Slightly more active against *H. influenza* and highly active against *Chlamydia*.

(Ref: Katzung-13th)

Viva Q. Justify once-daily dosing of azithromycin.

Ans.

Once-daily dosing of azithromycin: A 500-mg dose of azithromycin produces relatively low serum concentrations of approximately 0.4 mcg/mL. However, azithromycin penetrates into most tissues (except CSF) and phagocytic cells extremely well, with tissue concentrations exceeding serum concentrations by 10- to 100-fold. The drug is slowly released from tissues (tissue half-life of 2–4 days) to produce an elimination half-life approaching 3 days. These unique properties permit once-daily dosing and shortening of the duration of treatment in many cases. For example, a single 1-g dose of azithromycin is as effective as a 7-day course of doxycycline for chlamydial cervicitis and urethritis. Community-acquired pneumonia can be treated with azithromycin given as a 500-mg loading dose, followed by a 250-mg single daily dose for the next 4 days.

(Ref: Katzung-13th)

Q. Compare among macrolides. (DU-16Ju)

Q. Write down the differences between erythromycin and azithromycin. (DU-12Ju, SU-12Ju)

Q. Compare and contrast between erythromycin and azithromycin. (DU-15J, 11Ju, 10Ju, 09J, 08J, CU-16J, 15J, RU-08Ju; SU-17J, 15Ju, 14Ju/J, 13Ju/J, 12Ju)

Ans.

Comparison between erythromycin and azithromycin:

Traits	Erythromycin	Clarithromycin	Azithromycin
1. Volume of distribution	Low	Large	Larger
2. Tissue penetration	Less	More	More
3. Acid stability	Acid labile	Acid stable	Acid stable
4. Duration of action	Short	Prolonged	More prolonged
5. Half life	1.5 hours	6 hours	3 days
6. Absorption	Delayed	Rapid	Rapid
7. Food interferes with the absorption	Yes	No, rather increases absorption.	Yes
8. Excretion	Bile	Kidney & bile	Bile
9. Dose interval	6 hourly	12 hourly	Once daily
10. Duration of therapy	Longer	Long	Short
11. Tolerability	Less tolerated	Well tolerated	Well tolerated
12. Antibacterial spectrum	Gram +ve & -ve	Virtually identical to that of erythromycin except that clarithromycin is more active against <i>Mycobacterium avium</i> complex. Active against <i>M leprae</i> and <i>Toxoplasma gondii</i> .	Virtually identical to that of clarithromycin. More active against <i>H influenzae</i> . Highly active against <i>chlamydia</i> .
13. Drug interactions	Inhibit metabolism of a number of drugs	Inhibit metabolism of a number of drugs	No drug interactions
14. Resistance	Common	Show cross-resistance with erythromycin	Show cross-resistance with erythromycin

15. Contraindication	Hepatic failure	Renal failure	Hepatic failure
16. Cost	Cheap	Costly	Costly

(Ref: Lippincott's-6th; Katzung-13th)

Q. Compare azithromycin, doxycycline, and gentamicin with respect to their spectrum of activity. (CU-12J)

Ans.

Comparison among azithromycin, doxycycline, and gentamicin with respect to their spectrum of activity

Drug	Spectrum of activity
Azithromycin	Both Gram positive & Gram negative
Doxycycline	Good Gram negative activity but much less Gram positive activity
Gentamicin	Broad spectrum- active against many Gram positive and Gram negative bacteria, including anaerobes, rickettsiae, chlamydiae, mycoplasmas, and L forms and against some protozoa (eg, amebas).

Clindamycin

Group: Protein synthesis inhibitor

Mechanism of action: Clindamycin binds with the 50S ribosomal subunit (like macrolides) & inhibits protein synthesis by—

1. Interfering with the formation of initiation complexes
2. Interfering with aminoacyl translocation reactions

Pharmacokinetics

1. **Route:** Oral and IV.
2. **PPB:** The drug is about 90% protein-bound.
3. Clindamycin penetrates well into most tissues, except brain and CSF. It penetrates well into abscesses and is actively taken up and concentrated by phagocytic cells.
4. **Metabolism:** Liver
5. **Excretion:** Bile and urine.
6. **Half-life** is 2.5 hours in normal individuals, increasing to 6 hours in patients with anuria.
7. No dosage adjustment is required for renal failure.

Antibacterial activity:

1. Active against **Gram '+ve' cocci** including streptococci, staphylococci, and pneumococci.
2. Enterococci and gram-negative aerobes are resistant (*in contrast to their susceptibility to erythromycin*).
3. **Anaerobic infections** including bacteroides.

Resistance to clindamycin, which generally confers cross-resistance to macrolides, is due to

1. mutation of the ribosomal receptor site;
2. modification of the receptor by a constitutively expressed methylase; and
3. Enzymatic inactivation of clindamycin.

Gram-negative aerobic species are intrinsically resistant because of poor permeability of the outer membrane.

Clinical Uses

1. **Anaerobic infection** caused by bacteroides and other anaerobes.
2. Penetrating wounds of the abdomen and the gut; infections originating in the female genital tract, eg, septic abortion and pelvic abscesses; and aspiration pneumonia.

3. **Prophylaxis of endocarditis** in patients with valvular heart disease who are undergoing certain dental procedures.
4. *Pneumocystis jiroveci* pneumonia in AIDS patients (*Clindamycin plus primaquine*).
5. AIDS-related toxoplasmosis of the brain (*in combination with pyrimethamine*).
6. Staphylococcal infections of bones and joints.
7. Staphylococcal conjunctivitis as eye drops.

Adverse Effects

1. **Common:** Diarrhea, nausea, and skin rashes.
2. Impaired liver function (with or without jaundice)
3. Neutropenia (sometimes)
4. Severe diarrhea and enterocolitis.

(Ref: Katzung-13th)

Nucleic acid synthesis inhibitors

Q. List the antimicrobials that affect microbial nucleic acid. (SU-11J,09J)

Q. List the bacterial nucleic acid synthesis inhibitors. (CU-09J)

Ans.

Classification of nucleic acid synthesis inhibitors:

Mechanism of action		Class of drug
A. Direct	DNA synthesis inhibitor	▪ Quinolones ▪ Metronidazole
	RNA synthesis inhibitor	▪ Rifampicin ▪ Rifamycin
B. Indirect	Anti-folate drugs	▪ Sulfonamide ▪ Trimethoprim ▪ Pyrimethamine

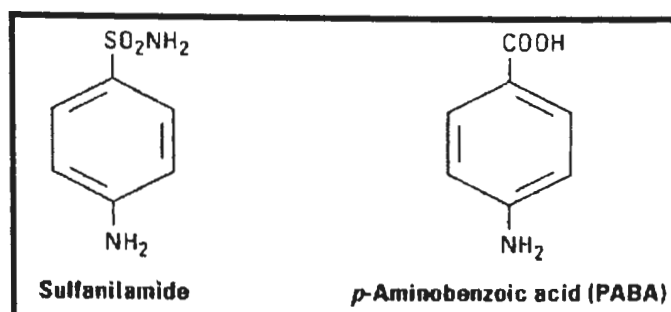
Antifolate drugs

Sulfonamides: They are-

1. Anti-microbial agents: Broad spectrum & Bacteriostatic
2. Diuretics
3. Oral hypoglycemic agents
4. Anti-leprosy agents (Dapsone)

Structure of sulfonamides:

1. Sulfonamides have structural similarity to *p*-aminobenzoic acid (PABA).
2. NH₂ group is responsible for pharmacodynamic property of drug.
3. SO₂-NH₂ group is responsible for pharmacokinetic property of drug.



Sulfa-Drugs

*Acid burn - Silver
Sulfadiazine
- tropical use*

Q. Classify sulfonamides.

Ans.

Classification of sulfonamides based on pharmacokinetics: Sulfonamides can be divided into three major groups: (1) oral, absorbable; (2) oral, nonabsorbable; and (3) topical.

Type		Drugs
1. Oral, absorbable: (Classified on the basis of their half-lives $t_{1/2}$)	Short acting	- Sulfisoxazole ($t_{1/2}$ = 6 hours) - Sulfamethizole ($t_{1/2}$ = 9 hours) - Sulfacytine
	Intermediate acting	- Sulfadiazine ($t_{1/2}$ = 10-17 hours) - Sulfamethoxazole ($t_{1/2}$ = 10-12 hours) - Sulfapyridine ($t_{1/2}$ = 17 hours)
	Long acting	- Sulfadoxine ($t_{1/2}$ = 7-9 days) - Sulfasalazine
2. Oral, nonabsorbable		Silver sulfadiazine (less toxic) <i>burn</i>
3. Topical (not absorbed in systemic circulation)		- Sodium sulfacetamide - Mafenide acetate

(Ref: Katzung-13th)

Q. Write down mechanism of action of co-trimoxazole. (DU-14J,12J,10Ju,09J, CU-07J; RU-06M, SU-17J,07Ju)

Q. Explain antimicrobial action of co-trimoxazole. (SU-08Ju)

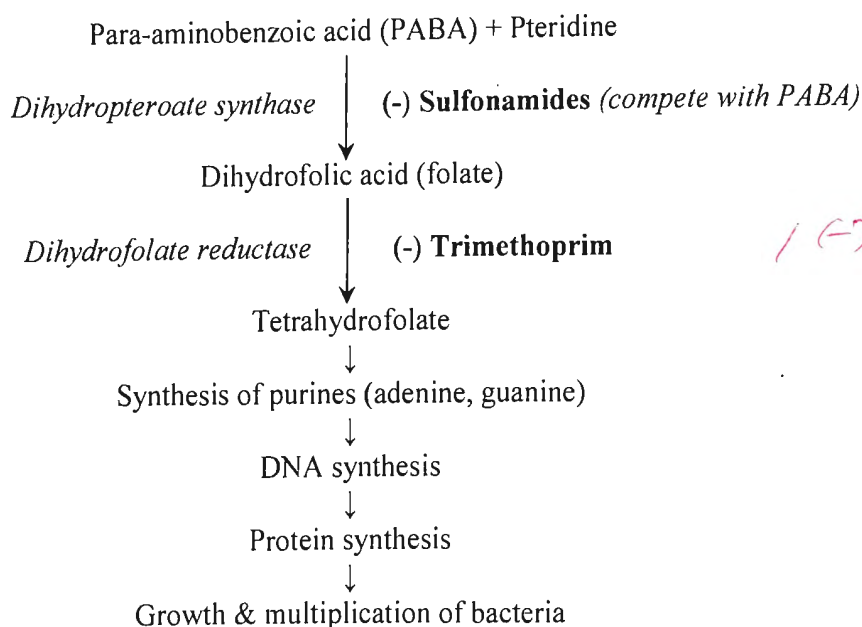
Q. What is the pharmacological basis of combination of sulfonamide with trimethoprim?

Q. Give the mechanism of action of sulfonamides. (DU-98J)

Q. Rationalize combination of Sulfamethoxazole and Trimethoprim. (RU-17J)

Ans.

Mechanism of action of cotrimoxazole/ sulfonamide: Sulfonamide-susceptible organisms, unlike mammals, cannot use exogenous folate but must synthesize it from PABA. This pathway is thus essential for production of purines and nucleic acid synthesis.

**Mechanism of action of Sulfonamide:**

- Sulfonamides are structural analogue of Para-aminobenzoic acid (PABA). PABA is a precursor of folic acid.
- Sulfonamides compete with PABA for the enzyme dihydropteroate synthase and inhibit folate synthesis. Folate is necessary for synthesis of bacterial DNA or RNA. Thereby sulfonamide inhibits bacterial growth.

Mechanism of action of Trimethoprim:

- Inhibit enzyme dihydrofolate reductase which is responsible for conversion of folic acid to active folate. Thereby trimethoprim inhibits bacterial growth.

Combination of a sulfonamide with an inhibitor of dihydrofolate reductase (trimethoprim or pyrimethamine) provides synergistic activity because of sequential inhibition of folate synthesis.

(Ref: Katzung-13th)

Viva Q. Why sulfonamides cannot inhibit nucleic acid synthesis in human cells?

Ans.

Sulfonamide act against those who synthesize their folate from PABA by the enzyme dihydropteroate synthase. Human cells (& other mammalian cells) lack the enzymes required for folate synthesis from PABA and depend on exogenous sources of folate; therefore, they are not susceptible to sulfonamides.

(Ref: Katzung-13th)

Viva Q. Why trimethoprim cannot inhibit nucleic acid synthesis in human cells?

Ans.

Trimethoprim selectively inhibits bacterial dihydrofolate reductase. Human cells have dihydrofolate reductase which converts exogenous folate to tetrahydrofolate. Trimethoprim is about 50,000 times less efficient in inhibition of human dihydrofolate reductase. This is why; Trimethoprim cannot inhibit nucleic acid synthesis in human cells.

(Ref: Katzung-13th)

Q. What are the fixed drug dose combinations of sulfonamide? (DU-02J)

Ans.

Fixed drug dose combinations of sulfonamide:

1. Co-trimoxazole = Trimethoprim (80 mg) + Sulfamethoxazole (400 mg)
2. Fansidar = Sulfadoxine (500 mg) + Pyrimethamine (25 mg)
3. Sulfadiazine (1 gm 4 times daily) + Pyrimethamine (25 mg daily) → Used for acute toxoplasmosis.

Q. What is the spectrum of activity of sulfonamides?

Ans.

Spectrum of activity of sulfonamides: Sulfonamides inhibit both gram-positive and gram-negative bacteria, nocardia, Chlamydia trachomatis, and some protozoa. Some enteric bacteria, such as E. coli, klebsiella, salmonella, shigella, and enterobacter, are also inhibited. It is interesting that rickettsiae are not inhibited by sulfonamides but are actually stimulated in their growth. Activity is poor against anaerobes.

(Ref: Katzung-13th)

Q. What is co-trimoxazole? (DU-17J, 12J, 09J; RU-06M, 04S)**Q. What are the constituents of co-trimoxazole? (DU-14J)**

Ans.

Co-trimoxazole:

- **Co** : for combination
- **Trim** : for trimethoprim 80mg
- **Oxazole**: for sulfamethoxazole. 400mg

So co-trimoxazole means combination of trimethoprim & sulfamethoxazole at the ratio of 1:5.

Q. Explain with example chemotherapeutic potentiation? (DU-05M, 04J)**Q. What is chemotherapeutic potentiation? How does Co-trimoxazole exhibit an Ideal example of it? (DU-03J)****Q. What are the advantages of combination of sulfamethoxazole and trimethoprim? (CU-02M, SU-02J)****Q. Justify combination of sulfonamide & trimethoprim. (CU-04S, SU-02J, RU-11J)****Q. Justify/rationalize the combination of sulfamethoxazole & trimethoprim. (DU-16J, CU-13Ju)**

Ans.

Chemotherapeutic potentiation: When two or more chemotherapeutic agents are used together, their effects are more than the sum of individual drug effects. This is called chemotherapeutic potentiation. e.g.

Sulfonamide (400 mg) + Trimethoprim (80 mg) (5 : 1)

Co-trimoxazole	Sulfonamide	Trimethoprim
• Bactericidal	• Bacteriostatic	• Bacteriostatic
• Broad spectrum	• Narrow spectrum	• Narrow spectrum
• Delayed resistance	• Bacteria can develop resistance easily	• Bacteria can develop resistance easily
• Cotrim 480 mg → Antimicrobial effect	• 400 x 10 mg → Same amount of antimicrobial effect.	• 80 x 10 mg → Same amount of antimicrobial effect.
• i.e, to achieve the effect of cotrim, we have to increase the dose of individual drug for 10 times, at least. Still we do not get the same effect.		
• Cotrim 480 mg → Less toxic effects.	• 4000 mg → more toxic effect.	• 800 mg → more toxic effect.
• i.e, combined therapy has less toxic effects. Individual therapy has more toxic effects.		

Q. Write down clinical uses of co-trimoxazole. (DU-17J,12J,10Ju,09J)

Q. What are the indications of sulfonamides? (

Q. What are the indications of co-trimoxazole? (RU-04S)

Ans.

Indications of sulfonamides / co-trimoxazole:

Sulfonamides	Co-trimoxazole
Oral absorbable sulfonamides 1. Urinary tract infection (UTI) 2. Acute toxoplasmosis (Sulfadiazine + pyrimethamine) 3. 2nd line therapy of malaria: Sulfadoxine + Pyrimethamine (Fansidar)	1. UTI 2. Community acquired pneumonia (CAP) 3. Otitis media 4. Respiratory tract infections (RTI), eg, pneumococcus, <i>Haemophilus</i> species, <i>Moraxella catarrhalis</i>, and <i>Klebsiella pneumoniae</i>. 5. <i>S aureus</i> strains, both methicillin-susceptible and methicillin-resistant. 6. Double strength tablet: Is used for — ▪ Pneumocystis jiroveci (carinii) pneumonia ▪ Shigellosis (bacillary dysentery) ▪ Enteric fever ▪ Prostatitis ▪ Non-tubercular mycobacterial infection.
Oral non-absorbable: Sulfasalazine is widely used in- 1. Ulcerative colitis 2. Enteritis 3. Other inflammatory bowel disease.	
Topical: 1. Bacterial conjunctivitis and adjunctive therapy for trachoma (Na Sulfacetamide). 2. Prevention of infection of burn wounds (Silver sulfadiazine).	

Indications of trimethoprim: Urinary tract infection (100 mg twice daily).

(Ref: Katzung-13th)

Q. Lists the antimicrobial spectrum of activity of co-trimoxazole. (SU-07Ju)

Ans.

Antimicrobial spectrum of activity of co-trimoxazole:

1. Most *S. aureus* strains (both methicillin susceptible & methicillin resistant)
2. *Pneumococcus*
3. *E. coli*
4. *H. influenza*
5. *Salmonella* & *Shigella*
6. *Klebsiella pneumoniae*

Sulfonamides,
Trimethoprim
— Sp. aureus
and systemic
use on burn
(Side eff +)

7. *Pneumocystis carinii* (*P. jiroveci*)
8. Non-tuberculous mycobacterium

(Ref: Katzung-13th)

Q. Enumerate advantages and disadvantages of co-trimoxazole as anti enteric fever drug. (CU04S)

Ans.

Advantages of co-trimoxazole:

1. Bactericidal effect
2. Broad spectrum antibiotic
3. Less dose requirement
4. Less adverse effect
5. Delayed drug resistance

Disadvantages of co-trimoxazole: Write adverse effects of co-trimoxazole.

Q. Mention the adverse effects of sulfonamides.

Q. Mention the adverse effects of co-trimoxazole. (DU-17J,14J,05S, RU-06M,04S, SU-05J, CU-08J)

Ans.

Adverse effects of co-trimoxazole / sulfonamides

Sulfonamides	Trimethoprim	Co-trimoxazole
1. Sulfonamide hypersensitivity: ▪ Fever ▪ Skin rashes ▪ Urticaria ▪ Photosensitivity ▪ Exfoliative dermatitis ▪ Steven Johnson syndrome (<i>Rare but a life threatening adverse effect</i>) 2. Urinary tract disturbances: Crystalluria, haematuria or even obstruction due to precipitation of sulfonamides at neutral or acid pH of urine. (<i>Patients are advised to intake 3 litres of water /day</i>). 3. GIT upset: Nausea, Vomiting 4. Haematopoietic disturbances: ▪ Hemolytic or aplastic anemia ▪ Granulocytopenia ▪ Thrombocytopenia ▪ Leukaemoid reaction 5. Others: ▪ Arthritis ▪ Hepatitis ▪ Polyarteritis nodosa (PAN) ▪ Psychosis	Trimethoprim produces the predictable adverse effects of an antifolate drug, especially 1. Megaloblastic anemia 2. Leucopenia 3. Granulocytopenia.	1. Crystalluria 2. Renal stone 3. Allergic reactions- Fever, skin rashes, urticaria, photosensitivity, exfoliative dermatitis, Steven Johnson syndrome 4. Megaloblastic anemia 5. Hemolytic anemia 6. Leukopenia 7. Granulocytopenia 8. Nausea, vomiting. 9. Central nervous system disturbances

(Ref: Katzung-13th)

Q. How bacterial resistance occurred against sulfonamides?

Ans.

Mechanisms of resistance to sulfonamides: Sulfonamide resistance may occur as a result of mutations that

1. Cause overproduction of PABA.
2. Cause production of a folic acid-synthesizing enzyme (plasmid mediated) that has low affinity for sulfonamides.
3. Impair permeability to the sulfonamide.

(Ref: Katzung-13th)

Q. Write down the contraindications of sulfonamides.

Q. Write down the contraindications of co-trimoxazole.

Ans.

Contraindications of sulfonamides & co-trimoxazole:

Sulfonamides	Co-trimoxazole
1. Hypersensitivity to sulfonamides	1. Hypersensitivity to co-trimoxazole
2. Renal & hepatic failure	2. Renal failure
3. Haemopoietic disorders	3. Pregnancy & lactation
4. Pregnancy (<u>cross placental barrier</u> → <u>Kernicterus of fetus</u>)	
5. Lactation	
6. Premature baby (<u>Sulfonamides replace bilirubin from plasma protein</u> → <u>CNS</u> → <u>Kernicterus</u>)	

Nice to know:

- **Trimethoprim:** Inhibit dihydrofolate reductase of bacteria → Antibacterial action
- **Pyrimethamine:** Inhibit dihydrofolate reductase of protozoa → Antiprotozoal action
- **Methotrexate:** Inhibit dihydrofolate reductase of human → Anticancer action

Fluoroquinolones / DNA-gyrase inhibitors

Quinolones are antibiotics obtained by chemical synthesis. They derive from quinoline. One of the first active molecules was nalidixic acid. Quinolones with a fluorine atom are called fluoroquinolones. Quinolones and fluoroquinolones inhibit topoisomerase II, also called DNA-gyrase.

Q. What are the quinolone derivatives / preparation? (DU-11J,06S; RU-07J,04J)

Ans.

Quinolone derivatives:

1. Nalidixic acid
2. Fluoroquinolones: See below

Q. Classify fluoroquinolones. (DU-04J, CU-08J,04S; SU-03J, RU-04J)

Q. Enlist fluoroquinolones according to their generation. (SU-17J)

Q. Mention the fluoroquinolones available in Bangladesh. (CU-04M)

Q. Mention the antimicrobial spectrum of fluoroquinolones. (DU-06S, SU-15Ju,14Ju/J,08/07Ju)

Q. Describe the antibacterial spectrum of second generation Fluoroquinolones. (CU-16J)

Ans.

Classification of fluoroquinolones:

A. Classification based on generation: Generations of drugs are based on their antimicrobial targets.

Generations	Drugs	Antibacterial spectrum
1. 1 st generation	▪ <u>Nalidixic acid</u>	▪ Least active against Gram -ve and Gram +ve bacteria ▪ Narrow spectrum usually confined to the urinary tract.
2. 2 nd generation	▪ Ciprofloxacin ▪ Lomefloxacin ▪ Ofloxacin ▪ Norfloxacin ▪ Pefloxacin ▪ Enoxacin	▪ Excellent Gram -ve activity and moderate to good activity against Gram +ve bacteria. ▪ Active against aerobic Gram -ve bacteria and intracellular organisms eg, <i>chlamydia</i> , <i>mycoplasma</i> , <i>legionella</i> .
3. 3 rd generation	▪ Levofloxacin ▪ Gatifloxacin ▪ Gemifloxacin ▪ Sparfloxacin	▪ Improved activity against Gram-positive bacteria.

4. 4 th generation	▪ Moxifloxacin ▪ Trovafloxacin	▪ Active against many anaerobic as well as Gram +ve organisms.
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(Ref: Lippincott's-6th)

B. According to half life:

1. Shorter half life (3-5 hours)	Ciprofloxacin, Norfloxacin
2. Intermediate half life (5-7 hrs)	Levofloxacin, Ofloxacin
3. Longer half life (>7 hours)	Gatifloxacin, Gemifloxacin, Lomefloxacin, Moxifloxacin

C. According to bioavailability:

1. Shorter bioavailability (70-90%)	Ciprofloxacin, gemifloxacin, moxifloxacin, norfloxacin
2. Longer bioavailability (> 90%)	Levofloxacin, gatifloxacin, lomefloxacin, ofloxacin

(Ref: Katzung-13th)

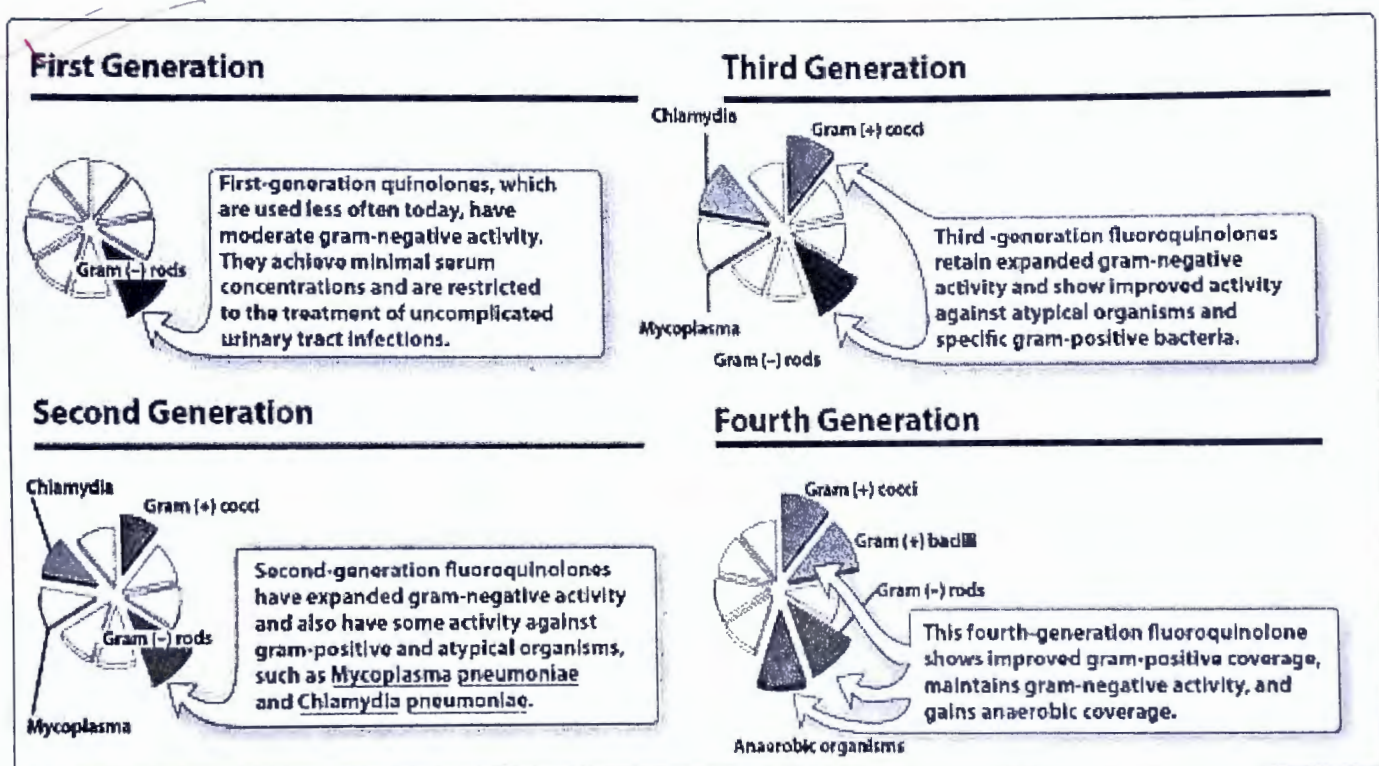


Figure. Summary of antimicrobial spectrum of quinolones.

Viva Q. Which fluoroquinolones are most active against Gram negative organisms?

Ans. 2nd generation fluoroquinolones are most active against Gram negative organisms.

(Ref- Katzung-13th)

Q. Enumerate common characteristics of fluoroquinolones. (CU-04S)

Q. Describe the pharmacokinetic profile of Fluroquinolone. (CU-16Ju)

Ans.

Common characteristics of fluoroquinolones:

1. Synthetic fluorinated compound of nalidixic acid
2. Both lipid soluble and water soluble
3. Pharmacokinetic profile:
 - Oral absorption is impaired by divalent cations, milk, food, antacid
 - Oral bioavailability is 80-95%
 - Distribution: Widely distributed in body fluids and tissues
 - Metabolism: Liver
 - Excretion: Kidney- by tubular secretion & glomerular secretion

4. Act on urinary tract and gastrointestinal tract
5. Extensively used- Broad spectrum, bactericidal
6. Less prone to develop resistance

Q. Write down the mechanism of action of ciprofloxacin/ fluoroquinolones / Sparfloxacin. (DU-16J,12Ju,11J, CU-17M,08J, SU-17M,13J,12Ju,11Ju,08J, RU-16J,13Ju,10J)

Q. What is the function of topoisomerase IV? (CU-16J)

Q. What are the functions of topoisomerase II and topoisomerase IV? (CU-16Ju)

Ans.

Mechanism of action of ciprofloxacin/ fluoroquinolones: Quinolones block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV.

1. **Inhibition of topoisomerase-II (DNA gyrase):** (Imp for Centre)

Fluoroquinolones inhibit DNA gyrase (topoisomerase-II) enzyme

↓
Prevents relaxation of positively super-coiled DNA

↓
Inhibits transcription and replication

↓
Inhibition of protein and DNA synthesis in bacteria

↓
Bacterial cell death

⇒ DNA strand breakage

2. **Inhibition of topoisomerase-IV:** Inhibition of topoisomerase IV by fluoroquinolones interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division. (Ref: Katzung-13th)

↓ chromosomal stabilization

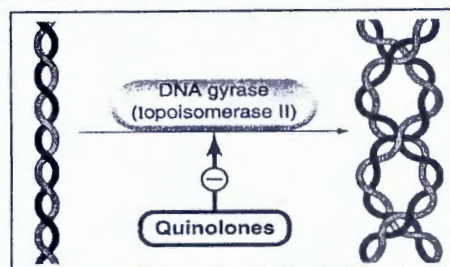


Fig. Schematic diagram of (left) the double helix and (right) the double helix in supercoiled form. In essence, the DNA gyrase unwinds the RNA-induced positive supercoil (not shown) and introduces a negative supercoil.

Q. Mention the antimicrobial spectrum of ciprofloxacin. (SU-13J,12J,10J, CU-10Ju)

Ans.

Antimicrobial spectra of ciprofloxacin: Ciprofloxacin has excellent Gram -ve activity and moderate to good activity against Gram +ve bacteria.

Highly susceptible	Moderately susceptible	Low / variable susceptibility
1. Enterobacteriaceae: <i>E. coli</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Proteus</i> , 2. <i>Klebsiella</i> , <i>Enterobacter</i> 3. <i>H. influenzae</i> 4. <i>N. gonorrhoeae</i> 5. <i>N. meningitidis</i> 6. <i>V. cholerae</i> 7. <i>C. jejuni</i>	1. <i>Pseudomonas aeruginosa</i> 2. <i>Staphylococcus aureus</i> (including Methicillin resistant <i>S. aureus</i>) 3. <i>Staphylococcus epidermidis</i> 4. <i>M. tuberculosis</i> 5. <i>Legionella</i> 6. <i>Brucella</i> 7. <i>Listeria</i> 8. <i>B. anthracis</i>	1. <i>Streptococcus pyogenes</i> 2. <i>Strept. faecalis</i> 3. <i>Strept. pneumoniae</i> 4. <i>Mycoplasma</i> 5. <i>Chlamydia</i> 6. Opportunistic mycobacterium

(Ref: Tripathi-6th/688-689)

Q. Write down the indications / uses of ciprofloxacin. (DU-14J, CU-08J,04M; RU-07J, SU-16J,15J)

Q. Write down the four (04) indications / uses of ciprofloxacin. (DU-16Ju)

Q. Write down the indications of fluoroquinolones. (DU-16J, CU-10/08Ju, SU-03S)

Q. Write down the indications of norfloxacin. (CU-01S)

Q. Write down the indications of pefloxacin. (SU-01M)

Ans.

Indications of ciprofloxacin/ fluoroquinolones/ pefloxacin:

1. Urinary tract infection (UTI).
2. Bacterial causes of diarrhea (shigella, salmonella, toxigenic E. coli & campylobacter)
3. Soft tissues, bones and joints infections.
4. Intra-abdominal infections such as peritonitis, diverticulitis, appendicitis etc.
5. Enteric fever.
6. Gonococcal infections (gonorrhoea).
7. Chlamydial urethritis and cervicitis.
8. Respiratory tract infections.
9. Prophylaxis & treatment of anthrax (drug of choice).
10. Second line agents in TB & atypical mycobacterium infection.
11. Eradication of meningococci from carrier state.
12. Chemoprophylaxis of infection in neutropenic patients.
13. Atypical pneumonia
14. Eradication of *Salmonella typhi* from carrier state.
15. Chronic bacterial prostatitis.

(Ref: Katzung-13th)

Q. Name the respiratory quinolones with justification. (RU-16J,12Ju,10J)

Ans.

Respiratory quinolones / fluoroquinolones having excellent activity in RTI:

1. Levofloxacin
2. Gatifloxacin
3. Gemifloxacin
4. Sparfloxacin
5. Moxifloxacin

(Ref: Tripathi-6th/690-693)

Justification: These drugs have enhanced **gram-positive activity** and activity against **atypical pneumonia agents** (eg, chlamydia, mycoplasma, and legionella) and are effective and used increasingly for treatment of upper and lower respiratory tract infections. So, they are called **respiratory quinolones**.

(Ref: Katzung-13th)

Q. Write down the adverse effects of fluoroquinolones. (DU-16J/Ju,11J, CU-17J; RU-07Jan, SU-17M,14J)

Q. Write down the adverse effects of ciprofloxacin. (DU-14J,12Ju, CU-13J, SU-16J,15J,06M; RU-13Ju)

Q. Write down the adverse effects of norfloxacin. (CU-01S)

Ans.

Adverse effects of ciprofloxacin / fluoroquinolones/ norfloxacin: Fluoroquinolones are extremely well tolerated.

1. **GIT upset:** Nausea, vomiting, diarrhea.
2. **CNS disturbances:** Headache, dizziness, insomnia, seizure, confusion.
3. **Photosensitivity:** Lomefloxacin, pefloxacin.
4. **Hepatotoxicity** (acute hepatitis & hepatic failure) by Trovafloxacin
5. **Prolonged QT interval:** Gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin.
6. Gatifloxacin causes **hyperglycemia** in diabetic patients and with **hypoglycemia** in patients also receiving oral hypoglycemic agents.
7. **Arthropathy in children:** Arthritis, fever, effusion (Fluoroquinolones may damage growing cartilages & can cause an arthropathy).

8. Tendinitis in adult & tendon rupture (in advanced age, renal insufficiency & co-administration of steroids).

(Ref: Katzung-13th)

Q. Short note: Ciprofloxacin. (DU-17J)

Ans. Write in brief from above.

Q. Justify the use of ciprofloxacin in the management of salmonella infection.

Q. Enumerate advantages & disadvantages of ciprofloxacin as anti-enteric fever drug. (CU-05J)

Ans.

Advantages of ciprofloxacin as a drug of enteric fever:

1. Bactericidal effect
2. Broad spectrum activity
3. Rapid onset of action
4. Prolonged duration of action, so less dose is required.
5. Short duration of therapy (7 days)
6. Less prone to develop resistance among anti-enteric fever drugs.
7. Less chance of toxicity
8. Eradication of *Salmonella typhi* from carrier state
9. Does not produce super infection
10. Does not produce serious adverse effects like aplastic anemia, GBS, nephrotoxicity, crystalluria, hematuria etc.
11. Patient's compliance is better.

Disadvantages of ciprofloxacin as anti-enteric fever drug:

1. Skin: Rash, pruritus, photosensitivity
2. CNS: Headache, dizziness, insomnia
3. Contraindicated in children below 18 years.

Q. What are the contraindications of ciprofloxacin?

Ans.

Contraindications of ciprofloxacin /fluoroquinolones:

1. Known hypersensitivity to ciprofloxacin
2. Pregnancy
3. Lactation
4. Children below 18 yrs
5. History of epilepsy
6. Psychosis
7. Tendinitis (athletes)

Q. Why ciprofloxacin is not used in children? (RU-04J)

Q. Discuss the probable outcome of using ciprofloxacin in children below 5 years of age. (DU-17M)

Ans.

Limitations of using ciprofloxacin in children below 18 years: Fluoroquinolones / Ciprofloxacin may damage growing cartilage and cause an **arthropathy**. Thus, these drugs are not routinely recommended for patients under 18 years of age. However, the arthropathy is **reversible**, and there is a growing consensus that fluoroquinolones may be used in children in some cases (eg, for treatment of pseudomonal infections in patients with cystic fibrosis).

(Ref: Katzung-13th)

Q. Compare Fluoroquinolone with Nalidixic acid. (CU-17J)

Ans.

Comparison between Fluoroquinolone with Nalidixic acid

Traits	Nalidixic acid	Fluoroquinolone
1. Structure	It is the first synthetic quinolone antibiotics derive from quinoline.	Quinolones with a fluorine atom are called fluoroquinolones.
2. Antibacterial spectrum	Gram-negative organisms (but not <i>Pseudomonas</i> species)	Both Gram negative & positive bacteria
3. Uses	Uncomplicated urinary tract infections	Wide clinical uses.
4. Activity against <i>pseudomonas</i>	No	Excellent
5. Use in systemic infections	No	Yes
6. Route of administration	Oral	Oral, IV
7. Excretion	Kidney	Kidney
8. Dose adjustment in renal failure	Required	Required
9. Current uses	Rarely used	Widely used

Q. Compare and contrast ceftriaxone, gentamicin & ciprofloxacin as antimicrobial drugs.

Ans.

Comparison among ceftriaxone, gentamicin & ciprofloxacin as antimicrobial drugs

Traits	Ceftriaxone	Gentamicin	Ciprofloxacin
1. Group	3 rd generation cephalosporin	Aminoglycosides	Fluoroquinolones
2. Mechanism of action	Inhibits bacterial cell wall synthesis	Inhibits bacterial protein synthesis	Inhibits bacterial DNA synthesis
3. Gram -ve activity	Good	Good	Excellent
4. Gram +ve activity	Good	Much less	Good
5. Activity against <i>pseudomonas</i>	No activity	Less than ciprofloxacin	Excellent
6. Bactericidal activity	Time dependent	Conc. dependent	Conc. dependent
7. Arthropathy in <18 years	No	No	Yes
8. Neurotoxicity	No	Yes	No
9. Ototoxicity	No	Yes (reversible)	No
10. Nephrotoxicity	No	Yes	No
11. Excretion	Liver	Kidney	Kidney
12. Dose adjustment in renal failure	Not required	Required	Required
13. Solubility	Lipid soluble	Water soluble	Lipid soluble

Q. Compare Ciprofloxacin, Levofloxacin & Co-trimoxazole in respect to their spectrum of activity. (CU-09J)

Ans.

Comparison among Ciprofloxacin, Levofloxacin & Co-trimoxazole

Traits	Ciprofloxacin	Levofloxacin	Co-trimoxazole
1. Group	2 nd generation fluoroquinolone	2 nd generation fluoroquinolone	Sulfonamide + trimethoprim
2. Gram +ve activity	Good	Good	Less
3. Gram -ve activity	Excellent	Excellent	Good but less than fluoroquinolones
4. Post-antibiotic effect	Against both gram +ve & -ve organisms	Against both gram +ve & -ve organisms	Only against gram +ve organisms
5. Use in enteric fever	Excellent & effective	Excellent & effective	Less effective than fluoroquinolones
6. <i>Pneumocystis carinii</i> infection in AIDS patient	Not used	Not used	Used in AIDS patients
7. Haemopoietic suppression	No	No	Yes
8. Hypersensitivity	Less frequent	Less frequent	More frequent (as a sulphur containing drug)

Clinical pharmacology of infectious diseases

Enteric fever

Q. Write down the treatment of enteric fever. (CU-13Ju)

Q. What are the drugs used in enteric fever? (DU-08J, SU-11J, CU-13J, RU-16Ju, 12/09J)

Q. Name the antimicrobials used in the treatment of enteric fever. (DU-15J, 08Ju, RU-09J)

Q. Which are the drugs used in enteric fever? Which one you prefer and why? (RU-03/01J, SU-03M)

Ans.

Drugs used in enteric fever:

Drugs	Dose
1. Ciprofloxacin (1 st choice)	500 mg 12 hourly for 2 weeks
2. Ceftriaxone	1.2 gm IV 12 hourly 14 days
3. Azithromycin	1 gm daily for 5-7 days
4. Amoxicillin	750 mg 6 hourly for 2 weeks
5. Co-trimoxazole	960 mg 12 hourly for 2 weeks
6. Chloramphenicol	500 mg 6 hourly for 2 weeks

Choice of antibiotic:

- Antibiotic therapy must be guided by in vitro **sensitivity testing**.
- **Fluoroquinolones are the drugs of choice (e.g. ciprofloxacin)** if the organism is susceptible, but resistance is common, especially in the Indian subcontinent.
- **Extended-spectrum cephalosporins (ceftriaxone and cefotaxime)** are useful alternatives but have a slightly increased treatment failure rate.
- **Azithromycin** (500 mg once daily) is an alternative where fluoroquinolone resistance is present but has not been validated in severe disease. Treatment should be continued for 14 days.
- Chloramphenicol, ampicillin and co-trimoxazole are losing their effect due to resistance in many areas of the world, especially South-east Asia.

Pyrexia may persist for up to 5 days after the start of specific therapy. Even with effective chemotherapy there is still a danger of complications, recrudescence of the disease and the development of a carrier state. Chronic carriers are treated for 4 weeks with ciprofloxacin; cholecystectomy may be necessary.

(Ref: Davidson's-22nd)

Q. Name the preferred drug to a pregnant mother suffering from enteric fever. (DU-12Ju)

Ans.

Drug to a pregnant mother suffering from enteric fever

1. Cephalosporins (2nd & 3rd generation), eg, cefuroxime, cefixime, ceftriaxone
2. Amoxicillin

Urinary tract infection (UTI)

Q. Mention the drugs used in UTI. (DU-09J,07J, RU-15Ju,14Ju)

Ans.

Antibiotics used in case of UTI:

UTI	Antibiotics
Upper UTI (including pyelonephritis)	▪ Trimethoprim ▪ Nitrofurantoin ▪ Co-amoxiclav ▪ Ciprofloxacin ▪ Norfloxacin ▪ Cefuroxime ▪ Gentamicin ▪ Cephalexin
Lower UTI	▪ Trimethoprim ▪ Ciprofloxacin ▪ Norfloxacin
Prophylactic or suppressive therapy	▪ Trimethoprim ▪ Co-amoxiclav ▪ Cephalexin

(Ref: Davidson's medicine-22nd)

Choice of antibiotics

- If urine culture has been performed, treatment may be started while awaiting the result.
- Treatment for 3 days is the norm.
- Trimethoprim is the usual choice for initial treatment.
- Nitrofurantoin, quinolone antibiotics such as ciprofloxacin and norfloxacin, and cephalexin are also generally effective.
- Co-amoxiclav or amoxicillin should only be used when the organism is known to be sensitive.
- Penicillins and cephalosporins are safe to use in pregnancy but trimethoprim, sulfonamides, quinolones and tetracyclines should be avoided.

(Ref: Davidson's medicine-22nd)

Q. Enlist drugs used for UTI in pregnancy. (RU-13Ju,12J)

Q. Name one drug of choice to treat UTI in pregnancy. Explain its mechanism of action. (RU-12/08J)

Q. A 30 yrs aged pregnant mother is suffering from UTI. Select two antibiotics for her stating their mechanism of action & toxic effect. (CU-07J, RU-06M, SU-11J)

Ans.

Drug of choice to treat UTI in pregnancy:

- **Cephalosporins:** Cephadrine, Cefixime, Cefuroxime, Cephalexin, Ceftriaxone.
- **Penicillins:** Amoxicillin, Ampicillin, Coamoxiclav.

Q. A pregnant lady complains of urinary hesitancy. Her physician prescribed her erythromycin and dicyclomine. Comment on selection of drugs and explain their role. (SU-14J)

*Ans.

Erythromycin treats urinary tract infection. Its pregnancy category is B.

Dicyclomine is an antispasmodic and anticholinergic (antimuscarinic) agent. Its pregnancy category is B. it relieves urinary hesitancy.

Infective diarrhea

Causes / organisms of infective bacterial diarrhea: *Shigella*, *Salmonella*, enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC).

Drugs used in cholera (caused by *V. cholera*): Tetracycline or Ciprofloxacin.

Q. List the antimicrobials that may be used in infective diarrhea caused by *Shigella*.

Q. Outline the management of shigellosis. (CU-17M)

Q. Select P-drug in this case and justify your choice? (CU-17M,06M)

Ans.

Management of shigellosis

- **Oral rehydration therapy** or, if diarrhoea is severe, intravenous replacement of water and electrolyte loss is necessary.
- **Antibiotics-**
 - Ciprofloxacin (500 mg twice daily for 3 days)
 - Ampicillin
 - 3rd and 4th generation cephalosporins
 - Co-trimoxazole
- Use of **antidiarrhoeal** medication should be avoided.

(Ref: Davidson's-22nd)

Ciprofloxacin is the P-drug of infective diarrhea caused by shigella because of

1. Bactericidal effect
2. Rapid onset of action
3. Prolong duration of action
4. Short duration of therapy
5. Less prone to develop resistance
6. Less change of toxicity

Respiratory tract infection (RTI)

	Organisms	Antibiotics
Community acquired pneumonia (CAP)	▪ <i>Streptococcus pneumoniae</i> ▪ <i>Chlamydia pneumoniae</i> ▪ <i>Mycoplasma pneumoniae</i> ▪ <i>Haemophilus influenzae</i>	▪ Cap. Amoxicillin or, ▪ Clarithromycin / Erythromycin (penicillin hypersensitive cases) ▪ Flucloxacillin / Clarithromycin (in case of <i>S. aureus</i>) ▪ Clarithromycin / Erythromycin (<i>Mycoplasma pneumoniae</i>)
Hospital acquired pneumonia	▪ <i>E. coli</i> ▪ <i>Pseudomonas aeruginosa</i> ▪ <i>S. aureus</i> ▪ <i>Klebsiella</i>	▪ 3rd generation cephalosporin (e.g. Cefotaxime / Ceftazidime) + Gentamicin or, ▪ Meropenem or, ▪ Aztreonam + Flucloxacillin

(Ref: Davidson's medicine-22nd)

Q. A patient aged 16 years, came to you with sore throat & fever. Outline the initial best treatment. Give rationale of each drug mentioned. (SU-09J)

Ans.

Diagnosis: The common cause of sore throat & fever in a 16 years aged patient is acute tonsillitis.

Initial treatment: Tablet phenoxymethylpenicillin (500 mg, 6 hourly), Cap. Amoxicillin 500 mg 3 hourly.

Rationale of the drugs: Sore throat & fever due to acute tonsillitis is due to streptococcal infection. Phenoxymethylpenicillin is a narrow spectrum antibiotic drug & still now very much effective against streptococcal infections. Moreover it is very cheap (3 taka per 500 mg tablet) in comparison to other drugs used in streptococcal infection. Amoxicillin is also very effective against streptococcal infections.

Meningitis

Common bacterial causes:

1. *N. meningitidis*
2. *E. coli*
3. *S. pneumoniae*
4. *H influenzae*
5. *Proteus*

Antibiotic treatment:

- Benzyl penicillin IV (pt with a typical meningococcal rash)
- Cefotaxime / Ceftriaxone IV (pt without a typical meningococcal rash)
- Vancomycin / Rifampicin (pt with penicillin resistant pneumococcal pneumonia)

(Ref: Davidson's medicine-22nd)

Anti-tubercular drugs

Mycobacteria are intrinsically resistant to most antibiotics. Because they grow slowly compared with other bacteria, antibiotics that are most active against growing cells are relatively ineffective. Mycobacterial cells can also be dormant and thus completely resistant to many drugs or killed only very slowly. The lipid-rich mycobacterial cell wall is impermeable to many agents. Mycobacterial species are intracellular pathogens, and organisms residing within macrophages are inaccessible to drugs that penetrate these cells poorly. Finally, mycobacteria are notorious for their ability to develop resistance. Combinations of two or more drugs are required to overcome these obstacles and to prevent emergence of resistance during the course of therapy. The response of mycobacterial infections to chemotherapy is slow, and treatment must be administered for months to years, depending on which drugs are used.

(Ref- Katzung-13th)

Anti-mycobacterial drugs:

- ✓ Anti-tubercular drugs
- ✓ Anti-leprosy drugs

Q. Categorize the anti-tubercular drugs on the basis of their preference. (CU-11Ju, RU-16Ju)

Q. Write down the category wise anti-tubercular regimens. (DU-13Ju)

Q. List the tuberculocidal drugs. (CU-17J)

Q. Lists the 1st line anti-tubercular drugs. (DU-17J,15/13J, CU-12/11J,09Ju; RU-14/13Ju,12J,08Ju, SU-09Ju)

Q. Lists the 2nd line anti-tubercular drugs. (CU-17M,15J)

Ans.

Anti-tubercular drugs:

First line drugs: (in approximate order of preference)- These drugs have high antitubercular efficacy as well as low toxicity & are used routinely.

1. Isoniazid (H)
2. Rifampicin (R)
3. Pyrazinamide (Z)
4. Ethambutol (E)
5. Streptomycin (S)

Second line drugs: These drugs have either low antitubercular efficacy or high toxicity or both & are used in special circumstances.

- ✓ 1. Amikacin
2. Aminosalicylic acid
3. Capreomycin
4. Ciprofloxacin
5. Clofazimine
- ✓ 6. Cycloserine
7. Ethionamide
8. Levofloxacin, moxifloxacin
9. Rifabutin
10. Rifapentine

(Ref- Katzung-13th)

Nice to know

Difference between 1st line & 2nd line anti-tubercular drugs:

1 st line anti-tubercular drugs	2 nd line anti-tubercular drugs
1. More potent	1. Less potent
2. Less toxic	2. More toxic
3. More chance to develop resistance on monotherapy	3. Less chance to develop resistance
4. High therapeutic index (TI)	4. Low therapeutic index
5. Given initially	5. Reserve drugs
6. Can be given by a graduate doctor or maintenance by a health worker	6. Always need specialized opinion. Cannot be given by a graduate doctor
7. More convenient	7. Less convenient
8. Less expensive	8. More expensive

Pharmacokinetics & pharmacodynamics of anti-tubercular drugs:

	Rifampicin	Isoniazid	Ethambutol	Pyrazinamide	Streptomycin
Route of administration	Oral	Oral/ Parenteral	Oral	Oral	Parenteral
Absorption	Well absorbed from GIT	Well absorbed from GIT	Well absorbed from GIT	Well absorbed from GIT	Not absorbed orally
Distribution	all body fluids and tissues	all body fluids and tissues	Widely distributed	Widely distributed	mainly extracellular
Metabolism	Liver	Liver	Liver		
Excretion	Liver	Kidney	Kidney (50%), liver (20%)		
Anti-bacterial action	Bactericidal	Bactericidal	Bacteriostatic	Bactericidal	Bactericidal
Intracellular	Intracellular & extracellular	Intracellular & extracellular		Intracellular	Extracellular
Drug resistance	Develops rapidly	Develops rapidly	Develops rapidly		

Q. Mention the indications of isoniazid. (DU-09J)

Q. Mention the indications of rifampicin. (CU-02J)

Ans.

Indications of anti-tubercular drugs:

Drugs	Indications
Isoniazid	▪ TB ▪ Latent TB
Rifampicin	▪ TB ▪ Leprosy ▪ To eliminate meningococcal & staphylococcal carriage. ▪ As prophylaxis in contacts of children with <i>Haemophilus influenzae</i> type b disease. ▪ Serious staphylococcal infections such as osteomyelitis and prosthetic valve endocarditis.
Pyrazinamide	▪ TB
Ethambutol	▪ TB
Streptomycin	▪ Life-threatening forms of TB, eg, meningitis and disseminated disease. ▪ MDR TB.

(Ref- Katzung-13th)

Q. Lists the 1st line anti-tubercular drugs with their common adverse effects. (DU-17J)

Q. Mention the important side effects of each anti-tubercular drug. (DU-17M,16J,14J)

Q. Mention one toxic effect of each anti-tubercular drugs. (DU-13J,12J,11Ju, CU-13J, SU-08Ju, RU-12J)

Q. Write down the important adverse effects of INH. (DU-13Ju,10/09J, RU-08J,04S; CU-06M; SU-09Ju)

Q. Write down the adverse effects of rifampicin. (DU-13Ju,10J; SU-09Ju; RU-10Ju,03S)

Q. Explain the adverse/toxic effects of pyrazinamide /PZA. (RU-16Ju,08J)

Q. Mention the adverse effects of ethambutol. (RU-14Ju,05S)

Ans.

Adverse effects of the anti-tubercular drugs:

Drugs	Adverse effects
Isoniazid	1. Hepatitis: This is the most common major toxic effect. 2. Peripheral neuropathy: In 10-20% patients. It is more likely to occur in slow acetylators. 3. Immunological reactions: Fever and skin rashes, SLE. 4. GIT upset: Nausea, vomiting 5. Hematologic abnormalities

	6. CNS disturbances: - Convulsion - Hallucination - Memory loss - Psychosis (Ref- Katzung-13th)
Rifampicin	- Causes harmless orange/red coloration of saliva, urine, sweat, tears, and contact lenses. - Hepatitis & cholestatic jaundice. - Light chain proteinuria. - Flu-like syndrome. - Induction of drug metabolizing enzymes. (Ref: Katzung-13th)
Pyrazinamide	- Hepatotoxicity (in 1-5% patients) - Hyperuricemia leading to acute gouty arthritis - GIT upset: Nausea, vomiting - Drug fever (Ref: Katzung-13th)
Ethambutol	Retrolbulbar neuritis, resulting in loss of visual acuity and red-green color blindness.
Streptomycin	- Ototoxicity - Nephrotoxicity (Ref: Katzung-13th)

Q. Mention the hepatotoxic anti-tubercular drugs. (RU-13J)

Ans.

Hepatotoxic anti-tubercular drugs

- Isoniazid
- Rifampicin
- Pyrazinamide

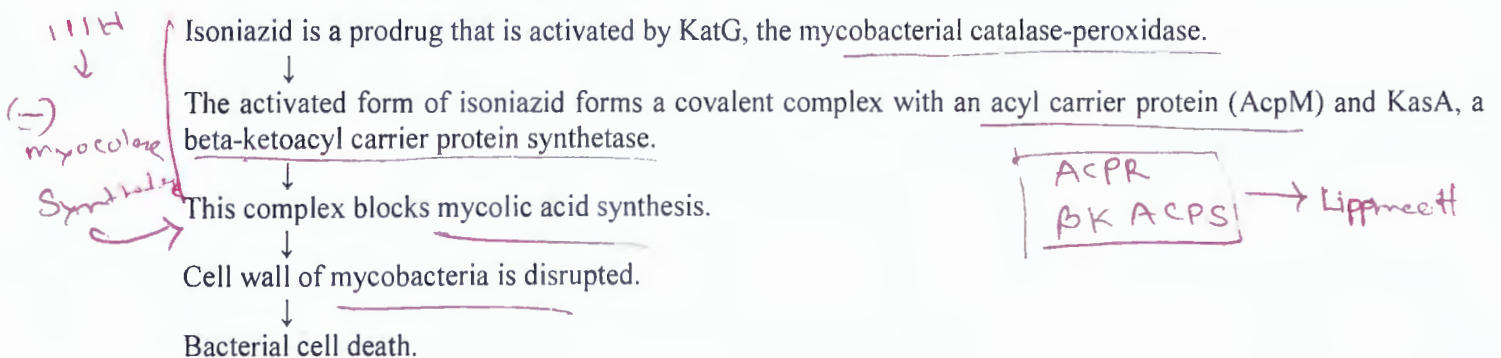
Isoniazid / INH

Q. Write the mechanism of action of INH. (DU-10J; CU-14Ju, SU-09Ju; RU-16Ju)

Q. Explain the anti-tubercular mechanism of isoniazid. (RU-08J, CU-12Ju)

Ans.

Mechanism of action of INH: Isoniazid inhibits synthesis of mycolic acids, which are essential components of mycobacterial cell walls.



(Ref- Katzung-13th)

Q. Discuss the mechanism of bacterial resistance against INH. (SU-07Ju)

Ans.

Mechanism of bacterial resistance against INH: Resistance to isoniazid is associated with

- mutations resulting in overexpression of inhA, which encodes an NADH-dependent acyl carrier protein reductase;
- mutation or deletion of the katG gene;
- promoter mutations resulting in overexpression of ahpC, a putative virulence gene involved in protection of the cell from oxidative stress; and

(ACP)

4. mutations in *kasA*.

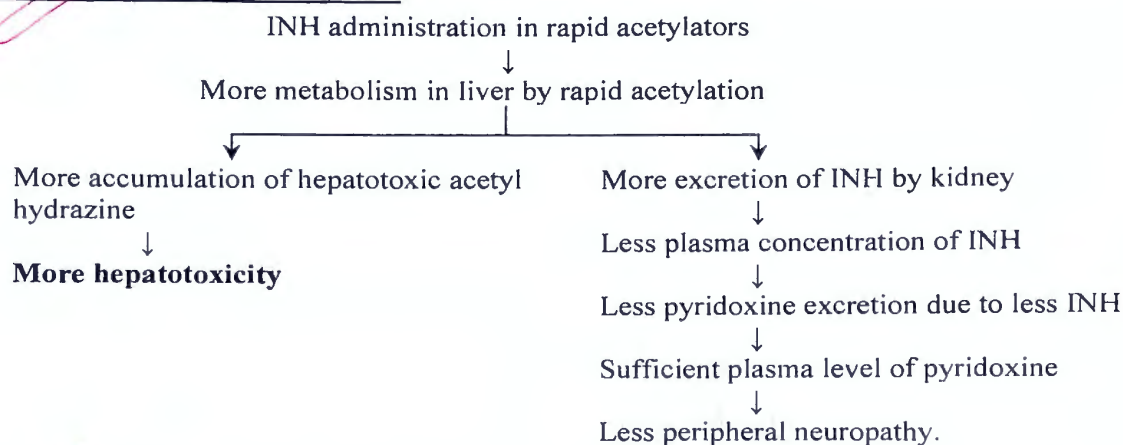
Overproducers of *inhA* express low-level isoniazid resistance and cross-resistance to ethionamide. KatG mutants express high-level isoniazid resistance and often are not cross-resistant to ethionamide.

(Ref- Katzung-13th)

Nice to know:

Metabolism of INH: INH is metabolized in the liver first by **acetylation** and then by hydrolysis. $\text{INH} \rightarrow \text{Acetyl INH (by acetylation)} \rightarrow \text{Isonicotinic acid} + \text{acetyl hydrazine (by hydrolysis)}$. Acetyl hydrazine produced as a metabolite of INH is highly hepatotoxic. Metabolism of isoniazid, especially acetylation by liver **N-acetyltransferase**, is genetically determined. The average plasma concentration of isoniazid in **rapid acetylators** is about one third to one half of that in **slow acetylators**, and average half-lives are less than 1 hour and 3 hours, respectively.

Hepatotoxicity in rapid acetylator:



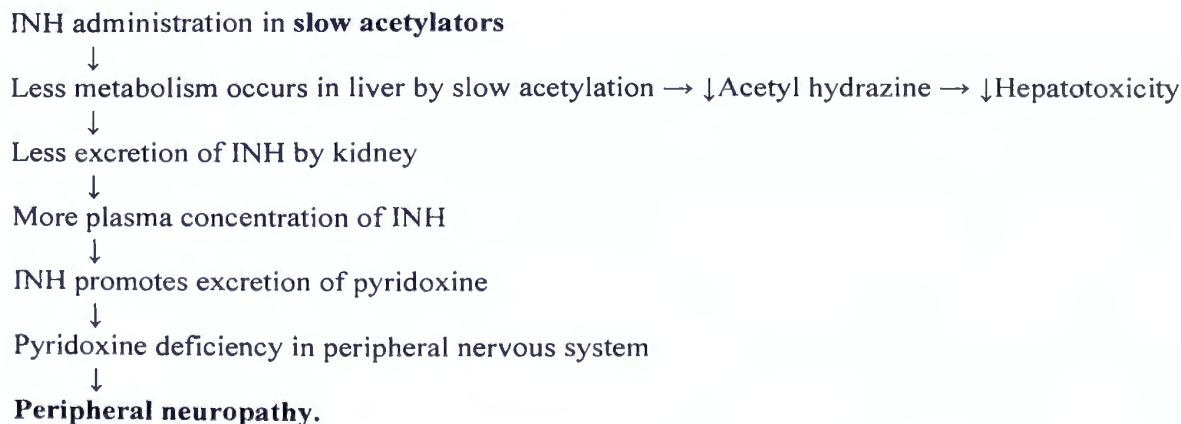
Q. How does INH produce peripheral neuropathy? (CU-14Ju)

Ans.

Isoniazid induced peripheral neuropathy: Peripheral neuropathy is observed in 10–20% of patients given dosages greater than 5 mg/kg/d but is infrequently seen with the standard 300 mg adult dose. It is more likely to occur in **slow acetylators** and patients with predisposing conditions such as malnutrition, alcoholism, diabetes, AIDS, and uremia. Neuropathy is due to a relative **pyridoxine deficiency**. This toxicity is readily reversed by pyridoxine in a dosage as low as 10 mg/d.

(Ref- Katzung-13th)

Pathogenesis of INH induced peripheral neuropathy



(Ref- Katzung-13th)

Q. Suggest the measures to avoid the adverse effects of INH. (CU-06M)

Q. Justify the use of pyridoxine with INH. (RU-15Ju, 13Ju)

Q. Rationalize combination of INH and Vit B6. (RU-17J)

Ans.

Measures to avoid adverse effects of INH:

1. **To avoid peripheral neuropathy:** Peripheral neuropathy is due to a relative pyridoxine deficiency. Isoniazid promotes excretion of pyridoxine, and this toxicity is readily reversed by administration of **pyridoxine** in a dosage as low as 10 mg/day.
2. **To avoid hepatotoxicity:** Liver function test should be carried out before therapy and should be monitored at 2-4 months interval. If SGPT level is 5 times normal, discontinuation of INH is recommended.

Q. Why isoniazid is a must in antitubercular regimen?

Ans.

Rationale of using INH in anti-tubercular drug regimen: The lipid rich mycobacterial cell wall is impermeable to many antibacterial drugs. Isoniazid disrupts mycobacterial cell wall by blocking mycolic acid synthesis. So, other antitubercular drugs can enter readily through disrupted mycobacterial cell wall & thus INH provides a chemotherapeutic synergism. For this reason, Isoniazid is a must in antitubercular regimen.

Q. Write down advantages and disadvantages of isoniazid as anti-tubercular drug.

Q. Discuss the role of INH as anti-tubercular drug. (CU-16J, 13Ju)

Ans.

Advantages of INH:

1. Isoniazid is the most active drug for the treatment of tuberculosis caused by susceptible strains.
2. It penetrates into macrophage & is active against both intracellular and extracellular tubercle bacilli.
3. It has bactericidal effect for actively growing tubercle bacilli.
4. Responsible for chemotherapeutic potentiation by enhancing entry of other antitubercular drugs into the cytoplasm of tubercle bacilli.

Disadvantages of INH:

1. Less active against slowly multiplying tubercle bacilli
2. Hepatitis
3. Peripheral neuropathy
4. CNS disturbances
5. GIT upset

Rifampicin

Q. Write down the mechanism of action of rifampicin. (DU-10J; SU-09Ju; RU-11Ju)

Q. Explain anti-tubercular action of rifampicin. (CU-12Ju, SU-14J, 12Ju, 08Ju)

Ans.

Anti-mycobacterial action / mechanism of action of rifampicin:

Rifampicin binds to the β -subunit of bacterial DNA-dependent RNA polymerase

↓

Inhibits RNA synthesis

↓

No protein synthesis

↓

No growth & multiplication of bacteria

↓

Rifampin is bactericidal.

Human RNA polymerase does not bind rifampin and is not inhibited by it.

(Ref- Katzung-13th)

Nice to know**Drug interaction of rifampicin:**

Rifampicin

↓
Induction of drug metabolizing enzymes by rifampicin

(↑ Cytochrome P450)

↓
↑ Drug metabolism↓
↓ Plasma concentration of drugs↓
Therapeutic failure

Drugs	Results
Rifampicin + OCP	Contraceptive failure → Unwanted pregnancy
Rifampicin + Anticoagulants	Anticoagulant failure → Increased thrombosis resulting in thromboembolic disorders, eg, MI, ischemic stroke.
Rifampicin + Anticonvulsants	Anticonvulsant failure → Convulsion

(Ref- Katzung-13th)

Q. Write down advantages and disadvantages of rifampicin as anti-tubercular drug. (CU-12/11J,09Ju)**Q. Outline role of rifampicin in tuberculosis. (CU-17J,16J,15Ju, SU-12Ju)****Q. Discuss the role of rifampicin as anti-tubercular drug. (CU-13Ju)**

Ans.

Advantages of rifampicin:

1. Rifampin is bactericidal for mycobacteria.
2. It readily penetrates most tissues and into phagocytic cells.
3. It can kill organisms that are poorly accessible to many other drugs, such as intracellular organisms and those sequestered in abscesses and lung cavities.
4. Active against both intracellular and extracellular tubercle bacilli.
5. There is no cross-resistance to other classes of antimicrobial drugs.
6. Excreted mainly through the liver into the bile. Dosage adjustment for renal or hepatic insufficiency is not necessary.

(Ref- Katzung-13th)

Disadvantages of rifampicin: See adverse effects of rifampicin.**Q. What advice will you give to the patient when you prescribe rifampicin?**

Ans.

Advice to a patient taking rifampicin:

1. Rifampicin causes harmless orange/red coloration of saliva, urine, sweat, tears, and contact lenses. So don't worry about this.
2. Monitor liver functions regularly.
3. Avoid other drugs without physician's consultation, because there may be drug interaction.

Pyrazinamide

Q. Explain the antitubercular mechanism of pyrazinamide. (CU-16J, RU-08J)

Q. What is the role of pyrazinamide in tuberculosis? (CU-15Ju, SU-14J)

Ans.

Anti-tubercular mechanism of pyrazinamide:

Pyrazinamide is taken up by macrophages.

↓

The drug is converted to pyrazinoic acid—the active form of the drug—by mycobacterial pyrazinamidase.

↓

The drug target and mechanism of action are unknown. It exerts its activity against mycobacteria residing within the acidic environment of lysosomes.

(Ref- Katzung-13th)

Q. Discuss the advantages of anti-tubercular regimen of 4 drugs including Pyrazinamide over that of 3 drugs without Pyrazinamide. (CU-07J)

Q. Write down advantages and disadvantages of pyrazinamide.

Q. Write down role of pyrazinamide in the treatment of TB. (CU-12Ju)

Ans.

Advantages of pyrazinamide in the treatment of TB:

1. It is much more active against dormant tubercle bacilli than the other anti-tubercular drugs.
2. **Prevention of relapse:** Pyrazinamide kills intracellular dormant bacilli. So, it prevents relapse of the TB which may be flared up by the dormant bacilli.
3. **Shortening of the duration:** An INH-Rifampicin combination take 9 months for cure. But the addition of pyrazinamide with the combination in the 1st 2 months reduce the total duration by 3 months (i.e. take 6 months for cure).
4. It is widely distributed over bone, avascular structures, meninges, so it is used to treat tubercular osteomyelitis and tubercular meningitis.
5. There is no cross resistance to other antimicrobial drugs.

Disadvantages: Write the adverse effects of pyrazinamide.

(Ref- Katzung-13th)

Ethambutol

Q. Describe the mechanism of action of Ethambutol. (CU-16Ju)

Ans.

Mechanism of action of Ethambutol: Ethambutol inhibits mycobacterial arabinosyl transferases, which are involved in the polymerization reaction of arabinoglycan, an essential component of the mycobacterial cell wall.

(Ref- Katzung-13th)

Q. What precaution is required to prescribe ethambutol? (CU-07J)

Ans.

Precaution of using ethambutol: The most common serious adverse event of ethambutol is retrobulbar neuritis, resulting in loss of visual acuity and red-green color blindness. This dose-related side effect is more likely to occur at doses of 25 mg/kg/d continued for several months. Periodic visual acuity testing is desirable if the 25 mg/kg/d dosage is used. Ethambutol is relatively contraindicated in children too young to permit assessment of visual acuity and red-green color discrimination.

(Ref- Katzung-13th)

Streptomycin

Q. Write down advantages & disadvantages of streptomycin.

Ans.

Advantages of streptomycin:

1. It is used to treat tubercular meningitis and miliary tuberculosis.
2. It is used to treat tuberculosis caused by resistant strains of other antitubercular drugs.

Disadvantages of streptomycin:

1. Active against only extracellular tubercle bacilli.
2. Always parenteral administration.
3. Serious adverse effects, eg, ototoxicity, nephrotoxicity, neuromuscular blockade.

(Ref- Katzung-13th)

Q. Outline role of ofloxacin and kanamycin in tuberculosis. (SU-12Ju)

Ans.

Role of kanamycin in tuberculosis: Kanamycin has been used for treatment of tuberculosis caused by streptomycin-resistant strains, but the availability of less toxic alternatives (eg, capreomycin and amikacin) has rendered it obsolete.

(Ref- Katzung-13th)

Role of ofloxacin in tuberculosis

1. Inhibit strains of *M tuberculosis* at concentrations less than 2 mcg/mL.
2. They are also active against atypical mycobacteria.
3. Can be used for strains that are resistant to first-line agents.

(Ref- Katzung-13th)

Treatment of TB

(Sheet)

TB ← Pulmonary
Extra pulmonary

Principles of anti-tubercular therapy: The basic principles of good TB treatment are-

1. Right combination of drugs to kill different bacterial populations.
2. Drugs are given for the right duration to kill the bacilli.
3. Drugs are given in the right dosage to achieve therapeutic but not toxic effect.

Aim of treatment

1. To cure the patient of TB
2. To prevent death from active TB or its late effects
3. To prevent relapse of TB
4. To decrease transmission of TB to others
5. To prevent the development of acquired drug resistance.
6. To kill a large number of actively multiplying bacilli (isoniazid achieves this).
7. To treat persisters i.e. semidormant bacilli that metabolize slowly or intermittently. Rifampicin and pyrazinamide are most efficacious.

(Ref: National guideline & operational manual for TB control-5th)

Treatment phases: Effective chemotherapy consists of 2 phases:

1. **Initial or intensive phase:** In this phase, drugs are administered daily for 2 months in new cases and 3 months in re-treatment cases. The aim of this phase is to rapidly reduce and eliminate the multiplying bacilli without allowing the development of acquired resistance to the prescribed drugs. During the intensive phase, the tubercle bacilli are killed rapidly. The infectious patients quickly become non-infectious (within approximately 2 weeks).
2. **Continuation phase:** It is essential to eliminate the remaining bacterial population. Drugs are administered daily for the rest of the treatment duration according to category.

within 15 days - Non infectious
within 2 months - 90% cases resolved

- Q. How will you treat a case of pulmonary tuberculosis by 6 months regimen? (DU-04J, CU-07/06J, 05M, RU-05S, SU-03S)
 Q. Name the drugs used in a 6 month antitubercular regimen. (DU-17M, 14J, 12J)
 Q. Outline the 6 months regimen of pulmonary tuberculosis. (SU-17J)
 Q. Write down the category I treatment regimen of pulmonary tuberculosis/ PTB. (RU-05S, SU-16J, 15J)
 Q. Explain the short course regimen for tuberculosis. (DU-07M, CU-14J)
 Q. Outline the treatment of category I tuberculosis. (DU-15J)
 Q. State category I treatment regimen of tuberculosis. (RU-14Ju, SU-16Ju)
 Q. Why initially four drugs are used for two months? (CU-14J)
 Q. Why anti-TB therapy requires prolonged duration of treatment? (RU-15Ju)

Ans.

Treatment regimens of pulmonary tuberculosis:

Patient category	Treatment regimens	
	Intensive phase (Daily)	Continuation phase (Daily)
I ▪ New smear positive PTB ▪ New smear negative PTB ▪ New extrapulmonary TB ▪ New concomitant/associated HIV/AIDS	2 months HRZE	4 months HR
II ▪ Sputum smear positive PTB with history of treatment of more than one month ▪ Relapse ▪ Treatment failure after category I ▪ After loss to follow-up ▪ Others	2 months (HRZE)S + 1 month HRZE	5 months (HR)E

H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; S = streptomycin.

(Ref: National guideline & operational manual for TB control-5th/21)

Nice to know

Dose of anti-TB drugs in 6 month-regimen:

Intensive phase (1st 2 months):

Drugs	Children	Adult	
		<50 kg	>50 kg
Rifampicin	10 – 20 mg/kg	450 mg	600 mg
Isoniazid	10 mg/kg	200 – 300 mg	
Pyrazinamide	20 – 35 mg/kg	20 – 35 mg/kg	
Ethambutol	25 mg/kg	25 mg/kg	

HRZE
↓ ↓ ↓
300 450 500 300 mg
5 8-12 20-35 25 mg/kg
day

Continuation phase: (last 4 months):

Drugs	Children	Adult	
		<50 kg	>50 kg
Rifampicin	10 – 20 mg/kg	450 mg	600 mg
Isoniazid	10 mg/kg	200 – 300 mg	

Q. Mr. Salamat hailing from Kanaighat aged about 55 years having a body weight of 55 kg attending you with the complaints of evening rise of fever, productive cough & gradual wt. reduction for several months. His sputum is Z-N stain positive and CXR shows apical patchy opacity. Make your diagnosis and give him treatment. Write one adverse effect of each drug used in this regimen. (SU-13Ju)

Ans.

Diagnosis: Pulmonary tuberculosis (category-I)

Treatment:

Intensive phase (Daily): 2 months HRZE

Continuation phase (Daily): 4 months HR

Adverse effect of each drug: Write from above.

Nice to know

Fixed dose combinations (FDC): FDC is combined tablet containing 4 or 2 anti-tubercular drugs. FDC tablets are composed as follows:

- **4-FDC:** Isoniazid 75mg + Rifampicin 150mg + Pyrazinamide 400mg + Ethambutol 275mg
- **2-FDC:** Isoniazid 75mg + Rifampicin 150mg

The doses of FDC tablets for adults are as follows:

Category I:

Pre-treatment weight (kg)	Intensive phase	Continuation phase
	Daily (1 st 2 months)	Daily (Next 4 months)
	Number of 4-FDC tablets	Number of 2-FDC tablets
30 – 37	2	2
38 – 54	3	3
55 – 70	4	4
> 70	5	5

Category II:

Pre-treatment weight (kg)	Intensive phase		Continuation phase	
	Daily (1 st 3 months)	Daily (1 st 2 months)	Daily (Next 5 months)	
	Number of 4-FDC tablets	Inj. Streptomycin	Number of 2-FDC tablets	Ethambutol 400 mg (No. of tablets)
30 – 37	2	500 mg	2	2
38 – 54	3	750 mg	3	3
55 – 70	4	1 gm*	4	3
> 70	5	1 gm*	5	4

*The dose of streptomycin should not exceed 750 mg daily after the age of 50 years.

(Ref: National guideline & operational manual for TB control-5th/22)

Q. Justify the rationale for multi-drug therapy and initial intensive phase in the management of pulmonary tuberculosis. (CU-06M, RU-09Ju, 04S)

Q. Justify the use of combination therapy in tuberculosis. (DU-17J, 13J, 12J, 08J; RU-12J, 08Ju, SU-17M)

Q. Justify administration of 4 drugs in the initial phase of 6 month anti-tubercular therapy. (CU-16Ju)

Q. Explain how the phenomenon of chemotherapeutic synergism has been exploited in the Rx of TB. (RU-04M)

Ans.

Justification of using multidrug / combination therapy in tuberculosis:

1. To broaden the spectrum coverage:

- Mycobacteria are intrinsically resistant to most antibiotics. Because they **grow slowly** compared with other bacteria, antibiotics that are most active against growing cells are relatively ineffective.
- Mycobacterial cells can also be **dormant** and thus completely resistant to many drugs or killed only very slowly.
- The lipid-rich mycobacterial cell wall is impermeable to many agents. Mycobacterial species are **intracellular pathogens**, and organisms residing within macrophages are inaccessible to drugs that penetrate these cells poorly.
- These problems are solved by using combination of drugs, eg,

1. Rifampicin	▪ Acts on <u>intracellular</u> and extracellular bacteria. ▪ Can kill organisms that are sequestered in <u>abscesses</u> and lung cavities.	x <i>Don't</i>
2. Isoniazid	▪ Acts on <u>intracellular</u> and extracellular bacteria. ▪ Acts on <u>rapidly multiplying</u> bacilli in tissues & even in CSF. ▪ Least active against <u>slowly multiplying</u> bacilli.	x <i>slowly multiplying</i> x <i>Don't</i>
3. Streptomycin	▪ Acts on <u>extracellular</u> bacteria. ▪ Acts on <u>rapidly multiplying</u> bacilli.	

4. Pyrazinamide	▪ Much more active against dormant tubercle bacilli than the other anti-tubercular drugs. ▪ Acts on intracellular bacteria. ▪ Acts on slowly multiplying bacilli.
5. Ethambutol	▪ Delays and prevents development of resistance.

2. **To prevent development of resistance:** Mycobacteria are notorious for their ability to develop resistance against drugs. Combinations of two or more drugs are required to overcome these obstacles and to prevent emergence of resistance during the course of therapy.
3. **To shorten duration of treatment:** Combination therapy reduces the total duration of treatment. An isoniazid-rifampin combination administered for 9 months will cure 95–98% of cases of tuberculosis caused by susceptible strains. The addition of pyrazinamide to an isoniazid-rifampin combination for the first 2 months allows the total duration of therapy to be reduced to 6 months without loss of efficacy.
4. **To reduce individual toxic effect of a large dose of a single drug.** Eg, retrobulbar neuritis is a dose-related adverse effect of ethambutol. This dose-related side effect is more likely to occur at doses of 25 mg/kg/d continued for several months. At 15 mg/kg/d or less, visual disturbances are very rare.
5. **To increase chemotherapeutic potentiation:** One drug potentiates the other drug. Eg,
 - Ethambutol enhances the activity of rifampicin.
 - Pyrazinamide enhances the sterilizing ability of rifampicin.

(Ref- Katzung-13th)

Q. Discuss DOTs for treatment of TB. (CU-17M)

Q. What is DOTs and why it has been implemented? (RU-13Ju)

Q. List the drugs used in DOTs for the treatment of tuberculosis. (DU-16J, 11Ju, 10J, RU-10Ju)

Q. Comments on DOTs therapy. (SU-14Ju)

Q. Short note: DOTs. (SU-17J, 16Ju/J, 15Ju, 15J)

Ans.

Directly observed therapy (DOT): Poor adherence to therapy is a major factor in prolonged infectious illness, risk of relapse, and the emergence of resistance. Directly observed therapy, in which supervised therapy is administered two or three times each week, has been advocated as a method of improving adherence and has become particularly important as a means of improving the control of TB in resource-poor nations.

(Ref: Davidson's-22nd)

Drugs used in DOTs for the treatment of tuberculosis:

1. Rifampicin
2. Isoniazid
3. Pyrazinamide
4. Ethambutol
5. Streptomycin

Q. When we consider / use the 2nd line drugs for TB?

Ans.

Conditions for using 2nd line anti-tubercular drugs: These drugs are usually considered only-

1. In case of resistance to 1st line anti-tubercular drugs
2. In case of failure of clinical response to conventional therapy
3. In case of serious treatment-limiting adverse drug reactions
4. When expert guidance is available to deal with the toxic effects.

(Ref- Katzung-13th)

Q. Write down the disadvantages of second line antitubercular drugs. (CU-17J)

Ans.

Disadvantages of second line antitubercular drugs

1. Less potent
2. More toxic
3. Low therapeutic index
4. Always need specialized opinion. Cannot be given by a graduate doctor
5. Less convenient
6. More expensive

Q. What are the indications of steroid along with anti-TB drugs?

Ans.

Indications of steroid along with anti-TB drugs: Corticosteroids should not be ordinarily used in tubercular patient. Corticosteroids reduce inflammation and limit tissue damage.

1. **Absolute indication:** Bilateral adrenal tuberculosis (replacement therapy).
2. **Relative indication:**
 - a. Tubercular meningitis (*to prevent adhesion*).
 - b. Tubercular pleural effusion (*to prevent adhesion*).
 - c. Tubercular peritonitis (*to prevent adhesion*).
 - d. Tubercular pericarditis (*to prevent adhesion*).
 - e. TB of ureter (*to prevent adhesion*).
 - f. Renal TB
 - g. Seriously ill patients such as in miliary TB, severe pulmonary TB to buy time for drugs to act.
 - h. In AIDS patients with severe manifestations of TB.
 - i. When hypersensitivity reactions occur to anti-tubercular drugs.

Corticosteroids are contraindicated in intestinal TB (silent perforation can occur). Corticosteroids, if given, should be gradually withdrawn when the general condition of the patient improves.

(Ref: Davidson's-22nd+Tripathi-6th/747-749)

Q. What are the causes of therapeutic failure in the management of TB? (CU-15J)

Ans.

Causes of therapeutic failure in the management of TB

1. Inadequate dose of drugs
2. Inadequate duration of treatment
3. Development of drug resistance
4. Poor patient compliance
5. Presence of co-infection, such as HIV.

Q. What is the anti-tubercular treatment in pregnancy?

Ans.

Anti tubercular treatment in pregnancy:

1. Isoniazid, rifampicin and ethambutol are the drug of choice.
2. Streptomycin is contraindicated through the pregnancy period, as it causes damage of 8th cranial nerve in fetus.
3. Pyrazinamide can be given in life threatening condition like tubercular meningitis.

Q. Define MDR-TB. (SU-10Ju)**Q. Write the drug treatment of MDR-TB. (SU-17M,14Ju,13J,11Ju)**

Ans.

Multi drug resistant tuberculosis (MDR-TB): MDR-TB is defined as resistance to **at least** isoniazid (INH) & rifampicin.

Treatment of MDR-TB: All MDR-TB regimens consist of two phases:

- **Intensive phase:** The period in which injectable agent is used.
- **Continuation phase:** It starts after the initial phase.

Ans.
2016
525

Amikacin
Levo & Loxam
Cycloserine

Strepto
mycin
Cipro

Antimicrobial drugs

Recommended standard MDR TB regimen:

8{Km - Z - Lfx (Ofx) - Eto - Cs} / 12 {Lfx (Ofx) - Eto - Cs - Z}

Phases	Duration	Drugs
<u>Intensive phase</u>	<u>8 months</u>	1. Kanamycin (Km) 2. Pyrazinamide (Z) 3. Levofloxacin (Lfx) / Ofloxacin (Ofx) 4. Ethionamide (Eto) 5. Cycloserine (Cs) Remember: K PLEC
<u>Continuation phase</u>	<u>12 months</u>	1. Pyrazinamide (Z) 2. Levofloxacin (Lfx) / Ofloxacin (Ofx) 3. Ethionamide (Eto) 4. Cycloserine (Cs) Remember: PLEC

(Ref: National guideline & operational manual for TB control-5th/54)

Nice to know:

- **Monoresistance:** Resistance to one anti-TB drug.
- **Polyresistance:** Resistance to more than one anti-TB drug other than isoniazid and rifampicin.
- **MDR-TB** is defined as resistance to **at least** isoniazid (INH) & rifampicin.
- **Extensive drug resistance tuberculosis (XDR-TB):** XDR TB is defined as resistance to at least 4 most effective bactericidal drugs, i.e. INH, rifampicin, a fluoroquinolone, one of three injectable second-line drugs (kanamycin / amikacin / capreomycin). The XDR TB is virtually untreatable; mortality is high.
- **Treatment failure case of TB:** Patients who remain or again become smear positive 5 months or later after commencing treatment are the treatment failure cases. Also one who was smear negative at start of therapy & becomes smear positive after the 2nd month.
- **Relapse of tuberculosis:** A patient declared cured from any form of TB in the past after receiving one full course of chemotherapy & now has become sputum positive.
- **Treatment after interruption (default):** A patient who interrupts the anti-tubercular treatment for 2 months or more & returns with sputum positive or clinically active TB. These patients may have resistant bacilli & are at greater risk of developing MDR-TB.
- **Chemoprophylaxis of TB:** The purpose is to prevent progression of latent tubercular infection to active diseases. This is indicated only in—
 1. Contacts of open cases that show recent Mantoux conversion.
 2. Children with positive Mantoux & a TB patient in the family.
 3. Neonate of tubercular mother.
 4. Patient of leukemia, DM, cirrhosis or those who are HIV positive but are not anergic, or are on corticosteroid therapy who show a positive Mantoux.
 5. Patients with old inactive diseases who are assessed to have received inadequate therapy.

Anti-leprosy drugs

Leprosy: Leprosy (**Hansen's disease**) is a chronic granulomatous disease affecting **skin** and **nerve**; it is caused by *Mycobacterium leprae*. The medical complications of leprosy are due to nerve damage, immunological reactions and bacillary infiltration. Nerve damage accompanying leprosy is a serious complication causing considerable morbidity.

(Ref: Davidson's-22nd)

Clinical features: Patients commonly present with skin lesions or the effects of a peripheral nerve lesion, weakness or an ulcer in an anesthetic hand or foot.

- **Skin lesions:** Macules or plaques.
- **Anaesthesia:** Loss of sensation in the area of skin supplied by a peripheral nerve.
- **Peripheral neuropathy.** Damage to peripheral nerve produces regional sensory loss and dysfunction of muscles supplied by that peripheral nerve. The CNS is not affected.
- **Eye involvement.** Blindness.

(Ref: Davidson's-22nd)

Cardinal features of leprosy

- **Skin lesions**, typically anesthetic at tuberculoid end of spectrum
- Thickened peripheral **nerves**
- **Acid-fast bacilli** on skin smears or biopsy.

(Ref: Davidson's-22nd)

Q. Write down the treatment of leprosy.

Q. Name the drugs used in leprosy. (RU-04S)

Ans.

Principles of leprosy treatment

- Stop the infection with chemotherapy
- Treat reactions
- Educate the patient about leprosy
- Prevent disability

(Ref: Davidson's-22nd)

Modified WHO-recommended multidrug therapy regimens in leprosy:

Type of leprosy	Monthly supervised drug treatment	Daily self-administered drug treatment	Duration of treatment
<u>Paucibacillary</u>	<u>Rifampicin 600 mg</u>	<u>Dapsone 100 mg</u>	<u>6 months</u>
<u>Multibacillary</u>	<u>Rifampicin 600 mg</u> <u>Clofazimine 300 mg</u>	<u>Clofazimine 50 mg</u> <u>Dapsone 100 mg</u>	<u>12 months</u>
<u>Paucibacillary single-lesion</u>	<u>Ofloxacin 400 mg</u> <u>Rifampicin 600 mg</u> <u>Minocycline 100 mg</u>		<u>Single dose</u>

- Paucibacillary single-lesion leprosy (one skin lesion)
- Paucibacillary (2-5 skin lesions)
- Multibacillary (more than 5 skin lesions).

In this field classification WHO recommends treatment of multibacillary patients for 12 months only.

(Ref: Davidson's-22nd)

Dapsone

Chemical name: Diaminodiphenylsulfone, a bacteriostatic sulfone (related to sulfonamides).

Mechanism of action: Like the sulfonamides, dapsone inhibits folate synthesis.

Pharmacokinetics:

- Well absorbed from the gut
- Widely distributed throughout body fluids and tissues
- Plasma half life 1-2 days
- Enterohepatic recycling
- Excreted through urine.

Resistance: Resistance against dapsone can emerge in large populations of *M leprae*, eg, in lepromatous leprosy, if very low doses are given. Therefore, the combination of dapsone, rifampin, and clofazimine is recommended for initial therapy.

Indications: Leprosy

1. To prevent and treat *Pneumocystis jiroveci* pneumonia in AIDS patients.
2. Dermatitis herpetiformis.

(Ref: Katzung-13th)

Q. Mention the adverse effects of dapsone. (DU-09J)

Ans.

Adverse effects:

1. Hemolytic anemia
2. Methemoglobinemia
3. GIT upset
4. Pruritus
5. Erythema nodosum leprosum
6. Anorexia
7. Fever
8. Allergic dermatitis
9. Neuropathy

(Ref: Katzung-13th)

Clofazimine

Mechanism of action: Its mechanism of action is unknown but may involve DNA binding. It has a leprostatic action.

Indications: Clofazimine is given for-

- ✓1. Sulfone-resistant leprosy or
- ✓2. When leprosy patients are intolerant to sulfones (dapsone).

Adverse effects:

- ✓1. Skin discoloration ranging from red-brown to nearly black.
- ✓2. GIT upset
- ✓3. Headache

Pharmacokinetics:

1. Oral administration
2. Prolonged plasma half life (2 months)
3. Distributed over reticulo-endothelial (RE) tissues and skin.

(Ref: Katzung-13th)

Antimalarial drugs

Q. Classify anti-malarial drugs according to their clinical use.

Q. Name anti-malarial drugs. (SU-13Ju, RU-12Ju)

Q. Name the tissue schizonticides.

Q. Name the drugs that are used to treat malaria. (DU-13Ju, RU-07Ju, 06S/M)

Q. Name the blood schizonticides. (DU-16Ju, CU-17M, 16J, 15J, 14Ju, SU-09J; RU-17J, 09J, 07Ju)

Q. Name the gametocidal drugs. (CU-01M)

Q. Outline role of chloroquine, quinine and primaquine in malaria. (SU-15Ju)

Ans.

Classification of antimalarial drugs:

Classes	Definition	Drugs
1. Tissue schizonticides	- Drugs that eliminate developing or dormant liver forms. - They cause a radical cure by acting on the parasites in the liver. - These drugs also destroy gametocytes and thus reduce the spread of infection.	Primary tissue schizonticides: Drugs for causal prophylaxis / chemoprophylaxis. - Proguanil - Mefloquine - Pyrimethamine - Doxycycline - Dapsone Latent tissue schizonticides: Drugs for radical cure - Primaquine - Tafenoquine
2. Blood schizonticides	- Drugs that act on erythrocytic parasites. - They are used to treat the acute attack. - They are also known as drugs for suppressive or clinical cure.	Highly efficacious: fast acting & can be used singly. - Chloroquine - Mefloquine - Quinine - Quinidine - Atovaquone - Artemisinins - Lumefantrine - Halofantrine Less efficacious: slow acting & always used in combination. - Pyrimethamine - Sulfadoxine - Proguanil
3. Gametocides	Drugs that kill sexual stages and prevent transmission to mosquitoes.	- Primaquine: For <i>P. falciparum</i> - Chloroquine: For <i>P. vivax</i>, <i>P. malariae</i>, <i>P. ovale</i>.
4. Causal prophylactic drugs	- Drugs that are capable of preventing erythrocytic infection. - They block the link between the exoerythrocytic stage and the erythrocytic stage and thus prevent the development of malarial attacks.	- Chloroquine - Mefloquine - Proguanil - Pyrimethamine - Dapsone - Doxycycline

(Ref: Katzung-13th; Rang & Dale's-8th)

Q. How will you treat a case of *Plasmodium vivax* infection? (DU-05M, RU-03M, SU-06J)

Q. How will you approach pharmacologically for the treatment of *P. vivax*? (DU-01S)

- Q. How do you treat a case of uncomplicated Vivax malaria? (SU-09J)
 Q. How will you treat a case of chloroquine sensitive malaria? (RU-06S)
 Q. Write down the treatment regimen of uncomplicated malaria. Explain why primaquine is added. (DU-16J)

Ans.

Treatment of Vivax malaria / Non-falciparum ('benign') malaria: These are usually due to *Plasmodium vivax* or less commonly to *Plasmodium ovale* or *Plasmodium malariae*; the drug of choice is **chloroquine**, which should be given by mouth as follows:

- 1st day: Chloroquine 10 mg/kg (4 tabs for adults)
- 2nd day: Chloroquine 10 mg/kg (4 tabs for adults)
- 3rd day: Chloroquine 5 mg/kg (2 tabs for adults)

Handwritten note: 10 mg/kg = 1 tab = 150 mg

For eradication of the hepatic parasites:

- 4th day: Primaquine, 15 mg daily for 14 days for adults (1 tab = 15 mg).
 For children, 0.3 mg/kg daily for 14 days.

(Ref: National guideline, 2011; Bennett & Brown-11th)

- Q. How will you treat a case of uncomplicated chloroquine resistant falciparum malaria? (DU-14Ju, 13Ju, 10Ju, 08/07Ju; RU-15J, 13Ju, 10Ju, 06/05M, SU-07/05/04J)
 Q. Write down the treatment of a case of falciparum malaria. (DU-06M, SU-14J, CU-04J)
 Q. List the drugs that are effective against chloroquine resistant plasmodium. (DU-12Ju, 11Ju, CU-10Ju, 09J)
 Q. Outline the drug treatment of multi-drug resistant malaria. (SU-14Ju)

Ans.

Uncomplicated chloroquine resistant *P. falciparum* malaria: *P. falciparum* is now resistant to chloroquine almost world-wide, so quinine is the drug of choice. If the patient can swallow and there are no serious complications such as impairment of consciousness, treatment options are as follows:

Handwritten note: Arrange 2000 Quinine → Coarctation

First line treatment: Artemether + Lumefantrine combination therapy (ACT)- 6 doses over 3 days.

Drug	Day	No. of dose	Time of dose	Number of tablets per dose			
				5 - <15 kg	15- <25 kg	25- <35 kg	> 35 kg
Artemether + Lumefantrine combination (ACT) <i>Coarctation</i>	Day 1	1 st	0 hour	1	2	3	4
		2 nd	8 hour	1	2	3	4
	Day 2	3 rd	24 hour	1	2	3	4
		4 th	36 hour	1	2	3	4
	Day 3	5 th	48 hour	1	2	3	4
		6 th	60 hour	1	2	3	4

Alternative treatment:

- Quinine 7 days + Tetracycline 7 days
- Quinine 7 days + Doxycycline 7 days
- Quinine 7 days + Clindamycin 7 days
- Or other WHO recommended artesunate combination therapies, eg, artesunate-mefloquine, artesunate-amodiaquine.

Dose:

- Quinine: 10 mg/kg 8 hourly for 7 days
- Tetracycline: 250 mg 6 hourly for 7 days
- Doxycycline: 100 mg once daily for 7 days
- Clindamycin: 10 mg/kg twice daily for 7 days

A single oral dose of Primaquine 0.75 mg/kg (45 mg base / 3 tabs for adult) should be added to kill gametocytes to reduce transmission after the end of 7 days course.

(Ref: National guideline, 2011)

Q. Short note: Coartem. (DU-17J)

Ans.

Coartem: Coartem is the trade name of Artemether and Lumefantrine combination. The combination came into medical use in 1992.

Route of administration: Oral

Indication: Chloroquine resistant *P. falciparum* malaria

Common side effects include-

1. Muscle and joint pains
2. Fever
3. Loss of appetite
4. Headache

Serious side effects include

1. Prolonged QT syndrome.
2. Anaphylaxis

Pregnancy category: C

Q. Write down the treatment of severe malaria/cerebral malaria/complicated malaria. (CU-07J, SU-09J)

Q. Describe the treatment of a case of acute severe unconscious falciparum malaria. (CU-16Ju, 15Ju)

Ans.

Treatment of cerebral malaria / severe malaria/ complicated malaria: Severe malaria is a medical emergency and cerebral malaria is the most common presentation and cause of death in adults with malaria. The management of severe malaria should include-

- Early and appropriate antimalarial chemotherapy
- Active treatment of complications
- Correction of fluid, electrolyte and acid-base balance

Quinine + DA 5-10J
↓
consciousness return
2 tabs. 5-7 days
Dextrose saline

1. **IV Artesunate** is preferred for severe malaria / cerebral malaria when available.
 - **Dose:** 2.4 mg/kg IV stat followed by 2.4 mg/kg daily until the patient can take oral medication.
2. **IV Quinine salt** is alternative if IV artesunate is not available.
 - **Loading dose:** 20 mg/kg as a loading dose (maximum 1.4 g) infused IV over 4 h.
 - **Maintenance dose:** 10 mg/kg 8 hourly.
3. **IM Artemether:**
 - **Loading dose:** 3.2 mg/kg IM.
 - **Maintenance dose:** 1.6 mg/kg IM daily until the patient can take oral medication.

After parenteral treatment, once the patient can take oral medication, it is essential to continue and complete treatment with an effective oral antimalarial using Artemether plus Lumefantrine or Artesunate (plus clindamycin or doxycycline) or Quinine (plus clindamycin or doxycycline).

A single oral dose of Primaquine 0.75 mg/kg (45 mg base / 3 tabs for adult) should be added to kill gametocytes to reduce transmission after the end of 7 days course.

(Ref: National guideline for malaria, 2011)

Q. Write down the chemoprophylaxis against malaria. (DU-05M, CU-07Ju, 05M)

Q. Describe chemoprophylaxis for *P. vivax* and *P. falciparum* malaria. (CU-14J)

Q. Discuss the drugs used in chemoprophylaxis against malaria. (SU-16Ju, 16J)

Ans.

Chemoprophylaxis against malaria: The following general principles apply:

1. Chemoprophylaxis is part of a broader regimen and only ever gives relative protection; travelers should protect against mosquito bites

2. Effective chemoprophylaxis requires that there be a plasmodicidal concentration of drug in the blood when the first infected mosquito bites, and that it be sustained safely for long periods.
3. Chemoprophylaxis is begun 1 week before entering the malarious area and should continue for at least 4 weeks after leaving an endemic area to kill parasites that are acquired about the time of departure, are still incubating in the liver and will develop into the erythrocyte phase.
4. Chloroquine and proguanil may be used for periods of up to 5 years, and mefloquine for up to 1 or 2 years.

Drugs for chemoprophylaxis:

Area	Antimalarial tablets	Adult prophylactic dose	Regimen
<u>Chloroquine resistance high</u>	Mefloquine <i>or</i> Doxycycline <i>or</i> Malarone	250 mg 100 mg 1 tablet from 1-2 days before travelling to 1 week after return	One tablet weekly Daily Daily
<u>Chloroquine resistance moderate</u>	Chloroquine <i>plus</i> Proguanil	150 mg base 100 mg	Two tablets weekly Two tablets daily
<u>Chloroquine resistance absent</u>	Chloroquine <i>or</i> Proguanil	150 mg base 100 mg	Two tablets weekly One or two tablets daily

(Ref: Davidson's-22nd)

Q. Define causal prophylaxis.

Ans.

Causal prophylaxis of malaria: Causal prophylaxis is preventing erythrocytic infection. Combination of Proguanil (200mg daily) with chloroquine (500mg weekly) is used. So, Proguanil should start before 1st week then weekly addition of chloroquine up to 4 wks even after leaving the endemic zone.

Nice to know

Clinical attacks of malaria may be preventable with drugs such as proguanil which attack the pre-erythrocytic form, and also by drugs such as atovaquone 250 mg plus proguanil 100 mg (Malarone), doxycycline, chloroquine or mefloquine after the parasite has entered the erythrocyte ('suppression').

(Ref: Davidson's-22nd)

Q. Name the anti-malarial drugs which can be prescribed in pregnancy safely. (DU-08Ju)

Ans.

Anti-malarial drugs in pregnancy

All trimesters	First line - Chloroquine - Quinine - <i>causes contraction of uterus</i> Second line - Artemether - Artesunate
2 nd / 3 rd trimesters	- Fansidar - Mefloquine

Q. What do you mean by radical cure of malaria and name the drugs to perform this cure? (RU-17J,16J,13Ju,10Ju,09J)

Q. How radical cure could be achieved? (RU-17J,09J)

Q. Give the radical treatment of malaria. (RU-04J)

Q. Short note: Radical cure of malaria? (RU-14Ju)

Ans.

Radical cure of malaria: Radical cure is eliminating both hepatic & erythrocytic state of malarial parasite. A radical cure is needed to prevent relapse of malaria. Drugs which attack the exoerythrocytic stage (hypnozoites) can be used for radical cure of malaria.

No single agent can reliably effect a radical cure

Drug for radical cure in malaria: Primaquine (15 mg/day for 14 days). - Acute vivax & ovale

Quinine & Quinidine

Pharmacokinetics of quinine & quinidine:

1. Quinine is rapidly absorbed after oral administration and is widely distributed in body tissue. Quinidine is much more water soluble than quinine.
2. Quinidine has a shorter half life than quinine.
3. Quinidine has a lower plasma level than quinine due to decreased protein binding.
4. Quinine is primarily metabolized in the liver
5. Quinine is excreted in the urine.

Cinchona Bark



Q. Mention the source of quinine. (CU-17J)

Ans.

Source of quinine

Natural Source: The bark of Cinchona Tree. The alkaloid quinine was purified in 1820,

Q. What are the pharmacodynamic effects of quinine? (DU-06M)

Q. What are the pharmacological effects of quinine? (SU-16Ju)

Ans.

Pharmacological / Pharmacodynamic effects of quinine & quinidine:

1. **Anti-malarial effect:** Quinine is a rapidly acting, highly effective blood schizonticide against the four species of human malaria parasites. The drug is gametocidal against *P vivax* and *P ovale* but not *P falciparum*. It is not active against liver stage parasites.
2. **Voltage gated Na⁺ channel blocker:**
 - Antiepileptic effect
 - Anti-arrhythmic effect
3. **Muscarinic antagonist property or vagolytic property:**
 - Tachycardia
 - Urinary retention
 - Constipation
 - Dry mouth & skin
 - Dry eye
4. **α-antagonistic property:**
 - Postural hypotension
 - Tachycardia
5. **Oxytocic property:** Having ability to contract uterus
6. **Increased insulin release** in massive dose: Hypoglycemic coma

Q. Write down the mechanism of action of quinine. (DU-99S, CU-17M/J, 16Ju/J, 14Ju)

Ans.

Mechanism of action of quinine: Quinine and its stereoisomer, quinidine, interfere with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite.

(Ref: Lippincott's-6th)

Nice to know

Mechanism of action of quinine: It binds to plasmodial DNA to prevent protein synthesis but its exact mode of action remains uncertain.

(Ref: Bennett & Brown-11th)

Q. Write the indications / uses of quinine. (CU-02J, SU-15J)

Ans.

Indications of quinine:

1. Severe falciparum malaria, eg, cerebral malaria. Used in parenteral route.
2. Uncomplicated chloroquine resistant falciparum malaria, used orally.
3. As anti-epileptic drug.
4. As anti-arrhythmic drug.
5. Babesiosis: Quinine is first-line therapy, in combination with clindamycin.

(Ref: Katzung-13th)

Q. Mention the adverse effects of quinine. (CU-04J, SU-16Ju, 15J)

Q. Enumerate the adverse effects of IV quinine administration. (CU-15Ju)

Ans.

Adverse effects of Quinine and Quinidine:

1. **GIT upset:** Nausea, vomiting, diarrhea, abdominal cramp.
2. **CNS disturbances: Cinchonism**
 - Ataxia
 - Tinnitus
 - Blurring of vision
 - Colour blindness
 - Nausea
 - Headache
 - Dizziness
3. **Hematological abnormalities:** Haemolysis, leucopenia, agranulocytosis & thrombocytopenia.
4. Chance of arrhythmia
5. Severe hypotension
6. Hypoglycemia.
7. **Hypersensitivity:** Skin rash, urticaria, angioedema & bronchospasm.
8. Black water fever (rare but severe).

(Ref: Katzung-13th)

Q. Write the contraindications of quinine & quinidine.

Ans.

Contraindications of quinine & quinidine:

1. Pregnancy
2. Should be discontinued if signs of severe cinchonism, hemolysis, or hypersensitivity occur.
3. Should be avoided if possible in patients with underlying visual or auditory problems.
4. Must be used with great caution in those with underlying cardiac abnormalities.
5. Should not be given concurrently with mefloquine.
6. Dosage must be reduced in renal insufficiency.

(Ref: Katzung-13th)

Chloroquine

Pharmacokinetic properties of chloroquine:

1. Oral administration
2. Rapidly and almost completely absorbed from GIT
3. Large volume of distribution
4. Anti-diarrheal agent kaolin and antacids interfere with the absorption of chloroquine.

(Ref: Katzung-13th)

Q. What are the pharmacological effects of chloroquine? (SU-16Ju)

Ans.

Pharmacological effects of chloroquine

1. Chloroquine is a highly effective blood schizonticide.

- It is also moderately effective against gametocytes of *P vivax*, *P ovale*, and *P malariae* but not against those of *P falciparum*.
- Chloroquine is not active against liver stage parasites.

(Ref: Katzung-13th/887)

Q. Write the indications of chloroquine. (DU-10Ju,05M, RU-06M,04S/J)

Q. Outline three indications of chloroquine. (RU-16J)

Ans.

Indications of chloroquine:

- Drug of choice for non-falciparum malaria & sensitive falciparum malaria.
- Preferred chemoprophylactic agent in malarious regions without resistant falciparum malaria.
- Anti-inflammatory to treat moderate degree of rheumatoid arthritis & SLE.
- Anti-amoebic drugs in amoebic liver abscess.

(Ref: Katzung-13th)

Q. Write down the mechanism of action of chloroquine. (CU-15J, RU-07Ju,06S, SU-13J)

Ans.

Mechanism of action of chloroquine: It has a complex mechanism of action that is not fully understood.

Chloroquine is uncharged at neutral pH and can, therefore, diffuse freely into the parasite lysosome.

↓
At the acid pH of the lysosome, it is converted to a protonated, membrane-impermeable form and is 'trapped' inside the parasite.

↓
Chloroquine prevents digestion of hemoglobin by the parasite and thus reducing the supply of amino acids necessary for parasite viability.

It also inhibits heme polymerase, which polymerizes toxic free heme to non-toxic hemozoin.

↓
The increased pH and accumulation of toxic heme result in oxidative damage to the membranes, leading to lysis of both the parasite and the red blood cells.

The binding to heme and prevention of its polymerization appear to be a crucial step in the drug's anti-plasmodial activity.

(Ref: Rang & Dale's-8th; Lippincott's-6th)

Nice to know

Mechanism of action of chloroquine: The drug probably acts by concentrating in parasite food vacuoles, preventing the biocrystallization of the hemoglobin breakdown product, heme, into hemozoin, and thus eliciting parasite toxicity due to the buildup of free heme.

(Ref: Katzung-13th/887)

Q. Write the adverse effects of chloroquine. (DU-06M; CU-15J,07Ju,06S; RU-07Ju, SU-16Ju)

Q. Outline three adverse effects of chloroquine. (RU-16J)

Ans.

Adverse effects of chloroquine: Chloroquine is very well tolerated. Dosing after meal may reduce some adverse effects.

- Hypersensitivity:** Pruritus, urticaria.
- GIT upsets:** Anorexia, nausea, vomiting, diarrhea, abdominal cramping pain.
- Long term & high dose administration (in case of rheumatic disease):**
 - Irreversible ototoxicity (impaired hearing)
 - Retinopathy
 - Myopathy
 - Peripheral neuropathy

4. Others:

- Headache
- Blurring of vision
- Rarely haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.
- Psychosis
- Confusion
- Seizure
- Agranulocytosis
- Exfoliative dermatitis
- Hypotension
- ECG change—QRS widening and T-wave abnormality. ↑ QT

(Ref: Katzung-13th)

Nice to know

- Chloroquine is considered safe in pregnancy and for young children.

Q. Write the contraindications of chloroquine.

Ans.

Contraindications of chloroquine:

1. Psoriasis or porphyria
2. Retinal or visual field abnormalities
3. Myopathy
4. Should be used with caution in patients with a history of liver disease or neurologic or hematologic disorders.

(Ref: Katzung-13th)

Q. Short note: Chloroquine. (SU-17J)

Ans. Write in short from above discussion.

Fansidar

Q. How does fansidar act? (CU-08J)

Ans.

Mechanism of action of fansidar:**Fansidar** is a fixed combination of—

1. Sulfonamide **sulfadoxine** (500 mg per tablet) &
2. Pyrimethamine (25 mg per tablet)

Folate $\xrightarrow{DHFR}$ DHF $\xrightarrow{DHPS}$ THF (Ref: Katzung-13th)**Mechanism of action of Sulfonamide:**

- Sulfonamides are structural analogue of para-aminobenzoic acid (PABA). PABA is a precursor of folic acid.
- Sulfonamides compete with PABA for the enzyme dihydropteroate synthase and inhibit folate synthesis. Folate is necessary for synthesis of bacterial DNA or RNA. Thereby sulfonamide inhibits bacterial growth.

Mechanism of action of Pyrimethamine:

- Inhibit enzyme dihydrofolate reductase of protozoa which is responsible for conversion of folic acid to active folate. Thereby pyrimethamine inhibits protozoal growth.

Combination of a sulfonamide with pyrimethamine provides synergistic activity because of sequential inhibition of folate synthesis.

(Ref: Katzung-13th)

Q. What are the indications of fansidar?

Ans.

Indications of fansidar:

1. Chloroquine-resistant falciparum malaria
2. Presumptive treatment for travelers who develop fever while traveling in endemic regions
3. Toxoplasmosis
4. *Pneumocystis carinii* infection

(Ref: Katzung-13th)

Q. Mention the adverse effects of fansidar. (CU-08J)

Ans.

Adverse effects of fansidar:

1. Uncommon but severe cutaneous reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.
2. Hematologic, gastrointestinal, central nervous system, dermatologic, and renal toxicity.
3. Folate antagonists should be used cautiously in the presence of renal or hepatic dysfunction.

(Ref: Katzung-13th)

Primaquine

Q. Explain the role of primaquine in the treatment of malaria. (CU-05J, RU-15J)

Ans.

Antimalarial action of primaquine: Primaquine is active against hepatic stages of all human malaria parasites. It is the only available agent active against the dormant hypnozoite stages of *P vivax* and *P ovale*. Primaquine is also gametocidal against the four human malaria species. Primaquine acts against erythrocytic stage parasites, but this activity is too weak to play an important role. The mechanism of antimalarial action is unknown.

(Ref: Katzung-13th)

Q. What are the indications of primaquine?**Q. Rationalize the use of primaquine in *P. vivax* malaria. (RU-12J)**

Ans.

Indications of primaquine:

1. **Radical cure of acute vivax & ovale malaria:** Primaquine eradicates liver hypnozoites and prevents relapse.
2. **Terminal prophylaxis of vivax & ovale malaria**
3. **Chemoprophylaxis of falciparum & vivax malaria** (0.5 mg/kg/day).
4. **Gametocidal action:** A single dose of primaquine (45 mg base) render *P falciparum* gametocytes noninfective to mosquitoes. This therapy is of no clinical benefit to the patient but will disrupt transmission.
5. **Pneumocystis jiroveci pneumonia.**

(Ref: Katzung-13th)

Q. Enlist four (04) adverse effects of primaquine. (DU-16Ju)

Ans.

Adverse effects of primaquine:

1. GIT upset
2. Leukopenia
3. Agranulocytosis
4. Leukocytosis
5. Cardiac arrhythmia
6. Hemolytic anemia in glucose 6 phosphate dehydrogenase deficiency

Q. What are the contraindications of primaquine?

Ans.

Contraindications of primaquine:

- 1. Pregnant women as fetus is relatively G6PD deficient
- 2. Glucose-6-Phosphate Dehydrogenase (G6PD) deficient patient
- 3. Granulocytopenia or Methemoglobinemia

Q. Why hemolytic anemia occurs after primaquine in a patient with G-6PD deficiency? (CU-04S)

Ans.

Primaquine-induced hemolytic anemia in glucose 6-phosphate dehydrogenase (G6PD) deficiency: Free radicals destroy cell membrane. G6PD is used in HMP shunt to produce NADPH. NADPH produces reduced glutathione (GSH) which destroys free radicals (such as H_2O_2) & maintains integrity of red cell membrane.

Mechanism of Primaquine-induced hemolytic anemia.

- Primaquine oxidizes reduced glutathione (GSH) to oxidized glutathione (GSSG) $\rightarrow$ $\downarrow$ GSH level.
- In case of G6PD deficiency $\rightarrow$ $\downarrow$ Production of NADPH $\rightarrow$ $\downarrow$ GSH level.

$\downarrow$
When primaquine is given to patients with G6PD deficiency-

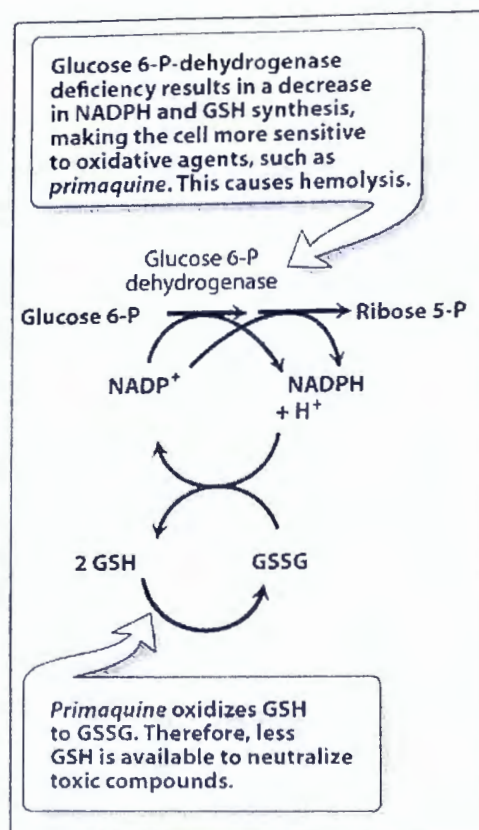
$\downarrow$
GSH level is greatly decreased

$\downarrow$
Oxidative free radicals are not properly destroyed

$\downarrow$
More damage of red cell membrane by the free radicals

$\downarrow$
Hemolytic anemia.

Figure. Mechanism of primaquine-induced hemolytic anemia. GSH = reduced glutathione; GSSG = oxidized glutathione.
(Ref: Lippincott's-6th)



Mefloquine

Pharmacokinetics of mefloquine:

1. Oral administration
2. Highly protein bound
3. Widely distributed in tissues
4. Plasma half life is about 20 days

(Ref: Katzung-13th)

Q. Write down the indications of mefloquine.

Ans.

Indications of mefloquine:

1. **Chemoprophylaxis:** Mefloquine is effective in prophylaxis against most strains of *P falciparum* and probably all other human malarial species as well.

2. **Treatment:** Mefloquine is effective in treating most falciparum malaria. The drug is not appropriate for severe or complicated malaria.

MDR to against 1st line (Ref: Katzung-13th)

Q. Write down the contraindications of mefloquine.

Ans.

Contraindications of mefloquine:

1. Epilepsy
2. Psychiatric disorders
3. Cardiac arrhythmia & conductive defect.
4. Hypersensitivity.

Exact mechanism unknown

(Ref: Katzung-13th)

Nice to know

Mefloquine is also now considered safe in young children. Available data suggest that mefloquine use is safe throughout pregnancy.

(Ref: Katzung-13th)

Atovaquone

Mechanism of action of atovaquone:

Atovaquone inhibits mitochondrial electron transport of malarial parasite

↓
No metabolism of food of malarial parasite
↓
No energy production
↓
Death of parasitic cells.

Indications of atovaquone:

1. Chloroquine resistant *P. falciparum* malaria (as malarone)
2. Chemoprophylaxis of chloroquine-resistant *P. falciparum* malaria (as malarone)
3. *Pneumocystis carinii* pneumonia
4. Toxoplasmosis

Adverse effects of atovaquone:

1. **GIT upset:** Nausea, vomiting, diarrhea.
2. **CNS:** Seizure, confusion, vertigo, diplopia.
3. QT prolongation

Contraindications of atovaquone:

1. Psychiatric patient
2. Cardiac arrhythmia
3. Pregnant women

Malarone: It is a fixed combination of atovaquone (250 mg) and proguanil (100 mg). it is highly effective for both the treatment and chemoprophylaxis of falciparum malaria.)

Malarone = Atovaquone (250 mg) + Proguanil (100 mg)juj

(Ref: Katzung-13th)

Proguanil

Mechanism of action: Same as Fansidar

Indications of proguanil:

1. Causal prophylaxis

2. To treat chloroquine resistant falciparum malaria
3. Toxoplasmosis
4. Pneumocystis carinii pneumonia

Adverse effects of proguanil:

1. GIT upset
2. Mouth ulcers
3. Alopecia
4. Megaloblastic anemia

Contraindications of proguanil: Renal & hepatic dysfunction.

Artesunate & Artemether

Pharmacokinetic properties of artemisinins:

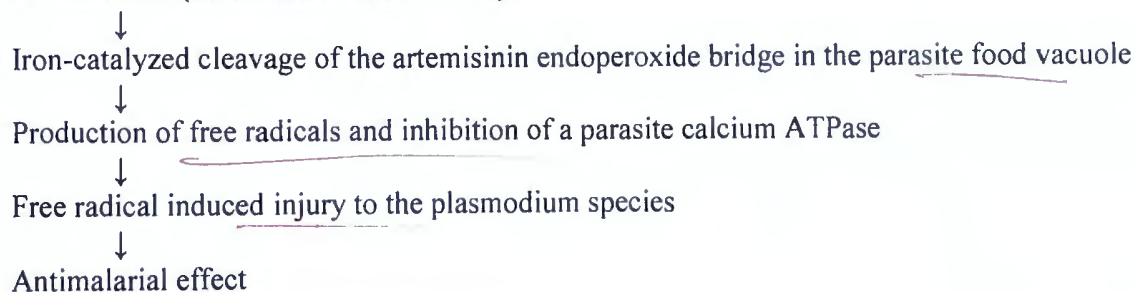
	Artesunate	Artemether
Solubility	Water soluble	Lipid soluble
Route of administration	Oral, IV, IM & rectal	Oral, IM and rectal
Absorption from gut	Rapid	Rapid
Half life	Short (45 minutes)	Long (4-11 hours)
Distribution	Wide	Wide

Q. Mention the mechanism of action of artesunate / artemether.

.Ans.

Mechanism of action of artesunate / artemether:

Artemisinins (artesunate / artemether)



(Ref: Katzung-13th)

Q. What are the indications of artemisinins?

Ans.

Indications of artemisinins / artesunate / artemether:

1. Multidrug-resistant *P falciparum* malaria.
2. Quinine-resistant malaria.
3. Uncomplicated & severe falciparum malaria.

(Ref: Katzung-13th)

Adverse effects of artemisinin derivatives:

1. GIT upset
2. Irreversible neurotoxicity

Contraindications of artemisinins: Pregnancy

Q. Mention the advantages & disadvantages of artemisinins as anti-malarial drugs. (DU-12Ju, 11Ju, CU-09J)

Ans.

Advantages of artemisinins:

1. Artemisinins—in particular artesunate and artemether—are playing an increasingly important role in the treatment of multidrug-resistant *P falciparum* malaria.

2. They are the only drugs reliably effective against quinine-resistant strains.
3. They are used for the treatment of uncomplicated & severe falciparum malaria.

(Ref: Katzung-13th)

Disadvantages of artemisinins:

1. Irreversible neurotoxicity
2. Contraindicated in pregnancy
3. Can cause GIT upset

Drugs for kala-azar

Types of leishmaniasis: 3 types—

1. Visceral leishmaniasis (Kala-azar): Caused by *L. donovani*
2. Cutaneous leishmaniasis (Oriental sore): Caused by *L. tropica*
3. Mucocutaneous leishmaniasis (Espundia): Caused by *L. braziliensis*

(Ref: LANGE Microbiology-12th edition)**Q. What are the anti-leishmanial / leishmanicidal drugs?****Q. Name two important drugs used clinically for Kala-azar. Mention two important side effects of each drug. (DU-08J)**

Ans.

Anti-leishmanial drugs:

Leishmaniasis	Drug of choice	Alternative drugs
Visceral leishmaniasis	Sodium stibogluconate	▪ Miltefosine ▪ Amphotericin B ▪ Paromomycin ▪ Meglumine antimonite ▪ Pentamidine
Cutaneous leishmaniasis	Sodium stibogluconate	▪ Meglumine antimonite ▪ Amphotericin ▪ Pentamidine ▪ Topical or intralesional therapies ▪ Ketoconazole ▪ Itraconazole

(Ref: Katzung-13th + Davidson's Medicine-22nd)**Q. Write down the treatment of visceral leishmaniasis (kala-azar).**

Ans.

Treatment of visceral leishmaniasis kala-azar:

1. **Treatment-A (Oral miltefosine):** First line of treatment for kala-azar patients.
 - Dose: 2.5 mg/kg body weight, in two divided doses by mouth after meal for 28 days.
 - For >12 years of age and weight ≥ 25 kg: 50 mg capsule twice daily for 28 days.
2. **Treatment-B (Sodium stibogluconate):** For kala-azar treatment failure cases with miltefosine and when miltefosine is not available.
 - Dose: 20 mg/kg body weight, daily IM or IV injection for 28 days.
3. **Treatment-C (Amphotericin-B deoxycholate or liposomal amphotericin-B):** Second line of treatment for kala-azar.
 - Dose: 1 mg/kg body weight, daily in the form of IV infusion (in 5% DA) for 20 days.

(Ref: National guideline of kala-azar)

Q. Name two important drugs used clinically for Kala-azar. Mention two important side effects of each drug. (DU-08J)

Ans.

Two important drugs used clinically in Kala-azar:

1. Sodium Stibogluconate
2. Miltefosine

Q. Mention the treatment of PKDL.

Ans.

Treatment of PKDL: Sodium stibogluconate.

Dose:

- Total 6 cycles.
- Each cycle consists of 20 mg/kg body weight, daily IM injection for 20 days, and there should be an interval of 10 days in between two cycles.

(Ref: National guideline of kala-azar)

Sodium stibogluconate

Route of administration: Parenteral (IM or IV).

Dose: Treatment is given once daily at a dosage of 20 mg/kg/day IM or IV for 20 days in cutaneous leishmaniasis and 28 days in visceral and mucocutaneous disease.

(Ref: Katzung-13th)

Mechanism of action:

Relatively nontoxic pentavalent antimonials act as prodrugs.

↓

These compounds are reduced to the more toxic Sb^{3+} species.

↓

Sb^{3+} kills amastigotes within the phagolysosomes of macrophages.

(Ref: Goodman & Gilman-12th edition)

Adverse effects of Na-stibogluconate: Few adverse effects occur initially, but the toxicity of stibogluconate increases over the course of therapy.

1. Pain at the injection site & lead to sterile abscess.
2. **GIT symptoms:** Nausea, vomiting, diarrhea, abdominal pain.
3. **Cardiac:** Arrhythmia, prolongation of QT interval & T inversion.
4. **Other:** Fever, headache, myalgia, arthralgia.
5. **Rarely:** Hemolytic anemia, liver & renal insufficiency.

Monitoring of Na-stibogluconate toxicity: By ECG, hepatic & renal function

Pharmacokinetics:

1. **Routes:** Always IM or Slow IV injection
2. Rapid absorption after administration.
3. Eliminated in two phases with short initial and much longer terminal half-lives.

(Ref: Rang Dale-8th & Katzung-13th)

Miltefosine

Miltefosine is an alkylphosphocholine analog that is the first effective oral drug for visceral leishmaniasis. It has recently shown excellent efficacy in the treatment of visceral leishmaniasis.

Dose: 2.5 mg/kg/d for 28 days.

Route of administration: Oral

Adverse effects of miltefosine:

1. **GIT upsets:** Mild to moderate vomiting, diarrhea
2. **In pregnancy:** Teratogenicity
3. Rarely Nephrotoxicity or skin allergy.

Contraindication of miltefosine:

1. Pregnancy
2. Women who may become pregnant within 2 months of treatment.

(Ref: Katzung-13th)

Caution of miltefosine therapy: Female patients are advised not to become pregnant for the duration of treatment & another 2 months, because its half life of nearly 1 week.

(Ref: Davidson's medicine-22nd)

Q. Write down the superiority of miltefosine over other leishmanicidal drugs.

Q. Why should miltefosine become the treatment of choice for leishmaniasis?

Ans.

Superiority of miltefosine:

1. Oral administration.
2. **Short-lived toxicities:** Nausea, vomiting, diarrhea
3. No evidence of resistance.

Amphotericin- B

This is an anti-fungal drug.

Dose: Once daily or on alternate days at a dose of 0.75 - 1.00 mg/kg for 15 to 20 doses.

Indications:

1. Na-stibogluconate failure
2. Na-stibogluconate resistant area
3. Kala-azar with pregnancy

Advantages:

1. Cure rate is nearly 100%
2. Only drug for kala-azar with pregnancy

Side effects / adverse effects:

1. Infusion-related side effects: High fever with rigor, thrombophlebitis, diarrhea & vomiting.
2. Renal toxicity.
3. Hepatic toxicity.
4. Hypokalemia.
5. Thrombocytopenia.
6. Myocarditis
7. Occasional death.

Formulations: Lipid formulations (amphotericin B- lipid complex) and liposomal amphotericin B are less toxic and have been tested widely for the treatment of VL.

(Ref: Davidson's medicine-22nd)

Pentamidine

Mechanism of action: Pentamidine binds to the parasite's DNA and interferes in the synthesis of RNA, DNA, phospholipid and protein of the parasite.

Indications:

1. Trypanosomiasis except caused by *T. cruzi*
2. Pneumocystis carinii infection in case of failure of co-trimoxazole or individuals who are allergic to sulfonamides.
3. Alternative drug to sodium stibogluconate in the treatment of leishmaniasis.

Adverse effects:

1. Reversible renal dysfunction.
2. Pancreatic toxicity may lead to hypoglycemia due to inappropriate insulin release.
3. **Due to rapid IV administration:** Severe hypotension, tachycardia, dizziness, dyspnea.
4. **Due to IM administration:** Pain at the site of injection, sterile abscess
5. **Inhaled pentamidine:** Cough, dyspnea, bronchospasm
6. **Others:**
 - Metallic taste
 - Fever
 - Rash
 - GI upset
 - Abnormal liver function test
 - Hypocalcemia
 - Thrombocytopenia
 - Hallucination

Pharmacokinetics:

- **Routes:** IM or IV or aerosol
- The drug is concentrated and stored in the liver and kidney for a long period of time.
- Because it does not enter the CSF, it is ineffective against the meningo-encephalitic stage of trypanosomiasis.
- The drug is not metabolized and is excreted very slowly into urine. Its half life is about 5 days.

(Ref: Katzung-13th & Lippincott's-6th)

Q. What are the anti-protozoal drugs? (SU-16Ju)

Ans.

Anti-protozoal drugs

1. Anti-malarial drugs
2. Anti-amebic drugs
3. Drugs for *Leishmaniasis*, *Pneumocystis jiroveci*, *Toxoplasma gondii*, *Trichomonas vaginalis*, *Trypanosomiasis*, etc.

(Ref: Katzung-13th)

Anti-amoebic drugs

Amoebiasis is caused by *Entamoeba histolytica*. Infection occurs when mature cysts are ingested and pass into the colon where they divide into trophozoites; these forms either enter the tissues or reform cysts. Amoebiasis occurs in two forms, both of which need treatment:

1. **Bowel lumen amoebiasis** is asymptomatic and trophozoites (noninfective) and cysts (infective) are passed into the faeces.
2. **Tissue-invading amoebiasis** gives rise to dysentery, hepatic amoebiasis and liver abscess.
(Ref: Bennett & Brown-11th)

Q. Classify anti-amoebic drugs. (CU-08J; SU-15Ju,09Ju,08J,06M, RU-03M)

Q. Enumerate the drugs used in amebiasis. (DU-14J,13J,11J, SU-09Ju, RU-05S)

Q. Outline pharmacotherapy for amebiasis. (RU-15Ju)

Q. List the drugs that are effective against *E. histolytica*. (CU-05S)

Q. Outline the treatment of a case of amebic dysentery. (DU-15Ju)

Ans.

Classification of anti-amoebic drugs:

1. Luminal amoebicides in large gut: Act on the ameba (cyst) in the lumen of the bowel	▪ Diloxanide furoate ▪ Iodoquinol ▪ Paromomycin
2. Systemic / Tissue amoebicides: Effective against ameba (trophozoite) in the intestinal wall and tissues eg, liver. These drugs are useful for treating liver abscesses or intestinal wall infections caused by amebas.	▪ Chloroquine ▪ Dehydroemetine
3. Mixed type of amoebicides: Effective against both luminal (cyst) and systemic forms (trophozoite) of the disease.	▪ Metronidazole ▪ Tinidazole ▪ Nitazoxanide ▪ Secnidazole ▪ Omidazole

(Ref: Lippincott's-6th)

Drug of choice for amoebiasis:

Clinical Setting	Drugs of Choice
Asymptomatic intestinal infection	Luminal agent: Diloxanide furoate, Iodoquinol, Paromomycin
Mild to moderate intestinal infection	Metronidazole or Tinidazole + Luminal agent
Severe intestinal infection	Metronidazole or Tinidazole + Luminal agent
Hepatic abscess, amoeboma & other extra-intestinal disease	Metronidazole or Tinidazole + Luminal agent

(Ref: Katzung-13th)

Q. Explain the management of a case of amoebic dysentery. (DU-07Ju)

Q. Write down the treatment of intestinal amoebiasis.

Ans.

Treatment of intestinal amoebiasis/ amoebic dysentery:

- Intestinal amoebiasis responds quickly to oral **metronidazole** (800 mg 8-hourly for 5 days) or **tinidazole** (2 g daily for 3 days).
- **Diloxanide furoate** 500 mg should be given orally 8-hourly for 10 days after treatment to eliminate luminal cysts.

(Ref: Davidson-22nd)

Q. Outline the treatment of hepatic amoebiasis / amoebic liver abscess. (RU-03J, SU-03S)

Q. Name the drugs used in amoebic liver abscess. (RU-04S)

Ans.

Treatment of hepatic amoebiasis / amoebic liver abscess:

Medical treatment:

- Early hepatic amoebiasis responds promptly to treatment with metronidazole (800 mg 8-hourly for 5 days) or tinidazole (2 g daily for 3 days).
- The luminal amoebicide diloxanide furoate (500 mg 8-hourly for 10 days) is given to eliminate the intestinal infection.

Surgical treatment:

- If the abscess is large or threatens to burst, or if the response to chemotherapy is not prompt, **aspiration** is required and repeated if necessary under ultrasonography guidance.
- Rupture of an abscess into the pleural cavity, pericardial sac or peritoneal cavity necessitates immediate aspiration or surgical drainage.
- Small serous effusions resolve without drainage.

(Ref: Davidson-22nd)

Metronidazole

Q. Write down mechanism of action metronidazole? (CU-13J, 09J, RU-03J, SU-16Ju, 15Ju, 13J)

Q. Write down the role of metronidazole? (SU-10Ju)

Q. Discuss pharmacodynamics of metronidazole. (CU-12J, 09Ju)

Q. Explain the pharmacological basis of using metronidazole in amoebiasis. (CU-06J)

Q. What is the role of anti-amoebic drugs? (SU-08J)

Ans.

Mechanism of action of metronidazole:

Metronidazole



Enters into anaerobic bacteria and sensitive protozoans (eg, ameba)



The nitro group of metronidazole is chemically reduced by accepting electron



Reduced cytotoxic compounds of metronidazole bind with proteins and DNA



Cell death

(Ref: Katzung-13th + Lippincott's-6th)

Viva Q. Explain selective toxicity of metronidazole towards anaerobic bacteria.

Ans. **Selective toxicity of metronidazole:** In the presence of oxygen, metronidazole is not reduced, rather oxygen is reduced. So, there is no production of reduced cytotoxic compounds of metronidazole → No toxic effect of metronidazole. This is why metronidazole is selectively toxic towards anaerobic bacteria.

Q. Outline the spectrum of activity of metronidazole. (CU-09J)

Ans.

Spectrum of activity of metronidazole:

1. **Protozoal infection:** Active against 3 protozoal infections; such as —

- *E. histolytica*
- *T. vaginalis*
- *G. lamblia*

2. **Bacterial infection:** Metronidazole is active against **anaerobic bacteria**, including

- *Bacteroides*
- *Clostridium*

- *Fusobacterium*
- *Peptococcus*
- *Peptostreptococcus*
- *Eubacterium*, and
- *Helicobacter*.

(Ref: Goodman & Gilman-12th edition)

Q. Mention the anti-bacterial indications of metronidazole. (DU-07J)

Q. Write down the uses / indications of metronidazole. (DU-15Ju,14J,13J,11J, CU-17M,06S; SU-16J,15Ju,15J,13J,10J,09Ju; RU-06J)

Ans.

Indications of metronidazole:

A. Anaerobic bacterial infection

1. Post surgical infection: Abdominal surgery, pelvic surgery, rectal surgery.
2. Intra-abdominal septicemia
3. PUD- Triple / quadruple therapy for *H. pylori*.
4. Endocarditis by *B. fragilis*
5. Pelvic infection
6. Brain abscess & lung abscess
7. Gingival & dental infection
8. Diabetic gangrene
9. Pseudomembranous colitis (caused by *C. difficile*)
10. Tetanus.
11. Suspected acute abdomen of GIT origin.
12. Aspiration pneumonia.
13. Prophylaxis of surgery- 2 days before & 2 days after.

B. Protozoal infection:

1. Lesions produced by *E. histolytica*:
 - Acute & chronic amoebic dysentery
 - Amoebic liver abscess
2. Trichomoniasis (vaginitis caused by *Trichomonas vaginalis*)
3. Giardiasis (diarrhea caused by *G. Lamblia*).

Q. Mention the adverse effects of metronidazole. (DU-15Ju,14J,13J,11J,08/07Ju; CU-10/09J, RU-05S, SU-16Ju,16J,15J,09Ju)

Q. What are the adverse effects of anti-amoebic drugs? (SU-08J)

Q. Mention adverse effects of any one drug that is effective against *E. histolytica*. (CU-05S)

Ans.

Adverse effects of metronidazole:

1. Metallic taste
2. Dry mouth
3. GIT upset: Nausea, vomiting, diarrhea. Taking the drug with meals lessens gastrointestinal irritation.
4. CNS intoxication: Headache, dizziness, insomnia, vertigo, paresthesia, ataxia.
5. Thrush, rash, dysuria, dark urine, and neutropenia.
6. Disulfiram like effect: Metronidazole has a disulfiram-like effect, so that nausea and vomiting can occur if alcohol is ingested during therapy.

(Ref: Katzung-13th)

Q. List the contraindications of metronidazole. (SU-16Ju)

Ans.

Relative contraindications of metronidazole:

1. Pregnant women
2. Lactating mother

3. Young children
4. Liver insufficiency

Nice to know

Drugs producing metallic taste:

1. Metronidazole
2. Tetracycline
3. Rifampicin
4. Pentamidine isothionate

Drugs possessing disulfiram like action:

1. Metronidazole
2. Cefotetan
3. Trimethoprim

Q. Short note: Metronidazole. (DU-12J)

Ans. Write M/A, indication, adverse effects, contraindications from above.

Q. Name two important drugs used clinically for giardiasis. (DU-08J)

Ans.

Drugs used to treat giardiasis:

- **Metronidazole** (treatment of choice for giardiasis): 2 g once daily for 3 days or 400 mg 8-hourly for 10 days.
- **Tinidazole**: 2 g single dose.

(Ref: Davidson-22nd)

Q. Write the treatment of *T. vaginalis* infection/trichomoniasis.

Ans.

Treatment of *T. vaginalis* infection/Trichomoniasis: Metronidazole is the treatment of choice. A single dose of 2 g is effective. Metronidazole-resistant organisms can lead to treatment failures. Tinidazole may be effective against some of these resistant organisms.

(Ref: Katzung-13th)

Q. What is the role of chloroquine in the treatment of hepatic amoebiasis? (CU-03J)

Ans.

Role of chloroquine in the treatment of hepatic amoebiasis: Chloroquine is used in combination with metronidazole and diloxanide furoate to treat and prevent amoebic liver abscesses. It eliminates trophozoites in liver abscesses.

(Ref: Lippincott's-6th)

Q. Explain disulfiram-like action of metronidazole.

Q. Write down the avulsive therapy of alcoholic patient?

Ans.

Disulfiram-like action of metronidazole:

Ethanol

↓ Alcohol dehydrogenase

Acetaldehyde

↓ Aldehyde dehydrogenase ← *Inhibits* Disulfiram / Metronidazole

Acetate

Oxidation of acetaldehyde is inhibited by disulfiram by inhibiting aldehyde dehydrogenase in the liver. When ethanol is consumed in the presence of disulfiram, acetaldehyde accumulates and causes an unpleasant reaction of facial flushing, nausea, vomiting, dizziness and headache. Metronidazole also inhibits aldehyde dehydrogenase

and can cause a disulfiram-like action if taken with ethanol. In the treatment of alcoholic patients, they are given alcohol along with metronidazole. As a result, they experience disulfiram-like effects of metronidazole and promise not to take alcohol again. This is called **avulsive therapy**.

Diloxanide furoate

In the gut, diloxanide furoate is split into diloxanide and furoic acid; about 90% of the diloxanide is rapidly absorbed and then conjugated to form the glucuronide, which is promptly excreted in the urine. The **unabsorbed diloxanide** is the active antiamebic substance. The mechanism of action of diloxanide furoate is unknown.

Indications: It is an effective luminal amoebicide but is not active against tissue trophozoites. It is used for complete eradication of cystic form of *E. histolytica*.

1. Drug of choice for asymptomatic luminal infections
2. Used with a tissue amebicide, usually metronidazole, to treat serious intestinal and extraintestinal infections.

Adverse effects of diloxanide furoate:

1. Flatulence- common
2. Nausea and abdominal cramps are infrequent and rashes are rare

Contraindications:

1. Pregnant women
2. Children under 2 years of age.

(Ref: Katzung-13th)

Nitazoxanide

It is rapidly absorbed and converted to tizoxanide and tizoxanide conjugates, which are subsequently excreted in both urine and feces. The active metabolite, tizoxanide, inhibits the pyruvate : ferredoxin oxidoreductase pathway.

Spectrum of activity:

1. *Giardia lamblia*
2. *Cryptosporidium parvum*
3. Metronidazole-resistant protozoal strains
4. *E histolytica*
5. *Helicobacter pylori*
6. *Ascaris lumbricoides*
7. Several tapeworms, and
8. *Fasciola hepatica*.

Dose: The recommended adult dosage is 500 mg twice daily for 3 days.

(Ref: Katzung-13th)

Anthelmintic drugs

Q. Name the common intestinal helminthic infections in Bangladesh. (CU-17M)

Ans.

Common intestinal helminthic infections in Bangladesh

Small intestine only

- *Ascaris lumbricoides* (Common round worm)
- *Ancylostoma duodenale* (Old world hookworm)
- *Strongyloides stercoralis*
- *Trichinella spiralis* (Trichina worm)

Cecum & vermiform appendix

- *Enterobius vermicularis* (Thread/pin worm)
- *Trichuris trichiura* (Whipworm)

Q. Classify anthelmintic drugs. (DU-15Ju, CU-17M; RU-03J/S)

Q. Name some anthelmintic drugs of clinical importance. (RU-04M)

Q. Describe the treatment of ankylostomiasis / hookworm. (RU-05S, 04M)

Q. Name the common intestinal helminthes & the drugs used against the helminthes you've listed. (CU-08J)

Ans.

Anthelmintic drugs

Anthelmintic drugs according to mode of action:

1. Inhibits ATP synthesis by inhibiting glucose uptake	▪ Albendazole ▪ Mebendazole ▪ Thiabendazole
2. Paralysis of worm and expel in feces	
▪ Neuromuscular blocker	▪ Pyrantel pamoate
▪ Increased influx of Cl ⁻ by activating GABA receptor	▪ Ivermectin
▪ Increased permeability of cell membrane of worm to Ca ²⁺	▪ Praziquantel
3. Destroy scolex	▪ Niclosamide

(Ref: Lippincott's-6th + Katzung-13th + Rang & Dale's-8th)

Nice to know:

Broad spectrum anthelmintic drugs:

1. Albendazole
2. Mebendazole
3. Pyrantel pamoate
4. Praziquantel

Albendazole & Mebendazole

Q. Describe the mechanism of action / anthelmintic action albendazole. (DU-15Ju, CU-17M, RU-05S)

Q. Discuss the mechanism of action / anthelmintic of mebendazole. (DU-07Ju; RU-04S)

Ans.

Mechanism of action / anthelmintic action of albendazole / mebendazole: Mebendazole / Albendazole acts by binding to and interfering with the assembly of the parasites' microtubules and also by decreasing glucose uptake. Affected parasites are expelled with the feces.

Nematodes

Mebendazole

Pyrantel pamoate

Thiabendazole

Trematodes

Praziquantel

Cestode

(Ref: K.D. Chatterjee-13th/200)

Aldendazole

Niclosamide

- Albendazole / mebendazole inhibits microtubule synthesis in nematodes.
- Irreversibly impair glucose uptake by the worm.

↓
↓ ATP synthesis required for survival
↓
Parasites are immobilized or die slowly
↓
Cleared out from intestine within 2-3 days.

(Ref: Lippincott's-6th)

Q. Write down the indications of albendazole. (CU-07J,05J)

Q. Write down the indications of mebendazole. (RU-04S)

Q. Write a short note on albendazole. (DU-13Ju; RU-06M)

Ans.

Indications of albendazole / mebendazole:

1. Round worm
2. Hook worm
3. Whip worm
4. Pin worm
5. Thread worm
6. Combined infection
7. Hydatid disease
8. Neurocysticercosis
9. Cutaneous & visceral larva migrans

(Ref: Katzung-13th)

Q. Mention the adverse effects of albendazole. (DU-05S, CU-05J; RU-05/04/03S)

Ans.

Adverse effects of albendazole / mebendazole:

In short term use:

- When used for 1–3 days, albendazole/ mebendazole is nearly free of significant adverse effects.
- Mild and transient epigastric distress, diarrhea, headache, nausea, dizziness, lassitude, and insomnia can occur.
- High-dose therapy of mebendazole may cause hypersensitivity reactions (rash, urticaria), agranulocytosis, alopecia, and elevation of liver enzymes.

In long-term use for hydatid disease:

- Albendazole is well tolerated, but it can cause abdominal distress, headaches, fever, fatigue, alopecia, increases in liver enzymes, and pancytopenia.

(Ref: Katzung-13th)

Viva Q. What investigations should be carried out during long term therapy of albendazole?

Ans.

Investigations during long term therapy of albendazole (in hydatid diseases):

- **Complete blood counts:** To see pancytopenia.
- **Liver function tests:** To see liver damage by the drug.

(Ref: Katzung-13th)

Q. Mention the contraindications of albendazole. (DU-15Ju)

Ans.

Contraindications of albendazole

1. Known hypersensitivity to the drug
2. Cirrhosis of liver
3. Pregnancy
4. Children younger than 2 years of age

(Ref: Katzung-13th)

Q. Short note: Albendazole. (DU-17J,14Ju,14J)

Ans. Write from above discussion.

Nice to know

Pharmacokinetics of albendazole:

1. Oral administration
2. Increased absorption with a fatty meal
3. Rapidly undergoes 1st pass hepatic metabolism
4. Active metabolite albendazole sulfoxide is produced in the liver
5. Widely distributed over bile, CSF and hydatid cysts.
6. Albendazole metabolites are excreted in the urine

Policy of albendazole administration: Albendazole is administered on an empty stomach when used against intraluminal parasites. Albendazole is administered with a fatty meal when used against tissue parasites

Dose of albendazole:

- Usual dose (ascariasis, trichuriasis, hookworm and pin worm infestation): 400 mg tablet, single dose.
- In hydatid cyst: 400 mg 12 hourly with meal for 1 month or longer. (1-3 months)
- In cysticercosis: 400 mg 12 hourly for 21 days.
- Cutaneous larva migrans: 400 mg daily for 3 days.
- Visceral larva migrans: 400 mg daily for 5 days.

Dose of mebendazole:

- Usual dose (ascariasis, trichuriasis, hookworm infestation): 100 mg tablet, 1 tablet 12 hourly, for 3 days.
- Pin worm infestation: 100 mg once. Repeated at two weeks.

(Ref: Katzung-13th)

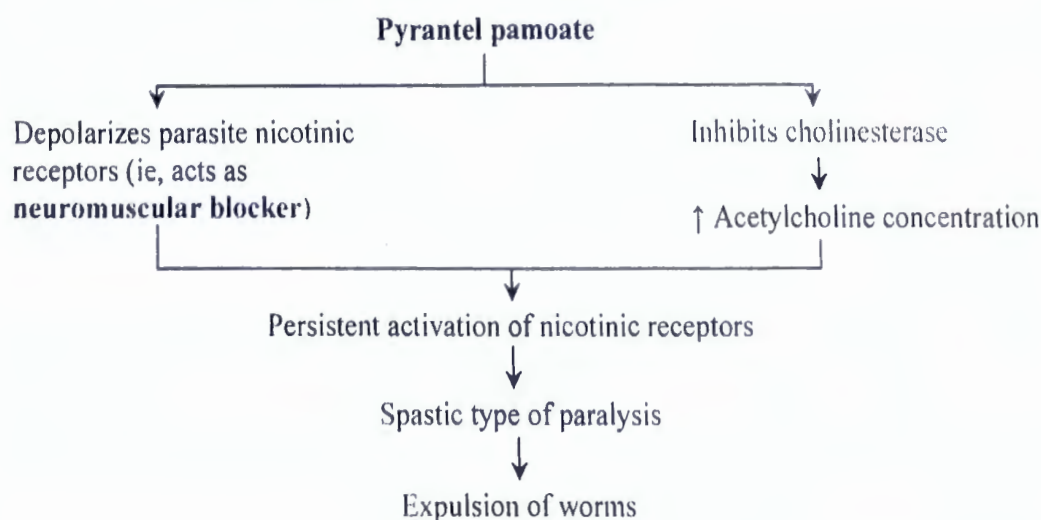
Pyrantel pamoate

Q. Write down the anthelmintic action of pyrantel pamoate. (DU-07Ju;CU-08Ju)

Ans.

Mechanism of action of pyrantel pamoate: Pyrantel is effective against mature and immature forms of susceptible helminths within the intestinal tract but not against migratory stages in the tissues or against ova. The drug is a neuromuscular blocking agent that causes release of acetylcholine and inhibition of cholinesterase; this results in paralysis, which is followed by expulsion of worms.

(Ref: Katzung-13th)



(Ref: Katzung-13th, Rang & Dale's-8th, Lippincott's-6th)

Q. Write down the clinical uses pyrantel pamoate.

Ans.

Indications / clinical uses of pyrantel pamoate:

1. Round worm
2. Hook worm
3. Pin worm

Q. Write down the adverse effects of pyrantel pamoate. (CU-08J)

Ans.

Adverse effects of pyrantel pamoate:

1. GIT upset
2. CNS adverse effects: Dizziness, drowsiness, headache, insomnia.
3. Rash
4. Fever
5. Weakness

Q. Mention the contraindications of pyrantel pamoate.

Ans.

Contraindications of pyrantel pamoate:

1. Pregnant women
2. Children under age of 2 years

(Ref: Katzung-13th)

Praziquantel

Q. Discuss the mechanism of action of praziquantel.

Ans.

Mechanism of action of praziquantel:

Praziquantel increases the permeability of the trematode and cestode cell membranes to Ca^{2+}

↓
↑Intracellular Ca^{2+} concentration

↓
Contraction of musculature

↓
Spastic paralysis

↓
Dislodgment

↓
Death of the parasites

(Ref: Katzung-13th)

Q. What are the indications of praziquantel?

Ans.

Indications of praziquantel:

1. Schistosomiasis
2. Clonorchiasis
3. Opisthorchiasis
4. Paragonimiasis
5. Taeniasis
6. Diphyllbothriasis
7. Neurocysticercosis
8. Hymenolepis nana

9. Hydatid Disease
10. Other Parasites-
 - Fasciolopsiasis
 - Metagonimiasis
 - Heterophyiasis

(Ref: Katzung-13th)

Q. Mention the adverse effects and contraindications of praziquantel?

Ans.

Adverse effects of praziquantel:

1. GIT upset
2. Pruritus
3. Urticaria
4. Arthralgia
5. Myalgia
6. Low grade fever
7. Eosinophilia
8. Dizziness

(Ref: Katzung-13th)

Contraindications of praziquantel:

1. Ocular cysticercosis
2. Spinal Neurocysticercosis
3. Children under age of 4 years
4. Pregnant women

(Ref: Katzung-13th)

Q. Name the anthelmintic drugs that are contraindicated in pregnancy?

Ans.

Anthelmintic drugs contraindicated in pregnancy:

1. Albendazole
2. Mebendazole
3. Ivermectin

(Ref: Lippincott's-6th)

Q. What is the treatment of filariasis?

Ans.

Treatment of filariasis: Treatment of the individual is aimed at reversing and halting disease progression.

1. **Diethylcarbamazine (DEC)** kills microfilariae and adult worms. The dose is 6 mg/kg daily orally in three divided doses for 12 days. The full dose must be reached slowly, starting with 50 mg and doubling daily unless serious allergic reactions ensue.
2. **Antihistamines or corticosteroids** may be required to control these allergic phenomena.
3. **Tight bandaging, massage and bed rest** with elevation of the affected limb may help to control the lymphedema.
4. **To prevent secondary infection:** Prompt diagnosis and antibiotic therapy.
5. **Plastic surgery** may be indicated in established elephantiasis. Great relief can be obtained by removal of excess tissue but recurrences are probable unless new lymphatic drainage is established.
6. **Surgery:** Hydroceles can be repaired surgically; chyluria can also be corrected surgically.

(Ref: Davidson's-22nd)

Anti-fungal drugs

- Q. Classify the antifungal drugs? (DU-15J,07M, CU-16Ju,13Ju,08J)
 Q. Name the local antifungal drugs. (RU-06M)
 Q. Enumerate systemic antifungal drugs. (DU-17J, RU-16Ju)
 Q. Name the drugs used in systemic fungal infection. (DU-07M)
 Q. Name topical antifungal drugs? (RU-15J)
 Q. Name 2 clinically used important drugs for oral candidiasis. (DU-05S)

Ans.

Antifungal drugs

A. On the basis of site of administration:

Site of administration	Drugs
1. Systemic antifungal drugs for systemic infections (oral or parenteral)	- Amphotericin-B - Flucytosine - Echinocandins: - Caspofungin - Micafungin - Anidulafungin - Azoles: - Imidazole groups: Ketoconazole - Triazole groups: Itraconazole, Fluconazole, Voriconazole & Posaconazole.
2. Systemic antifungal drugs for mucocutaneous infections (oral)	- Griseofulvin - Terbinafine
3. Topical antifungal drugs for mucocutaneous infections	- Nystatin - Amphotericin-B - Topical azoles: Miconazole, Clotrimazole & Ketoconazole. - Topical allylamines: Terbinafine, Naftifine.

(Ref: Katzung-13th)

B. On the basis of mechanism of action:

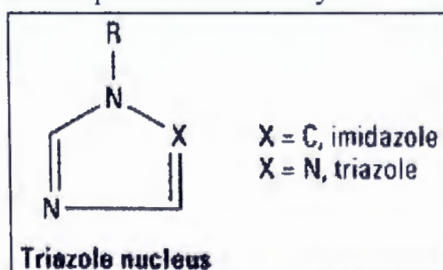
Mechanism of action	Drugs
1. Drugs that disrupt the fungal cell membrane	- Polynes: e.g. amphotericin - Azoles: imidazoles, e.g. ketoconazole, fluconazole - Allylamines: terbinafine
2. Drug that inhibits mitosis	Griseofulvin
3. Drug that inhibits DNA synthesis	Flucytosine

(Ref: Bennet & Brown-11th)

- Q. Name the azole anti-fungal drugs. (DU-09Ju)
 Q. Name the azole antibiotics. (DU-14Ju)
 Q. Name the azoles that can be used to treat fungal infections. (CU-06M)

Ans.

Azole anti-fungal drugs: The azoles are a group of synthetic fungistatic agents with nitrogen-containing five-membered azole ring and a broad spectrum of activity.



(Ref: Rang & Dale's-8th; Katzung-13th)

Classification of azole anti-fungal drugs:**A. According to site of administration:**

1. Systemic antifungal azoles for systemic infections	▪ Ketoconazole ▪ Itraconazole ▪ Fluconazole ▪ Voriconazole
2. Topical antifungal azoles for mucocutaneous infections	▪ Miconazole ▪ Clotrimazole ▪ Ketoconazole ▪ Econazole ▪ Oxiconazole ▪ Sulconazole

B. According to the number of nitrogen atoms in the five-membered azole ring:

▪ Imidazoles (contain 2 nitrogen atoms in the azole ring)	1. Ketoconazole 2. Miconazole 3. Fenticonazole 4. Clotrimazole 5. Isoconazole 6. Tioconazole
▪ Triazoles (contain 3 nitrogen atoms in the azole ring)	1. Fluconazole 2. Itraconazole 3. Voriconazole

(Ref: Katzung-13th)

Q. Name the mechanism of action of azole group. (DU-09Ju; CU-16J, RU-08Ju,06M)**Q. Describe the mechanism of action of econazole.** (CU-13Ju)**Q. Mention the mechanism of action of miconazole.** (CU-08J)**Q. How fluconazole produces its antifungal effects.** (DU-07J, RU-12J)**Q. Write the mechanism of action of ketoconazole.** (CU-16Ju)

Ans.

Mechanism of action of azole drugs: Azoles are predominantly fungistatic.

Azole drugs



Inhibit fungal cytochrome P450 enzyme



Inhibit conversion of lanosterol into ergosterol- the principal sterol of fungal cell membrane



Reduction of ergosterol synthesis



Disrupt membrane structure and function



Inhibit fungal cell growth.

The specificity of azole drugs results from their greater affinity for fungal than for human cytochrome P450 enzymes.

(Ref: Katzung-13th; Lippincott's-6th)

Q. What are the advantages of fluconazole over ketoconazole? (DU-07/06J; CU-04M; RU-16Ju,12Ju,06M)**Q. Write down the differences between fluconazole & ketoconazole.** (DU-12Ju)**Q. Compare & contrast between fluconazole & ketoconazole.** (RU-15J,11Ju,08J)

Ans.

Differences between fluconazole & ketoconazole:

Or, Advantages of fluconazole over ketoconazole: (write points 1, 4, 5, 7, 8, 9, 10, 11)

Traits	Ketoconazole	Fluconazole
1. Spectrum	Narrow	Expanded
2. Route of administration	Oral	Oral, IV
3. Half life	6-9 hours	30 hours
4. Frequency of dosing	More	Less
5. CSF penetration	No	Yes, so drug of first choice for most types of fungal meningitis
6. Renal excretion	No	Yes
7. Interaction with other drugs	Frequent, can increase toxicities of drugs, eg, cyclosporine, warfarin.	Occasional
8. Inhibition of mammalian sterol synthesis	Dose-dependent inhibitory effect, thus inhibits mammal androgen synthesis	No inhibition
9. Gastrointestinal side effects	More	Less
10. Endocrinological side effects	Gynecomastia, decreased libido, impotence, menstrual irregularities	No
11. Therapeutic index	Lower than fluconazole	Highest among the azoles

(Ref: Lippincott's-6th; Katzung-13th edition)

Q. What are the adverse effects of azole? (DU-09Ju)

Q. What are the adverse effects of ketoconazole? (DU-03M, CU-16Ju/J, SU-02S)

Q. What are the adverse effects of miconazole? (CU-08J)

Q. What are the adverse effects of griseofulvin? (DU-01M, CU-02M, SU-04S)

Q. What are the adverse drug reactions of Econazole? (CU-16J)

Ans.

Adverse effects of azole

Ketoconazole	1. Liver damage (rare but fatal) 2. GIT upset: Nausea, anorexia, vomiting 3. Headache 4. Pruritus 5. Photophobia 6. Endocrine effects such as gynecomastia, decreased libido in men, impotence, menstrual irregularities results from blocking of androgen and steroid synthesis. 7. Can increase toxicities of drugs, eg, cyclosporine, warfarin. 8. Teratogenesis
Fluconazole (it is generally very well tolerated.)	Unwanted effects, which are generally mild, include 1. Nausea 2. Headache 3. abdominal pain 4. elevation of liver enzymes and 5. Allergic rash
Miconazole	Adverse effects are uncommon, but include ▪ Transient hepatitis and hypokalemia. ▪ Prolonged use may lead to cardiac failure, especially in those with preexisting cardiac disease. Topical use may cause- ▪ Contact dermatitis, vulvar irritation, edema
Econazole	1. Local erythema 2. Burning

- | |
|-------------|
| 3. Stinging |
| 4. Itching |

(Ref: Lippincott's-6th, Bennett & Brown-11th, Rang&Dale's-8th; Goodman & Gillman-12th)

Q. Short note: Fluconazole. (DU-14J)

Ans. Write from above discussion.

Q. Write down the mechanism of action of griseofulvin.

Ans.

Mechanism of action of griseofulvin: Griseofulvin's mechanism of action at the cellular level is unclear, but it is deposited in newly forming skin where it binds to keratin, protecting the skin from new infection. Because its action is to prevent infection of these new skin structures, griseofulvin must be administered for 2–6 weeks for skin and hair infections to allow the replacement of infected keratin by the resistant structures. Nail infections may require therapy for months to allow regrowth of the new protected nail and is often followed by relapse.

(Ref: Katzung-13th)

Q. Mention the mechanism of action of amphotericin B. (DU-15J)

Ans.

Mechanism of action of amphotericin B: Amphotericin B is **selective** in its fungicidal effect because it binds to ergosterol of fungal cell membrane. It cannot bind to human cell membrane, which contains cholesterol, not ergosterol.

Amphotericin B binds to ergosterol



Alters the permeability of the cell by forming **pores** in the fungal cell membrane.



The pore allows the leakage of intracellular ions and macromolecules



Cell death.

(Ref: Katzung-13th)

Q. Mention the clinical uses of amphotericin B. (DU-15J)

Ans.

Clinical uses of amphotericin B

1. Localized and systemic candidemia
2. *Cryptococcus*
3. *Histoplasma*
4. *Blastomyces*
5. *Coccidioides*
6. *Aspergillus*

(Ref: Katzung-13th)

Viva Q. Why is amphotericin B selective for fungal cells?

Ans. Amphotericin B binds to **ergosterol**. It does not bind to **cholesterol** found in bacteria and human cells. This is why; it is selective for fungal cells.

Nice to know

Adverse effects of Griseofulvin and Amphotericin B:

Griseofulvin	1. Allergic syndrome much like serum sickness 2. hepatitis 3. gastrointestinal upsets 4. headache 5. photosensitivity 6. Drug interactions with warfarin and phenobarbital.
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Amphotericin B	Infusion-related toxicity: These infusion-related reactions are nearly universal and consist of- ▪ Fever ▪ Chills ▪ Muscle spasms ▪ Vomiting ▪ Headache, and ▪ Hypotension. <i>(They can be ameliorated by slowing the infusion rate or decreasing the daily dose. Premedication with antipyretics, antihistamines, meperidine, or corticosteroids can be helpful.)</i> Cumulative toxicity ▪ Renal damage is the most significant toxic reaction. ▪ Live damage ▪ Anemia (due to reduced erythropoietin production by damaged renal tubular cells) ▪ Seizures (after intrathecal therapy)
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(Ref: Katzung-13th)

Q. Briefly write down the pharmacological properties of nystatin.

Ans.

Pharmacological properties of nystatin

1. **Chemistry:** Nystatin is a polyene macrolide much like amphotericin B.
2. **Route of administration:** It is too toxic for parenteral administration and is only used topically.
3. **Preparations:** Creams, ointments, suppositories, and other forms for application to skin and mucous membranes.
4. **Toxicity:** It is not absorbed to a significant degree from skin, mucous membranes, GIT. As a result, nystatin has little toxicity.
5. **Indications:**
 - a. Oropharyngeal thrush
 - b. Vaginal candidiasis
 - c. Intertriginous candidal infections.

(Ref: Katzung-13th)

Anti-viral drugs

Viruses are obligate intracellular parasites; their replication depends primarily on synthetic processes of the host cell. Therefore, to be effective, antiviral agents must either block viral entry into or exit from the cell or be active inside the host cell. As a corollary, nonselective inhibitors of virus replication may interfere with host cell function and produce toxicity.

(Ref: Katzung-13th)

Q. Classify antiviral drugs according to mechanism of action.

Ans.

Classification of antiviral drugs:

Mechanism of action	Drugs
A. Early event inhibitors	
1. Viral entry inhibitors / fusion inhibitor	• Enfuvirtide
2. Viral uncoating inhibitors	• Amantadine • Rimantadine
B. Viral nucleic acid synthesis inhibitors	
1. Inhibitors of herpes viruses (HSV)	
▪ Nucleoside viral DNA polymerase inhibitors	• Acyclovir • Ganciclovir • Famciclovir • Valacyclovir • Cidofovir • Vidarabine • Iododeoxyuridine • Trifluorothymidine
▪ Non-nucleoside viral DNA polymerase inhibitors	• Foscarnet
2. Inhibitors of retroviruses	
▪ Nucleoside reverse transcriptase inhibitors	• Azidothymidine • Dideoxyinosine • Dideoxycytidine • Lamivudine • Stavudine • Abacavir • Tenofovir
▪ Non-nucleoside reverse transcriptase inhibitors	• Nevirapine • Delavirdine • Efavirenz
3. Inhibitors of other viruses	• Ribavirin • Adefovir
C. Protease inhibitors	• Saquinavir • Nelfinavir • Indinavir • Amprenavir • Ritonavir • Atazanavir
D. Viral protein synthesis inhibitors	• Interferon • Fomivirsen • Methisazone
E. Viral release inhibitors / neuraminidase inhibitor	• Zanamivir • Oseltamivir

(Ref: LANGE Microbiology-12th; Katzung-13th)

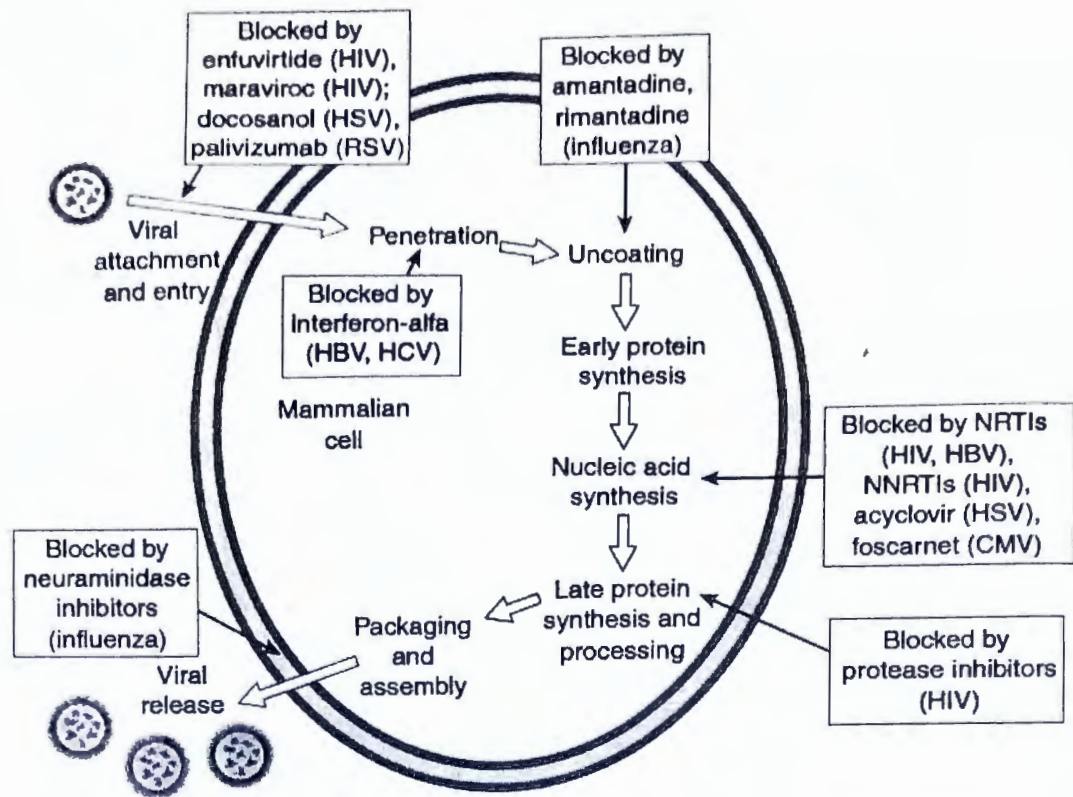


Figure: The major sites of antiviral drug action. (Ref: Katzung-13th edition)

Anti-hepatitis agent

Drugs used to treat chronic hepatitis B:

Drugs	Route
1. Lamivudine	Oral
2. Adefovir	
3. Entecavir	
4. Tenofovir	
5. Telbivudine	
6. Interferon alfa-2b	Subcutaneous or intramuscular
7. Pegylated interferon alfa-2a	Subcutaneous

(Ref: Katzung-13th)

Drugs used to treat hepatitis C virus:

Indication	Drugs	Route
Chronic hepatitis C	Pegylated interferon alfa-2a	Subcutaneous
	Pegylated interferon alfa-2b	Subcutaneous
	Ribavirin	Oral
	Interferon alfa-2a	Subcutaneous or intramuscular
	Interferon alfa-2b	Subcutaneous or intramuscular
	Interferon alfacon-1	Subcutaneous
Acute hepatitis C	Interferon alfa-2b	Subcutaneous or intramuscular

(Ref: Katzung-13th)

Treatment of AIDS / HAART

Replication of virus

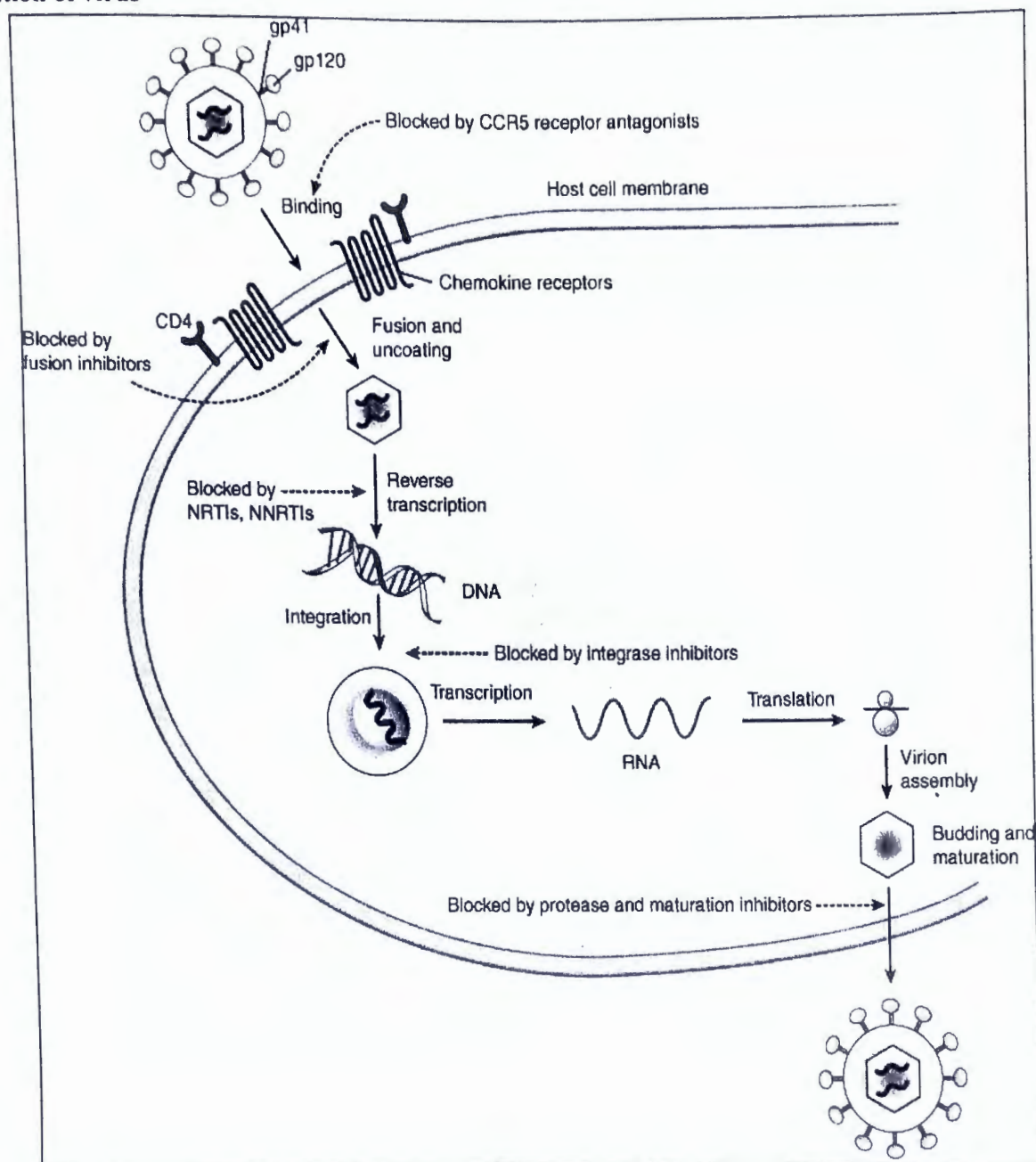


Figure: Life cycle of HIV. Binding of viral glycoproteins to host cell CD4 and chemokine receptors precedes fusion and entry into the cell. After uncoating, reverse transcription copies the single-stranded HIV RNA genome into double-stranded DNA, which is integrated into the host cell genome. Gene transcription by host cell enzymes produces messenger RNA, which is translated into proteins that assemble into immature noninfectious virions that bud from the host cell membrane. Maturation into fully infectious virions is through proteolytic cleavage. NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors.

Antiretroviral agents: Six classes of antiretroviral agents are currently available for use:

1. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
2. Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
3. Protease inhibitors (PIs)
4. Fusion inhibitors
5. CCR5 receptor antagonists, and
6. Integrase inhibitors.

1. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	• Abacavir • Delavirdine • Didanosine (ddI) • Efavirenz • Emtricitabine • Etravirine • Lamivudine • Stavudine • Tenofovir • Zalcitabine • Zidovudine
2. Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	• Etravirine • Nevirapine
3. Protease inhibitors (PIs)	• Atazanavir • Darunavir • Fosamprenavir • Indinavir • Lopinavir/ritonavir • Nelfinavir • Ritonavir • Saquinavir • Tipranavir
4. Fusion inhibitors	• Enfuvirtide
5. CCR5 inhibitor	• Maraviroc
6. Integrase inhibitor	• Raltegravir

(Ref: Katzung-13th)

Q. Short note: HAART.

Ans.

HAART:

Definition: Combination therapy with maximally efficacious and potent antiviral agents reduces viral replication to the lowest possible level, restores the number of CD4+ cells and immunocompetency to the host and decreases the likelihood of emergence of resistance. This multi drug regimen is commonly referred to as highly active antiretroviral therapy, or HAART. HAART typically consists of 3–4 antiretroviral agents and has become the standard of care.

(Ref: Katzung-13th; Lippincott's-6th)

Component drugs of HAART: The current recommendation for primary therapy is-

1. Two NRTIs plus
2. A protease inhibitor or an NNRTI.

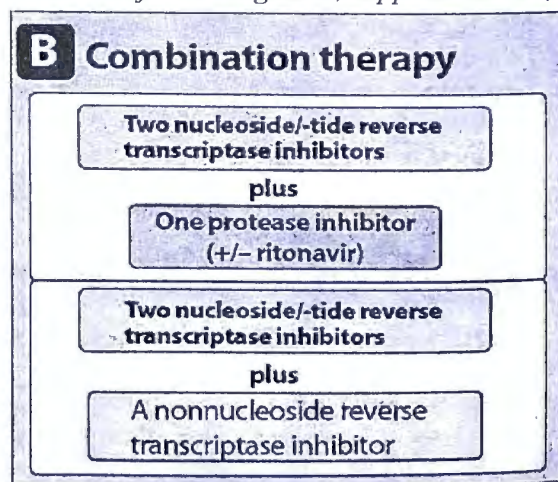
Goals of HAART: The goals of therapy are-

1. To maximally and durably suppress viral load replication.
2. To restore and preserve immunologic function.
3. To reduce HIV-related morbidity and mortality.
4. To improve quality of life.

(Ref: Lippincott's-6th)

Disadvantages of HAART:

1. The regimen is complex, has many unwanted effects.



2. It is difficult to adhere to and may well have to be lifelong because HIV will not have been eradicated.
(Ref: Rang & Dale's-8th)

Anti-influenza agent

Drugs for influenza virus:

1. Oseltamivir
2. Amantadine
3. Rimantadine
4. Zanamivir

Oseltamivir

It is a prodrug (activated by hepatic esterase).

- **Route:** Oral
- **Absorption:** Taking oseltamivir with food does not interfere with absorption and may decrease nausea and vomiting.
- **Dosage:** 75 mg twice daily for treatment and 75 mg once daily for prevention
- **Half life:** 6-10 hours
- **Distribution:** Widely distributed throughout the body
- **Excretion:** Kidney (So dosage must be modified in renal insufficiency)
- **Mechanism of action:** The neuraminidase inhibitors oseltamivir interfere with release of progeny influenza virus from infected to new host cells, thus halting the spread of infection within the respiratory tract. Early administration is crucial because replication of influenza virus peaks at 24–72 hours after the onset of illness.
- **Indication:** Influenza A and influenza B (**Bird flu, Swine flu**).
- **Adverse effects:** Nausea, vomiting, headache, fatigue, diarrhea.
- **Resistance:** In adults, resistance during therapy is rare but may cause fatal disease.

(Ref: Katzung-13th)

MCQ

- Q. Advantage of combination therapy in tuberculosis are to-** (DU-17M)
- avoid drug resistance
 - obtain better therapeutic efficacy
 - reduce the toxicity of drug
 - reduce the spectrum
 - increase duration of action of drug
- a. T, b. T, c. T, d. F, e. F*
- Q. β -lactam antibiotics are-** (DU-17M)
- penicillin
 - cephalosporin
 - vancomycin
 - meropenem
 - cilastatin
- a. T, b. T, c. F, d. T, e. F*
- Q. Nephrotoxic drugs are-** (DU-17M)
- ampicillin
 - azithromycin
 - amphotericin
 - rifampicin
 - tobramycin
- a. F, b. F, c. T, d. F, e. T*
- Q. Chloroquine may cause-** (DU-17M)
- pruritus
 - hypertension
 - impaired hearing
 - peptic ulcer
 - hypotension
- a. T, b. F, c. T, d. F, e. T*
- Q. Drugs safe in children below 05 years old are-** (DU-17M)
- erythromycin
 - cloxacillin
 - ciprofloxacin
 - tetracycline
 - streptomycin
- a. T, b. T, c. F, d. F, e. F*
- Q. Chemoprophylaxis of malaria is done by-** (DU-17M)
- proguanil
 - mefloquine
 - quinine
 - doxycycline
 - chloroquine
- a. T, b. T, c. F, d. T, e. T*
- Q. Bacterial protein synthesis inhibitors are-** (DU-17J)
- azithromycin
 - flucloxacillin
 - tetracycline
 - gentamicin
 - cotrimoxazole
- a. T, b. F, c. T, d. T, e. F*
- Q. The following are anthelmintics-** (DU-16J)
- albendazole
 - metronidazole
 - clotrimazole
 - pyrantal pamoate
 - piperazine
- a. T, b. F, c. F, d. T, e. F*
- Q. Drug induced ototoxicity is produced by-** (DU-15Ju)
- furosemide
 - bromocriptine
 - lithium carbonate
 - streptomycin
 - chloroquine
- a. T, b. F, c. F, d. T, e. T*
- Q. Topical sulphonamides are-** (DU-15Ju)
- sulfisoxazole
 - sodium sulfacetamide
 - mafenide acetate
 - sulfamethoxazole
 - silver sulfadiazine
- a. F, b. T, c. T, d. F, e. F*
- Q. Antibacterial drugs useful against *pseudomonas aeruginosa* are-** (DU-15Ju)
- Carbenicillin
 - cephradine
 - erythromycin
 - gentamycin
 - ciprofloxacin
- a. F, b. F, c. F, d. T, e. T*
- Q. Drugs used for eradication of *Helicobacter pylori* are-** (DU-15Ju)
- clarithromycin
 - tetracycline
 - quinolone
 - antacid

- e. metronidazole
a. T, b. F, c. F, d. F, e. T
- Q. Advantages of combination therapy in TB is to- (DU-15Ju)**
a. avoid drug resistance
b. have better therapeutic efficacy
c. reduce drug toxicity
d. reduce spectrum of activity
e. increase duration of action of drug
a. T, b. T, c. T, d. F, e. F
- Q. Chemoprophylaxis of malaria is done by- (DU-14Ju)**
a. proguanil
b. mefloquine
c. quinine
d. doxycycline
e. chloroquine
a. T, b. T, c. F, d. T, e. T
- Q. Rifampicin- (DU-14Ju)**
a. is a bactericidal drug
b. is a protein synthesis inhibitor
c. inhibits DNA gyrase enzyme
d. can cause hepatitis
e. can cause enzyme induction
a. T, b. T, c. F, d. T, e. T
- Q. Highly active anti retroviral therapy (HAART) includes- (DU-14Ju)**
a. didarosine
b. ganciclovir
c. acyclovir
d. lamivudine
e. ritonavir
a. T, b. F, c. F, d. T, e. T
- Q. The following are systemic anti-fungal drugs- (DU-14Ju)**
a. clotrimazole
b. cotrimoxazole
c. fluconazole
d. miconazole
e. itraconazole
a. F, b. F, c. T, d. F, e. T
- Q. Tinnitus, dizziness, blurred vision and headache are indicative of toxicity of following drugs: (CU-14Ju)**
a) primaquine
- b) Quinine
c) Pyrimethamine
d) Quinidine
e) Sulfadoxine
a. F, b. T, c. F, d. T, e. F
- Q. First generation Cephalosporin ineffective against: (CU-14Ju)**
a) Bacteroids
b) *Neisseria*
c) *Haemophilus*
d) *E. coli*
e) *Klebsiella*
a. F, b. T, c. T, d. F, e. F
- Q. Following statements about Antimicrobial drug therapy are: (CU-14Ju)**
a) Should be based exclusively on in vitro sensitivity tests.
b) Surgical chemoprophylaxis is best done by combination of drugs.
c) In mycobacterial infections combination of drugs is used primarily to increase efficacy.
d) Narrow-spectrum one is preferred in definitive therapy.
e) Pseudomembranous colitis is the common risk with broad-spectrum antibacterial drugs.
a. F, b. F, c. F, d. T, e. T
- Q. β -lactam antibiotics are- (DU-14J)**
a. cephradine
b. erythromycin
c. flucloxacillin
d. amoxicillin
e. streptomycin.
a. T, b. F, c. T, d. T, e. F
- Q. Tetracycline- (DU-14J)**
a. binds to 50s subunit of bacterial ribosome.
b. inhibits nucleic acid synthesis.
c. produces brown discoloration of teeth in children.
d. is a drug of choice in rickettsial infection.
e. chelates divalent cations.
a. F, b. F, c. T, d. T, e. T
- Q. The followings are protein synthesis inhibitors- (DU-14J)**
a. chloramphenicol
b. amoxicillin

- c. tetracycline
- d. levofloxacin
- e. streptomycin
- a. T, b. F, c. T, d. F, e. T*

Q. Gentamicin- (DU-14J)

- a. is effective when used topically
- b. is poorly absorbed from the gut
- c. can easily penetrate into CSF.
- d. Can cause irreversible 8th nerve damage
- e. Acts by inhibiting cell wall synthesis.
- a. T, b. T, c. F, d. T, e. F*

Q. Chloroquine may cause- (DU-14J,13Ju)

- a. Pruritus.
- b. hypotension.
- c. impaired hearing.
- d. peptic ulcer.
- e. hypertension.
- a. T, b. T, c. T, d. F, e. F*

Q. Antibiotics which act against beta-lactamase are- (DU-13Ju)

- a. vancomycin.
- b. penicillin.
- c. cefixime.
- d. flucloxacillin.
- e. sulbactam.
- a. T, b. F, c. T, d. T, e. T*

Q. The following are antifungal drugs- (DU-13J)

- a. fluconazole.
- b. metronidazole.
- c. clotrimazole.
- d. cotrimoxazole.
- e. albendazole.
- a. T, b. F, c. T, d. F, e. F*

Q. Penicillin G- (DU-13J)

- a. is a natural penicillin .
- b. alters cell membrane permeability.
- c. is a penicillinase resistant antibiotic.
- d. is effective in treating gas gangrene.
- e. can cause hypersensitivity.
- a. T, b. F, c. F, d. T, e. T*

Q. The following antibiotic are bacteriostatic- (DU-13J)

- a. isoniazide.
- b. co-trimoxazole.
- c. tetracycline.

- d. sulfonamide.
- e. erythromycin.
- a. F, b. F, c. T, d. T, e. T*

Q. Bacterial 30s ribosomal subunit inhibitors are- (SU-13J)

- a. Amikacin
- b. Streptomycin
- c. Erythromycin
- d. Doxycycline
- e. Chloramphenicol
- a. T, b. T, c. F, d. T, e. F*

Q. Adverse effects of antimicrobials- (SU-13J)

- a. Chloramphenicol causes bone deformity
- b. INH causes neuropathy
- c. Ceftriaxone may cause cross allergic reaction with penicillin
- d. Sulfonamides causes crystaluria
- e. Erythromycin is teratogenic
- a. F, b. T, c. T, d. T, e. T*

Q. Antimicrobial spectrum of gentamicin- (SU-13J)

- a. Effective in pneumococcal infection
- b. Not crosses meningeal membrane
- c. Exert time-dependent killing
- d. Causes vestibular damage
- e. Active against anaerobes
- a. F, b. T, c. T, d. T, e. F*

Q. Systemic antifungal agents include- (DU-12Ju)

- a. Griseofulvin (F)
- b. Nystatin (F)
- c. Amphotericin (T)
- d. Fluconazole (T)
- e. Clotrimazole (F)

Q. Following drugs are protein synthesis inhibitor- (DU-12Ju)

- a. Rifampicin (T)
- b. Ciprofloxacin (F)
- c. Cefuroxime (F)
- d. Erythromycin (T)
- e. Gentamicin (T)

Q. HAART includes- (DU-12Ju)

- a. Zidovudine (T)
- b. Lamivudine (T)
- c. Oseltamivir (F)

- d. Rimantadine (F)
e. Acyclovir (F)
- Q. Drugs not safe in children below 5 years old- (DU-12Ju)**
a. Erythromycin (F)
b. Cloxacillin (F)
c. Ciprofloxacin (T)
d. Tetracycline (T)
e. Streptomycin (T)
- Q. Following drugs are commonly effective in staphylococcal infection- (DU-12J)**
a. Ampicillin (F)
b. Coamoxiclav (T)
c. Ciprofloxacin (F)
d. Flucloxacillin (T)
e. Metronidazole (F)
- Q. Tetracycline- (DU-12J)**
a. Binds to 50S subunit of bacterial ribosome. (F)
b. Inhibits nucleic acid synthesis. (F)
c. Produces brown discoloration of teeth in children. (T)
d. Is a drug of choice in rickettsial infection. (T)
e. Chelates divalent cation. (T)
- Q. Gentamicin- (DU-11Ju)**
a. Is effective in pneumococcal pneumonia (F)
b. Is poorly absorbed from gut (T)
c. Can easily penetrate into CSF (F)
d. Can cause irreversible 8th nerve damage. (T)
e. Acts by inhibiting cell wall synthesis. (F)
- Q. Rifampicin- (DU-11Ju)**
a. Inhibits bacterial DNA gyrase. (F)
b. Is highly protein bound (?)
c. Is excreted mainly through the liver into bile. (T)
d. Inhibits cytochrome P450 enzyme (F)
e. Commonly causes hepatitis and cholestatic jaundice. (T)
- Q. The following drugs are bactericidal- (DU-11J)**
a. Sulfonamides (F)
b. Tetracycline (F)
c. Aminoglycosides (T)
d. Chloramphenicol (F)
e. Rifampicin (T)
- Q. Erythromycin- (DU-11J)**
a. Inhibits cell wall synthesis (F)
b. Is a quinolone preparation (F)
c. Is a broad spectrum antibiotic (F)
d. Can cause enzyme inhibition (T)
e. Is indicated in pertussis (T)
- Q. The following are anti-protozoal drugs- (DU-11J)**
a. Chloroquine (T)
b. Metronidazole (T)
c. Flucloxacillin (F)
d. Ciprofloxacin (F)
e. Azithromycin (F)
- Q. Penicillin G- (DU-10Ju)**
a. is a natural penicillin (T)
b. alters cell membrane permeability (F)
c. is a penicillinase resistant antibiotic (F)
d. is effective in treating gas gangrene (T)
e. can cause hypersensitivity (T)
- Q. The followings are antifungal drugs- (DU-10Ju)**
a. Fluconazole (T)
b. Metronidazole (F)
c. Clotrimazole (T)
d. Cotrimoxazole (F)
e. Albendazole (F)
- Q. Ciprofloxacin- (DU-10J)**
a. is a DNA synthesis inhibitor (T)
b. is widely distributed in body fluids (T)
c. can cause enzyme induction (F)
d. is safe in children (F)
e. can cause convulsion along with aspirin (T)
- Q. The followings are antimalarial drugs- (DU-10J)**
a. chloroquine (T)
b. dapsone (F)
c. sulfadoxine-pyrimethamine combination (T)
d. primaquine (T)
e. metronidazole (F)

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Chapter 8

Autacoids

Q. Define the autacoids. (DU-14J, 12Ju, 11J/Ju, 08J; CU-08J, 06M; RU-09/08Ju; SU-09/07J)

Q. Name the lipid derived autacoids. (RU-13Ju, 08J)

Q. Classify autacoids. (DU-12Ju, RU-09Ju, 08Ju, 06S, SU-13J, 09/08J, 07J)

Q. Name some autacoids. (CU-15J)

Q. What are eicosanoids? (DU-09J)

Ans.

Autacoids: Autacoids means self remedy. Autacoids are biological factors which act like local hormones, have a brief duration, act near the site of synthesis to protect from local injuries and then decay or are destroyed enzymatically and are not blood borne.

Classification of autacoids:

1. Eicosanoids / lipid-derived autacoids	- Prostaglandins (PGs) - Thromboxanes (TXs) - Leukotrienes (LTs)
2. Decarboxylated amino acids (amine)	- Histamine - Serotonin
3. Vasoactive peptides	Vasoconstrictor - Angiotensin - Neuropeptide Y - Endothelin - Eurotensin Vasodilator - Vasoactive Intestinal Peptides (VIP) - Kinins: (Bradykinin & kallidin) - Substance P - Nitric oxide

Histamine

Q. Outline the synthesis, storage & release of histamine. (CU-00M)

Ans.

Synthesis of histamine: Histamine is formed by decarboxylation of the amino acid L-histidine, a reaction catalyzed in mammalian tissues by the enzyme histidine decarboxylase. Once formed, histamine is either stored or rapidly inactivated.



Storage of histamine:

1. Mast cell
2. Basophil
3. Epidermis of skin
4. Cells in the gastric mucosa
5. Neurons in the CNS

Sites of storage of histamine:

A. **Mast cell histamine:** Mast cells are especially rich at sites of potential tissue injury, eg—

1. Nose
2. Mouth
3. Feet
4. Internal body surfaces
5. Blood vessels, particularly at pressure points and bifurcations.

B. **Non-mast cell histamine** is found in several tissues, including-

1. Brain, where it functions as a neurotransmitter. Endogenous neurotransmitter histamine may play a role in many brain functions such as
 - Neuroendocrine control
 - Cardiovascular regulation
 - Thermal and body weight regulation, and
 - Arousal.
2. Enterochromaffin-like (ECL) cells of the stomach. ECL cells release histamine which stimulates parietal cells to secrete HCl.

Release of histamine:

1. **Immunologic release:** IgE mediated histamine release in type I hypersensitivity. This type of release also requires energy and calcium.
2. **Physical factors:** Scratch, burn, soap, exposure to sun, radiation.
3. **Chemical factors:** Dextran, polysaccharide, bile salts, lecithin, radio-contrast media.

4. *Foods like crab, lobsters*

(Ref: Katzung-13th)

Q. Name the histamine releasing drugs/agents. (RU-12Ju,09Ju,07J)

Q. Enumerate the agents that can cause the release of histamine. (RU-17J,15J,11J,10J)

Ans.

Drugs causing histamine release:

1. **Chemotherapeutic agents:** Chlortetracycline, polymyxin B, pentamidine.
2. **Spasmolytic agents:** Atropine.
3. **Vasodilators:** Hydralazine, tolazoline
4. **Centrally acting drugs:** Morphine, pethidine
5. **Sympathomimetic agents:** Amphetamine, Phenylethylamine
6. **Neuro-muscular blocking agents:** D-tubocurarine, Gallamine
7. **Others:**
 - Succinylcholine
 - Codeine
 - Penicillin

Tripathi and 12

(Ref: Katzung-13th & Tripathi-6th/155)

Other substances causing histamine release:

4. **Immunologic release:** IgE mediated histamine release in type I hypersensitivity.
5. **Physical factors:** Scratch, burn, soap, exposure to sun, radiation.
6. **Chemical factors:** Dextran, polysaccharide, bile salts, lecithin, radio-contrast media.
7. **Foods** like crabs, lobster etc.

Q. Name the histamine receptors with their location. (RU-04S)

Ans.

(G-protein coupled receptor)
Histamine receptors with their location:

Receptor subtype	Distribution	Postreceptor mechanism
H ₁	<i>Bronchioles, bladder, GIT</i> Smooth muscle, endothelium, brain (post synaptic)	Gq, ↑IP ₃ , DAG
H ₂	Gastric mucosa, cardiac muscle, mast cells, brain (post synaptic)	Gs, ↑cAMP
H ₃	Presynaptic: brain, myenteric plexus, other neurons	Gi, ↓cAMP
H ₄	Eosinophils, neutrophils, CD4 T cells	Gi, ↓cAMP

(Ref: Katzung-13th)

Q. Enumerate the agonists & antagonists of H₁-receptors. (RU-09J)

Ans.

Agonists & antagonists of histamine receptors:

	Agonists	Antagonists
H ₁ -receptors	2-Methyl histamine 2-Pyridylethyl amine 2-Thiazolylethyl amine	See in the <u>anti-histamine drugs</u> .
H ₂ -receptors	4-methyl histamine - Dimaprit - Impromidine	See drugs for <u>peptic ulcer</u> in the <u>GIT chapter</u> .
H ₃ -receptors	α-Methyl- histamine	

Q. Write down the physiological roles of histamine. (RU-16J, 13J, 08Ju, 07Ju)

Q. What are the pharmacological effects of histamine? (CU-06M; RU-09J, 07J)

Ans.

Pharmacological effects of histamine:

1. Cardiovascular effects of histamine:

- Decrease in systolic and diastolic blood pressure: Caused by the direct vasodilator action of histamine on arterioles and precapillary sphincters.
- Histamine induced edema: Results from the H₁ receptor-mediated increased permeability in the postcapillary vessels.
- Effect of histamine on heart: Direct cardiac effects of histamine via H₂ receptors include both increased force of contraction and increased heart rate.

2. Nervous system effect:

- Histamine stimulates sensory nerve endings via H₁ receptors and produce pain and itching. This effect is an important component of urticaria and reactions to insect and nettle stings.
- H₃ agonists reduce the release of ACh, amine & peptide transmitters in the brain and peripheral nerves.

3. Bronchiolar smooth muscle: Histamine causes bronchoconstriction mediated by H₁ receptors. Patients with asthma are very sensitive to histamine. An allergic reaction is a predisposing factor of acute asthmatic attack.

4. GIT Smooth Muscle: Histamine causes contraction of intestinal smooth muscle (via H₁ receptor contraction), leading to diarrhea.

5. Genitourinary smooth muscle: In pregnant women with anaphylactic shock histamine induced uterine contraction may lead to abortion.

6. Secretory effect: (via H₂-receptor)

- Gastric acid secretion.
- Gastric pepsin and intrinsic factor of castle production to a lesser extent.

7. Triple response: Intradermal injection of histamine causes a characteristic red spot, edema, and flare response.

8. Other effects:

- Local stimulation of peripheral nerve endings (H₃ & H₁ receptor)
- Nociception in the CNS.

(Ref: Katzung-13th)

Q. What is the triple response of histamine? (RU-01J)

Q. Discuss the "triple response of wheal" caused by insect bite and write down the drug management of it. (DU-02J)

Ans.

Triple response of histamine/ triple response of wheal: Intradermal injection of histamine causes a characteristic **red spot, edema, and flare** response that was first described over 60 years ago by Lewis. This phenomenon is called the triple response / triple response of wheal. The effect involves three separate cell types:

1. smooth muscle in the microcirculation
2. capillary or venular endothelium, and
3. sensory nerve endings.

Mechanisms of the 3 responses:

1. **Redness:** At the site of injection, a reddening appears due to direct vasodilation effect of histamine on the small vessels.
2. **Edema:** An edematous wheal at the injection site due to increased capillary permeability.
3. **Flare:** A red irregular flare surrounding the wheal occurs due to histamine induced axon reflex that causes vasodilation indirectly.

A sensation of itching may accompany these effects.

Drug management of the triple response: Antihistamine.

(Ref: Katzung-13th)

Q. What are the manifestations of histamine release? How it can be managed? (CU-06M)

Q. Name possible consequences of histamine release. (RU-10J)

Q. Mention the adverse effects of histamine.

Ans.

Manifestations / consequences / adverse effects of histamine release:

1. Itching
2. Flushing
3. Hypotension
4. Tachycardia
5. Bronchoconstriction (dyspnea)
6. Diarrhea
7. Gastric acid secretion (hyperacidity)
8. Peripheral edema
9. Anaphylactic shock (severe hypotension & bronchoconstriction due to massive histamine release).

Management:

1. Anti-histamines (chlorpheniramine, promethazine etc.)
2. Adrenaline (in anaphylactic shock)
3. Mast cell stabilizer
4. Supportive care: Care of the oral cavity, skin, eye & other orifices.

Q. Mention the clinical uses of histamine.

Ans.

Clinical uses of histamine: In pulmonary function laboratories, histamine aerosol has been used as a provocative test of **bronchial hyper-reactivity**. Histamine has no other current clinical applications.

(Ref: Katzung-13th)

$H_1 = G_q$ (at excitation) $\rightarrow$ Endothelium $\rightarrow$ Vasodilation $\rightarrow$ Vaso-~~ular~~ permeability $\Rightarrow$ $\downarrow$ BP
 $\downarrow$ Smooth muscle $\rightarrow$ Bronchus $\Rightarrow$ Bronchoconstriction
 Receptor $\rightarrow$ GIT $\Rightarrow$ Diarrhea
 Brain $\Rightarrow$ REM sleep $\Rightarrow$ Alertness

$H_2 = G_s \Rightarrow$ Heart $\Rightarrow$ $\uparrow$ HR, $\uparrow$ FOC
 Stomach $\Rightarrow$ $\uparrow$ Gastric acid secret.

$H_3 = G_i \Rightarrow$ Brain $\Rightarrow$ $\downarrow$ Release of neurotransmitters

Anti-histamine

Q. Classify antihistamines. (SU-11J,09Ju,07J)

Q. Write down about histamine antagonist. (CU-06M)

Q. How can you antagonize the effects of histamine? (RU-13J,11J)

Ans.

Anti-histamine / Histamine antagonist:

A. Physiological antagonist	Adrenaline (Adrenaline acts over adrenoceptors which opposes the action of histamine) <i>Histamine: Vasodilatation, bronchospasm.</i> <i>Adrenaline: Vasoconstriction, bronchodilation.</i> <i>Indication of physiologic antagonist: Anaphylactic shock.</i>
B. Histamine release inhibitors	- Cromolyn, Nedocromil-sodium β_2-agonist: Salbutamol, Terbutaline β_2-agonists (salbutamol, terbutalin) $\rightarrow$ Degranulation of mast cell $\rightarrow$ Decrease histamine release.
C. Histamine receptor antagonists	- H₁-receptor antagonists - H₂-receptor antagonists - H₃ & H₄-receptor antagonist

(Ref: Katzung-13th)

Q. Classify H₁ receptor blockers/ antagonists. (RU-12/11J,09J, SU-17J,16Ju/J,09Ju)

Q. Classify H₁ receptor antagonists according to generation. (RU-14J)

Q. Lists clinically useful antihistamines. (CU-12/11J,09/09Ju,04M)

Q. Name the 2nd & 3rd generation antihistamine with indications. (RU-10J)

Q. List the 2nd generation antihistamine with their advantage and use. (RU-17J,15J)

Q. List the 1st & 2nd generation H₁ receptor antagonists. (DU-09/08Ju, SU-12J)

Q. List the 2nd generation H₁ receptor antagonists. (RU-16J)

Q. Enumerate non sedative H₁ receptor antagonists. (CU-05M)

Q. List the non sedative antihistamines (H₁ blockers). (CU-17J)

Q. Enlist the classical antihistamines. (DU-16Ju)

Ans.

Clinical classification of H₁ receptor antagonists:

A. According to their generation:

1. 1 st generation H ₁ -receptor antagonists	Ethanolamines - Carbinoxamine - Dimenhydrinate - Diphenhydramine
	Piperazine derivatives - Hydroxyzine - Cyclizine - Meclizine
	Alkylamines - Brompheniramine - Chlorpheniramine
	Phenothiazine derivative Promethazine
	Miscellaneous Cyproheptadine

2. 2 nd generation H ₁ -receptor antagonists	Piperidine • Fexofenadine
	Miscellaneous • Loratadine • Cetirizine → <i>Allatol</i>

(Ref: Katzung-13th)

B. According to degree of sedative effect:

1. Highly sedative	✓ Diphenhydramine ✓ Dimenhydrinate ▪ Promethazine ▪ Hydroxyzine
2. Moderately sedative	▪ Pheniramine ▪ Cyproheptadine ✓ Meclizine ▪ Buclizine
3. Mildly sedative	▪ Chlorpheniramine ▪ Dexchlorpheniramine ▪ Cyclizine ▪ Dimethindene ▪ Triprolidine
4. Least or non-sedative	▪ Cetirizine ▪ Levocetirizine ✓ Fexofenadine ▪ Loratadine ▪ Desloratadine ▪ Azelastine ▪ Mizolastine ▪ Ebastine ▪ Rupatadine

(Ref: Tripathi-6th/156)

Q. Mention the pharmacological action of clinically useful antihistamines. (CU-12/11J,09/08Ju,SU-09J,RU-08Ju)

Ans.

Pharmacological action of clinically useful antihistamines:

Receptor blockade	Pharmacological action
1. Antihistamine action: By H ₁ -receptor blockade	▪ Decreases allergic inflammation, itching, sneezing & rhinorrhoea. ▪ Increased sedation (<i>A common effect of first-generation H₁ antagonists</i>) ▪ Decreases cognitive & psychomotor performance ▪ Increases appetite ▪ Anti nausea & emesis ▪ Anti-parkinsonian effect
2. Anticholinergic actions (By M ₂ receptor blockade. Many first-generation agents, especially diphenhydramine and promethazine)	▪ Dry mouth & skin ▪ Sinus tachycardia ▪ Urine retention ▪ Constipation ▪ Blurred vision & mydriasis
3. Anti-adrenergic actions: By α-receptor blockade	▪ Postural hypotension ▪ Dizziness ▪ Reflex tachycardia

*H₁, M₂, α , 5HT, Anesthetics
(Not channel)*

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4. Serotonin-blocking action (mainly cyproheptadine)	▪ Increases appetite
5. Local Anesthesia: By Na ⁺ channel blockade.	▪ Several first-generation H ₁ antagonists are potent local anesthetics. Diphenhydramine and promethazine are actually more potent than procaine as local anesthetics.

(Ref: Katzung-13th; Lippincott's-6th)

Nice to know

Antihistamines with actions not caused by histamine receptor blockade

1. Anti-histamines with strong sedative effect: Doxylamine, Hydroxyzine, Promethazine.
2. Anti-histamines with anti-nausea & anti-emetic action: Diphenhydramine, Meclizine, Cyclizine, Promethazine, Doxylamine.
3. Anti-histamines with anti-parkinsonian effect: Promethazine, Diphenhydramine.
4. Anti-histamines with anti-cholinergic effect: Promethazine, Diphenhydramine, Dimenhydrinate
5. Anti-histamines with α -adrenoceptor blocking activity: Promethazine
6. Anti-histamines with additional anti-5HT receptor blocking activity: Cyproheptadine
7. Anti-histamines with local anesthetic activity: Diphenhydramine, Promethazine (They are more potent than procaine & they block Na⁺ channel).
8. Others: Cetirizine is used in allergic rhinitis as it inhibits histamine release from mast cell & inhibits to release inflammatory mediators but this action is not due to H₁-receptor blockade.

(Ref: Katzung-13th)

Q. Mention the indications of H₁-blocker. (DU-09Ju,07Ju; CU-13J,07J, RU-14J,10J,06/05S, SU-17J,11J,09Ju)

Q. Mention the indications of chlorpheniramine. (DU-14Ju)

Q. Mention the indications of promethazine. (RU-12/11J,09Ju)

Q. List the uses of antihistamines. (SU-14J)

Q. Mention the common uses of 2nd generation H₁-receptor blockers. (RU-16J)

Ans.

Indications of H₁-blocker:

Indications/ clinical uses	Drugs
1. <u>Allergic conditions:</u> • Itching. • Urticaria. • Allergic rhinitis • Chronic urticaria • Atopic dermatitis • Seasonal hay fever • Drug hypersensitivity	▪ Cetirizine ▪ Levocetirizine ▪ Fexofenadine ▪ Loratadine ▪ Desloratadine
2. <u>Motion sickness or vestibular disturbances</u>	▪ Diphenhydramine ▪ Promethazine ▪ Dimenhydrinate ▪ Cyclizine ▪ Meclizine
3. <u>Nausea and vomiting in pregnancy (morning sickness)</u>	▪ Cyclizine ▪ Meclizine ▪ Doxylamine
4. <u>For sedation</u>	▪ Promethazine
5. <u>Parkinsonism</u>	
6. <u>Non-allergic rhinorrhoea</u>	
7. <u>Local anesthetic</u>	▪ Diphenhydramine ▪ Promethazine (They are occasionally used to produce local anesthesia in patients allergic to conventional local anesthetic drugs.)

*Common cold
Rhinitis*

8. Pre-anesthetic medication

To prevent histamine release during surgery and subsequent complication

(Ref: Katzung-12th/279,280 + Tripathi-6th/159-161)

Q. Mention the adverse effects of clinically useful antihistamine. (CU-11J,09Ju)

Q. Write down the adverse effects of H₁-receptor antagonists. (SU-16Ju/J,11J, CU-05S ;RU-06S)

Q. List the adverse effects of new generation H₁ receptor antagonists? (RU-05S)

Ans.

Adverse effect of antihistamine / H₁-receptor antagonists:

1. Sedation
2. Dizziness
3. Fatigue
4. Tinnitus
5. Dry mouth & skin
6. Tachycardia
7. Urine retention
8. Constipation
9. Blurred vision
10. Postural hypotension
11. Reflex tachycardia
12. Excitation in children
13. Convulsions (at toxic doses).

(Ref: Katzung-13th; Lippincott's-6th)

Q. Differentiate between 1st & 2nd generation H₁-receptor antagonists. (DU-09/08Ju)

Q. Differentiate between older (classical) & new generation antihistamines. (DU-07Ju; CU-04M)

Q. How does promethazine differ from loratadine? (DU-14J, SU-08Ju)

Q. Compare promethazine and fexofenadine as anti-histamine. (SU-17M)

Ans.

Difference between older & new generation / 1st & 2nd generation antihistamines:

Traits	Older / Classical / 1 st generation antihistamines	New / 2 nd generation antihistamines
1. Lipid solubility	More	Less
2. CNS penetration	Marked	Less or not at all
3. Duration of action	Short (4 - 6 hrs)	Long (12 - 24 hrs)
4. Sedation	Marked	Less or not at all
5. Anti muscarinic effects	Present	Less / No
6. α ₂ -receptor blockade	Present	Less / No
7. 5 HT receptor blockade	Present	Less / No
8. Therapeutic efficacy	More effective	Less effective

(Ref: Katzung-13th & Tripathi-6th/158)

Q. What is the commonest adverse effect of older H₁-receptor antagonists? Name 3 H₁ antagonists which are free from that adverse effect. (CU-07J)

Ans.

Sedation is the commonest adverse effect of older (first generation) H₁-receptor antagonists. Loratadine, cetirizine & fexofenadine are non-sedative.

Q. Mention the expected advantages of 2nd & 3rd generation antihistamines over 1st generation antihistamines? (RU-10J)

Q. What are the advantages of 2nd generation antihistamine over 1st generation? (DU-16Ju, RU-16J, 15J, 09Ju, SU-14Ju, 12J, CU-13J)

Q. What are the advantages of loratadine over promethazine (older)? (DU-11J, SU-09Ju, RU-11J)

Q. Mention few advantages of new generation H-blockers over conventional antihistamines. (DU-07J)

Ans.

Advantages of 2nd generation antihistamines (loratadine) over 1st generation antihistamines (promethazine): 2nd generation antihistamine drugs have-

1. Less / no sedation
2. Less systemic effects, eg, less anti-muscarinic, anti-adrenergic, anti-serotonin effects.
3. Less lipid solubility
4. Less CNS penetration
5. Long duration of action

(Ref: Katzung-13th & Tripathi-6th/158)

Q. Name two most important drugs that can be used for prophylaxis of motion sickness. (DU-07J)

Q. Enlist the anti-emetic drugs used for motion sickness. (DU-15Ju)

Ans. *Write from below*

Motion sickness: It is a condition of sickness of motion characterized by vertigo, nausea, vomiting due to vestibular disturbances. It is due chiefly to **overstimulation of the vestibular apparatus** (and does not occur if the labyrinth is destroyed). Motion sickness is more easily prevented than cured.

Drugs that are used for motion sickness include the **antimuscarinic** agents-

1. Cinnarizine
2. Cyclizine
3. Meclizine
4. Dimenhydrinate
5. Hyoscine
6. Promethazine.

For prophylaxis an antiemetic is best taken 1 h before exposure to the motion. About 70% protection may be expected by the right dose given at the right time. Once motion sickness has started, oral administration of drugs may fail, and the i.m., s.c. or rectal routes are required.

(Ref: Bennett & Brown-11th)

5-HT₂ - vasocon. , ^{↑ blood} _{agg.} bronchoconstrict (smooth muscle contract)

5-HT₃ - Emesis , Bradycardia , ↓BP
(Drift)

5-HT₄ - Prokinetic

↓ ⇒ Depression, ↑ ⇒ BPD

Serotonin / 5-hydroxytryptamine / 5-HT

Synthesis of serotonin / 5-HT:

Tryptophan
↓ Hydroxylase
5-hydroxytryptophan
↓ Decarboxylase
5-hydroxytryptamine (5-HT)

monoamine Derivative
90% in guts, 10% in CNS
(EC₄)

Source: Meat, banana, egg, milk, etc

Hydroxylation by hydroxylase is the rate-limiting step.

(Ref: Katzung-13th)

Serotonin receptors subtypes and their distribution

5-HT ₁	CNS, Enteric nervous system, choroid plexus, adrenergic nerve terminal
5-HT ₂	Platelets, smooth muscle, CNS, stomach fundus, choroid
5-HT ₃	PNS (Sensory and enteric nerves)
5-HT ₄	CNS and myenteric neurons, smooth muscle
5-HT ₅	Brain
5-HT _{6,7}	Brain

(Ref: Katzung-13th)

Pharmacological effects of serotonin:

A. Nervous System

- Vomiting reflex:** 5-HT₃ receptors in the gastrointestinal tract and in the vomiting center of the medulla participate in the vomiting reflex. They are particularly important in vomiting caused by chemical triggers such as cancer chemotherapy drugs.
- Pain and itch:** Like histamine, serotonin is a potent stimulant of pain and itch sensory nerve endings and is responsible for some of the symptoms caused by insect and plant stings.
- Bradycardia & hypotension:** By 5-HT₃ receptor (present on the afferent vagal nerve endings) mediated **chemoreceptor reflex**, serotonin causes marked bradycardia & hypotension.

B. Respiratory System

- Bronchoconstriction
- Hyperventilation as a result of the chemoreceptor reflex or stimulation of bronchial sensory nerve endings.

C. Cardiovascular System

- Vasoconstriction** by 5-HT₂ receptors: In humans, serotonin is a powerful vasoconstrictor except in skeletal muscle and heart, where it dilates blood vessels.
- Platelet aggregation** by 5-HT₂ receptors
- A **triphasic blood pressure response** is often seen following injection of serotonin in experimental animals. Initially, there is a decrease in heart rate, cardiac output, and blood pressure caused by the chemoreceptor response. Following this decrease, blood pressure increases as a result of vasoconstriction. The third phase is again a decrease in blood pressure attributed to vasodilation in vessels supplying skeletal muscle.

D. Gastrointestinal Tract

- Causes contraction of gastrointestinal smooth muscle and increases tone by 5-HT₂ smooth muscle receptors. This facilitates peristalsis.
- Activation of 5-HT₄ receptors in the enteric nervous system causes increased acetylcholine release and thereby mediates a motility-enhancing or "prokinetic" effect of selective serotonin agonists such as cisapride.

- Skeletal Muscle:** 5-HT₂ receptors are present on skeletal muscle membranes, but their physiologic role is not understood.

(Ref: Katzung-13th)

Q. Mention the 3 serotonin receptor agonist with their clinical utility. (DU-12Ju)

Q. Name two serotonin agonists with their clinical indications. (DU-14J, 11Ju)

Ans.

Serotonin agonists: Serotonin has no clinical applications as a drug. However, several receptor subtype-selective agonists have proved to be of value.

Receptor	Agonist	Clinical uses
5-HT _{1A} agonist	<u>Buspirone</u>	Non-benzodiazepine <u>anxiolytic</u>
5-HT _{2C}	<u>Dexfenfluramine</u>	Was widely used as an <u>appetite suppressant</u> but was withdrawn because of toxicity.
5-HT _{1D/1B} agonists	<u>Sumatriptan</u>	Effective in the treatment of <u>acute migraine</u> and cluster headache attacks.
5-HT ₄ agonist	<u>Cisapride</u>	Was used in the treatment of gastroesophageal reflux and motility disorders. <u>1. laxative</u>
Newer 5-HT ₄ partial agonist	<u>Tegaserod</u>	Irritable bowel syndrome with constipation <u>Motility ↑</u>

(Ref: Katzung-13th)

Q. What are the indications of drugs acting on 5-HT receptors? (SU-06S)

Q. Write down the clinical uses of serotonin agonists.

Ans.

Indications of serotonin agonists:

1. As a non-benzodiazepine anxiolytic: Buspirone, Gepirone, Ipsapirone (5-HT_{1A} partial agonist).
2. Anti-depressant: Fluoxetine & other SSRI (selective serotonin reuptake inhibitor).
3. Appetite suppressant: Dexfenfluramine (5-HT_{2C} agonist)
4. Acute migraine: Sumatriptan (5-HT_{1D} agonist) & other 5-HT_{1B/1D} receptor selective agonists constrict cerebral blood vessels & are used in the treatment of acute migraine headache.
5. In irritable bowel syndrome with constipation: Prokinetic drugs.
 - Cisapride (5-HT₄ agonist)
 - Tegaserod (5-HT₄ partial agonist)
 - Metoclopramide (5-HT₄ agonist).

(Ref: Katzung-13th; Tripathi-6th/166)

Q. Write down the adverse effects of serotonin agonists.

Ans.

Adverse effects of serotonin agonists:

1. Flushing
2. Tingling
3. Dizziness
4. Chest discomfort
5. Muscle weakness
6. Neck pain
7. Vomiting
8. Bradycardia
9. Hypotension
10. Bronchoconstriction
11. Diarrhea
12. Malignant hyperthermia

(Ref: Katzung-13th)

Q. What are indications of serotonin antagonists?

Q. Mention the 3 serotonin receptor antagonist with their clinical utility. (DU-12Ju)

Q. Name two serotonin antagonists with their clinical indications. (DU-14J, 11Ju)

Ans.

Indications of serotonin antagonists:

1. **Carcinoid tumors:** The carcinoid tumors produce massive amount of 5-HT. Cyproheptadine, ketanserin & methysergide are the 5-HT₂ receptor blockers & used for relaxation of smooth muscle in carcinoid tumor.
2. **Cold-induced urticaria** (Cyproheptadine)
3. **Asthma:** Ketotifen is a 5-HT₂ receptor blocker & used in the prophylaxis of bronchial asthma.
4. **Anti-emetic** (Ondansetron, granisetron & tropisetron are the 5-HT₃ antagonists & used as anti-emetic in cancer chemotherapy).
5. **Post-gastrectomy dumping syndrome** (Cyproheptadine)
6. **Antiplatelet drug (ketanserin)** for the treatment of hypertension and vasospastic conditions.

(Ref: Rang & Dale's-8th & Katzung-13th)

Q. What are the triptans? Mention their uses.

Ans.

Triptans: Triptans are the selective 5-HT_{1D/1B} agonists. They are —

1. Sumatriptan
2. Rizatriptan
3. Zolmitriptan
4. Almotriptan
5. Eletriptan
6. Frovatriptan
7. Naratriptan

Indications of triptans: Triptans are exclusively used in the treatment of **acute migraine headache**. Sumatriptan and its congeners are currently **first-line therapy** for acute severe migraine attacks in most patients.

Mechanism of action in migraine: The mechanisms of action of drugs used in migraine are poorly understood. Two primary hypotheses have been proposed to explain the actions of these drugs.

- First, the triptans activate 5-HT_{1D/1B} receptors on presynaptic trigeminal nerve endings to inhibit the release of vasodilating peptides.
- Second, the vasoconstrictor actions of the triptans may prevent vasodilation and stretching of the pain endings.

It is possible that both mechanisms contribute in the case of some drugs.

Adverse effects: Most adverse effects are mild and include-

1. Altered sensations (tingling, warmth, etc)
2. Dizziness
3. Muscle weakness
4. Neck pain
5. Injection site reactions (for parenteral sumatriptan)
6. Chest discomfort
7. Rare but serious cardiac events: Coronary artery vasospasm, transient myocardial ischemia, atrial and ventricular arrhythmias, and myocardial infarction, predominantly in patients with risk factors for coronary artery disease.

(Ref: Katzung-13th)

Contraindication:

1. Coronary artery disease, eg, angina.
2. Cerebrovascular disease, eg, stroke.
3. Peripheral vascular disease.
4. Uncontrolled hypertension
5. Naratriptan is contraindicated in patients with severe renal or hepatic impairment.

(Ref: Goodman & Gilman-12th edition)

Eicosanoids

The eicosanoids, so called because of their derivation from a 20-carbon unsaturated fatty acid, arachidonic acid, are obtained from membrane phospholipids and synthesized de novo at the time of cellular stimulation.

(Ref: Modern pharmacology with clinical application-6th/425)

Q. What are eicosanoids? (DU-09J)

Ans.

Eicosanoids / lipid-derived autacoids:

- Prostaglandins (PGs)
- Thromboxanes (TXs)
- Leukotrienes (LTs)

Q. What are the prostanoids?

Ans.

Prostanoids:

1. Prostaglandins
2. Prostacyclin
3. Thromboxane

Principal Inflammatory Actions of Arachidonic Acid Metabolites (Eicosanoids)

Action	Eicosanoid
Vasodilation	PGI ₂ (prostacyclin), PGE ₁ , PGE ₂ , PGD ₂
Vasoconstriction	Thromboxane A ₂ , leukotrienes C ₄ , D ₄ , E ₄
Increased vascular permeability	Leukotrienes C ₄ , D ₄ , E ₄
Chemotaxis, leukocyte adhesion	Leukotriene B ₄ , HETE

(Ref: Robbins & Cotran-9th edition)

Q. What are the drugs which inhibit PG synthesis with their mechanism of action? (DU-13J, 10J, RU-13Ju; SU-09J/Ju)

Ans.

Drugs that inhibit prostaglandin synthesis:

1. Corticosteroids.
2. Non-steroidal anti inflammatory drugs (NSAIDs).

Nice to know

Prostanoid membrane receptors:

Endogenous agonist	Receptor type
PGD ₂	DP
PGE ₂	EP1, EP2, EP3, EP4
PGI ₂	IP
PGE ₂ α	FP
TXA ₂	TP

(Ref: Katzung-13th)

Q. Outline the biosynthesis of eicosanoids with drugs on different steps inhibiting synthesis. (RU-14Ju)

Q. Describe the cyclooxygenase pathway of arachidonic acid metabolism. (CU-04M)

Q. Enumerate the steps of synthesis of prostaglandins. (RU-10J, 05M; SU-06M)

Q. Draw a diagram showing the site of action of NSAIDs in the pathway of prostaglandin synthesis. (CU-07J)

Q. Outline the synthesis of leukotrienes. (SU-07J)

Ans.

Steps of synthesis of eicosanoids / prostaglandins:

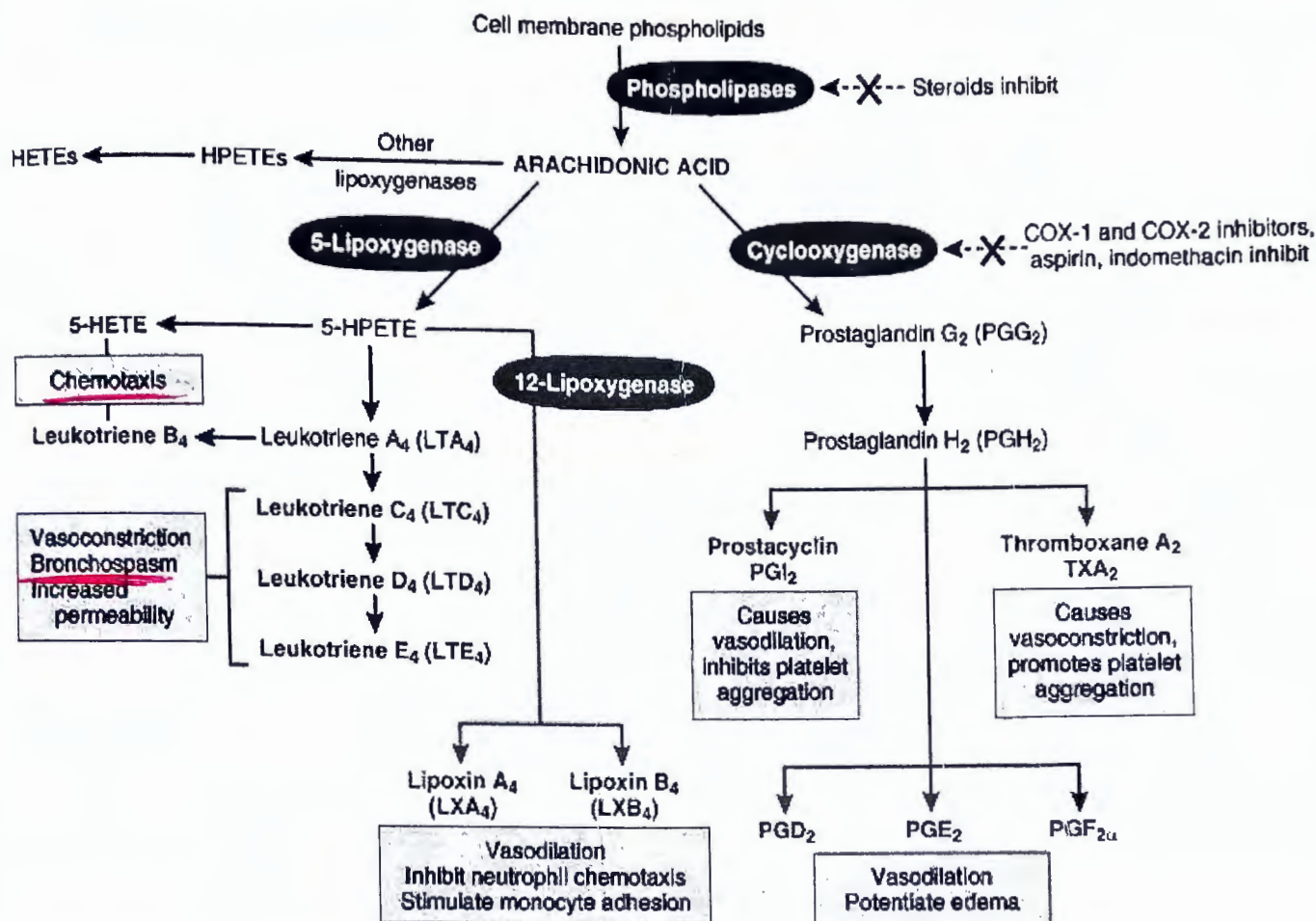


Fig. Eicosanoid synthesis pathway. COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid.

(Ref: Robbins & Cotran-9th edition)

Q. What is the physiological role of prostaglandin in our body? (DU-09/08J, CU-08J; RU-15Ju,08J,06J,05M)

Q. Mention the pharmacological effects of eicosanoids.

Q. Mention the pharmacological effects of Prostaglandins. (CU-17J)

Ans.

Physiological role of prostaglandin / Pharmacological effects of prostaglandins / eicosanoids:

A. Smooth muscle:

1. Vascular:

- Vasodilatation : PGE_2 , & PGI_2
- Vasoconstriction : $PGF_{2\alpha}$, TXA_2 , LTs
- Platelet aggregation : TXA_2

2. Airway:

- Bronchodilatation : PGE_2 , PGI_2
- Bronchoconstriction : $PGF_{2\alpha}$, PGD_2 , TXA_2 , LTs

3. Gastrointestinal tract:

- Contraction
- Cytoprotection:
 - ➔ Increased HCl secretion $\leftarrow PGI_2$
 - ➔ Decreased HCO_3^- secretion $\rightarrow PGE_1, PGE_2$
 - ➔ Increased mucous secretion
 - ➔ Increased water and electrolyte in large gut

$PGI_2, PGE_2 \rightarrow$ dilation
 $PGF_2, TXA_2 \rightarrow$ constriction

B. Reproductive organs:1. **Female reproductive organs:**

- a) Contraction of uterine smooth muscles: TXA_2 , $\text{PGF}_{2\alpha}$, PGE_2 (low conc.)
- b) Relaxation of uterine smooth muscle: PGI_2 , PGE_2 (high conc.)

2. **Male reproductive organs:**

- ✓ Penile erection: PGE_1
- Fertile men contain PGE & PGF in their semen.

C. Kidney:

- Increased GFR
- Increased sodium & H_2O excretion | PGE_2 , PGI_2 (By vasodilation)
- Increased renin release
- Increased intra-renal vasoconstriction → Hypertension (TXA_2)

D. Central and peripheral nervous system:

- Fever : PGE_2 , PGI_2 , $\text{PGF}_{2\alpha}$
- Sleep : PGD_2
- Decrease release of NE from postganglionic sympathetic nerve endings: PGE

E. Eye: Increased outflow of aqueous humor → Decreased IOP (PGE & PGF derivatives)**F. Inflammation & immunity:**

- Increased vascular permeability & leukocyte infiltration : PGE_2 , PGI_2
- Chemo-attraction, lymphocyte migration : PGD_2

G. Neuro-endocrine:

- Release of GH, Prolactin, TSH, ACTH, FSH & LH: PGE
- LHRH, LH : LTC_4 , LTD_4

H. Bone metabolism: Stimulation of bone resorption & formation: PGE_2

(Ref: Katzung-13th)

Q. What do you mean by "house-keeping" action of prostaglandin? (RU-09J)

Ans.

Housekeeping action of prostaglandin: COX-1 is responsible for the production of prostaglandins that are involved in both inflammation and homeostatic functions (e.g., fluid and electrolyte balance in the kidneys, cytoprotection in the gastrointestinal tract). These homeostatic functions of prostaglandins are called "house-keeping" effect of prostaglandin.

Nice to know**Physiological role of prostaglandins in our body:**

- 1. ✓ Cytoprotection of GIT
- 2. Parturition
- 3. Patency of neonate's ductus arteriosus during surgery.
- 4. ✓ Renal perfusion
- 5. **Mediators of inflammatory reactions:** Vasodilatation, pain, pyrexia, platelet infiltration, chemotaxis.

o male fertility

Q. Discuss the clinically used prostaglandin analogues with their indication. (DU-16J, 14Ju, 13J, 12J, 10/08J, SU-17M, 16Ju, 15J, 13Ju/J, 12J, 11Ju, 09/06J, CU-13J, 09Ju, RU-16Ju, 15Ju, 12Ju, 10Ju)**Q. Write down about clinical pharmacology / therapeutics of prostaglandins. (DU-07J)****Q. What are the therapeutic approach/uses of prostaglandin in gynecology? (RU-14Ju, 08/06J)****Q. Briefly outline the role of different prostaglandins in pharmacotherapy. (DU-09Ju; CU-04M; SU-09Ju, 06M)****Q. State the therapeutic uses of synthetic prostaglandins in eye and gynecology? (RU-13Ju, 11Ju)**

Q. Discuss the prostaglandins used clinically. (SU-16J)

Ans.

Indications of prostaglandins and prostaglandin analogues:

1. **Induction of abortion:** Dinoprostone (PGE₂), Mifepristone + Misoprostol (PGE₁) & Carboprost tromethamine (These drugs can terminate pregnancy at any stage by promoting uterine contractions. The drugs are used for first- and second-trimester abortion and for priming or ripening the cervix before abortion.)
2. **Induction of labour:** Dinoprostone (PGE₂) & PGF₂α (Initiate & stimulate labour)
3. **Cytoprotection of GIT:** Misoprostol (PGE₁)
4. **Erectile dysfunction:** Alprostadil (PGE₁)
5. **Maintenance of patency of the neonate's ductus arteriosus during surgery:** Alprostadil (PGE₁)
6. **Pulmonary hypertension:** Epoprostenol (PGI₂), Iloprost & Treprostinil.
7. **Thromboembolic disorder:** Epoprostenol (PGI₂)
8. **Glaucoma:** Latanoprost (PGF₂α), Bimatoprost, Travoprost, Unoprostone.

(Ref: Katzung-13th)

Q. Write down the adverse effects of prostaglandins / prostaglandin analogues. (DU-16J)

Ans.

Adverse effects of prostaglandins and prostaglandin analogues:

A. When used in abortion & labour:

1. Prolonged vaginal bleeding
2. Severe menstrual cramp
3. Cardiovascular: Hypotension &/or hypertension, syncope.
4. GIT upsets: Diarrhea, Vomiting
5. Fever
6. Bronchospasm
7. Hypersensitivity reaction
8. Dizziness
9. Flushing

PGE₂
Dinoprostone - Abortion, Labour

PGE₁
Misoprostol - Cytoprotection
Alprostadil - Erectile dysfunction, Patency of PDA

PGF₂α
Latanoprost - Glaucoma

B. In erectile dysfunction: Penile pain, priapism (painful persistent erection of penis).

C. GIT: Abdominal discomfort, diarrhea.

D. Cardiac: Bradycardia, hypotension, hyperpyrexia, apnea.

E. Others:

1. Bone Pain
2. Hyperostosis
3. Kidney stones

Q. What are the contraindications of prostaglandins?

Ans.

Contraindications of prostaglandins

1. Active cardiac / renal / hepatic / pulmonary diseases
2. Active pelvic inflammatory diseases
3. Hypertension (PGF₂α increases BP)
4. Hypotension (PGE₂ decreases BP)
5. Asthma
6. Epilepsy

Q. Short note: Misoprostol. (DU-15J)

Ans. Write indication, adverse effects, contraindication from above.

Ergot alkaloids

Ergot alkaloids are produced by *Claviceps purpurea*, a fungus that infects grain—especially rye—under damp growing or storage conditions. This fungus synthesizes histamine, acetylcholine, tyramine, and other biologically active products in addition to a score or more of unique ergot alkaloids. These alkaloids affect α -adrenoceptors, dopamine receptors, 5-HT receptors.

(Ref: Katzung-13th)

Q. Classify ergot alkaloids?

Ans.

Classification of ergot alkaloids:

A. Natural ergot alkaloids:

1. *Amine alkaloids*: Ergometrine (ergonovine) which is oxytocic.
2. *Amino acid alkaloids*: They are vasoconstrictor & α -adrenoceptor blockers.
 - Ergotamine
 - Ergotamine (mixture of ergocristine, ergocornine & ergocryptine).

B. Semi-synthetic ergot alkaloids:

1. *Anti-adrenergic, cerebro-protective*: Dihydroergotamine (DHE). Dihydroergotoxine.
2. *Dopaminergic agonist*: Bromocriptine
3. *Anti-serotonergic*: Methysergide

C. Synthetic non-lysergic acid derivative: They pharmacologically resemble ergot alkaloids.

1. Pergolide.
2. Lergotril
3. Metergoline
4. Lisuride

(Ref: Tripathi-6th/167)

Nice to know

Mechanism of action of ergot alkaloids: The ergot alkaloids act on several types of receptors. Their effects include agonist, partial agonist, and antagonist actions at α -adrenoceptors and serotonin receptors (especially 5-HT_{1A} and 5-HT_{1D}; less for 5-HT₂ and 5-HT₃); and agonist or partial agonist actions at CNS dopamine receptors. There is a powerful stimulant effect on the uterus that seems to be most closely associated with agonist or partial agonist effects at 5-HT₂ receptors.

(Ref: Katzung-13th)

Q. Write down the pharmacological effects of ergot derivatives.

Q. Explain uterine action of ergometrine. (SU-06M)

Q. Explain the role of ergometrine on uterine dysfunction. (SU-12Ju)

Ans.

Pharmacological effects of ergot derivatives:

A. Central nervous system: D₂-receptor mediated (e.g. Bromocriptine, pergolide, cabergoline)-

- Hallucination
- Bromocriptine plays important roles in **extrapyramidal motor control** by acting on Dopamine receptors in the CNS.
- Bromocriptine, cabergoline, and pergolide directly suppress prolactin secretion from pituitary cells by activating regulatory dopamine receptors.

B. Vascular smooth muscle: Vasoconstriction → Sustained rise in BP (due to partial agonistic effects mainly over α -adrenoceptor & partly over 5-HT receptors).

C. Uterine smooth muscle: Ergot alkaloids cause contraction of the uterus by acting on α -adrenoceptor, serotonin and other receptors. The sensitivity of the uterus to the stimulant effects of ergot increases

dramatically during pregnancy, perhaps because of increasing dominance of α_1 receptors as pregnancy progresses. As a result, ***the uterus at term is more sensitive to ergot than earlier in pregnancy and far more sensitive than the nonpregnant organ.***

- In very small doses of ergot: Rhythmic contraction and relaxation of the uterus.
- At higher doses of ergot: Powerful and prolonged contracture.

Ergonovine is more selective than other ergot alkaloids in affecting the uterus and is the agent of choice in obstetric applications of these drugs.

- D. **GIT:** Ergots cause contraction of intestinal smooth muscle via serotonin receptors → Nausea, vomiting & diarrhea.

(Ref: Katzung-13th)

Q. Briefly mention the clinical uses of ergometrine with reasoning. (DU-09Ju)

Ans.

Clinical uses of ergometrine:

1. **Migraine:**
 - a. **Ergotamine** can be effective during the prodrome of an attack.
 - b. **IV Dihydroergotamine** → For intractable migraine.
 - c. **Intranasal dihydroergotamine** may also be effective.
2. **Hyperprolactinemia:** Bromocriptine, cabergoline.
3. **Parkinsonism:** Bromocriptine
4. **In postpartum hemorrhage (PPH):** Ergonovine maleate (*It is given at the time of delivery of the placenta or immediately afterward if bleeding is significant.*)
5. **Diagnosis of Variant Angina:** IV Ergonovine.
6. **Senile Cerebral Insufficiency:** Dihydroergotoxine is used for senility and Alzheimer's dementia.
7. **Carcinoid syndrome:** Methysergide.

In spite of their significant toxicities, ergot alkaloids are still widely used in patients with migraine headache or pituitary dysfunction, and occasionally in the postpartum patient.

(Ref: Katzung-13th)

Q. Mention the adverse effects of ergometrine.

Ans.

Adverse effects of ergometrine:

1. **GIT:** Diarrhea, nausea, vomiting (most common) & bowel infarction rarely.
2. **CNS:** Drowsiness
3. **CVS:** Ischemic chest pain, arrhythmias.
4. Vascular ischemia (due to prolong vasospasm) & gangrene.
5. **Chronic use of methysergide:** Connective tissue proliferation in the retroperitoneal space, pleural cavity & endocardial tissue & hallucination.
6. Hydronephrosis.

(Ref: Katzung-13th)

Q. What are the contraindications of ergot alkaloids?

Ans.

Contraindications of ergot alkaloids:

1. Obstructive vascular diseases / peripheral vascular diseases.
2. Collagen diseases.
3. Ischemic heart diseases.
4. Hypertension.
5. Pregnancy.
6. Renal & hepatic failure.

(Ref: Katzung-13th; Tripathi-6th/168)

Drugs causing uterine contraction

Q. Name three important receptors present in uterus. (CU-15Ju)

Q. Name the receptors present in the uterus and drugs acting on these receptors. (CU-17J, 15J)

Ans.

Receptors present in uterus

1. **β_2 adrenoceptors**: adrenaline, acting on β_2 adrenoceptors, inhibits uterine contraction,
2. **α -adrenoceptors**: noradrenaline, acting on α -adrenoceptors, stimulates contraction.
3. **Serotonin receptors** (5-hydroxytryptamine receptors)

Q. What are ecbolics? (CU-02M)

Q. What are the oxytocics? (DU-09J/Ju; RU-13J, 10J, SU-16Ju)

Q. Name the drugs affecting motility of uterus. (RU-09J)

Q. Name the drugs causing contraction of the uterus. (RU-11Ju)

Q. Name 3 drugs that act on pregnant uterus. (CU-14J)

Q. Name drugs that act on pregnant uterus. (SU-17J)

Ans.

Ecbolics or oxytocics: The agents that cause the contraction of the gravid uterus and help the expulsion of its contents are called oxytocics or ecbolics.

Oxytocic / ecbolics in obstetrics:

1. Oxytocin
2. Ergot derivatives
3. Prostaglandins (E & F)

Q. List the tocolytics. (DU-09Ju, SU-16Ju)

Q. Name the tocolytics with their indications in different purposes. (RU-13J)

Ans.

Tocolytics: The agents that inhibit uterine contraction are called tocolytics.

(Ref: Dutta Obstetrics-6th/498)

Tocolytic agents

- **β_2 agonist**: Terbutaline, Ritodrine, Fenoterol, Salbutamol
- **Calcium-channel blocker**: Nifedipine. It is one of the most commonly used tocolytic agent.
- **Oxytocin antagonist**: Atosiban.
- **NSAIDs**: Indomethacin, Sulindac.
- **Magnesium sulphate**
- **Nitric oxide (NO) donors**: Glyceryl trinitrate (GTN)

(Ref: Dutta Obstetrics-6th/508)

Indication: Tocolytics are used to suppress preterm labor and delivery in order to improve the perinatal outcome. The therapy also buys time for the administration of betamethasone, a glucocorticoid drug which greatly accelerates fetal lung maturity, but takes one to two days to work.

(Ref: Dutta Obstetrics-6th/507)

Q. Compare & contrast oxytocic drugs. (SU-16Ju)

Q. Compare & contrast oxytocin, ergometrine & prostaglandins with respect to their effects on uterus and clinical uses. (RU-15Ju)

Q. Compare & contrast oxytocin, ergometrine & prostaglandins as uterine stimulant / ecbolics. (DU-10Ju, 09J; RU-10J, 09J, CU-16J, 09J, 06M/S)

Q. Compare & contrast oxytocin & ergometrine. (CU-17J, RU-16Ju)

Q. Compare & contrast oxytocin & ergometrine as ecbolics. (CU-15J, 12Ju, 09Ju, RU-11Ju, 09Ju; SU-16J, 08J)

Q. Compare the M/A & effects of ergometrine & oxytocin on uterine contractility. (SU-07J)

- Q. Enlist the clinically used uterotonic & compare their actions with each other. (SU-06J,05S)
 Q. Name the indications of oxytocics in different purposes. (RU-13J)
 Q. Discuss the role of oxytocin on uterus. (CU-14J)
 Q. Short note: Oxytocin & ergometrine. (DU-13J)

Ans.

Comparison among oxytocin, ergometrine & prostaglandins

Traits	Oxytocin	Ergometrine	Prostaglandin
1. Source	Animal- Para-ventricular nucleus of hypothalamus	Plant- Alkaloid of rye	Arachidonic acid metabolism.
2. Nature	Peptide hormone.	Amine.	Eicosanoid
3. Route of administration	IV, IM	Oral, IV, IM, Aerosol	Vaginal, Oral, IV.
4. Effect on non-pregnant uterus	Immature uterus- <u>No action</u> Mature uterus- <u>Slight contraction</u>	<u>Contraction</u>	<u>Contraction</u>
5. Effect on gravid uterus	<u>Small doses</u> : Intermittent, rhythmic & forceful uterine contraction. <u>High doses</u> : Produces <u>Sustained uterine contraction</u> .	<u>Very small doses</u> : <u>Rhythmic contraction & relaxation</u> of the uterus. <u>High doses</u> : <u>Sustained uterine contraction</u>	<u>Strong uterine contraction</u> .
6. Indications / clinical uses	- Active management of 3rd stage of labor - Induction of labor. - Augmentation of labor - Management of postpartum hemorrhage (PPH) - Inevitable abortion - Incomplete abortion.	- Management of PPH. - After evacuation of product of conception. - After evacuation of molar tissue.	- Induction of labor at or near term. - Induction of abortion.
7. Side effects	- Fetal distress. - Placental abruption. - Uterine rupture. - Hypotension. - Excessive fluid retention or water intoxication leading to hyponatremia, heart failure, convulsion & death.	- Nausea. - Vomiting. - Sudden rise of BP.	- GIT symptoms (with oral route). - Fever. - Uterine hyper-stimulation.
8. Contraindication	- Grand multiparity - Contracted pelvis / CPD. - Malpresentation. - Having scarred uterus, - Cardiac disease. - Obstructed labor. - Uncoordinated uterine action.	- Cardiac disease. - Hypertension. - Rh negative women having Rh positive husband. - After delivery of 1st twin. - Migraine	- Hypersensitivities - Glaucoma. - Bronchial asthma (relative contraindication). - Patients in whom oxytocin is contraindicated. - Malpresentation.
9. Milk ejection	Ejects <u>milk</u>	Not so.	Not so.

Q. Name the drugs used for induction of labour. (CU-07J)

Q. Name the drugs used in the management of labour. (CU-12Ju)

Ans.

Induction of labour: Induction of labor means the initiation of uterine contractions (after the period of viability) by any method (medical, surgical or combined) for the purpose of vaginal delivery.

Drugs used for medical induction:**1. Prostaglandins:**

- Dinoprostone (PGE₂): Intra-cervical application of dinoprostone (PGE₂) gel is the gold standard for cervical ripening.
- Misoprostol (PGE₁)
- Dinoprost (PGF_{2α}).

2. Oxytocin**3. Steroid receptor antagonist:**

- Mifepristone
- Onapristone

4. Relaxin

(Ref: Dutta Obstetrics-6th/520,521)

Q. Name the effective drugs used to prevent post partum hemorrhage. (CU-06M)

Ans.

Post-partum hemorrhage (PPH): Any amount of bleeding from or into the genital tract following birth of the baby upto the end of puerperium which adversely affects the general condition of the patient evidenced by rise in pulse rate and falling blood pressure is called post-partum hemorrhage (PPH).

(Ref: Dutta Obstetrics-6th/411)

Effective drugs in post-partum hemorrhage (PPH):

1. Ergometrine.
2. Oxytocin.

Q. Compare & contrast oxytocin, ergometrine & prostaglandins as oxytocic agents. Briefly mention their clinical use with reasoning. (DU-09Ju)

Q. What is the role of ergometrine in labour/uterine dysfunction? (RU-12Ju/J)

Ans.

Oxytocin:

- **For induction of labour & abortion:** Oxytocin produces, almost immediately, rhythmic contractions with relaxation between, i.e. it mimics normal uterine activity. So, oxytocin is used IV in the induction of labour & abortion.
- **For postpartum hemorrhage (PPH):** Oxytocin is used to control PPH after vaginal or cesarean delivery.

Ergometrine:

- **For postpartum hemorrhage (PPH):** The uterus at term is extremely sensitive to the stimulant action of ergometrine, and even moderate doses produce a prolonged and powerful spasm of the muscle quite unlike natural labor. Therefore, ergot derivatives **should be used only for control of postpartum hemorrhage (PPH) and should never be given before delivery.**

(Ref: Katzung-13th)

Prostaglandins:

- **For induction of labour & abortion:** Prostaglandin effectively initiates and stimulates labor. So it is used in the **induction of labor**. Prostaglandin can terminate pregnancy at any stage by promoting uterine contractions. So it is used to **terminate pregnancy**, including missed or partial abortion. The drugs are used for first- and second-trimester abortion and for **priming or ripening the cervix** before abortion.

(Ref: Katzung + Bennett & Brown)

Drugs for Migraine

Migraine is a triad of paroxysmal headache, nausea and/or vomiting, and an 'aura' of focal neurological events (usually visual). Patients with all three of these features are said to have migraine with aura ('**classical**' migraine). Those with paroxysmal headache (with or without vomiting) but no 'aura' are said to have migraine without aura ('**common**' migraine). Typically, a classical migraine attack starts with a non-specific prodrome of malaise and irritability followed by the 'aura' of a focal neurological event, and then a **severe, throbbing, hemicranial headache** with **photophobia** and **vomiting**. During the headache phase, patients prefer to be in a quiet, darkened room and to sleep. The headache may persist for several days.

(Ref: Davidson's medicine, -22nd)

Patho-physiology of migraine: The acute migraine attack appears to begin in **serotonergic (5-HT)** and **noradrenergic neurons** in the brain. These monoamines affect the cerebral and extracerebral vasculature and also cause release of further vasoactive substances such as histamine, prostaglandins and neuropeptides involved in pain, i.e. there is neurogenic inflammation that can be inhibited by specific antimigraine drugs.

The throbbing headache is due to **dilatation of pain-sensitive arteries** outside the brain, including scalp arteries.

Precipitating factors:

1. Stress (exertion, excitement, anxiety, fatigue, anger)
2. Food containing vasoactive amines (chocolate, cheese)
3. Food allergy
4. Bright lights and loud noise
5. Hormonal changes (menstruation and oral contraceptives)
6. Hypoglycemia.

These precipitants may initiate release of vasoactive substances stored in nerve endings and blood platelets. Many attacks, however, have no obvious trigger.

Q. Mention the drugs used in migraine? (DU-16Ju)

Q. Mention the drugs used in acute attack and prophylaxis of migraine headache? (DU-14Ju)

Q. Enlist four drugs used in migraine. (DU-15Ju)

Ans.

Drugs used in the treatment of migraine:

A. Drugs for acute migraine headache:

1. **5-HT₁ agonists:** Triptans (Sumatriptan, rizatriptan, zolmitriptan, almotriptan, frovatriptan).
2. **NSAIDs:** Paracetamol, Aspirin, Diclofenac, Ibuprofen, Naproxen.
3. **Anti-emetic:** Domperidone, Metoclopramide.
4. **Ergot alkaloid :** Ergotamine (uncommonly used now)

B. Drugs for prophylaxis of migraine:

1. **Anti-histamine & serotonin (5-HT) antagonist :** Pizotifen
2. **β-blocker :** Propranolol
3. **Tricyclic anti-depressant:** Amitriptyline.
4. **Both Ca²⁺ & Na⁺-channel blocker:** Flunarizine.
5. **Other drugs:** Less commonly used.
 - Selective serotonin reuptake inhibitors (SSRIs).
 - Ca²⁺-channel blockers: Verapamil, Nifedipine.
 - Valproic acid.
 - Methysergide.
 - Gabapentin.

(Ref: Tripathi-6th/169-170; Kumar & Clark-6th/1248)

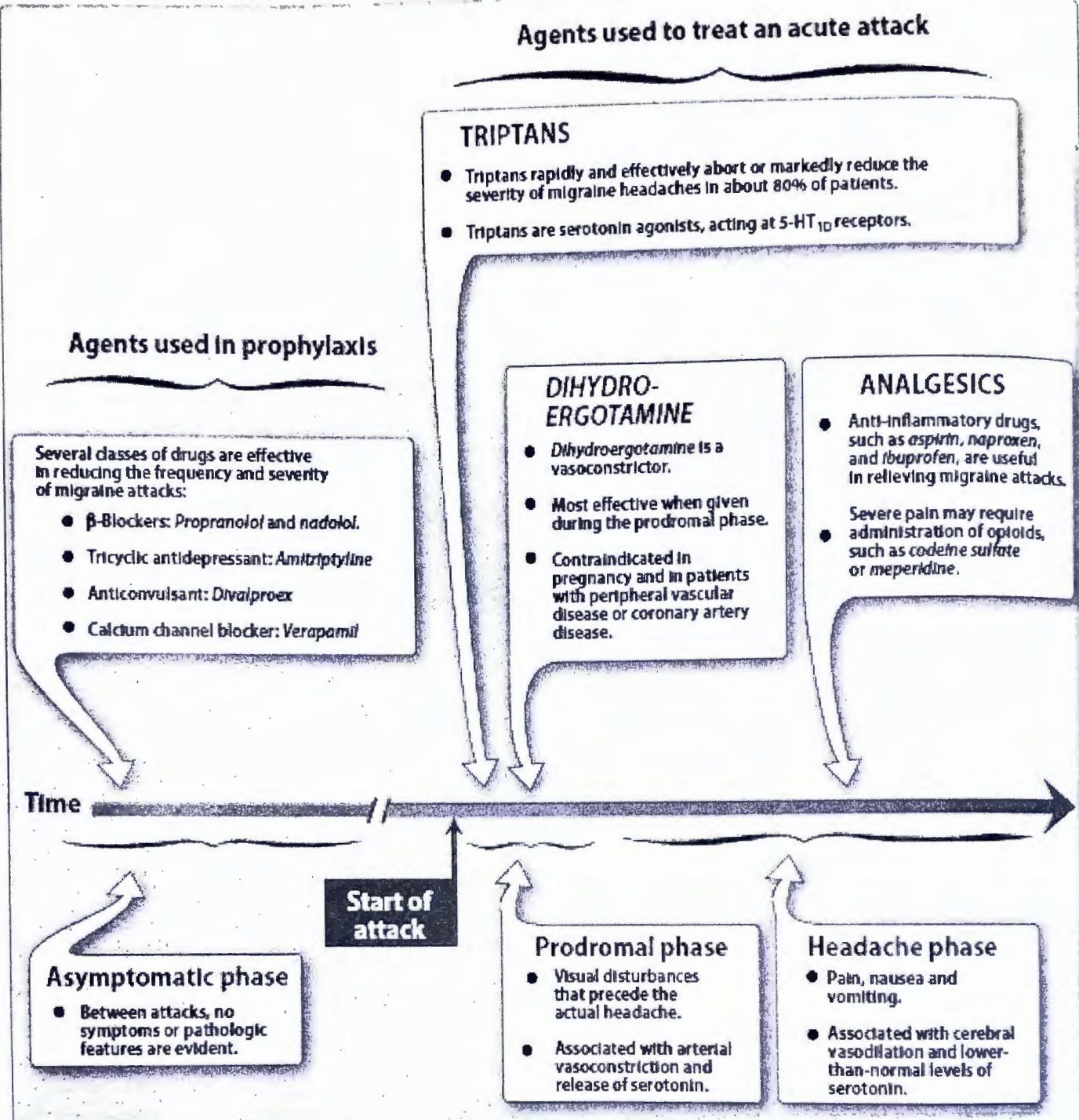


Figure. Drugs useful in the treatment and prophylaxis of migraine headaches.

Mechanism of action / Role of different drugs in migraine:

Anti-migraine drugs	Mechanism of action
1. Triptans (Rizatriptan, Zolmitriptan, Sumatriptan)	They selectively activate 5-HT _{1B/1D} receptor → Constriction of dilated cranial extra-cerebral blood vessels → Relief of headache
2. Ergot alkaloid (Ergotamine)	Same as triptans
3. NSAIDS	Inhibit release of prostaglandins (which is a vasodilator)
4. Pizotifen	Block H ₁ & 5-HT ₁ receptors → Prevent cerebral vasoconstriction → Prevent migraine attack.
5. β -blockers	beta-adrenoceptor blockade

6. Tricyclic antidepressant (TCA)	Acts on 5-HT _{1D} receptors which are located on pre-synaptic trigeminal nerve endings → inhibit the release of vasodilating peptides.
7. SSRI	Same to TCA
8. Flunarizine	Cerebro-selective vascular Ca ²⁺ channel blockade → Prevention of vasoconstriction → Prevents migraine attack

Q. How propranolol improves migraine? (DU-05J)

Ans.

Prevention of migraine by propranolol:

Propranolol



Membrane stabilizing effect (inhibits release of serotonin, substance P, PG, histamine)



Vasoconstriction & weak serotonin antagonistic effect



Prevents migraine attack.

Q. Explain the mode of action of pizotifen in migrainous headache. (DU-02M)

Ans.

Mode of action of pizotifen in migrainous headache: Pizotifen is a serotonin antagonist acting mainly at the 5-HT₁, 5-HT_{2A} and 5HT_{2C} receptors. It also has some activity as an antihistamine as well as some anticholinergic activity

Pizotifen → Block H₁ & 5-HT₁ receptors → Prevent cerebral vasoconstriction → Prevents migraine attack.

Q. Justify the role of pizotifen in acute migraine. (DU-15Ju)

Ans.

Role of pizotifen in acute migraine: Pizotifen prevents migraine attack by preventing cerebral vasoconstriction. But pizotifen cannot relieve acute migraine attack.

Drugs used in vertigo

Vertigo: Vertigo is defined as an abnormal perception of movement of the environment and occurs because of an abnormality in sensory information from the eyes, limb proprioception and the vestibular system about a person's position in space. Vertigo commonly arises from inappropriate input from the labyrinthine apparatus. Vertigo caused by labyrinthine disorders is usually short-lived, though it may recur, whilst vertigo arising from central (brain-stem) disorders is often persistent and accompanied by other signs of brain-stem dysfunction. A careful analysis of the history will reveal the likely cause in most patients.

(Ref: Davidson's-22nd)

Q. What are the drugs used in vertigo?

Ans.

Drugs used for vertigo:

A. **Labyrinthine suppressants:** They suppress end organ receptors or inhibit central cholinergic pathway (in vestibular nuclei).

Antihistamines	• Cinnarizine • Cyclizine • Dimenhydrinate • Diphenhydramine
Anti-emetic phenothiazine	• Prochlorperazine: Parenteral Prochlorperazine is the most effective drug to control violent vertigo & vomiting. • Thiethylperazine
Anticholinergics	• Atropine • Hyoscine

B. **Vasodilators:** They improve blood flow to labyrinth & brainstem.

1. Betahistine
2. Codergocrine
3. Nicotinic acid
4. Naftidrofuryl

C. **Anxiolytics & anti-depressants:** They appear to modify the sense of vertigo.

1. Diazepam
2. Amitriptyline

D. **Diuretics:** They decrease labyrinthine fluid pressure.

1. Acetazolamide
2. Thiazide
3. Frusemide

E. **Corticosteroids:** They suppress intra-labyrinthine edema due to viral infection or other cause.

1. Dexamethasone
2. Hydrocortisone

(Ref: Tripathi-6th/160)

MCQ

Q. 1st generation antihistamines include- (DU-17J)

- a. cetirizine
- b. chlorpheniramine
- c. promethazine
- d. loratadine
- e. fexofenadine

a. F, b. T, c. T, d. F, e. F

Q. Pharmacological antagonist of histamine H₁ receptors are- (DU-15Ju)

- a. epinephrine
- b. fexofenadine
- c. chlorpheniramine
- d. promethazine
- e. salbutamol

a. F, b. T, c. T, d. T, e. F

Q. Following drugs have antihistamine with antiemetic property: (CU-14Ju)

- a) Orphenedrine.
- b) Meclizine
- c) Cyproheptadine.
- d) Promethazine.
- e) Diphenhydramine.

a. F, b. T, c. F, d. T, e. T

Q. Pharmacological effects of classical antihistamines (H₁-receptor antagonists) include: (CU-14Ju)

- a) Sedation with low doses.
- b) Convulsion with low doses
- c) Prevention of motion sickness.
- d) Inhibition of gastric acid secretion
- e) An antipruritic effect.

a. T, b. F, c. T, d. T, e. T

Q. Clinically used prostaglandins are- (DU-14J)

- a. dinoprostone
- b. metoprolol
- c. misoprostol
- d. buspirone
- e. epoprostenol

a. T, b. F, c. T, d. F, e. T

Q. Less-sedative antihistamine are- (DU-13Ju)

- a. diphenhydramine.
- b. cetirizine.
- c. promethazine.

d. loratidine.

e. terfenadine.

a. F, b. T, c. F, d. T, e. T

Q. Statements related to eicosanoids- (SU-13J)

- a. COX-1 is absent in gastric mucosa
- b. COX-2 is absent in site of inflammation
- c. Arachidonic acid forms both PGs & LTs
- d. Leukotrienes cause bronchoconstriction
- e. NSAIDs inhibits cyclooxygenase only

a. F, b. F, c. T, d. T, e. T

Q. Actions of classical antihistamines- (SU-13J)

- a. Sedation is common
- b. 2nd generations are more sedative
- c. Increase salivation
- d. Some have anti-emetic action
- e. Beneficial for heart failure

a. T, b. F, c. F, d. T, e. F

Q. Clinically useful prostaglandins are- (DU-12Ju)

- a. Dinoprostone (T)
- b. Epoprostenol (T)
- c. Misoprostol (T)
- d. Buspirone (F)
- e. Metoprolol (F)

Q. Prostaglandin pathway inhibitor is- (DU-12J)

- a. Corticosteroids (T)
- b. Aspirin (T)
- c. Montelukast (F)
- d. Misoprostol (F)
- e. PPI (F)

Q. H₁-blockers are useful in treatment of- (DU-12J)

- a. Urticaria (T)
- b. Motion sickness (T)
- c. Bronchial asthma (F)
- d. Urinary retention (F)
- e. Common cold (T)

Q. Loratadine- (DU-10Ju)

- a. Is a H₁-blocker (T)
- b. Can easily cross the BBB (F)
- c. Is used in allergic rhinitis (T)
- d. Can be used in treating EPS (T)
- e. Is a muscle relaxant (F)

Q. Followings are bronchodilators- (DU-10J)

- a. salmeterol (T)
- b. prednisolone (F)
- c. cromoglycate (F)
- d. ipratropium (T)
- e. aminophylline (T)

Chapter 9

Non-steroidal Anti-inflammatory Drugs / NSAIDs

NSAIDs

Main criteria of non-steroidal anti-inflammatory drugs / NSAIDs:

1. NSAIDs are a chemically heterogeneous group of compounds, often chemically unrelated (although most of them are organic acids), which nevertheless share certain therapeutic actions and adverse effects.
2. They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoïd biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects.
3. All NSAIDs, including the subclass of selective COX-2 inhibitors, have three main therapeutic effects-
 - an anti-inflammatory effect: modification of the inflammatory reaction.
 - an analgesic effect: reduction of certain types of (especially inflammatory) pain.
 - an antipyretic effect: lowering of body temperature when this is raised in disease (i.e. fever).
4. In addition, all the NSAIDs share, to a greater or lesser degree, the same types of mechanism-based side effects. These include:
 - gastric irritation, which may range from simple discomfort to ulcer formation.
 - an effect on renal blood flow in the compromised kidney.
 - a tendency to prolong bleeding through inhibition of platelet function.
 - controversially, it is argued that they may also all-but especially COX-2 selective drugs-increase the likelihood of thrombotic events such as myocardial infarction by inhibiting prostaglandin (PG) I₂ synthesis.
5. They don't produce narcosis.
6. They have peripheral effect.
7. They have least central effect.
8. They are given orally, because they do not undergo hepatic first pass metabolism.
9. They have high therapeutic index (TI).

(Ref: Goodman & Gilman-12th edition; Lippincott's-6th; Rang & Dale's-8th)

Q: Classify NSAIDs. (CU-15Ju,06S/M; RU-07J; SU-17J,16Ju,09J,09Ju)

Q: Enumerate the NSAIDs according to efficacy. (DU-11Ju)

Q: Enumerate the NSAIDs according to anti-inflammatory efficacy. (DU-17M)

Q: Name 4 NSAIDs belonging to different chemical groupings with principal pharmacological effects. (RU-10J)

Q: What are the cyclooxygenase inhibitors? (DU-06M) / non-selective COX inhibitors. (RU-12Ju)

Q: Name the NSAIDs with strong anti-inflammatory effects. (DU-12Ju,11J, RU-16Ju,15J,14J,11Ju,06M)

Q: Name 4 NSAIDs with strong anti-inflammatory effects. (DU-16J,14J)

Q: Classify NSAIDs according to COX selectivity with 4 common example of each group. (CU-16Ju, RU-16J,08Ju,07Ju)

Q: Enlist selective COX-2 inhibitors. (DU-09J, SU-16Ju,10J, CU-17J,13J)

Q: Name the anti-pyretic drugs used commonly. (CU-14Ju, RU-14Ju,13J,04J)

Q: Name the non-narcotic/non-opioid analgesics.

Ans.

Classification of NSADs:

A. According to their chemical nature & structure:

1. Salicylates: Aspirin
2. Propionic acid derivatives: Ibuprofen, Naproxen, fenoprofen, ketoprofen, flurbiprofen and oxaprozin.
3. Acetic acid derivatives: Indomethacin, sulindac, and etodolac.
4. Fenamic acid derivatives: Mefenamic acid and meclofenamate.
5. Heteroaryl acetic acids: Diclofenac, aceclofenac and tolmetin.
6. Oxicam derivatives: Piroxicam, tenoxicam and meloxicam.
7. Nabumetone
8. Pyrrolo-pyrrolo derivative: Ketorolac.
9. Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone.

10. **Benzoxazocine derivatives:** Nefopam.
11. **COX-2 inhibitors:** Celecoxib, Rofecoxib.
12. **Para-aminophenol derivative:** Paracetamol (acetaminophen)

(Ref: Lippincott's-6th; Tripathi-6th/184)

B. According to efficacy/ degree of anti-inflammatory effect:

1. Weak anti-inflammatory / Low efficacious	▪ Para-aminophenol derivative: Paracetamol
2. Moderate anti-inflammatory/ Moderate efficacious	▪ Propionic acid derivatives: Ibuprofen, Naproxen, ketoprofen, flurbiprofen. ▪ Fenamic acid derivatives: Mefenamic acid.
3. Strong anti-inflammatory/ High efficacious	▪ Salicylates: Aspirin ▪ Heteroaryl acetic acids: Diclofenac, Aceclofenac. ▪ Oxicam derivatives: Piroxicam, Tenoxicam. ▪ Pyrrolo-pyrrolo derivative: Ketorolac. ▪ Acetic acid derivatives: Indomethacin. ▪ Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone.

C. According to COX isoenzyme selectivity:

1. **COX-2 selective NSAIDs**, whose selectivity for inhibiting COX-2 is at least 5 times that for COX-1. The group includes
 - Rofecoxib
 - Celecoxib
 - Meloxicam
 - Etodolac and
 - Nabumetone
2. **Non-COX-2 selective NSAIDs**, which comprise all other NSAIDs. These drugs inhibit COX-1 as much as, or even more than, COX-2.

(Ref: Bennett & Brown-11th edition)

C. According to plasma half-life:

1. Short acting NSAIDs ($t_{1/2} < 6$ hrs)	▪ Aspirin ▪ Diclofenac ▪ Ibuprofen ▪ Fenoprofen ▪ Indomethacin ▪ Ketoprofen
2. Intermediate acting NSAIDs ($t_{1/2}$ 6-26 hours)	▪ Celecoxib ▪ Rofecoxib ▪ Naproxen ▪ Ketorolac ▪ Etodolac
3. Long acting NSAIDs ($t_{1/2} > 26$ hours)	▪ Nabumetone ▪ Piroxicam ▪ Oxaprozin

Q. Enlist the NSAIDs of clinical importance. (DU-15Ju)

Q. Name some important NSAIDs. (DU-09Ju)

Ans.

Some clinically important NSAIDs: Following drugs are commonly used clinically-

1. Diclofenac.
2. Aceclofenac
3. Ketorolac.

4. Indomethacin.
5. Naproxen.
6. Aspirin
7. Ibuprofen
8. Ketoprofen
9. Mefenamic acid
10. Etoricoxib

Nice to knowPharmacokinetics of NSAIDs:

1. **Chemical nature:** All NSAIDs except nabumetone are weak organic acids.
2. **Absorption:** Most of the drugs are well absorbed & foods cannot change their bioavailability.
3. **Metabolism:** Most of the NSAIDs are highly metabolized by CYP3A or CYP2C families of P450 enzymes in the liver.
4. **Distribution:** Most of the NSAIDs are highly protein binds (98%) & usually with albumin.
5. **Excretion:** Renal excretion is most important route of final excretion of NSAIDs. In spite of that nearly all NSAIDs undergo varying degree of biliary excretion & reabsorption (possesses entero-hepatic circulation).
6. Drugs with short half lives remain in the joints longer while drugs with longer half lives disappear from the synovial fluid relatively quickly.

(Ref: Katzung-13th)

Q. Write down the mechanism of action of NSAIDs.

Q. Draw a diagram showing the site of action of NSAIDs in the pathway of prostaglandin synthesis. (CU-07J)

Q. Outline the cyclooxygenase pathway along with drugs that inhibit the pathway. (RU-16Ju)
Ans.

Mechanism of action of NSAIDs: The single common mode of action of NSAIDs is to **block prostaglandin synthesis** by inhibiting **cyclooxygenase (COX)** enzyme. Nonselective NSAIDs inhibit both COX-1 and COX-2 enzymes; whereas COX-2 selective NSAIDs selectively inhibit only COX-2 enzyme.

Cell membrane



Phospholipids

↓ Phospholipase ← Inhibits Steroid

Arachidonic acid

↓ Cyclooxygenase enzyme (COX) ← Inhibits NSAID

Prostaglandins

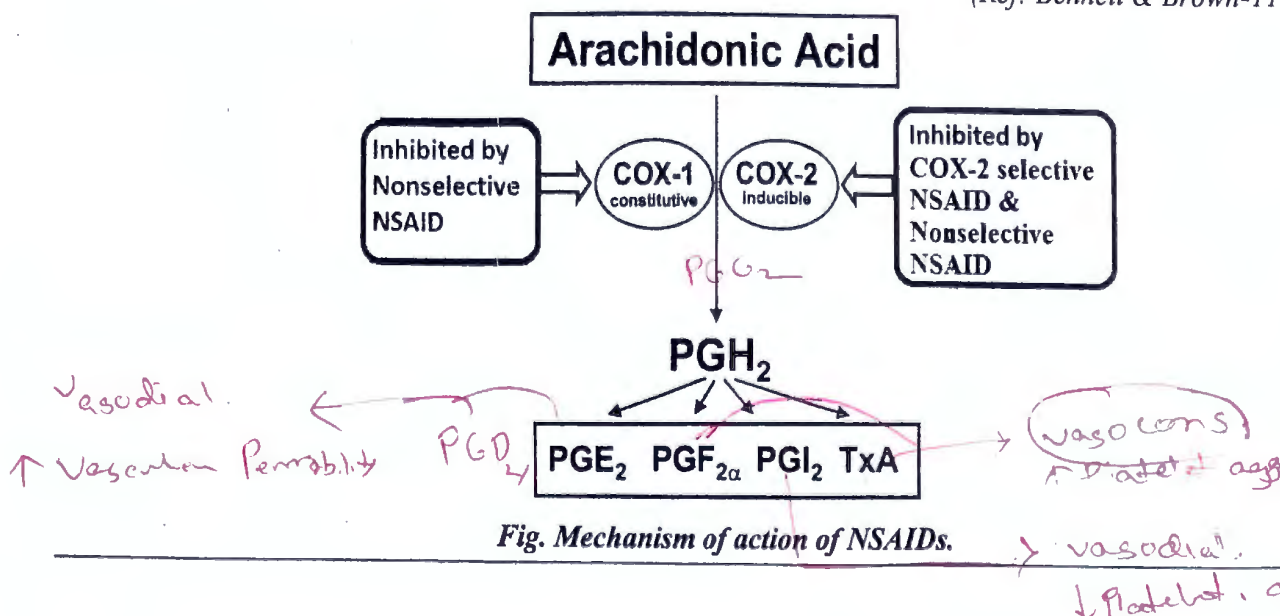
(Ref: Bennett & Brown-11th edition)

Fig. Mechanism of action of NSAIDs.

Nice to know

Regarding mechanism of action of NSAIDs: Various NSAIDs have other actions that may contribute to differences between the drugs and these include: the inhibition of lipoxygenases (diclofenac, indomethacin); superoxide radical production and superoxide scavenging; effects on neutrophil aggregation and adhesion, cytokine production and cartilage metabolism.

(Ref: Bennett & Brown-11th edition)

Q. Describe the mechanism of action of aspirin. (DU-14J, 09Ju, RU-12Ju)

Ans.

Mechanism of action of aspirin:

Aspirin



Inhibits cyclooxygenase (COX) enzyme **irreversibly**



No production of different prostaglandins from arachidonic acid



Anti-inflammatory action

(NB: NSAIDs other than aspirin are competitive & reversible inhibitor of COX)

Q. Name principal pharmacological effects of NSAIDs. (RU-11/10J)

Q. What are the pharmacological effects of aspirin? (DU-00M, 01J)

Q. Write down the pharmacological actions of non-narcotic / non-opioid analgesics. (SU-09J, CU-06M/J)

Q. Write down the pharmacological effects of ibuprofen. (DU-13Ju, SU-14J)

Ans.

Pharmacological effects of NSAIDs/ Aspirin / Ibuprofen:

1. Anti-inflammatory effects
2. Analgesic effect
3. Anti-pyretic effect.
4. Anti-platelet effects.
5. Closure of the ductus arteriosus in newborn.

(Ref: Katzung-13th edition)

Q. Explain the analgesic effects of diclofenac. (RU-16Ju)

Q. Explain the analgesic effects of ketorolac. (DU-09J, 07Ju)

Q. How does diclofenac reduce pain? (RU-08Ju, 06M)

Q. Explain the analgesic effect of NSAIDs.

Q. Explain the analgesic mechanism of aspirin. (SU-11J, RU-11J)

Q. Mention how paracetamol relieves pain. (DU-17J)

Q. A female patient complains of large joint pain and is being treated with indomethacin. How does indomethacin help her? (SU-12Ju)

Ans.

Analgesic effect of ketorolac / diclofenac / ibuprofen / naproxen / other NSAIDs:

NSAIDs / aspirin/ ketorolac/ diclofenac /ibuprofen /naproxen inhibit cyclooxygenase enzyme



Decreased production of prostaglandin E₂ (PGE₂)



Decreased level of bradykinin, histamine, interleukins, TNF- α & other chemical mediators at the site of inflammation (They are released at the nerve ending in response to inflammatory process)



No stimulation of 'A δ ' & 'C' nerve fibre



No transmission of pain.



Relief of pain / the sensation of pain.

Central pain transfer

So NSAIDs are therefore more effective against pain associated with inflammation.

(Ref: Lippincott's-6th; Tripathi-6th/185)

Nice to know

- **Antiplatelet dose of aspirin (low dose aspirin):**
 - 75 – 150 mg per day (Ref: Bennett & Brown-10th edition)
 - 75 – 150 mg/ day (Ref: Davidson's-21st edition)
- **Anti-inflammatory dose of aspirin:** >350 mg
- **Analgesic dose of aspirin:** 300-900 mg every 4-6 h
- No operation within 1 week of administration of aspirin → If done, more bleeding.
(Ref: Bennett & Brown-11th edition)

- Q. Explain the anti-platelet effects of aspirin. (DU-10J,07J; RU-17J; SU-17J,16Ju,09J)
 Q. How does low dose aspirin act as anti-platelet action? (DU-09J, RU-10J)
 Q. Explain the mechanism of antiplatelet action of low dose aspirin. (DU-08J, SU-06J)
 Q. Justify the use of low dose aspirin in the management of thromboembolic diseases. (CU-17J,08J, SU-03S)

Ans.

Mechanism of antiplatelet action of low dose aspirin: Low dose aspirin inhibits platelet aggregation by inhibiting **thromboxane A₂** formation.

Aspirin (acetylsalicylic acid)

↓
Acetylates and thus inactivates cyclooxygenase (COX) irreversibly

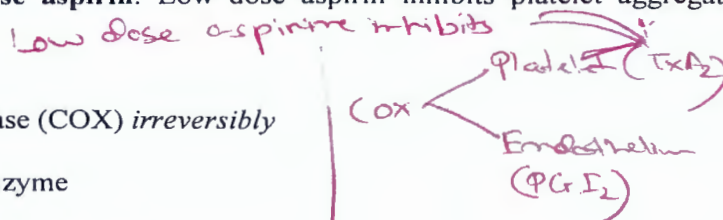
↓
The platelets are unable to synthesize new enzyme

↓
COX activity is lost for the platelet life time (8 - 10 days)

↓
Prevention of formation of both thromboxane A₂ and prostacyclin.

↓
Thromboxane A₂ causes platelet aggregation but prostacyclin inhibits platelet aggregation. Low dose aspirin (75 to 150 mg/day by mouth) will abolish synthesis of thromboxane A₂ without significant impairment of prostacyclin formation.

↓
Thus low dose aspirin Inhibits platelet aggregation.



12th edition: 81-325 low dose mg/day

By preventing platelet aggregation, low dose aspirin prevents formation of **thrombus**. This is how aspirin prevents thromboembolic diseases, eg, MI, stroke, deep vein thrombosis, etc.

(Ref: Bennett & Brown-11th edition)

Q. Why aspirin is stopped one week before surgery? (SU-14Ju)

Ans.

Aspirin is stopped one week before surgery: Antiplatelet effect is due to permanent inactivation of COX in platelets, preventing synthesis of thromboxane. Being non-nucleated, platelets cannot regenerate the enzyme as can nucleated cells, and the resumption of thromboxane production is dependent on the entry of new platelets into the circulation (platelet life-span is 8 days). If aspirin is stopped one week before surgery, the platelets inhibited by the aspirin are removed from the circulation by this time and then new platelets come to the circulation, which can control bleeding during surgery.

(Ref: Bennet & Brown-11th)

Nice to know

Inflammation: A normal inflammatory response is essential to fight **infections** and is part of the **repair** mechanism and **removal of debris** following tissue damage. Inflammation can also cause **disease**, due to damage

of healthy tissue. This may occur if the response is overvigorous, or persists longer than is necessary. Anti-inflammatory drugs reduce inflammation and relieve us from unwanted effects of inflammation.

Activated leukocytes at a site of inflammation release compounds which enhance the inflammatory response. These inflammatory mediators include eicosanoids (eg, prostaglandins, thromboxanes, leukotrienes), cytokines, complement products.

(Ref: Bennett & Brown-11th)

Q. How does diclofenac produce anti-inflammatory effect? (RU-07J; SU-06M)

Q. Explain the anti-inflammatory effects of aspirin. (RU-06M, SU-17J)

Q. Explain the anti-inflammatory effects of ketoprofen. (SU-09/06J)

Q. How naproxen produces anti inflammatory effects? (DU-06M)

Q. Give the mechanism of anti inflammatory effects of NSAID? (RU-16J,15J)

Ans.

Anti-inflammatory effects of aspirin / ketoprofen / other NSAIDs:

1. The anti-inflammatory activity of the NSAIDs is mediated **chiefly** through **inhibition of biosynthesis of prostaglandins** by inhibiting cyclooxygenase.
2. Various NSAIDs have additional possible mechanisms of action, including-
 - Inhibition of chemotaxis
 - Down-regulation of interleukin-1 production
 - Decreased production of free radicals and superoxide, and
 - Interference with calcium-mediated intracellular events.
 - Decreased the sensitivity of vessels to bradykinin and histamine
 - Decreased lymphokine production from T lymphocytes.

(Ref: Katzung-13th)

The NSAIDs reduce mainly those components of the inflammatory and immune response in which prostaglandins, mainly derived from COX-2, play a significant part. These include:

1. vasodilatation
2. edema
3. pain.

(Ref: Rang & Dale's-8th)

Q. Outline the patho-physiology of fever. (DU-04J)

Ans.

Patho-physiology of fever

Substances that cause fever are called pyrogens. For example, bacterial products such as lipopolysaccharide (exogenous pyrogen), IL-1 & TNF (endogenous pyrogen).

↓
Exogenous pyrogens stimulate leukocytes to release cytokines such as IL-1 & TNF

↓
Cytokines stimulate cyclooxygenase enzyme to produce prostaglandin E₂ in the hypothalamus

↓
Increased **prostaglandin E₂** (PGE₂) in the hypothalamus

↓
In hypothalamus, PGE₂ stimulates production of neurotransmitters such as cAMP, which function to reset the **temperature set point** at a higher level

↓
All the mechanisms for increasing body temperature are brought into play

↓
Fever

(Ref: Guyton-11th/898; Robbins & Cotran-9th)

Q. Name the commonly used anti-pyretics? (RU-15Ju)

Ans.

Commonly used anti-pyretics

1. Paracetamol
2. Diclofenac
3. Aspirin

Q. How do the anti-pyretic drugs reduce fever? (RU-15Ju,13J,12J)

Q. Explain anti-pyretic action of paracetamol. (DU-17M,16J,13Ju, CU-14Ju,14J, SU-10J)

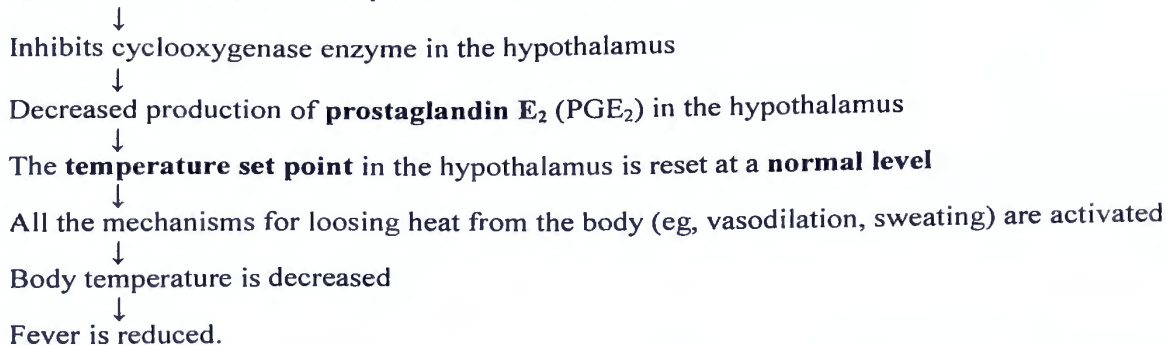
Q. How does paracetamol reduce fever? (DU-12Ju,11J, CU-06J; RU-14Ju,10/09Ju)

Q. How does aspirin reduce fever? (DU-08J, RU-07J, SU-11J)

Ans.

Anti-pyretic action of paracetamol / diclofenac / aspirin:

Paracetamol / diclofenac / aspirin/ other NSAIDs



(Ref: Katzung-13th; Bennett & Brown-11th)

Q. Mention the indications/uses of aspirin. (DU-09Ju,08J,07J; RU-17J)

Q. Mention the indications of low dose aspirin with justification. (RU-15J,14J,12Ju)

Q. Give 3 indications of low dose aspirin. (DU-15Ju)

Ans.

Indications of aspirin:**1. Thromboembolic disorder (only low dose aspirin):**

- Myocardial infarction (MI)
- Unstable angina (UA).
- Ischemic stroke.
- Transient ischemic attack (TIA).
- Deep vein thrombosis (DVT)

2. Musculoskeletal disorders (in high dose):

- Rheumatoid arthritis (RA)
- Arthritis of rheumatic fever (RF)
- Osteoarthritis
- Acute gouty arthritis
- Ankylosing spondylitis
- Other acute musculoskeletal pain

3. Mild to moderate somatic or inflammatory pain**4. Preeclampsia-eclampsia****5. Colonic and rectal carcinoma**

Q. Describe the role of mefenamic acid in the management of dysmenorrhea.

Ans.

Role of mefenamic acid in the management of dysmenorrhea: Dysmenorrhea means painful menstruation. In dysmenorrhea, prostaglandins cause uterine hypercontractility and pain. Mefenamic acid is used to reduce the production of PGs by the uterus, thus mefenamic acid reduces pain during menstruation.

(Ref: Bennett & Brown-11th)

Aspirin → ↑ Vasodilation → X

Q. Mention the indications of NSAID.

Q. Lists the clinical indications of non-opioid analgesics. (CU-06M)

Ans.

Indications of NSAID

1. **Analgesia:** NSAIDs are effective for pain of mild to moderate intensity including musculoskeletal and postoperative pain, and osteo- and inflammatory arthritis; they have the advantage of not causing dependence, unlike opioids.
2. **Anti-inflammatory action:**
 - All types of arthritis
 - Musculoskeletal conditions and
 - Pericarditis.
3. **Antipyretic action**
4. **Antiplatelet function:** Aspirin is indicated for the treatment and/or prevention of myocardial infarction, transient ischemic attacks and embolic strokes.
5. **Prolongation of gestation and labour:** inhibition of PG synthesis by the uterus during labour by **indomethacin** will prolong labour.
6. **Patency of the ductus arteriosus:** as PGs maintain the patency, **indomethacin** given to a new-born child with a patent ductus can result in closure, avoiding the alternative of surgical ligation.
7. **Primary dysmenorrhea:** **Mefenamic acid** is used to reduce the production of PGs by the uterus which causes uterine hypercontractility and pain.

(Ref: Bennett & Brown-11th)

Q. Mention the common adverse effects of NSAIDs. (DU-09J, 09Ju; CU-04M, SU-17M)

Q. Mention the adverse effects of diclofenac. (SU-17J)

Q. Mention the adverse effects of diclofenac on GIT. (RU-08Ju, 06M)

Q. Mention the adverse effects of non-opioid analgesics. (CU-07J)

Q. What are the adverse effects of anti-pyretics? (DU-04J)

Q. Mention the adverse effects of ketoprofen. (SU-06J)

Q. Mention the adverse effects of aspirin. (DU-14J, SU-11J)

Q. Mention the adverse effects of indomethacin. (SU-12Ju)

Q. Discuss the risks of NSAIDs when used in postoperative pain management. (CU-06S)

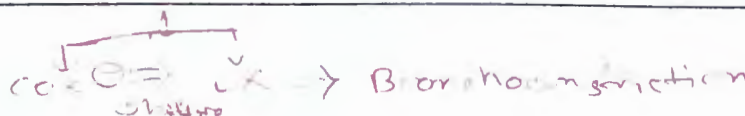
Q. What are the adverse effects of aspirin on GIT? (RU-03M/J)

Q. Elaborate NSAID induced gastric mucosal damager. (CU-15Ju)

Ans.

Adverse effects of NSAIDs/ diclofenac/ ketoprofen/aspirin:

1. **GIT adverse effects:** These are caused by inhibition of prostaglandin synthesis which play cytoprotective role in the GI tract.
 - Indigestion
 - gastro-esophageal reflux
 - Nausea, vomiting, abdominal pain.
 - Erosions
 - Peptic ulcer
 - Gastrointestinal hemorrhage eg, hematemesis and melena
 - perforation
 - Small and large bowel ulceration
2. **Renal effects:** Renal blood flow is reduced because the synthesis of vasodilator renal prostaglandins is inhibited; the result is sodium and fluid retention and arterial hypertension. Renal failure may occur.
3. **Salicylism:** With higher doses of aspirin, patients may experience **salicylism**—vomiting, tinnitus, decreased hearing, headache, dizziness and vertigo—reversible by reducing the dosage.
4. **Hepatic:** Abnormal liver functions, liver failure & hepatic encephalopathy (in case of toxic overdose).
6. **Pulmonary:** **Bronchoconstriction** by reducing bronchodilator prostaglandin synthesis. Thus aspirin & other NSAIDs aggravate bronchial asthma.



7. **Hematological:** Bleeding tendency & rarely thrombocytopenia, neutropenia, agranulocytosis or even aplastic anemia.
8. **Cutaneous effects:** Urticaria, severe rhinitis and asthma occur in susceptible individuals, e.g. with nasal polyposis, who are exposed to NSAIDs, notably aspirin.
9. **Reye syndrome:** Aspirin given to children for viral infection has been associated with Reye syndrome characterized by fatal, fulminating hepatitis with cerebral edema.
10. **Teratogenesis.**

(Ref: Katzung-13th; Bennett & Brown-11th, Lippincott's-6th)

Adverse effects of individual NSAIDs:

Diclofenac	• Gastrointestinal distress • Occult gastrointestinal bleeding • Gastric ulceration • Diclofenac at a dosage of 150 mg/d appears to impair renal blood flow and GFR. • Elevation of serum aminotransferases.
Naproxen	• Incidence of upper GI bleeding is low. <i>Rare side effects include-</i> • Allergic pneumonitis • Leukocytoclastic vasculitis • Pseudoporphyria
Ketorolac	• Toxicities are similar to those of other NSAIDs, although renal toxicity may be more common with chronic use.
Ibuprofen	• Gastrointestinal irritation • Rash • Pruritus • Tinnitus • Dizziness • Headache • Aseptic meningitis (particularly in patients with SLE) • Fluid retention • Ibuprofen antagonizes the irreversible platelet inhibition induced by aspirin. Thus, treatment with ibuprofen in patients with increased cardiovascular risk may limit the cardioprotective effects of aspirin. <i>Rare side effects are-</i> • Hematologic: Agranulocytosis, aplastic anemia • Renal: Acute renal failure, interstitial nephritis, nephrotic syndrome • Hepatitis
Ketoprofen	• GIT: Nausea, vomiting, diarrhea • CNS: Headache, dizziness, vertigo, confusion
Indomethacin	• GIT: Abdominal pain, diarrhea, GI hemorrhage, pancreatitis • CNS: Headache, dizziness, confusion, depression, • Psychosis with hallucinations (Rare) • Hepatic abnormalities (Rare) • Hematologic: Thrombocytopenia, aplastic anemia • Hyperkalemia • Renal papillary necrosis • At higher dosages, at least a third of patients have reactions to indomethacin requiring discontinuance.

(Ref: Katzung-13th edition)

Nice to know

Analgesic nephropathy: Mixtures of NSAIDs (rather than single agents) taken repeatedly cause grave and often irreversible renal damage, notably **chronic interstitial nephritis**, **renal papillary necrosis** and **acute renal failure**; these effects appear to be due at least in part to ischemia through inhibition of formation of locally produced vasodilator prostaglandins. The condition is most common in people who take high doses over years, e.g. for severe chronic rheumatism and patients with personality disorder.

(Ref: Bennett & Brown-11th)

Q. Write down the limitations of using aspirin. (DU-07J)

Q. Mention the contraindications of aspirin. (CU-01M)

Ans.

Contraindications of NSAIDs / aspirin:

1. Active bleeding peptic ulcer
2. Chronic peptic ulcer disease (PUD)
3. Chronic liver disease (CLD)
4. During elective surgery (should stop 1 week before surgery, otherwise there is chance of bleeding)
5. Bronchial asthma
6. Immediately after burn (after burn there may be curling ulcer. So NSAIDs are contraindicated)
7. Undiagnosed acute abdominal pain.
8. In influenza & swine flu (due to risk of Reye's syndrome)
9. Gout
10. Bleeding disorders.
11. Pregnancy (paracetamol is the safest in pregnancy among NSAIDs).

Q. Short note: Reye's syndrome. (RU-15Ju)

Ans.

Reye's syndrome:

Reye's syndrome is a rare but serious condition that causes swelling in the liver and brain. Reye's syndrome most often affects children and teenagers recovering from a viral infection, most commonly the flu or chickenpox.

Causes: The exact cause of Reye's syndrome is unknown, although several factors may play a role in its development.

1. Using **aspirin** to treat a viral infection, such as flu, chickenpox or an upper respiratory infection.
2. Having an underlying fatty acid oxidation disorder.

Clinical features:

1. Rash on hands and feet
2. Persistent, heavy vomiting
3. Confusion
4. Fatty liver
5. Cerebral edema
6. Coma
7. Seizures
8. Multiple organ failure
9. Death

Aspirin is **not** safe in pregnancy
(Diclofenac is)
Misoprostol abortion agent

Q. What precautions you should take before prescribing NSAIDs? (RU-10J, SU-17M)

Q. How can the adverse effects of indomethacin be reduced? (SU-12Ju)

Q. Elaborate the prevention of NSAID induced gastric mucosal damager. (CU-15Ju)

Ans.

Precautions before prescribing NSAIDs:

A. Prevention of GIT irritation:

- An anti-ulcerant drug (preferably a proton pump inhibitor, eg, omeprazole) should be added to prevent GIT irritation.
- The drug should be taken after meal.

Misoprostol
PGI₂ analog

- B. **Caution in case of comorbid conditions:** The comorbid conditions may be aggravated by NSAIDs. So in these cases, NSAIDs should be avoided or used with caution.
- Asthma, COPD or any sort of obstructive airway diseases
 - Signs or history of hepatic impairment
 - Signs or history of renal impairment
 - History of present active bleeding or any type of bleeding disorders
 - In case of edema, HTN, or CNS disorder (headache, tinnitus, dizziness) decision should be taken according to the severity of the diseases & need for analgesia & other options.
- C. Any history of hypersensitivity reaction to any NSAIDs should be taken.
- D. In pregnancy, the NSAIDs except paracetamol should be avoided.

Q. Name 2 effective NSAIDs preferred in postoperative pain management. (CU-09Ju)

Ans.

NSAIDs in postoperative pain management:

1. Diclofenac*
2. Ketorolac*
3. Ibuprofen
4. Naproxen
5. Indomethacin
6. Etodolac

*Note * indicates most commonly used drug in postoperative pain management in our country.*

Q. What are the advantages of propionic acid derivatives over aspirin? (DU-01J)

Ans.

Advantages of propionic acid derivatives over aspirin

1. Very potent
2. Low toxicity
3. Can enter into synovial space & may retain in high concentration, even though plasma concentration declines. That is why it is the drug of choice in inflammatory musculoskeletal pain.

Q. Short note: Diclofenac. (CU-14J)

Ans. Write in M/A, indication, adverse effects, contraindications in brief from above.

*Pre-operative 72hr
2 hrs → Opioid
2 hrs → Kete rob*

Ketorolac

Ketorolac is an NSAID promoted for systemic use mainly as an analgesic, not as an anti-inflammatory drug (although it has typical NSAID properties). The drug is an effective analgesic and has been used successfully to replace morphine in some situations involving mild to moderate postsurgical pain. It is most often given IM or IV, but an oral dose formulation is available. When used with an opioid, it may decrease the opioid requirement by 25–50%. An ophthalmic preparation is available for ocular inflammatory conditions. Toxicities are similar to those of other NSAIDs, although renal toxicity may be more common with chronic use.

(Ref: Katzung-13th)

Paracetamol (Acetaminophen)

Paracetamol is a domestic drug. It has **weak anti inflammatory effect**. For this reason, most of the pharmacologists **do not consider it to be an NSAID**. It may be better named as **non-narcotic analgesic-antipyretic drug**.

Pharmacological effects

1. It has analgesic and anti-pyretic effect.
2. It has little or no anti-inflammatory effect.
3. It has no anti-platelet effect.

Aspirine peripherally, Paracetamol centrally

Paracetamol **inhibits prostaglandin synthesis** in the CNS. This explains its analgesic and anti-pyretic properties. Paracetamol has less effect on cyclooxygenase enzyme in the peripheral tissues, which accounts for its weak anti-inflammatory effect.

(Ref: Lippincott's-6th)

Q. Write down the indications of paracetamol. (DU-17J)

Ans.

Indications of paracetamol:

1. Fever
2. Mild to moderate pain
 - a. Migraine headache
 - b. Myalgia
 - c. Dysmenorrhea
 - d. Postpartum pain
3. Analgesic adjunct to anti-inflammatory therapy.

Adverse effects of paracetamol:

1. With normal therapeutic doses, paracetamol is virtually free of any significant adverse effects.
2. Allergic reactions and skin rash.
3. Heavy, long-term daily use → chronic kidney disease (CKD).

(Ref: Bennett & Brown-11th + Lippincott's-6th)

Dose. The oral dose is 0.5 to 1 g every 4 to 6 h, maximum daily dose 4 g.

Q. Name the formulations of paracetamol. (RU-12J)

Ans.

Formulations of paracetamol

1. Tablet
2. Syrup
3. Pediatric drop
4. Suppository
5. In combination with other drugs:
 - Paracetamol + Caffeine
 - Paracetamol + Tramadol
 - Paracetamol + Methionine

2mg bronchoconstriction in 2hr

Q. How does poisoning occur due to paracetamol overdose? (CU-08J)

Q. How paracetamol is biotransformed?

Ans.

Poisoning due to paracetamol overdose/biotransformation of paracetamol: Under normal conditions, paracetamol is conjugated in the liver to form inactive glucuronidated and sulfated metabolites. A portion of paracetamol is hydroxylated to form N-acetylbenzoiminoquinone (NABIQ) - a highly reactive and potentially dangerous metabolite that reacts with sulfhydryl groups. At normal doses of paracetamol, the NABIQ reacts with the sulfhydryl groups of glutathione, forming a non-toxic substance. With large doses, the available glutathione in the liver becomes depleted, and the NABIQ reacts with the sulfhydryl groups of hepatic proteins (eg, key enzymes of liver), forming covalent bonds. Hepatic necrosis, a very serious and life-threatening condition, can result. Renal tubular necrosis can also occur.

NAPQI /
NABQI

Paracetamol → NABIQ $\xrightarrow{\text{Glutathione}}$ Inactivation

(Ref: Lippincott's-6th)

Q. Mention the management of paracetamol overdose. (CU-17J,08J)

Ans.

Management of acute paracetamol overdose

Acute overdose. Severe hepatocellular damage and renal tubular necrosis can result from taking 150 mg/kg (about 10 or 20 tablets) in one dose

Clinical features:

1. Jaundice, abdominal pain, hepatic tenderness do not become apparent for 24-18 h
2. Liver failure occurs between 2 and 7 days after the overdose.

Investigations

1. Blood for paracetamol level should be taken immediately.
2. Monitoring of the therapy and liver and kidney damage by-
 - Prothrombin time (INR)
 - Serum creatinine.
 - Blood pH

Treatment: Treatment depends on the interval between overdose and presentation and on the plasma concentration of paracetamol.

1. Gastric lavage (within 4 hours of ingestion)
2. **Antidote:**
 - a. **N-acetylcysteine (NAC)** by IV route.
 - b. **Methionine** if NAC is not available.
3. IV steroid and antihistamine to combat pseudoallergic reactions of N-acetylcysteine.

If patient presents after 16 hours of overdose:

1. Maintain fluid & electrolyte balance.
2. Maintain blood glucose level
3. Hemorrhage should be treated with fresh frozen plasma.
4. Hemoperfusion or liver transplantation (in hepatic failure).

Q. How N-acetylcysteine (NAC) and methionine act in paracetamol poisoning?

Ans.

N-acetylcysteine (NAC) and **methionine** are effective as they are precursors for the synthesis of **glutathione**. NAC is more effective because its conversion into glutathione requires fewer enzymes; also, it is administered by IV infusion which is an advantage if the patient is vomiting. Methionine alone may be used to initiate treatment when facilities for infusing NAC are not immediately available.

(Ref: Bennett & Brown-11th)

Q. Write differences between aspirin and paracetamol. (SU-15J)

Ans.

Differences between aspirin and paracetamol

Traits	Aspirin	Paracetamol
1. Anti-platelet effects.	Yes	No
2. Anti-inflammatory effects	Yes	Little or no
3. GIT adverse effects	More	Less
4. Salicylism	Yes	No
5. Aggravate bronchial asthma	Yes	No
6. Increases bleeding tendency	Yes	No
7. Reye syndrome	Yes	No
8. Teratogenesis	Yes	No

Q. What are the hepatotoxic drugs? (CU-14J)

Ans.

Hepatotoxic drugs

Pattern of hepatotoxicity	Drug
Cholestasis	- Chlorpromazine - High-dose estrogens
Cholestatic hepatitis	- NSAIDs - Co-amoxiclav - Statins
Acute hepatitis	- Rifampicin - Isoniazid
Non-alcoholic steatohepatitis	Amiodarone
Venous outflow obstruction	- Busulfan - Azathioprine
Fibrosis	Methotrexate

Drug Interactions

NSAIDs + Steroids → ↑ Ulcer

" + Warfarin → ↑ Bleeding
(Anti-P) (Anti-coag)

" + Diuretics → Hypotension
Vasopressor (↑ GFR to 2000 mg)

" + Penicillins → Prolongation of action

" + ACEi → Hypotension

" + OHA → Hypoglycemia
(Ref: Davidson's-22nd edition)

Selective COX-2 inhibitors / Coxibs

COX-1 and COX-2:

The COX enzyme exists in at least two isoforms. **COX-1** is a constitutive or "housekeeping" isoform that is responsible for the basal production of prostaglandins, prostacyclins, and thromboxanes. **COX-2** is inducible by cytokines and other inflammatory stimuli and is believed to predominate during chronic inflammation.

(Ref: Modern pharmacology with clinical application-6th/425)

Difference between COX-1 & COX-2 isoenzymes:

Traits	COX-1	COX-2
1. Type	PGH Synthase-1	PGH Synthase-2
2. Expression	It is a constitutive enzyme present in most cells (i.e. its activity is not changed once the cell is fully grown)	COX-2 enzyme normally present in insignificant amount. It is induced by cytokines, growth factors & other factors of inflammatory response.
3. Distribution	GIT, kidney & platelets.	Kidney, inflammatory and immune cells
4. Stimulatory effect	Following humoral stimulation, COX-1 isoenzyme increases 2-4 folds.	Following stimulation by growth factors, tumor promoters, cytokines & endotoxin, COX-2 isoenzyme increases 10-18 folds.
5. Function	Eicosanoids produced by COX-1 enzyme participate in physiological (house keeping) functions; such as- - Secretion of mucous for protection of gastric mucosa - Homeostasis. - Maintenance of renal function.	Eicosanoids produced by COX-2 enzyme play role in inflammatory & pathological changes. ← COX-2 inhibitor 273 adu 274 + 275 Hemorrhagic Inc. 275

Q. Enlist selective COX-II inhibitors. (DU-09Ju, CU-17J, SU-16Ju)

Q. Name the COXIBs. (RU-17J)

Ans.

COX-2 inhibitors / Coxibs

1. Celecoxib
2. Etoricoxib

3. Meloxicam
4. Lumiracoxib
5. Parecoxib

Rofecoxib and valdecoxib have been withdrawn from the market due to their increasing CVS risk.

(Ref: Katzung-13th)

Q. Characterize selective COX-II inhibitors. (SU-10J)

Cardiovascular

Ans.

Characteristics of selective COX-II inhibitors:

1. COX-2 inhibitors have analgesic, antipyretic, and anti-inflammatory effects similar to those of nonselective NSAIDs.
2. They have no anti-platelet effect.
3. They have limited or no GIT bleeding.
4. They don't precipitate bronchial asthma.
5. They have increased chance of renal injury & cardiovascular thrombotic events, eg, MI.

(Ref: Katzung-13th)

Q. Mention the advantages of COXIBs over traditional NSAIDs. (RU-17J, SU-16Ju)

Ans.

Advantages of COXIBs over traditional NSAIDs

1. They have limited or no GIT bleeding.
2. They don't precipitate bronchial asthma.
3. They do not cause gastric mucosal damage.

Q. What are the adverse effects of selective COX-II inhibitors? (CU-16Ju, SU-16Ju)

Ans.

Adverse effects of selective COX-II inhibitors

1. Increased chance of renal injury
2. Increased risk of cardiovascular thrombotic events, eg, MI.

Q. Describe the mechanism of action of COX-II inhibitors. (CU-04J)

Ans.

Mechanism of action of COX-II inhibitors: COX-2 selective inhibitors or coxibs inhibit prostaglandin synthesis by the COX-2 isoenzyme induced at sites of inflammation without affecting the action of the constitutively active "housekeeping" COX-1 isoenzyme found in the gastrointestinal tract, kidneys, and platelets. COXibs selectively bind to and block the active site of the COX-2 enzyme much more effectively than that of COX-1. Thus COX-2 inhibitors show analgesic, antipyretic, and anti-inflammatory effects similar to those of nonselective NSAIDs but they have no anti-platelet effect and minimum GI bleeding.

(Ref: Katzung-13th)

Q. Comment on present therapeutic status of selective COX-2 inhibitors. (SU-14Ju)

Q. What are the risks of using COX-II inhibitors in CVS patients? (CU-13J)

Ans.

COX-II inhibitors may increase the risk of thromboembolic complications, such as MI, stroke. Such complications caused withdrawal of rofecoxib and valdecoxib from the market.

This is why, selective COX-2 inhibitors should be used only in patients at high risk of peptic ulcer, perforation or bleeding. They should be used in the lowest dose for the shortest period of time.

(Ref: Katzung-13th)

Q. Mention the contraindications of COX-2 selective drugs.

Ans.

Contraindications of COX-2 selective drugs:

1. Ischemic heart disease, eg, MI.
2. Hypertension
3. Cardiac failure
4. Cerebro-vascular diseases (CVD), eg, ischemic stroke.

(Ref: Tripathi-6th/197)

Q. How do traditional NSAIDs vary with coxibs? (RU-10)

Q. Compare non-selective & selective inhibitors of COX enzymes as non steroidal anti-inflammatory effects. (CU-09J)

Q. Compare rofecoxib with diclofenac with regard to mechanism of action and adverse effect profile. (RU-13Ju)

Ans.

Differences between non-selective COX inhibitor & selective COX inhibitors:

Traits	Non-selective COX inhibitors / diclofenac	Selective COX inhibitors/ rofecoxib
1. Mechanism of action	Inhibit prostaglandin synthesis by the inhibiting cyclooxygenase (COX) enzyme	Inhibit prostaglandin synthesis by the inhibiting COX-2 isoenzyme.
2. Analgesic, antipyretic, and anti-inflammatory effects	Yes	Yes
3. Antiplatelet effect	Yes	No
4. Precipitation of asthma	Yes	No
5. Gastric mucosal damage	Yes	No
6. Incidence of GI bleeding	More	Less
7. Renal injury	Less	More
8. Cardiovascular risk	Less	More

(Ref: Katzung-13th edition + Tripathi-6th/186-187)**Drugs used in rheumatoid arthritis (RA)****A. Non-steroidal anti inflammatory drugs (NSAIDs)****B. Disease modifying anti-rheumatic drugs / DMARDs:**

1. Immunosuppressants:
 - Methotrexate
 - Azathioprine
 - Cyclosporine
2. Sulfasalazine
3. Leflunomide
4. Chloroquine & hydroxychloroquine
5. Cyclophosphamide
6. D-Penicillamine
7. Gold
8. Auranofin

C. Biologic response modifiers:

1. TNF- α inhibitors:
 - a. Etanercept
 - b. Infliximab
 - c. Adalimumab
2. Interleukin-1 antagonist: Anakinra

Disease modifying anti-rheumatic drugs / DMARDs

Drugs	Mechanism of action	Adverse effects
Methotrexate	Direct inhibitory effects on proliferation & stimulates apoptosis in immune-inflammatory cells. At low dose it inhibits "amino imidazole carboxamide ribonucleotide" (AICAR) transformylase & thymidylate synthetase with secondary effects on neutrophil chemotaxis. Inhibit dihydro-folate reductase enzyme.	Nausea, stomatitis & mucosal ulcer (most common), hepatotoxicity, rash, alopecia, acute pneumonitis.
Azathioprine	Converts into metabolite 6-thioguanine which suppresses inosinic acid synthesis, B-cell & T-cell function, Ig production & IL-2 secretion.	Bone marrow suppression, GIT upset, stomatitis, hepatitis.
Cyclosporine	Inhibits IL-1 & IL-2 receptor production & secondarily inhibits macrophage-T cell interaction and T cell responsiveness. T cell dependent B cell function is also affected.	Significant nephrotoxicity, HTN, hyperkalaemia, hepatotoxicity, gingival hyperplasia & hirsutism.
Sulfasalazine	Sulfasalazine is metabolized into sulfapyridine & 5-amino-salicylic acid → Inhibit the release of inflammatory cytokines; such as IL-1, 6, 12 & TNF-α.	GIT upset is commonest (nausea, vomiting), headache, neutropenia, thrombocytopenia, hepatitis & rash.
Leflunomide	Converts into active metabolite → Inhibits dihydroorotate dehydrogenase → ↓ribonucleotide synthesis → ↓Cell growth, inhibits T-cell proliferation & production of auto-antibodies by B- cells.	Diarrhea (25%), nausea, hepatotoxicity, HTN, weight gain, alopecia
Chloroquine & hydroxychloroquine	Suppression of T-lymphocyte responses to mitogens, ↓leukocyte chemotaxis, stabilization of lysosomal enzymes, inhibition of DNA & RNA synthesis & trapping of free radicals	Irreversible ototoxicity, retinopathy, myopathy, peripheral neuropathy, GIT upset (dyspepsia, nausea, vomiting, abdominal pain), rash.
Cyclophosphamide	Converts into active metabolite (phosphoramidate mustard) → Cross-links with DNA → Prevents cell replication and suppress T-cell & B-cell function.	Nausea, GIT upset alopecia, cystitis, bone marrow suppression, azoospermia & anovulation.

(Ref: Katzung-13th; Davidson's medicine-22nd)

Drugs used in gout

Drugs causing hyperuricemia:

1. Pyrazinamide
2. Thiazide diuretics (hydrochlorothiazide)
3. Loop diuretics (furosemide)
4. Cyclosporine

(Ref: Davidson-22nd)

Pathogenesis of gout:

Precipitation of urate crystals in the synovial fluid



Chemotactic factors are produced & granulocyte migration into the joint



Granulocytes phagocytose the urate crystals & release a glycoprotein which aggravates the inflammatory processes



- Increase lactic acid production from the inflammatory cells → ↓Local pH → More urate crystals are precipitated in the affected joint
- Release of lysosomal enzymes → Joint destruction

(Ref: Tripathi-6th/206)

Drugs for gout:

Drugs for acute gout	1. NSAIDs - <i>Indomethacin</i> 2. Colchicine 3. Corticosteroids (intra-articular)
Drugs for chronic gout	Uricosuric drugs: 1. Probenecid 2. Sulfipyrazone 3. Benzbromarone Uric acid synthesis inhibitors: 1. Allopurinol.

Indomethacin

(Ref: Tripathi-6th/205)

Allopurinol

Role of allopurinol in gout:

Allopurinol inhibits xanthine oxidase



No oxidation of xanthine and hypoxanthine



No production of uric acid



Decreased uric acid level



Decreased uric acid crystal formation

(Ref: Tripathi-6th/209)

Adverse effects of allopurinol:

1. Hypersensitivity (rash, fever, malaise, muscle pain etc)
2. Steven Johnson syndrome (rare but serious)
3. Gastric irritation, nausea.
4. Headache, dizziness.

(Ref: Tripathi-6th/209)

MCQ

Q. Pharmacological actions of diclofenac are-
(DU-17M)

- a) antiplatelet
- b) antianginal
- c) analgesic
- d) antiinflammatory
- e) antipyretic

a. T, b. F, c. T, d. T, e. T

Q. Low dose aspirin- (DU-17J)

- a. inhibits TxA_2 formation in platelet
- b. is indicated in MI
- c. inhibits PG I_2 formation
- d. may cause GIT bleeding
- e. is useful in rheumatoid arthritis

a. T, b. T, c. T, d. T, e. F

Q. Aspirin- (DU-14Ju)

- a. inhibits cyclooxygenase irreversibly
- b. causes bronchoconstriction
- c. depresses the respiratory centre
- d. has a long plasma half life
- e. exhibits first order kinetics at high dose

a. T, b. T, c. F, d. T, e. F

Q. Aspirin- (DU-13Ju)

- a. irreversibly block the cyclooxygenase enzyme.
- b. has a long plasma half life.
- c. can cause bronchoconstriction.
- d. can protect vascular occlusion.
- e. depress the respiratory centre.

a. T, b. T, c. T, d. T, e. F

Q. Aspirin- (DU-11J)

- a. Non-selectively inhibits COX enzyme (T)
- b. Not contraindicated in asthma (F)
- c. Causes PUD (T)
- d. Has no effect on bleeding time (F)
- e. Stimulates the respiratory center (F)

Chapter 10

Drugs used to treat Diseases of BLOOD

Anti-thrombotic drugs

Hemostasis: Hemostasis is the process of forming clots in the walls of damaged blood vessels and preventing blood loss while maintaining blood in a fluid state within the vascular system.

(Ref: Ganong-24th)

Steps of hemostasis: When a small blood vessel is ruptured or severed, hemostasis is achieved by the following steps:

1. Vascular spasm (or vasoconstriction)
2. Formation of platelet plug
3. Blood coagulation
4. Fibrous organization or dissolution of blood clot.

Formation of platelet plug:

Platelet adhesion: When the endothelium is injured, platelets adhere to the subendothelial collagen by **von Willebrand factor (vWF)**.

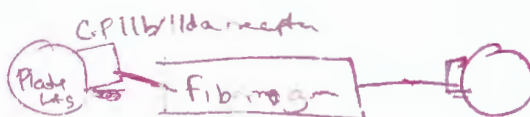
Platelet activation: After adhesion, platelets undergo morphologic changes and become activated and then release granules containing **adenosine diphosphate (ADP)**, **thromboxane A₂**, serotonin, platelet-activation factor (PAF), and thrombin.

Platelet aggregation: ADP, thromboxane A₂, serotonin, and PAF bind to the resting platelets circulating nearby and activate them. **Intracellular Ca²⁺ increases** in these activated platelets.

Increased cytosolic Ca²⁺ leads to

- Release of platelet granules containing ADP and serotonin that activate other platelets.
- Activation of thromboxane A₂ synthesis.
- Activation of the **glycoprotein (GP) IIb/IIIa receptors**.

Activated GP IIb/IIIa receptor binds with fibrinogen



One fibrinogen molecule binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet-cross-linking and **platelet aggregation**. (Formation of platelet plug)

(Ref: Lippincott's-6th)

Importance of platelet plug for closing vascular holes: If the hole in the vessel is small, the platelet plug by itself can stop blood loss, but if there is a large hole, a blood clot in addition to the platelet plug is required to stop the bleeding.

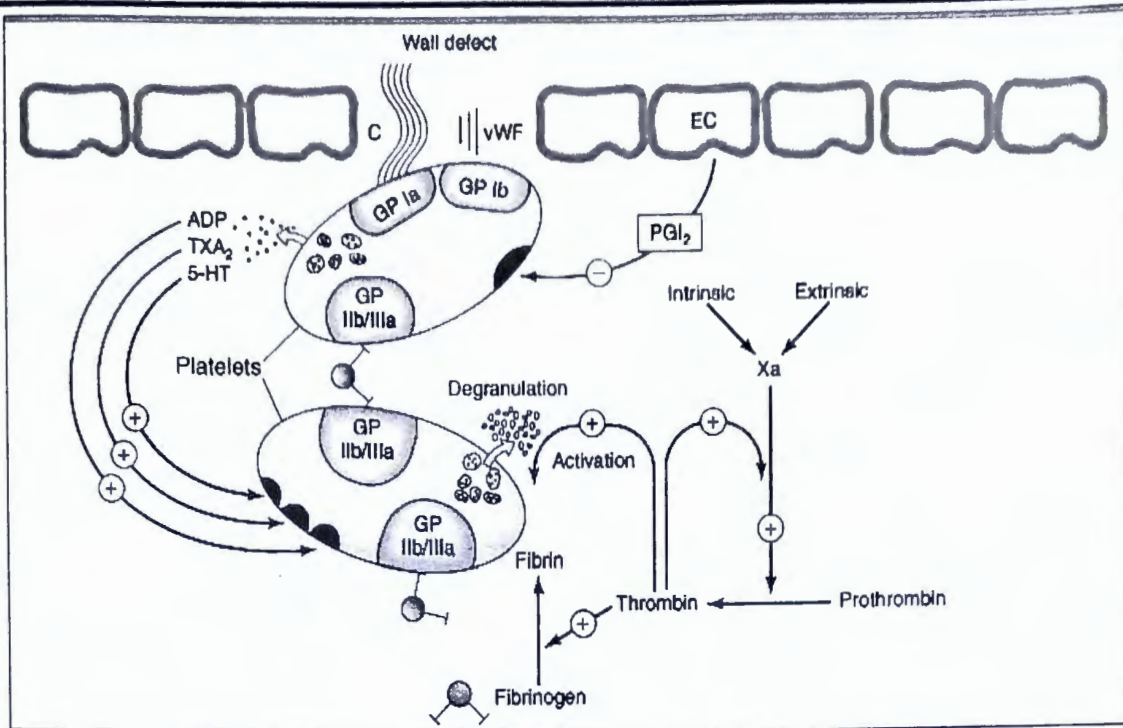


Figure: **Thrombus formation at the site of the damaged vascular wall** (EC, endothelial cell) and the role of platelets and clotting factors. Platelet membrane receptors include the glycoprotein (GP) Ia receptor, binding to collagen (C); GP Ib receptor binding von Willebrand factor (vWF), and GP IIb/IIIa, which binds fibrinogen and other macromolecules. **Aggregating substances** released from the degranulating platelet include **ADP**, **thromboxane A₂ (TXA₂)**, and **serotonin (5-HT)**.

(Ref: Katzung-13th)

Anti-thrombotic drugs include-

- Anti-platelet drugs
- Anti-coagulant drugs

Antiplatelet drugs

Q. List the anti-platelet drugs. (DU-17M,16J,11Ju,09J,08Ju; CU-16Ju,08Ju; RU-13J,10J,05M; SU-09/06J)

Q. Categorize anti-platelet drugs. (CU-14J)

Ans.

Classification of anti-platelet drugs:

1. Cyclooxygenase inhibitors: Inhibition of prostaglandin synthesis	Aspirin
2. ADP receptor inhibitors: Inhibition of ADP induced platelet aggregation.	Clopidogrel Prasugrel Ticlopidine
3. Inhibitor of glycoprotein IIb/IIIa receptors on platelets (intravenous use only)	Abciximab Eptifibatide Tirofiban
4. Additional antiplatelet-directed drugs	
• Phosphodiesterase inhibitor	Cilostazol
• Inhibitor of adenosine uptake and cGMP phosphodiesterase	Dipyridamole

(Ref: Katzung-13th)

Q. Name 3 clinically useful antiplatelet drugs. (CU-07Ju)

Ans.

3 clinically useful anti-platelet drugs:

1. Low dose aspirin (75 - 150 mg per day)

2. Clopidogrel
3. Abciximab

- Q. How does low dose aspirin act as anti-platelet action? (DU-17M,09J)
Q. Explain the mechanism of antiplatelet action of low dose aspirin. (DU-11Ju,0807/J;RU-05M,SU-09J,08J)
Q. Justify the use of low dose aspirin in the management of thromboembolic diseases. (CU-08J,SU-03S)
Q. How does aspirin produce antiplatelet effect? (DU-16J,07J; RU-05M,04M; SU-09J,03S/J)
Q. Give explanation of anti-platelet effect low dose aspirin. (RU-10J)
Q. Explain the role of low dose aspirin in heart disease/IHD. (SU-13J,12Ju)
Q. Short note: Low dose aspirin. (DU-12Ju,11J)

Ans.

Mechanism of antiplatelet action of low dose aspirin: Low dose aspirin inhibits platelet aggregation by inhibiting thromboxane A₂ formation.

Aspirin (acetylsalicylic acid)

↓
Acetylates and thus inactivates cyclooxygenase enzyme (COX) *irreversibly*

↓
The platelets are unable to synthesize new enzyme

↓
COX activity is lost for the platelet life time (8 - 10 days)

↓
Prevention of formation of both thromboxane A₂ and prostacyclin.

↓
Thromboxane A₂ causes platelet aggregation but prostacyclin inhibits platelet aggregation. Low dose aspirin (75 to 150 mg/day by mouth) will abolish synthesis of thromboxane A₂ without significant impairment of prostacyclin formation.

↓
Thus low dose aspirin Inhibits platelet aggregation.

By preventing platelet aggregation, low dose aspirin prevents formation of **thrombus**. This is how aspirin prevents thromboembolic diseases, eg, myocardial infarction, stroke, deep vein thrombosis, etc.

(Ref- Bennett & Brown-11th)

- Q. Explain the mechanism of action of clopidogrel as antiplatelet drug. (CU-16Ju, SU-17M,06/05J)

Ans.

Mechanism of action of Clopidogrel / Ticlopidine: Clopidogrel and ticlopidine reduce platelet aggregation by inhibiting the ADP pathway of platelets.

Clopidogrel / Ticlopidine

↓
Irreversibly blocks the ADP receptor on platelet membrane

↓
No binding of ADP with ADP receptor

↓
No activation of the glycoprotein IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other

↓
No platelet aggregation (antiplatelet effect).

By preventing platelet aggregation, clopidogrel prevents formation of **thrombus**. This is how clopidogrel prevents thromboembolic diseases, eg, MI, stroke, deep vein thrombosis, etc.

(Ref: Katzung-13th +Lippincott's-6th)

Q. What do you mean by low dose aspirin? (CU-15Ju)

Q. Briefly discuss about low dose aspirin with clinical importance. (SU-13Ju)

Ans.

Low dose aspirin: A daily dose of **75 – 150 mg** of aspirin is called low dose aspirin. Low dose aspirin inhibits platelet aggregation by inhibiting **thromboxane A₂** formation.

Clinical importance: Write indications from below.

Nice to know

Reference of low dose aspirin

- 75 – 150 mg per day (Ref- Bennett & Brown-10th edition)
- 75 – 150 mg/ day (Ref: Davidson's-21st edition)

Q. Mention the indications of low dose aspirin with justification. (DU-08J, RU-14J, 12Ju)

Q. Name 4 indications of aspirin for anti-platelet effect. (RU-10J)

Ans.

Indications of low dose aspirin / clopidogrel:

1. Myocardial infarction (MI)
2. Unstable angina (UA)
3. Ischemic stroke
4. Transient ischemic attacks (TIA)
5. Peripheral vascular diseases (PVD)
6. Following coronary artery angioplasty & bypass grafting.
7. Patient with prosthetic valve.
8. Deep vein thrombosis.
9. Atrial fibrillation.

Clopidogrel is used either alone or in combination with aspirin. It is given to patients who cannot tolerate aspirin such as patients with peptic ulcer disease (PUD) with active bleeding, severe bronchial asthma; because aspirin aggravates PUD and asthma.

Q. Rationalize the use of antiplatelet drugs in a patient with cerebro-vascular accident. (RU-13J)

Ans.

Antiplatelet drugs prevent platelet aggregation and thus prevent formation of thrombus. If a patient of cerebro-vascular accident (ischemic stroke) receives antiplatelet drugs, these drugs **prevent further attack** of cerebro-vascular accident.

Q. Mention the adverse effects of low dose aspirin? (DU-11Ju, SU-06M)

Ans.

Adverse effects of aspirin:

1. Gastric irritation
2. Gastric hemorrhage
3. Gastric perforation (drug induced peptic ulcer perforation)
4. Precipitation of asthma.

Q. Mention the contraindications of aspirin?

Ans.

Contraindications of aspirin:

1. Peptic ulcer disease / active bleeding PUD
2. Coagulation disorder
3. Asthma
4. Chronic obstructive pulmonary disease (COPD)
5. Pregnancy (1st trimester).

Q. Mention the adverse effects of ticlopidine. (CU-16Ju)

Ans.

Adverse effects of ticlopidine:

1. Nausea
2. Dyspepsia
3. Diarrhea
4. Hemorrhage
5. Ticlopidine causes life threatening blood abnormalities such as neutropenia, agranulocytosis, thrombotic thrombocytopenic purpura (TTP) & aplastic anemia. For these adverse effects it is reserved for the patients who are not suitable for aspirin / clopidogrel therapy.

(Ref: Lippincott's-6th; Katzung-13th)

Q. Mention the adverse effects of clopidogrel.

Ans.

Adverse effects of clopidogrel

1. Thrombotic thrombocytopenic purpura
2. Clopidogrel is rarely associated with neutropenia.

Viva Q. Which one is preferred- ticlopidine or clopidogrel?

Ans.

Because of its superior side effect profile and dosing requirements, clopidogrel is preferred over ticlopidine. The antithrombotic effects of clopidogrel are dose-dependent; within 5 hours after an oral loading dose of 300 mg, 80% of platelet activity will be inhibited. The maintenance dose of clopidogrel is 75 mg/d, which achieves maximum platelet inhibition. The duration of the antiplatelet effect is 7–10 days.

(Ref: Katzung-13th)

Q. Compare the mechanism of antiplatelet action of aspirin & clopidogrel. (DU-08Ju)

Q. Compare the mechanism of action & adverse effects of aspirin & clopidogrel when used as antiplatelet drug. (CU-08Ju)

Q. Write down differences between aspirin and clopidogrel. (SU-03M/S/J; RU-05M)

Ans.

Differences between Aspirin & Clopidogrel:

Traits	Aspirin	Clopidogrel
1. Mechanism of action	Inhibits thromboxane A ₂ synthesis	Block ADP receptor on platelet membrane
2. Anti-inflammatory effect	Present	Absent
3. Anti-pyretic effect	Present	Absent
4. Effectiveness	Less effective	More effective
5. Cost	Cheap	Expensive
6. Thrombotic thrombocytopenic purpura	No	Yes
7. Aggravates peptic ulcer diseases	Yes	No
8. Use in bronchial asthma	No	Yes

Q. Short note: Aspirin & clopidogrel as antiplatelet drugs. (RU-14Ju)

Q. Short note: Clopidogrel. (RU-16J)

Ans. Write in brief from above.

Viva Q. Which anti-platelet drug will you prefer for a patient of MI who has history of bronchial asthma?

Ans.

Clopidogrel.

Anticoagulant drugs

Blood coagulation:

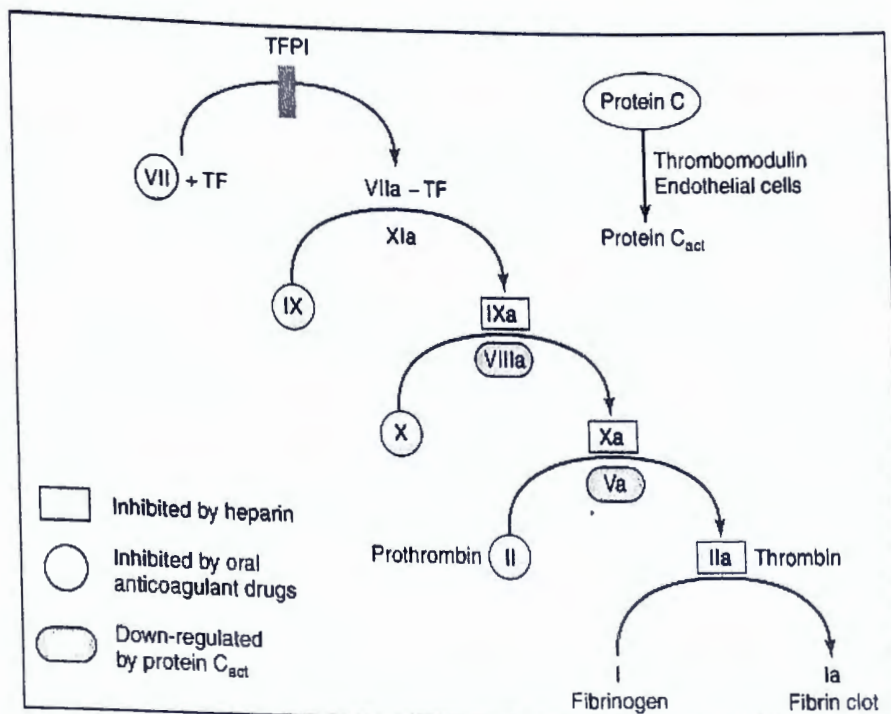


Fig. A model of blood coagulation. With tissue factor (TF), factor VII forms an activated complex (VIIa-TF) that catalyzes the activation of factor IX to factor IXa. Activated factor Xa also catalyzes this reaction. Tissue factor pathway inhibitor (TFPI) inhibits the catalytic action of the VIIa-TF complex. The cascade proceeds as shown, resulting ultimately in the conversion of fibrinogen to fibrin, an essential component of a functional clot. The two major anticoagulant drugs, heparin and warfarin (an oral anticoagulant), have very different actions. Heparin, acting in the blood, directly activates anticlotting factors, specifically antithrombin, which inactivates the factors enclosed in rectangles. Warfarin, acting in the liver, inhibits the synthesis of the factors enclosed in circles. Proteins C and S exert anticlotting effects by inactivating activated factors Va and VIIIa.

(Ref: Katzung-13th)

Q. How fluidity of blood is maintained in vivo? (CU-16Ju)

Ans.

Fluidity of blood is maintained in vivo by preventing intravascular coagulation by the following factors-

- 1. Endothelial surface factor:** Probably the most important factors for preventing clotting in the normal vessel are-
 - a. Smoothness of the endothelial surface** prevents contact activation of the intrinsic pathway.
 - b. Glycocalyx layer on the endothelial surface** repels the platelets & clotting factors and thereby prevents activation of clotting.
 - c. Thrombomodulin**, a thrombin-binding protein, is produced by endothelial cells. It acts by two ways-
 - It binds with thrombin $\rightarrow$ $\downarrow$ thrombin $\rightarrow$ $\downarrow$ clotting.
 - Thrombomodulin-thrombin complex activates protein C.
- 2. Speed of blood flow:** This prevents intravascular clotting of blood.
- 3. Presence of natural anticoagulants:**
 - a. Heparin:** Secreted by basophil & mast cell. It acts as a co-factor for antithrombin III.
 - b. Antithrombin III:** It combines with the thrombin and thus, blocks the effect of thrombin on the fibrinogen. The complex of antithrombin III & heparin inhibits the activated factors IX, X, XI and XII.

- c. **Fibrin:** It has antithrombin action. When a clot is forming, about 85 – 90 % of thrombin becomes absorbed to the fibrin fibers as they develop. This prevents the spread of thrombin into the remaining blood and, therefore, prevents excessive spread of the clot.
 - d. **Protein C:** Activated protein C (APC), along with its cofactor protein S, inactivates factors V and VIII and inactivates an inhibitor of tissue plasminogen activator, increasing the formation of plasmin.
 - e. **Protein S:** Acts as cofactor for protein C.
 - f. **Heparin sulfate**
 - g. **α_2 macroglobulin:** Binds some clotting factors & prevents their action.
4. **Plasmin (Fibrinolysin):** This enzyme lyses fibrin and fibrinogen, with the production of fibrinogen degradation products (FDP) that inhibit thrombin.

(Ref: Guyton-13th; Ganong-25th; Concise-6th/72,73)

Q. Classify anticoagulants. (RU-06S, SU-13J,08J, CU-12J,09Ju)

Q. Mention the different anticoagulants. (DU-16Ju,14J)

Q. Enumerate in-vivo anticoagulants. (DU-05S)

Q. Name the orally acting anticoagulants. (CU-06S)

Q. Name the low molecular weight heparin (LMW) preparations. (DU-10/08/07J; CU-06M, RU-12J)

Ans.

Anticoagulant drugs: Anticoagulants are the drugs which are used to prevent unwanted coagulation.

A. Anticoagulants acting in vitro: (in vitro)

1. Heparin
2. Ca chelating agents
 - 3.8% Na citrate
 - Na⁺-oxalate

B. Anticoagulants acting in vivo: (in vivo)

1. Parenteral anticoagulant drugs	
▪ Indirect thrombin inhibitors	1. Unfractionated heparin (UFH) / standard heparin / regular heparin 2. Low-molecular weight (LMW) heparin / fractionated heparin / irregular heparin: • Enoxaparin • Dalteparin • Tinzaparin 3. Synthetic pentasaccharide • Fondaparinux
▪ Parenteral direct thrombin inhibitors	• Hirudin • Lepirudin • Bivalirudin • Argatroban
2. Oral anticoagulant drugs	
▪ Coumarin anticoagulants	• Warfarin • Dicumarol
▪ Oral direct thrombin inhibitors	• Ximelagatran (withdrawn from the market because of hepatic toxicity) • Dabigatran

C. Anticoagulants acting in vivo & vitro: Heparin.

Acidic in nature
MW: 3000-30000

Heparin

Heparin is a heterogeneous mixture of sulfated mucopolysaccharides. It binds to endothelial cell surfaces and a variety of plasma proteins.

Viva Q. Why heparin is not administered orally?

Ans.

Heparin is not administered orally, because-

1. Digestion of heparin by amylase as it is mucopolysaccharide.
2. Less absorption due to negative charge.

Synthesis & Production in human

Source

→ Natural → Most common
Bovine
→ Synthetic → Beef lung
Intestinal mucin

Viva Q. Why heparin is not administered intramuscularly?

Ans.

Heparin is not administered intramuscularly because there will be hematoma formation at the site of injection. IM injection of heparin → Bleeding → ↓Coagulation due to action of heparin → More bleeding → Hematoma formation.

Q. What do you mean by LMW heparin? (RU-07J,06S)

Q. Name the low molecular weight heparin (LMWH). (RU-13Ju)

Q. Briefly discuss about low molecular weight heparin with clinical importance. (SU-13Ju)

Q. Short note: Low molecular weight heparin. (DU-13J,12J,SU-15Ju,12Ju)

Ans.
Low molecular weight heparin (LMWH): The LMWHs are heterogeneous compounds (one-third the size of unfractionated heparin) produced by the chemical or enzymatic depolymerization of unfractionated heparin. Because they are free of some of the drawbacks associated with the polymer, they are replacing the use of heparin in many clinical situations.

(Ref: Lippincott's-6th)

Q. Explain the anticoagulant mechanism of heparin. (DU-13Ju,11Ju, CU-13Ju,07J; RU-07J, SU-07S)

Q. How does LMWH acts? (SU-09J)

Q. Explain the anticoagulant action of enoxaparin. (SU-17M,11Ju)

Q. Short note: Enoxaparin. (SU-14Ju)

Ans.

Anticoagulant mechanism of heparin: Its biologic activity is dependent upon the endogenous anticoagulant **antithrombin III (AT-III)**.

Active heparin binds tightly with AT-III



Conformational change in AT-III molecule



More rapid interaction of AT-III with the serine proteases (activated clotting factors IIa, IXa, Xa).



Formation of AT-III-Serine protease complex.



Heparin functions as a **cofactor** for the 'AT-III-Serine protease complex' reaction without being consumed. It actually potentiates the action of AT-III by 1000 times.



Inactivation of serine proteases (IIa, IXa, Xa) by the AT-III.

- High-molecular-weight fractions of heparin with high affinity for antithrombin markedly inhibit blood coagulation by inhibiting all three factors, especially thrombin (IIa) and factor Xa.
- In contrast, LMW heparin inhibit factor Xa but have less effect on thrombin.

(Ref: Katzung-13th)

Viva Q. Why LMW Heparin inhibits only Xa by AT-III?

Ans.

To inhibit factors other than factor Xa, ≥ 18 monosaccharide units are required. But LMW heparin has only 15 monosaccharide units. So, LMW heparin produces an anticoagulant effect mainly through inhibition of Xa by AT-III.

(Ref: Goodman Gilman-12th edition)

Q. Mention the indications of heparin. (DU-07J,04S, SU-15J, CU-02J, RU-04M)

Q. Mention the therapeutic/clinical uses of heparin. (CU-13Ju; SU-10)

Q. Mention the important indications of LMW heparin. (DU-07J, RU-13Ju,12J)

Q. Mention the clinical uses of enoxaparin. (DU-16Ju)

Ans.

Indications / clinical uses of Heparin/ LMW heparin / Enoxaparin:

1. Acute MI
2. Unstable angina
3. Deep vein thrombosis (DVT)
4. Pulmonary embolism
5. Angiogram
6. Prophylaxis of deep vein thrombosis (DVT) & pulmonary embolism in high risk patient undergoing surgery / stroke or other immobilized patients
7. To maintain the patency of cannula & shunts in dialysis patients & in extra-corporal circulation.
8. Disseminated intravascular coagulation (DIC)
9. Cerebral infarction
10. Thoracic surgery

• Thromboembolic disease
• Dialysis
• ICU
• Bypass surgery

(Ref: Lippincott's-6th)

Q. What are the adverse effects of heparin? (DU-11Ju, CU-02J, RU-04M)

Ans.

Adverse effects of heparin:

1. Hemorrhage.
2. Hypersensitivity reactions (chills, fever, urticaria or anaphylactic shock)
3. Thrombosis (due to reduction of antithrombin-III).
4. Thrombocytopenia.
5. Osteoporosis leading to pathological fracture.
6. Transient alopecia.

Q. Mention the contraindications of heparin. (SU-15J)

Ans.

Contraindications of heparin:

1. Hypersensitivity reaction
2. **Bleeding disorders:** Hemophilia, thrombocytopenia, purpura.
3. **Preexisting hemorrhagic state:** Chronic liver disease (CLD), hepatic failure, renal failure.
4. Active bleeding peptic ulcer disease.
5. Recent cerebral hemorrhage / intracranial hemorrhage.
6. Uncontrolled hypertension
7. Subacute bacterial endocarditis
8. Active tuberculosis
9. Threatened abortion
10. Large visceral carcinoma
11. Recent surgeries especially to eye or CNS.
12. Lumbar puncture or regional anesthetic block.
13. Heparin should be used in pregnant women only when clearly indicated.

(Ref: Katzung-13th)

Ans.

(73) ~~more~~ insulin 3500

- (Ref: Bennett & Brown-11th)

(Ref: Bennett & Brown-11th)

Ans.

(Ref: Tripathi-6th/599)

Ans.

(Ref: Katzung-13th edition)

Q. Compare & contrast standard & low molecular weight heparin as anticoagulant. (CU-15Ju, RU-09J)

Q. Differentiate between LMWH and UFH (unfractionated heparin). (CU-06M; SU-08J)

Q. Compare the clinical status of low molecular weight heparin with unfractionated heparin. (DU-13Ju)
Ans.

Differences between LMWH and traditional/conventional/unfractionated heparin

Traits	LMW Heparin	Unfractionated heparin
1. Molecular weight	4500 Dalton	12000 Dalton
2. Monosaccharide unit	15	40
3. Effect on APTT	No	Prolonged
4. Plasma protein binding	Less	More
5. Pharmacokinetics	More predictable	Unpredictable
6. Plasma $t_{1/2}$	Longer	Shorter
7. Bioavailability	More	Less
8. Activity	Inhibits factor Xa	Inhibits factor IIa, IXa, Xa
9. Dosing interval	Less frequent (Once or twice a day)	More frequent
10. Monitoring	Not required	Required (by APTT)
11. Use	More convenient to use	Less convenient
12. Suitability	Suitable for outpatient.	Not suitable for outpatient
13. Thrombocytopenia	Less frequent	More frequent
14. Hemorrhagic complications	Lower incidence	Higher incidence

Q. How would you manage a case of bleeding from excessive anticoagulant action of heparin? (RU-15Ju)
Ans.

Management of bleeding from excessive anticoagulant action of heparin:

1. Stop heparin
2. Inj. protamine sulfate:
 - When infused slowly, it combines ionically with heparin to form a stable, 1:1 inactive complex.
 - Dose of protamine sulfate: 1 mg for every 100 units of heparin administered.
3. Close monitoring of the activated partial thromboplastin time (APTT) is necessary in patients receiving heparin.

(Ref: Lippincott's-6th/301)

Warfarin

Q. Explain mechanism of action of warfarin. (DU-17J, RU-16Ju, 14Ju, 05S, CU-04J, SU-08Ju, 07J)

Q. Discuss how warfarin acts as anticoagulant. (DU-14J)

Q. Discuss the mechanism of action of dicumarol? (RU-03S, SU-03J)

Q. How does orally acting anticoagulant produce their action? (CU-06S)

Ans.

Mechanism of action of warfarin/ dicumarol/ oral anticoagulant: The vitamin K-dependent factors II, VII, IX and X are produced as inactive proteins. These factors are rich in glutamic acid (Gla) residues, which must be further carboxylated to enable the proteins to maintain an active tertiary structure. The carboxylase enzyme responsible for this in the liver requires vitamin K as a co-factor. Vitamin K is converted to an epoxide in this reaction and must be regenerated to its active form by a reductase enzyme. This reductase is inhibited by warfarin/ dicumarol, which results in inhibition of the carboxylation cycle and is the basis of the anticoagulant effect of coumarins.

Warfarin / dicumarol → inhibits vitamin-K epoxide reductase → Inhibition of conversion of vitamin-K epoxide to its active form → Inhibits carboxylation of glutamic acid residues in factors II, VII, IX & X → No activation of factors II, VII, IX & X → Anticoagulant effect.

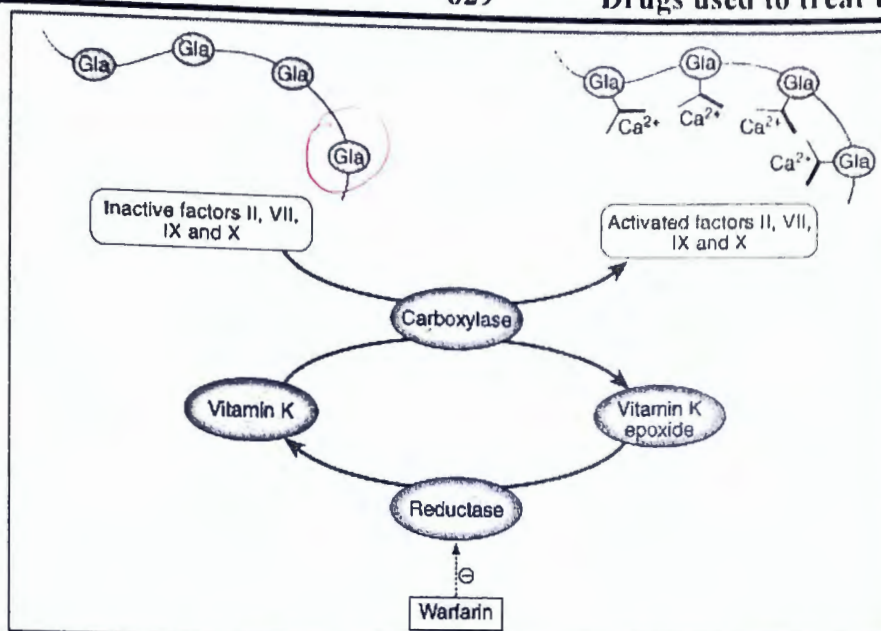


Figure. The role of vitamin K in clotting and the mechanism of action of warfarin.

(Ref: Davidson's medicine-22nd)

Q. Why are oral anti-coagulants indirectly acting? (DU-09Ju)

Ans.

Warfarin exerts its anticoagulant effect by inhibiting vitamin-K epoxide reductase enzyme which results in decreased synthesis of vitamin K dependent clotting factors. As warfarin / oral anticoagulants do not exert their action by direct interference in the coagulation cascade, they are also called indirect acting anti-coagulants.

Q. Why there is a delay in the mechanism of action of warfarin? (SU-07J)

Ans.

Delay in anticoagulant action of warfarin: Warfarin inhibits vitamin-K epoxide reductase enzyme. As a result, the synthesis of vitamin K dependent clotting factors (factors II, VII, IX & X) is decreased. There is an 8- to 12-hour delay in the action of warfarin. Its anticoagulant effect results from a balance between partially inhibited synthesis and unaltered degradation of the four vitamin K-dependent clotting factors. The resulting anticoagulation is dependent on their degradation half-lives in the circulation. These half-lives are 6, 24, 40, and 60 hours for factors VII, IX, X, and II, respectively. Larger initial doses of warfarin hasten the onset of the anticoagulant effect.

(Ref: Katzung-13th)

Q. Discuss pharmacokinetics of warfarin. (SU-07J)

Ans.

Pharmacokinetic properties of warfarin:

1. **Route:** Oral
2. **Bioavailability:** 100%
3. **Onset of action:** At least 8-12 hours after administration.
4. **Duration of action:** 3 - 6 days.
5. **Plasma Protein Binding:** 99 % is bound to albumin
6. **Volume of distribution:** Low
7. **Plasma half life ($t_{1/2}$):** 36 - 48 hours
8. **Metabolism:** Liver
9. **Excretion:** Kidney
10. **Others:** It crosses placenta & it may secrete in breast milk.

(Ref: Katzung-13th; Tripathi-6th/601)

Q. Write down the indications of oral anticoagulants. (DU-09Ju)

Q. Mention the indications of warfarin. (RU-05S, SU-03J)

Ans.

Indications of oral anticoagulants / warfarin:

1. Myocardial infarction (MI).
2. Deep vein thrombosis
3. Hip arthroplasty
4. Fractured femur operation
5. Pulmonary embolism
6. Systemic embolism
7. Mitral stenosis with embolism
8. Transient ischemic attacks
9. Atrial fibrillation
10. Heart failure.

(Ref: Katzung-13th)

Q. Write down the adverse effects of oral anticoagulants. (DU-09Ju)

Q. Why warfarin is not suitable in pregnancy? (DU-11Ju)

Q. Write down adverse effects of warfarin therapy. (DU-17J, CU-14J, RU-03S; SU-03J)

Ans.

Adverse effects of warfarin:

1. **Bleeding disorders:** Bleeding is the commonest complication of warfarin therapy. Hemorrhage is most likely to occur in the alimentary and renal tracts, and in the brain in those with cerebrovascular disease.
2. **Skin reactions:** purpura, ecchymoses, hypersensitivity, rash and alopecia.
3. **Skin necrosis** due to a mixture of hemorrhage and thrombosis occurs rarely where induction of warfarin therapy is over-abrupt and/or the patient has a deficiency of protein C or protein S.
4. **Infarction of the breast, fatty tissues, intestine, and extremities.**
5. **Hemorrhagic infarction in venous thrombosis** is caused by warfarin-induced depression of protein C synthesis.
6. **Teratogenesis:**
 - Warfarin crosses the placenta readily and can cause a hemorrhagic disorder in the fetus.
 - The drug can cause a serious birth defect characterized by-
 - Skeletal disorders (5%) (bossed forehead, sunken nose, foci of calcification in the epiphyses).
 - Absence of the spleen.
 - CNS abnormalities (microcephaly, cranial nerve palsies).

Thus, warfarin should never be administered during pregnancy.

(Ref: Bennett & Brown-11th + Katzung-13th)

Q. How will you manage warfarin toxicity?

Q. What is the antidote of warfarin toxicity? (RU-03S; SU-03J)

Ans.

Management of warfarin toxicity: Excessive anticoagulant effect and bleeding from warfarin can be reversed by-

1. Stopping the drug
2. **Antidote:** Oral or parenteral vitamin K₁ (phytonadione)
3. Fresh-frozen plasma
4. Prothrombin complex concentrates
5. Recombinant factor VIIa (rFVIIa).

(Ref: Katzung-13th)

Q. Write down monitoring of warfarin therapy. (RU-03S; SU-03J)

Ans. ~~X~~

Monitoring of warfarin therapy: Monitoring of therapy is by the **prothrombin time**. Usually the test is carried out with a standardized thromboplastin and the result is expressed as the **International Normalised Ratio (INR)**.

Normal range of INR:

- ✓ for a healthy person is **0.9–1.3**.
- ✓ for people on warfarin therapy, **2.0–3.0**.
- higher in patients with a mechanical heart valve.

(Ref: Bennett & Brown-11th)

Nice to know

International normalized ratio (INR): It is the ratio of the prothrombin time in the patient to that in a normal (non-anticoagulated) person—taking account of the sensitivity of the thromboplastin used. INR reliably reflects the degree of prothrombin activity.

The result (in seconds) for a prothrombin time performed on a normal individual will vary depending on what type of analytical system it is performed. The INR was devised to standardize the results. The INR is the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the ISI (International Sensitivity Index) value for the analytical system used.

$$INR = \left(\frac{PT_{\text{test}}}{PT_{\text{normal}}} \right)^{ISI}$$

Interpretation: A high INR level such as $INR=5$ indicates that there is a high chance of bleeding, whereas if the $INR=0.5$ then there is a high chance of having a clot.

Q. Mention the contraindications of anticoagulants.

Ans.

Contraindications of anticoagulants

1. Hematological: Pre-existing bleeding tendency like
 - Hemophilia
 - Purpura
 - Thrombocytopenia
 - Active bleeding
2. Cardiovascular:
 - Long standing hypertension
 - Infective endocarditis.
3. Neurological:
 - Stroke due to intracranial hemorrhage (within 3 wks)
 - Recent surgery: Brain or eye surgery
 - Lumbar puncture or regional block
4. Renal impairment
5. Pregnancy (Oral anticoagulant crosses the placental barrier → Dicumarol syndrome)
6. Hypersensitivity reaction (Heparin)
7. Alcohol dependence.
8. Active pulmonary TB
9. Ulcerative lesions of GIT
10. Threatened abortion.

Q. How does heparin differ from warfarin? (DU-07Ju, SU-08Ju, CU-01S)

Q. Compare the mechanism of action & possible adverse effects of warfarin & heparin. (CU-12J, 09Ju)

Q. Compare & contrast heparin & warfarin as anticoagulant. (DU-07Ju/J, CU-16Ju; RU-06J; SU-09Ju)

Ans.

Differences between heparin & warfarin:

Traits	Heparin	Warfarin
1. Source	Animal source: Hog lung, Pig intestine	• Plant source, eg, sweet clove • Synthetic
2. Chemical nature	Mucopolysaccharide	Coumarin derivatives
3. Route of administration	Parenteral (SC or IV)	Oral
4. Activity	Both in vivo & in vitro	Only in vivo
5. Plasma $t_{1/2}$	Shorter	Larger
6. PPB	Less	High
7. Volume of distribution	High	Low
8. Onset of action	Rapid (within 5-10 min)	Delayed (1 - 3 days)
9. Duration of action	4 - 6 hours	3 - 6 days
10. Placental barrier	Cannot cross	Can cross
11. Teratogenic effect	Absent	Present
12. Individualization of dose	No need	Needed
13. Excretion	Renal	Renal and GIT
14. Histamine release	Occurs	Does not occur
15. Mechanism of action	Heparin binds with AT-III and inactivates factors II, X, IX, VII.	Warfarin inhibits synthesis of vitamin K-dependant clotting Factors
16. Monitoring of therapy	By APTF or CT	By PT, INR
17. Effect over lipoprotein lipase	Stimulatory effect.	Has no effect
18. Use	To initiate anticoagulant therapy	For maintenance of anticoagulant therapy
19. Antidote of toxicity	Protamine sulfate	Vitamin-K

(Ref: Tripathi-6th/604)

Q. Mention the drug interaction of oral anticoagulant (warfarin).

Ans.

Drug interaction of warfarin:

A. Drugs that potentiate warfarin action:

1. Drugs that inhibit hepatic drug metabolism	• Cimetidine • Chloramphenicol • Ciprofloxacin • Metronidazole • Amiodarone • Ketoconazole • Fluconazole
2. Drugs that inhibit platelet functions	• NSAIDs (aspirin) • Carbenicillin • Moxalactam
3. Drugs that displace warfarin from albumin	• NSAIDs (aspirin) • Chloral hydrate
4. Drugs that inhibit reduction of vitamin K	• Cephalosporins
5. Drugs that decrease availability of vitamin K	• Broad spectrum antibiotics- (ciprofloxacin, sulfonamides, tetracyclines, amoxicillin, ampicillin)

B. Drugs that inhibit warfarin action

1. Physiological / disease state	• Pregnancy • Hypothyroidism
2. Vitamin K	
3. Drugs that induce drug metabolizing enzymes	• Rifampicin • Carbamazepine • Barbiturates • Griseofulvin
4. Drugs that decrease absorption	• Colestyramine

(Ref: Rang & Dale's-8th)

Fibrinolytic / Thrombolytic drugs

Q. Mention the fibrinolytic / thrombolytic drugs. (DU-16Ju,07Ju; CU-14Ju, RU-14J,12Ju,11J,08Ju)

Q. Short note: Fibrinolytics. (SU-15Ju)

Ans.

Fibrinolytic / thrombolytic drugs: Acute thromboembolic disease may be treated by the administration of agents that activate the conversion of plasminogen to plasmin- a serine protease that hydrolyzes fibrin and, thus, dissolves clots.

1. Streptokinase
2. Alteplase
3. Urokinase
4. Tissue plasminogen activator (t-PA)
5. Reteplase
6. Tenecteplase

First generation: Streptokinase

Second generation: Alteplase

Third generation: Reteplase

Q. Explain the mechanism of action of streptokinase. (RU-14J,12Ju,11J,08Ju)

Q. Explain the role of streptokinase in acute ischemia. (SU-14J)

Q. Explain the pharmacological basis of the use of streptokinase in the management of acute myocardial infarction. Enumerate the alternative to streptokinase in this clinical condition. (CU-06M)

Q. Short note: Streptokinase. (DU-12J, RU-15J)

Ans.

Mechanism of action of streptokinase:

Streptokinase combines with plasminogen

↓

Streptokinase-plasminogen complex

↓

Conversion of plasminogen to plasmin

↓

Degradation of fibrinogen, fibrin, clotting factors V & VII by plasmin

↓

Dissolution of clot in the embolus or thrombus

↓

Re-opening of the blood vessel.

↓
Increased blood flow to the myocardium.
↓
Relief of myocardial ischemia / infarction.

(Ref: Lippincott's-6th)

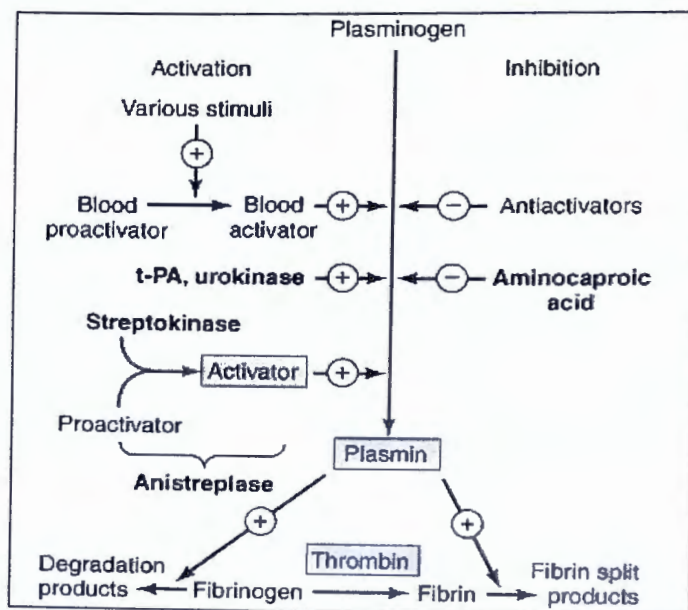


Fig. Schematic representation of the fibrinolytic system. Plasmin is the active fibrinolytic enzyme. Several clinically useful activators are shown on the left in bold. Anistreplase is a combination of streptokinase and the proactivator plasminogen. Aminocaproic acid (right) inhibits the activation of plasminogen to plasmin and is useful in some bleeding disorders. (t-PA, tissue plasminogen activator.)

(Ref: Katzung-13th edition)

Q. Mention the indications of streptokinase? (RU-12Ju)

Q. Mention the indications of thrombolytic/fibrinolytic drugs. (RU-14J,11J)

Ans.

Indications of streptokinase:

1. Acute myocardial infarction (ST elevated MI, within 12 hours of onset of pain)
2. Acute pulmonary embolism
3. Severe deep venous thrombosis:
 - Superior venacaval syndrome
 - Ascending thrombophlebitis
4. Peripheral vascular disease
5. Occluded arterio-venous shunts.

(Ref: Lippincott's-6th)

Q. Mention the role of streptokinase in IHD. (SU-13J)

Q. Explain the pharmacological basis for the use of Streptokinase in the management of acute MI. Enumerate the alternatives to Streptokinase in this clinical condition. (CU-06M)

Ans.

Use of streptokinase In MI: Ideally streptokinase (thrombolytics) should be administered as soon as possible after the onset of symptoms. They act to dissolve the thrombus, salvage the myocardium, and limit the extent of damage.

Alternate to streptokinase:

- Alteplase
- Reteplase

- Tissue plasminogen activator (tPA)
- Tretceplase
- Recombinant prourokinase

Q. Write down the adverse effects of streptokinase. (RU-12Ju,08Ju, SU-05M)

Q. Write down the limitations of fibrinolytic drugs. (RU-14J)

Ans.

Adverse effects of streptokinase:

1. **Bleeding disorders:** due to dissolution of haemostatic plugs by elevated levels of plasmin.
2. **Hypersensitivity reaction:** Streptokinase is a foreign protein and is antigenic. Fever, rash & rarely anaphylaxis occur.
3. **GIT:** Nausea, vomiting
4. Multiple micro-emboli
5. Cardiac arrhythmias from reperfusion of ischemic areas.

(Ref: Katzung-13th)

Q. Mention the contraindications of streptokinase?

Ans.

Contraindications of streptokinase:

1. Recent trauma.
2. Recent surgery (within 6 months).
3. Hemorrhagic stroke.
4. Severe hypertension.
5. Active bleeding peptic ulcer disease.
6. Aneurysm.
7. Bleeding disorder.
8. Acute pancreatitis.
9. Diabetes mellitus.

(Ref: Tripathi-6th/607 & 608)

Fibrinolytic inhibitors / Drugs used to stop bleeding

Q. Name the drugs used to stop bleeding.

Q. Name the anti-fibrinolytic drugs.

Ans.

Drugs used to stop bleeding/ Fibrinolytic inhibitors/ Anti-fibrinolytic drugs:

1. Aminocaproic acid / epsilon aminocaproic acid (EACA) → 4 hrs to 12 hrs Hospital
2. Tranexamic acid (an analog of aminocaproic acid). → 12 hrs to 12 hrs Tablet 1000 mg
3. Protamine sulfate (antidote of heparin)
4. Vitamin K₁ / phytonadione (antidote of warfarin) → umbilical cord & a bleeding at birth of (stale) 1-2 months
5. Aprotinin (serine protease inhibitor)

(Ref: Lippincott's-6th)

Q. Write down the mechanism of action of aminocaproic acid / tranexamic acid.

Ans.

Mechanism of action of aminocaproic acid / tranexamic acid: Aminocaproic acid and tranexamic acid are synthetic inhibitors of fibrinolysis.

Aminocaproic acid / Tranexamic acid

↓
Competitively inhibits the binding of plasminogen and t-PA to fibrin

↓

Thus inhibits plasminogen activation



No plasmin



No degradation of fibrinogen, fibrin, clotting factors V & VII.



Bleeding is stopped by the action of these clotting factors and fibrin.

(Ref: Katzung-13th + Bennet & Brown-11th)

Q. What are the indications of aminocaproic acid / tranexamic acid?

Ans.

Ruptured oesophageal
varices
Incomplete abortion

Indications of aminocaproic acid / tranexamic acid:

1. Adjunctive therapy in hemophilia
2. Overdose of fibrinolytic drugs (streptokinase / urokinase / alteplase)
3. Prophylaxis for rebleeding from intracranial aneurysms
4. Postsurgical gastrointestinal bleeding and postprostatectomy bleeding, after tonsillectomy, tooth extraction in hemophilic patient, uterine cervical conisation.
5. Bladder hemorrhage secondary to radiation- and drug-induced cystitis
6. Gynecological: Abruptio placenta, post-partum hemorrhage (PPH) & certain cases of menorrhagia.
7. After cardio-pulmonary bypass surgery.
8. Recurrent epistaxis, ocular trauma & bleeding peptic ulcer disease.
9. Thrombocytopenia: To reduce the risk of hemorrhage.

(Ref: Katzung-13th; Bennett & Brown-11th)

Q. Mention the adverse effects of aminocaproic acid / tranexamic acid.

Ans.

Adverse effects of aminocaproic acid / tranexamic acid:

1. Intra-vascular thrombosis.
2. CVS: Hypotension, bradycardia & arrhythmia.
3. GIT: Nausea, diarrhea, abdominal discomfort.
4. Headache, giddiness.
5. Myopathy
6. Nasal stuffiness.

(Ref: Katzung-13th)

Contraindication of aminocaproic acid / tranexamic acid: The drug should not be used in patients with-

1. Disseminated intravascular coagulation
2. Genitourinary bleeding of the upper tract, eg, kidney and ureters, because of the potential for excessive clotting.

(Ref: Katzung-13th)

Life threatening condition → Adverse effects
Acute Presentation

HDL ↓ ⇒ HF

Smoking, Diet, ↓ M ⇒ ↓ HDL

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Drugs used to treat the diseases of Blood

Lipid lowering agents

Lipoproteins: Four major groups of plasma lipoproteins have been identified:

1. **Chylomicrons:** Transport dietary TG, cholesterol and cholesteryl esters from intestine to the peripheral tissue.
2. **Very low density lipoproteins (VLDL):** Transport TG from liver to peripheral tissue.
3. **Low-density lipoproteins (LDL):** Transport cholesterol from liver to peripheral tissue.
4. **High-density lipoproteins (HDL):** Transport cholesterol from peripheral tissues to the liver (Reverse cholesterol transport).

Classification of Hyperlipidemia / Dyslipidaemia:

Disease	Elevated lipid results	Elevated lipoprotein	CHD risk
Predominant hypercholesterolaemia	TC ± TG	LDL ± VLDL	+
• Familial hypercholesterolaemia	TC ± TG	LDL ± VLDL	+++
• Hyperalphalipoproteinaemia	TC	HDL	--
Predominant hypertriglyceridaemia	TG	VLDL ± LDL	Variable
• Lipoprotein lipase deficiency	TG > TC	Chylomicron	?
• Familial hypertriglyceridaemia	TG + TC	VLDL + Chylo	?
Mixed hyperlipidemia	TC + TG	VLDL + LDL	Variable
• Familial combined hyperlipidemia	TC and/or TG	LDL and VLDL	++
• Dysbetalipoproteinaemia	TC and/or TG	IDL	+++

(Ref: Davidson's medicine-22nd)

	Desirable mg/dL (mmol/L)	Borderline to High mg/dL (mmol/L)	High
Total cholesterol	< 200 (5.2)	200–239 (5.2–6.2)	> 240 (6.2)
LDL cholesterol	< 130 (3.4)	130–159 (3.4–4.1)	> 160 (4.1)
HDL cholesterol			> 60 (1.55)
Men	> 40 (1.04)		
Women	> 50 (1.30)		
Triglycerides	< 120 (1.4)	120–199 (1.4–2.3)	> 200 (2.3)

(Ref: Katzung-13th)

Q. Enlist the lipid lowering agents. (DU-16Ju, RU-13Ju, 11Ju, CU-14J, 12Ju)

Q. Enlist important /clinically used lipid lowering agents. (DU-14J, 12/10Ju)

Q. Categorize drugs used in hyperlipidemia/dyslipidemia. (CU-12J, RU-12Ju)

Q. Name the statin preparations used as hypolipidemic agent. (RU-07J)

Q. Name four lipid lowering agents. (DU-17M)

Ans.

Lipid lowering agents:

A. Predominantly cholesterol lowering agents:

1. HMG-CoA reductase inhibitors (Statins): (↓cholesterol synthesis & ↑LDL catabolism)	▪ Lovastatin ▪ Atorvastatin ▪ Fluvastatin ▪ Pravastatin ▪ Simvastatin ▪ Rosuvastatin
2. Cholesterol absorption inhibitors	▪ Ezetimibe

3. Bile acid-binding resins	▪ Colestipol ▪ Cholestyramine ▪ Colesevelam
4. Niacin (Vit-B3)	

B. Predominantly TG lowering agents:

1. Fibrates / fibric acid derivatives	▪ Gemfibrozil ▪ Fenofibrate ▪ Bezafibrate
2. Highly poly-unsaturated long-chain n-3 fatty acids	▪ Eicosapentanoic acid ▪ Docosahexanoic acid

(Ref: Davidson's medicine-22nd; Lippincott's-6th)

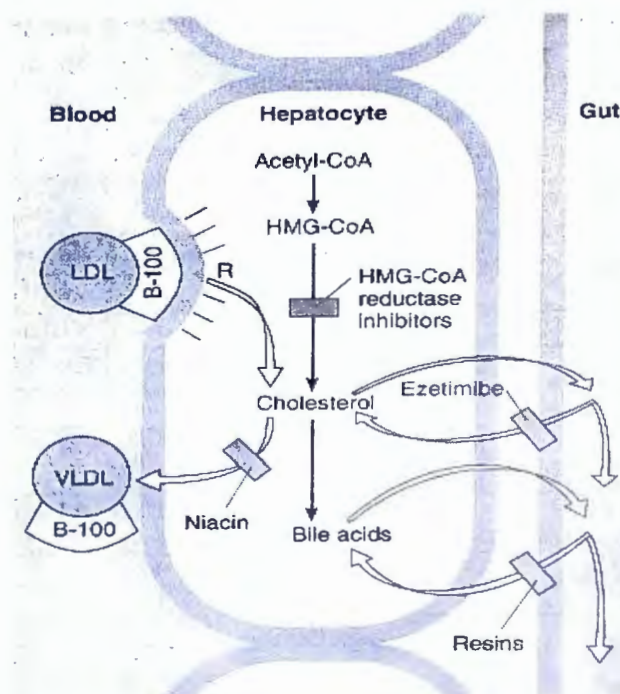


Fig. Sites of action of HMG-CoA reductase inhibitors, niacin, ezetimibe, and resins used in treating hyperlipidemias. LDL receptors (R) are increased by treatment with resins and HMG-CoA reductase inhibitors.

(Ref: Katzung-13th)

Atorvastatin

Q. Short note: Atorvastatin. (DU-14Ju, 11Ju, 10J)

Q. Short note: Statin. (RU-15J)

Ans. Write in brief from below.

Q. How does statins decrease serum cholesterol level? (DU-17M, RU-12Ju, 11Ju)

Q. Write down the mechanism of action of statin. (DU-16Ju, 14J)

Q. Write down the mechanism of action & indications of atorvastatin. (DU-12/10Ju)

Q. Write down the mechanism of action fluvastatin. (RU-13Ju)

Q. Write down the mechanism of action simvastatin. (CU-14J)

Q. Explain the role of atorvastatin in heart disease/IHD. (SU-13J, 12Ju)

Ans.

Rate limiting step HMG CoA → mevalonate

Mechanism of action of Atorvastatin / Fluvastatin / Simvastatin / HMG CoA reductase inhibitors / statins:

- **Inhibition of HMG CoA reductase:** All Statins have strong affinity for HMG CoA reductase enzyme. So, they compete effectively to inhibit HMG CoA reductase enzyme → Block the rate limiting step of cholesterol synthesis → ↓Cholesterol synthesis → ↓VLDL → ↓LDL.
- **Increase in LDL receptors:** Depletion of intra-cellular cholesterol due to decrease in its synthesis → ↑Cell surface LDL-receptor → ↑Binding of LDL with its receptor & ↑Internalization occurs → ↑Catabolism LDL → ↓Plasma cholesterol.

(Ref: Lippincott's-6th)

Nice to know

Therapeutic Uses & Dosage: HMG CoA reductase inhibitors (atorvastatin) are useful in lowering plasma cholesterol levels in all types of hyperlipidemia.

Q. Why statins are preferred to administer in the evening? (RU-13Ju)

Ans.

Statins are preferred to administer in the evening: Because cholesterol synthesis occurs predominantly at night, reductase inhibitors—except atorvastatin and rosuvastatin—should be given in the evening if a single daily dose is used. Absorption generally (with the exception of pravastatin) is enhanced by food.

(Ref: Katzung-13th)

Q. Write down the adverse effects of statin. (DU-14J)

Q. What are the adverse effects of atorvastatin? (DU-10Ju)

Ans.

Adverse effects of statins/ atorvastatin: Serious side effects are rare (well below 2%)

1. **Liver function:** Biochemical abnormalities of liver function may occur. So, liver function should be evaluated periodically.
2. **Muscle:** Myopathy, myalgia, myositis & rhabdomyolysis (rarely).
3. **Drug interaction:** May increase warfarin level, thus increasing bleeding tendency. So, it is important to evaluate prothrombin time frequently.

(Ref: Lippincott's-6th)

Q. Mention the contraindications of statins / atorvastatin.

Ans.

Contraindications of statins:

1. Pregnancy or women who are likely to become pregnant
2. Nursing mother.
3. Children & teenagers.

(Ref: Lippincott's-6th)

Fenofibrate

Mechanism of Action: These agents function primarily as ligands for the nuclear transcription receptor, peroxisome proliferator-activated receptor-alpha (PPAR-α). They increase lipolysis of lipoprotein triglyceride via lipoprotein lipase (LPL) resulting in decrease in triglyceride in plasma. Intracellular lipolysis in adipose tissue is decreased. Levels of VLDL decrease. Only modest reductions of LDL occur in most patients. HDL cholesterol increases moderately.

Indication:

1. Hypertriglyceridemias in which VLDL predominate
2. Dysbetalipoproteinemia
3. Hypertriglyceridemia that results from treatment with viral protease inhibitors

(Ref: Katzung-13th)

Q. What are the adverse effects of fibrates/fenofibrates?

Ans.

Adverse effects of fibrates / fenofibrates:

- 1. **GIT:** Mild GIT disturbances.
- 2. **Muscle:** Myalgia, myopathy, myositis.
- 3. **Biliary tree:** Increases risk of gall stone formation
- 4. Abnormal liver function tests
- 5. **Drug interaction:** Increase warfarin level, thus increasing bleeding tendency.

(Ref: Lippincott's-6th)

Q. What are the contraindications of fibrates/fenofibrates?

Ans.

Contraindications of fibrates/fenofibrates:

- 1. Pregnancy
- 2. Lactation
- 6. Renal failure
- 7. Hepatic failure
- 8. Pre-existing gall bladder pathology.

(Ref: Lippincott's-6th)

Nice to know

Characteristics of antihyperlipidemic drug families

Type of drug	Effect on LDL	Effect on HDL	Effect on triacylglycerols
Statins	↓↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑↑	↓↓↓↓↓
Niacin	↓↓	↑↑↑↑↑	↓↓↓
Bile acid-binding resins (Cholestyramine)	↓↓↓	↑	Minimal
Cholesterol absorption inhibitors (Ezetimibe)	↓	↑	↓

(Ref: Lippincott's-6th)

Hematinics (Fe, Vit-B₁₂, Folic Acid)

Erythropoiesis: Erythropoiesis means the process of formation of erythrocyte under normal physiological conditions. It starts in the 3rd week of intrauterine life.

Essential nutrients and factors required for normal erythropoiesis: They are as follows:

1. Iron
2. Vitamin B₁₂
3. Folic acid
4. Hemopoietic growth factors, eg, erythropoietin.

Anemia: Anemia means a deficiency of hemoglobin, which can be caused by either too few red blood cells or too little hemoglobin in the cells.

(Ref: Guyton-12th/420)

Q. List hematinics. (DU-15J, RU-11J, SU-09J)

Q. List commonly used hematinics. (CU-14J)

Q. List hematinic drugs. (DU-11J, 09Ju)

Q. Write anti-anemic drugs. (CU-11Ju; RU-12J)

Ans:

Hematinic drugs: Hematinics are the drugs which increase erythropoiesis resulting in increase in the number of RBC or hemoglobin content or both and ultimately correction of anemia.

List of hematinics / anti-anemic drugs:

1. Iron preparations
2. Vitamin B₁₂-preparations
3. Folic acid preparations
4. Hematopoietic growth factors, eg, Erythropoietin

Q. Name the hematinics used during pregnancy. (RU-10J)

Ans.

Hematinics safe during pregnancy:

1. Iron preparations: Iron salts (oral) & iron dextran (IV or IM) both are safe.
2. Folic acid.
3. Vitamin B₁₂.

IRON

Total body iron is 3-5 g (40-50 mg/kg) (male > female).

Q. Describe the pharmacokinetics of iron. (CU-11Ju)

Ans.

Pharmacokinetics of iron

Iron absorption:

- **Average dietary iron contents:** 10 - 15 mg/day (Dietary iron remains in the ferric form (Fe³⁺))
- **Amount of daily absorption:** About 5-10% of dietary contents (0.5-1 mg/day)
- **Form of absorption:** Iron is exclusively absorbed in ferrous (Fe²⁺) form.

Iron transport: Fe is transported in the plasma by binding with transferrin (an α-globulin) that specifically binds with two molecules of Fe²⁺.

Storage of iron:

Forms of storage iron	1. Ferritin 2. Haemosiderin
Site of storage	1. Reticulo-endothelial cells: Spleen, liver, bone marrow. 2. Hepatic parenchymal cells 3. Skeletal muscles.

Importance of ferritin level: Ferritin is detectable in serum. Since the ferritin present in serum is in equilibrium with storage ferritin in RE tissues, the “serum ferritin level” can be used to estimate total body Fe stores.

Elimination of Iron:

- There is no mechanism for Fe excretion.
- Small amounts are lost in the faeces by exfoliation of intestinal mucosal cells.
- Trace amounts are excreted in bile, urine & sweat.

(Ref: Katzung-13th + de Gruchy-5TH/38-40)

Q. How oral iron preparations are absorbed from GIT? (DU-06M; RU-14Ju,09Ju,06/05S)

Q. How iron is absorbed from GIT? (CU-16Ju,14J)

Q. Describe mechanism of Iron absorption. (CU-16J)

Ans:

Absorption of oral iron preparations: Oral iron preparations contain iron in the ferrous (Fe^{2+}) form. Fe^{2+} is soluble and is readily absorbed. Iron crosses the luminal membrane of the intestinal mucosal cell by two mechanisms: active transport of ferrous iron and absorption of iron complexed with heme. The divalent metal transporter, DMT1, efficiently transports ferrous iron across the luminal membrane of the intestinal enterocyte. Together with iron split from absorbed heme, the newly absorbed iron can be actively transported into the blood across the basolateral membrane, probably by the transporter IREG1, also known as ferroportin1. Excess iron can be stored in the mucosal cell as ferritin, a water-soluble complex consisting of a core of ferric hydroxide covered by a shell of a specialized storage protein called apoferritin.

(Ref: Katzung-13th)

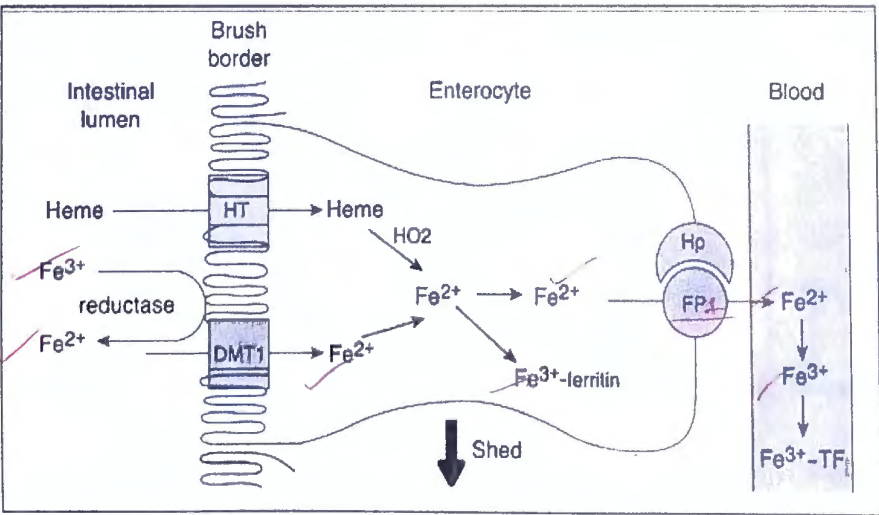


Fig. Absorption of oral iron (Ref: Ganong-24th edition)

Q. Describe the factors that can hasten & retard the absorption of the oral iron preparations from the gut. (CU-11J,09/08Ju)

Ans.

Factors affecting iron absorption:

Factors/conditions increasing absorption	Factors/conditions decreasing absorption
1. Iron deficiency anemia & other anemia 2. Pregnancy 3. Growing age 4. Vitamin-C 5. Meat 6. Citric acid 7. Sugar 8. Amino acid 9. A low phosphorus diet	1. Malabsorption syndrome 2. Partial or total gastrectomy 3. Tannin (in tea) 4. A high phosphorus diet (bread, cereals & milk) 5. Salts of phosphate, bicarbonate, phytates 6. Phytic acid (cereals) 7. Drugs: Antacid, tetracycline, L-dopa, ciprofloxacin, desferrioxamine.

Q. Name the different iron preparations. (RU-16J,13,11J,09Ju, SU-12J)

Q. Name the oral iron preparations. (DU-16Ju,10J,06M; CU-11J,09/09Ju,06M; RU-17J,14J,10J,06S)

Q. Name 3 oral iron preparations. (DU-16J)

Q. Enumerate the parental iron preparations. (RU-14Ju)

Q. Name the drugs in microcytic hypochromic anemia. (RU-06J)

Q. Short note: Oral iron preparations. (SU-15Ju)

Ans:

Iron preparations

A. Oral iron preparations	Tablet form	• Ferrous sulfate • Ferrous fumarate • Ferrous gluconate • Ferrous succinate • Ferrous glycine-SO₄
	Liquid form	• FeSO₄ pediatric mixture • Polysaccharide iron complex
	Sustained release form	• Slow-Fe • Sytron • Na-Fe edetate
B. Parenteral iron preparations	IV iron	• Iron dextran • Iron sucrose
	IM iron	• Iron dextran • Iron sorbitol citric acid

(Ref: Katzung-12th/585)

Q. Write down the advantages & disadvantages of oral iron preparations. (DU-10J)

Q. Mention the advantages of different formulations of iron. (DU-03J)

Ans.

Advantages & disadvantages of different formulations of iron: Oral tablet, IV and IM injections.

	Advantages	Disadvantages
Oral iron preparations: Tablet	1. Easy to administer 2. Good patient compliance 3. No pain & scar mark.	1. Daily administration needed 2. Blackening of stool may confuse / misguide as black tarry stool. 3. Anemia recovers slowly. So, can't be given to establish the quick recovery of Fe store. 4. Can't be stored.

Elixir	1. Can be given in small children and adults who prefer this.	1. It stains the teeth.
Parenteral iron preparations	1. Daily administration is not needed 2. Quick recovery from anemia is possible. 3. Given to patients for whom iron can't be absorbed from intestine. 4. Can be given to patients who can't be relied on to take it. 5. Patients with intolerable gut symptoms. 6. No blackening of stool.	1. Not easy to administer. 2. Pain & blackening of the injection site. 3. Patient's compliance is not good. 4. Haemopoietic response is not quicker than that of oral preparation. 5. Ionized salts are unsuitable for parenteral preparations.

Note: Elixir is the sweetened aromatic solution of alcohol and water, serving as a vehicle for medicine.

Q. What are the indications of iron therapy? (DU-01J, CU-06M/S, RU-06S, SU-05S)

Q. Mention the indications of oral iron therapy? (RU-13J)

Q. Where is iron therapy needed? (DU-06M)

Q. What are the indications of parenteral iron therapy? (RU-14Ju)

Ans:

Indications of iron therapy: Iron therapy is indicated in the treatment or prevention of **iron deficiency anemia**. Iron deficiency anemia occurs in the following conditions where iron therapy is needed-

Inadequate intake	1. Nutritional deficiency: • Ignorance & poverty • Repeated pregnancy • Milk injury & improper feeding of the baby 2. Gastrectomy 3. Coeliac disease 4. Tropical sprue
Increased demand	1. In childhood: During the period of growth, mostly between 6-24 months. 2. Menstruation. 3. Pregnancy. 4. Lactation.
Excessive blood loss	1. Hookworm infestation 2. Hemorrhage: Accidental & surgical 3. Peptic ulcer disease 4. Bleeding hemorrhoids 5. Ruptured esophageal varices 6. Ca stomach 7. Ca colon
Defective utilization	1. Malabsorption syndrome 2. Partial or total gastrectomy 3. Gastrojejunostomy 4. Chronic diarrhea 5. Achlorhydria

Indications of Parenteral Iron Therapy: Parenteral therapy should be reserved for patients with documented iron deficiency who are unable to tolerate or absorb oral iron and for patients with extensive chronic anemia who cannot be maintained with oral iron alone. This includes patients with-

1. Advanced chronic renal disease requiring hemodialysis and treatment with erythropoietin
2. Various postgastrectomy conditions and previous small bowel resection

3. Inflammatory bowel disease involving the proximal small bowel, and
4. Malabsorption syndromes.

(Ref: Katzung-12th/585)

Q. How would you treat a case of iron deficiency anemia? (DU-15J, 11J, 09Ju, RU-06J, SU-11Ju)

Q. Enumerate the principles of Iron therapy. (CU-16Ju)

Ans.

Treatment of a case of iron deficiency anemia (IDA) / principles of Iron therapy:

1. Orally administered ferrous sulfate is the treatment of choice for iron deficiency.
2. **Ferrous sulphate** 200 mg 8-hourly (195 mg of elemental iron per day) is more than adequate and should be continued for **3-6 months** to replete iron stores.
3. If ferrous sulphate causes dyspepsia and altered bowel habit, its dose can be reduced to **200 mg 12-hourly** or a switch to ferrous gluconate 300 mg 12-hourly (70 mg of elemental iron per day).
4. **Haemoglobin** should rise by **1 g/dL every 7-10 days** and a **reticulocyte count** will be increased within a week.
5. A failure to respond adequately may be due to non-compliance, continued blood loss, malabsorption or an incorrect diagnosis.
6. Patients with malabsorption or chronic gut disease may need **parenteral iron therapy** with single or multiple doses of intravenous iron dextran or iron sucrose. **Doses** required can be calculated based on the patient's starting Hb and body weight. Observation for **anaphylaxis** following an initial test dose is recommended

(Ref: Davidson's-22nd; Goodman & Gillman-12th)

Q. Describe the total dose infusion for parenteral Iron therapy. (CU-16J)

Ans.

Total dose infusion for parenteral Iron therapy: Doses required for total dose infusion for parenteral iron therapy can be calculated based on the patient's starting Hb and body weight.

$$\begin{aligned} \text{Iron to be injected (mg)} &= \text{Total iron deficit} \\ &= \text{Body weight [kg]} \times (\text{Target Hb} - \text{Actual Hb}) [\text{g/dL}] \times 2.4 + 500\text{mg} \end{aligned}$$

500 mg is added to replenish the iron store if body weight >35kg.

Most adult patients require a cumulative dose of elemental Fe of at least 1 g.

Q. A 26 year old woman came to the OPD with the complaint of rapid heart rates and easy fatigability, laboratory workup reveals low hemoglobin and microcytic red cells. Discuss your diagnosis; write causes & treatment of this clinical condition. (SU-13Ju)

Ans.

Diagnosis: Iron deficiency anemia (IDA).

Cause: Most common causes of IDA in this young woman are-

1. Menstruation.
2. Pregnancy.
3. Lactation.

Treatment: Oral iron therapy.

Q. Mention the side effects of iron therapy? (DU-09Ju)

Q. What are the adverse/toxic effects of oral iron therapy? (RU-17J, 14J, 13J, 06S/J, 04J; SU-05S)

Q. Mention the adverse effects of parenteral Fe therapy. (CU-06S; RU-04S, 03J)

Q. Mention the adverse effects of ferrous sulphate. (RU-16J)

Ans:

Adverse effects of iron therapy:

A. Adverse effects of oral iron therapy:

1. Nausea & vomiting (sometimes causes intense nausea & vomiting).

2. Epigastric discomfort
3. Abdominal cramps
4. Constipation
5. Diarrhea
6. Black stool: This has no clinical significance, but it may obscure the diagnosis of continued GIT blood loss.

B. Adverse effects of parenteral iron therapy:

- **Intra-muscular iron therapy:**
 1. Local pain
 2. Tissue staining around the injection site
- **Intra-venous iron therapy:**
 1. Headache
 2. Light-headedness
 3. Fever
 4. Arthralgia
 5. Nausea & vomiting
 6. Back pain
 7. Flushing
 8. Bronchospasm
 9. Urticaria
 10. Anaphylaxis (rarely).

(Ref: Katzung-13th)

Q. Mention how long time ferrous sulphate is to be used to correct anemia and why. (RU-16J)

Q. Why oral Fe therapy should be continued for more than 3 months? (CU-09J)

Ans:

Treatment with oral iron should be continued for **3–6 months** after correction of the cause of the iron loss. This corrects the anemia and replenishes iron stores.

(Ref: Katzung-13th)

Q. How can you assess the effective iron therapy? (DU-16J,10J)

Ans.

Assessment of effective iron therapy:

1. **Clinical assessment:** Clinically effective iron therapy is assessed by improvement of anemia and the patient's complaints such as weakness, tiredness, appetite, lethargic condition etc.
2. **Biochemical assessment:**
 - Hemoglobin percentage (Hb %) will be increased.
 - Serum iron and serum ferritin level will be increased
 - Serum iron binding capacity will be decreased.
3. **Increase in reticulocyte count**

Q. What are the manifestations of acute iron toxicity? How do you manage the condition? (DU-05J, RU-17J,11J, CU-06M)

Ans:

Acute iron toxicity: Acute iron toxicity is seen almost exclusively in young children who accidentally ingest iron tablets. Although adults are able to tolerate large doses of oral iron without serious consequences, as few as **10 tablets** of any of the commonly available oral iron preparations can be **lethal** in young children.

Clinical features of acute iron toxicity:

1. Necrotizing gastroenteritis
2. Vomiting

3. Abdominal pain
4. Bloody diarrhea
5. Shock
6. Lethargy
7. Dyspnea
8. Metabolic acidosis
9. Coma and death.

Management: Urgent treatment is necessary.

1. **Whole bowel irrigation** should be performed to flush out unabsorbed pills.
2. **Deferoxamine**, a potent iron-chelating compound, can be given systemically to bind iron that has already been absorbed and to promote its excretion in urine and feces.
3. Appropriate supportive therapy for gastrointestinal bleeding, metabolic acidosis, and shock must also be provided.

(Ref: Katzung-13th)

Vitamin B₁₂

Vitamin B₁₂ (cobalamin) serves as a cofactor for several essential biochemical reactions in humans. Although deficiency of vitamin B₁₂ due to an inadequate supply in the diet is unusual, deficiency of B₁₂ in adults—especially older adults—due to inadequate absorption of dietary vitamin B₁₂ is a relatively common and easily treated disorder.

Active forms of vitamin B₁₂:

1. Deoxyadenosylcobalamin
2. Methylcobalamin

Q. What are the causes of vitamin B₁₂ deficiency?

Ans:

Common causes of vitamin B₁₂ deficiency:

1. Pernicious anemia
2. Partial or total gastrectomy
3. Malabsorption syndrome
4. Inflammatory bowel disease
5. Small bowel resection.

(Ref: Katzung-13th)

Q. What are the diseases caused by vitamin B₁₂ deficiency?

Ans:

Diseases caused by vitamin B₁₂ deficiency:

1. Megaloblastic anemia.
2. Combined degeneration of spinal cord (*Demyelination of large nerve fibers of the spinal cord especially of lateral column*).
3. Gastrointestinal symptoms.

(Ref: Katzung-13th)

Q. Name the drugs used in megaloblastic anemia. (RU-05M)

Ans:

Drugs used in megaloblastic anemia:

1. Vitamin B₁₂
2. Folic acid

Q. Name the vitamin B₁₂ preparations.

Ans:

Vitamin B₁₂ preparations:

Preparations		Route	Dose
1. Parenteral vitamin B ₁₂	Cyanocobalamin	I/M or S/C	10-1000 mcg/ml
	Hydroxocobalamin	I/M only	1000 mcg/ml
2. Oral vitamin B ₁₂	Cyanocobalamin	Orally	1000 mcg/ml/day

Q. "Folic acid should be administered only after exclusion of Vit-B₁₂ deficiency anemia"-Explain. (CU-09J)

Q. A physician has treated with folic acid of a megaloblastic anemic patient due to vitamin B₁₂ deficiency. What will be the hazards? (RU-06J)

Ans:

Rationale of using Folic acid after confirming the diagnosis: People with megaloblastic anemia due to vitamin B₁₂ deficiency are usually identified because of signs and symptoms of anemia, which typically occur before neurologic symptoms. So if this anemia is corrected by administration of folic acid, vitamin B₁₂ deficiency will remain undiagnosed and will be more and more severe. The most dangerous hazards of this deficiency-

“demyelination of nerve fibers” & “combined degeneration of spinal cord” may develop. But folic acid *does not* prevent the potentially irreversible neurologic damage caused by vitamin B₁₂ deficiency. So, before treatment the exact cause of megaloblastic anemia should be detected- whether it is due to vitamin B₁₂ or folic acid deficiency.

(Ref: Katzung-13th)

Folic acid

RDA: 100-200 µg/day

Source: Green leafy vegetables, whole grains, cereals, liver, kidney, yeast and eggs.

Active from: Tetrahydrofolate

Functions of folic acid:

1. Tetrahydrofolate (THF) can carry one-carbon units attached to N-5 (formyl, formimino, or methyl groups), N-10 (formyl group), or bridging N-5 to N-10 (methylene or methenyl groups) for the biosynthesis of a variety of bio-molecules (eg, methionine, serine etc).
2. It is involved in tyrosine metabolism and formation of RBC.

(Ref: Harper's-26th/493)

Causes of folic acid deficiency:

1. Inadequate dietary intake
2. Defective absorption
3. Use of anticonvulsant drugs (phenobarbitone, phenytoin)
4. Increased demand eg, in pregnancy.

Q. Briefly discuss the deficiency feature of folic acid.

Ans.

Deficiency feature of folic acid: Folic acid deficiency is probably the most common vitamin deficiency, observed primarily in the pregnant women.

1. Megaloblastic anemia.
2. Growth failure
3. Neural tube defect in the fetus eg, spina bifida, anencephaly (when deficiency in pregnant mother)
4. Glossitis
5. Gastrointestinal disturbances

Indications of folic acid:

1. Megaloblastic anemia due to folic acid deficiency
2. Pregnancy
3. Hemolytic anemia
4. Live diseases
5. Spina bifida
6. Skin diseases
7. Alcoholic

Contra-indication:

1. Megaloblastic anemia due to vitamin B₁₂ deficiency
2. Folate dependant cancer.

Erythropoietin therapy

Erythropoietin: It is a 34-39 kDa glycoprotein & is a human hematopoietic growth factor & produced by the peritubular cells of **kidney**.

Function: Erythropoietin stimulates erythroid proliferation & differentiation by interacting with erythropoietin receptors on red cell progenitors and thus increases red cell production.

Recombinant human erythropoietin

1. Epoetin alfa (*administered three times a week*)
2. Darbepoetin alfa (*administered weekly*)
3. Methoxy polyethylene glycol epoetin beta (*administered as a single IV or SC dose at 2-week or monthly intervals*)

Indications: Erythropoietin is useful for the treatment of **anemia** in the following cases-

1. Chronic renal failure.
2. Cancer patients treated with myelosuppressive cancer chemotherapy
3. Primary bone marrow disorder (eg, aplastic anemia, myeloproliferative and myelodysplastic disorders, multiple myeloma and perhaps other chronic bone marrow malignancies).
4. HIV-infected patients treated with zidovudine
5. Patients scheduled to undergo elective, noncardiac, nonvascular surgery: It reduces the need for transfusion in these patients.

Adverse effects: Hypertension, thrombotic complications (most serious), flu-like syndrome, hypersensitivity.
(Ref: Katzung-13th)

Nice to know

Blood doping: Highly competitive athletes have used epoetin alfa to increase their hemoglobin levels ("blood doping") on the hope that this will increase oxygen delivery to muscles and improve performance. Unfortunately, this misuse of the drug has been implicated in the deaths of several athletes and is strongly discouraged. Erythropoietin is one of the drugs banned by the International Olympic Committee.

(Ref: Katzung-13th edition; Goodman & Gilman-12th edition)

Plasma volume expander

Q. Enlist the plasma volume expander.

Ans.

Plasma volume expanders:

1. Human albumin
2. Dextran
3. Degraded gelatin polymer (polygeline)
4. Hydroxyethyl starch (HES)
5. Polyvinylpyrrolidone (PVP)

Indications:

1. Severe burn
2. Severe hypovolemic shock including severe hemorrhage.
3. Severe trauma.
4. Extensive tissue damage.

Contraindications: Severe anemia, cardiac failure, pulmonary edema, renal failure.

(Ref: Tripathi-6th/622-623)

MCQ

Q. Low dose aspirin- (DU-16J)

- a) binds with COX enzyme reversibly
 - b) inhibits TXA₂ formation in platelet
 - c) may cause GIT bleeding
 - d) inhibits PGI₂ formation
 - e) blocks platelet ADP receptors
- a. F, b. T, c. T, d. T, e. F*

Q. Adverse effect of heparin includes- (DU-15Ju)

- a. alopecia
- b. hemorrhage
- c. DIC
- d. osteoporosis
- e. myopathy

a. T, b. T, c. F, d. T, e. F

Q. Following are the manifestations of Folic acid deficiency: (CU-14Ju)

- a) Enteritis.
- b) Spina bifida in the offspring.
- c) Loss of ankle reflex
- d) Hallucination
- e) Glossitis

a. T, b. T, c. F, d. F, e. T

Q. Drugs preventing platelet aggregation are- (DU-14J)

- a. clopidogrel
- b. streptokinase
- c. ticlopidine
- d. warfarin
- e. dipyridamol.

a. T, b. F, c. T, d. F, e. T

Q. Following are the fibrinolytic agents- (DU-13Ju)

- a. alteplase.
- b. streptokinase.
- c. clopidogrel.
- d. tranaxaemic acid.
- e. abciximab.

a. T, b. T, c. F, d. F, e. F

Q. Enoxaparin- (DU-13Ju)

- a. is a LMWH.
- b. is injected subcutaneously.
- c. requires intense monitoring.
- d. bioavailability is less than HMW one.
- e. can cross the placental barrier.

a. T, b. T, c. F, d. F, e. F

Q. Warfarin is used in the following clinical situations- (DU-13Ju)

- a. angina pectoris.
- b. implant prosthetic valve.
- c. chronic atrial fibrillation.
- d. venous thromboembolism.
- e. cerebrovascular stroke.

a. F, b. T, c. T, d. T, e. F

Q. The following drugs prevent platelet aggregation- (DU-13J)

- a. clopidogrel.
- b. ticlopidine
- c. warfarin.
- d. low dose heparin.
- e. streptokinase.

a. T, b. T, c. F, d. T, e. F

Q. The following are adverse effects of heparin therapy- (DU-13J)

- a. osteoporosis.
- b. alopecia.
- c. thrombocytopenia.
- d. diarrhea.
- e. fetal cleft palate.

a. T, b. F, c. T, d. F, e. T

Q. The advantages of LMWH include- (DU-11J)

- a. No need of monitoring (T)
- b. Low risk of bleeding (T)
- c. High plasma protein binding drug (F)
- d. Administered IV (T)
- e. Less bioavailability (F)

Q. The following drugs prevent platelet aggregation- (DU-10Ju)

- a. Clopidogrel (T)
- b. Ticlopidine (T)
- c. Warfarin (F)
- d. Low dose aspirin (T)
- e. Streptokinase (F)

Q. Regarding warfarin- (DU-10Ju)

- a. It is given orally (T)
- b. It can cause bleeding (T)
- c. It acts within 24 hours of administration (T)
- d. Its effect can be antagonized by protamine sulfate (F)
- e. It causes fibrinolysis (F)

Q. Heparin- (DU-10J)

- a. is effective if given orally (F)
- b. can cause osteoporosis (T)
- c. acts by inhibiting vit K dependent coagulation factors (F)
- d. may cause thrombocytopenia (T)

Q. Aspirin- (DU-10J)

- a. inhibits PGs synthesis (T)
 - b. inhibits LTs synthesis (F)
 - c. can cause sodium retention & edema (T)
 - d. excretion can be enhanced by giving ammonium chloride (F)
 - e. can cause premature closure of the ductus arteriosus if given in late pregnancy (F)
-

Chapter 11

Gastrointestinal Pharmacology

Drugs used in acid-peptic diseases

Acid-peptic diseases include-

1. Peptic ulcer diseases (PUD)
2. Gastro-esophageal reflux diseases (GERD)
3. Stress-related ulcer.

Q. Define peptic ulcer diseases and mention the sites of peptic ulcer formation.

Ans.

Peptic ulcer diseases (PUD): Peptic ulcer diseases are chronic, most often solitary lesions that occur in any portion of the gastrointestinal tract exposed to aggressive action of acid peptic juices.

(Ref- Robbins and Cotran-9th)

Common sites of peptic ulcer

1. First part of duodenum.
2. Stomach (usually antrum).
3. Gastro-esophageal junction.
4. Within the margins of a gastro-jejunostomy.
5. Throughout the GIT in Zollinger-Ellison syndrome.
6. Within or adjacent to an ileal Meckel's diverticulum that contains ectopic gastric mucosa.

(Ref- Robbins and Cotran-9th)

Nice to know

Defense mechanisms of gastro-duodenal mucosa:

1. Surface mucous secretion
2. Bicarbonate secretion into mucus.
3. Increased mucosal blood flow that washes out H^+ .
4. Apical surface membrane transport.
5. Quick regenerative capacity of lining epithelium.
6. Elaboration of prostaglandin that increases mucus secretion, blood flow & epithelial regeneration.

Pathogenesis of peptic ulcer: Peptic ulcer is produced by an imbalance between —

1. Gastro-duodenal mucosal defense mechanism &
2. Damaging force.

1. **Impairment of defense mechanism:** By the followings —

- ↓ Mucus secretion.
- ↓ Bicarbonate secretion in mucus.
- ↓ Mucosal blood flow,
- ↓ Prostaglandin elaboration.
- ↓ Apical surface membrane transport.
- ↓ Epithelial regenerative capacity.

Caused by- Ischemia, shock, delayed gastric emptying (gastric ulcer), rapid gastric emptying (duodenal ulcer), psychological.

2. **Increased damaging force:**

- ↑ Gastric acidity.
- NSAIDs.
- Steroid.
- Cigarette, alcohol.
- Duodenal gastric reflux.
- *Helicobacter pylori*.

Complications of peptic ulcer:

(Ref- Robbins and Cotran-9th)

1. **Bleeding:** Occurs in 15 - 20% patients, may be life-threatening.
2. **Perforation:** Occurs in about 5% of patients, accounts for two thirds of ulcer deaths.
3. **Obstruction** from edema and scarring: Occurs in about 2% of patients.
4. Acquired pyloric stenosis.

(Ref- Robbins and Cotran-9th)

Q. Discuss the role of *H. pylori* in the pathogenesis of peptic ulcer disease? (CU-16J,15J,14Ju,13Ju)

Ans.

Role of *H. pylori* in the pathogenesis of peptic ulcer:

1. Peptic ulceration is strongly associated with *H. pylori* infection. Around 90% of duodenal ulcer patients and 70% of gastric ulcer patients are infected with *H. pylori*; the remaining 30% of gastric ulcers are due to NSAIDs.
2. Four features are linked to *H. pylori* virulence:
 - a. **Flagella**, which allow the bacteria to be motile in viscous mucus.
 - b. **Urease**, which generates ammonia from endogenous urea and thereby elevates local gastric pH.
 - c. **Adhesins** that enhance their bacterial adherence to surface foveolar cells.
 - d. **Toxins**, such as cytotoxin-associated gene A (CagA) may be involved in ulcer development.
3. *H. pylori* infection results in increased acid production and disruption of normal gastric and duodenal protective mechanisms.
4. *H. pylori* gastritis is, therefore, the result of an imbalance between gastroduodenal mucosal defenses and damaging forces that overcome those defenses.

(Ref- Robbins and Cotran-9th)

Q. Name the drugs used in PUD/ peptic ulcer. (DU-16J,13J,12J,09J/Ju; CU-13J,12Ju, SU-17J,16J,09J/Ju;RU-10J)

Q. Lists the drugs used in the treatment of hyperacidity. (DU-09Ju)

Q. Enlist the drugs that inhibit gastric acid secretion. (DU-06M)

Q. Lists anti-ulcer drugs. (SU-09Ju)

Q. Name the anti-secretory drugs used in the management of PUD. (CU-16J,15J, SU-11J, RU-17J,15J,13J,09Ju/J)

Q. Lists the peptic ulcer healing drugs. (SU-12J, CU-04M)

Q. Mention the cytoprotective agents used in PUD. (DU-14Ju)

Q. Mention the gastroprotective agents used in PUD. (RU-16Ju)

Ans.

Drugs for peptic ulcer diseases (PUD):

Types of anti-ulcerant drugs	Name of drugs
A. Acid neutralizers	
1. Antacids	• Sodium bicarbonate, NaHCO_3 • Calcium carbonate, CaCO_3 • Magnesium hydroxide, Mg(OH)_2 • Aluminium hydroxide, Al(OH)_3
B. Antisecretory: Agents that reduce HCl secretion	
1. H_2 -receptor blockers	• Ranitidine • Famotidine • Nizatidine • Cimetidine
2. Proton pump inhibitors (PPI)	• Omeprazole • Esomeprazole • Pantoprazole • Lansoprazole • Rabeprazole
3. Anti-muscarinic drugs	• Dicyclomine • Pirenzepine • Telenzepine

C. Agents that kill the causative bacteria (<i>Helicobacter pylori</i>)	
1. Antibiotics	• Metronidazole • Amoxicillin • Tetracycline • Clarithromycin
D. Agents that enhance mucosal resistance (ulcer healing drugs) / gastroprotective	• Sucralfate • Prostaglandin analog (Misoprostol) • Colloidal bismuth compounds. (Bismuth subsalicylate)

(Ref: Katzung-13th & Goodman & Gilman's-12th)

Q. Discuss the approaches of treatment of peptic ulcer. (CU-09Ju)

Q. Outline the therapeutic approaches in the treatment of a case of acute peptic ulcer. (SU-06J)

Q. Write down the management of PUD. (SU-16Ju)

Ans.

Principles / approaches of treatment of PUD:

1. Eradication of *H. pylori* infection
2. Decrease in gastric acidity: by H_2 -receptor blockers, PPI.
3. Increase in mucosal protections: by sucralfate, misoprostol.
4. Avoidance of risk factors (smoking, stress, spicy food etc.).

Q. List the drugs used to treat NSAID induced peptic ulcer. (CU-06M)

Ans.

Drugs used to treat NSAID induced peptic ulcer

1. Stop the drug (NSAID).
2. H_2 -receptor blockers
3. Proton pump inhibitors (PPIs)
4. Increasing the mucosal resistance by Prostaglandins / Sucralfate / Colloidal bismuth compound.

Antacids

Q. Classify antacids. (RU-06J)

Ans.

Antacids:

Antacids	Properties
Non-systemic antacids: 1. Calcium carbonate, $CaCO_3$ 2. Magnesium hydroxide, $Mg(OH)_2$ 3. Magnesium trisilicate 4. Aluminium hydroxide, $Al(OH)_3$	• Not absorbed into the systemic circulation. • Insoluble • Produces no acid-base abnormality. • Diarrhea, constipation are common side effects.
Systemic antacids: 1. Sodium bicarbonate, $NaHCO_3$ 2. Sodium carbonate, Na_2CO_3	• Absorbed into the systemic circulation. • Soluble • Produces acid-base abnormality. • Quick onset of action.

(Ref: Katzung-13th)

Q. What is the mechanism of action of antacids?

Q. What is the role of antacids in PUD? (SU-16Ju)

Ans.

Mechanism of action of antacids:

1. As antacids are weak base, they **directly neutralize** gastric acidity.
2. They may also **promote mucosal defense** by stimulation of mucosal PG production.
3. Cannot prevent secretion of gastric acid.

(Ref: Katzung-13th)

Q. Mention the indications antacids.

Q. Describe the therapeutic profile of antacids. (CU-17M)

Ans.

Indications of antacids: Now-a-days, antacids are uncommonly prescribed.

1. Intermittent heartburn
2. Dyspepsia
3. Peptic ulcer disease (to reduce quick reduction of intra-gastric acidity)

(Ref: Katzung-13th)

Q. What are the advantages of combined antacids? (SU-09J)

Ans.

Advantages of using combined $Mg(OH)_2$ & $Al(OH)_3$ antacids:

- $Mg(OH)_2 + 2HCl \rightarrow MgCl_2 + 2H_2O$ (Unabsorbed $MgCl_2 \rightarrow$ Osmotic diarrhea)
- $Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O$ (Unabsorbed $AlCl_3 \rightarrow$ Constipation)

So if we use $Mg(OH)_2$ & $Al(OH)_3$ in the same preparation, osmotic diarrhea by $MgCl_2$ is antagonized by constipating effect of $AlCl_3$. So combined use of $Mg(OH)_2$ & $Al(OH)_3$ minimize the GIT adverse effects.

(Ref: Katzung-13th)

Q. Write down the limitations of using systemic antacids. (RU-06J;SU-07Ju)

Q. What are the disadvantages of $NaHCO_3$? (RU-06J)

Q. What are the consequences of long-term use of antacids? (SU-11J)

Ans.

Systemic antacids: The antacids which are completely absorbed into the systemic circulation are called systemic antacids. These antacids cause systemic alkalosis.

Adverse effects of systemic antacids:

Systemic antacids	Adverse effects
1. $NaHCO_3$: $NaHCO_3 + HCl \rightarrow NaCl + CO_2 + H_2O$	1. Gastric distention & belching (CO_2) 2. Metabolic alkalosis 3. $NaCl$ absorption: Can exacerbate HF, HTN & renal insufficiency (rarely)
2. $CaCO_3$ $CaCO_3 + 2HCl \rightarrow CO_2 + CaCl_2 + H_2O$	1. Belching 2. Metabolic alkalosis (milk-alkali syndrome) 3. hypercalcemia (in high doses) 4. Renal insufficiency.
3. $Mg(OH)_2$ & $Al(OH)_3$: $Mg(OH)_2 + 2HCl \rightarrow MgCl_2 + 2H_2O$ $Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O$	1. Unabsorbed $MgCl_2 \rightarrow$ Osmotic diarrhea 2. Unabsorbed $AlCl_3 \rightarrow$ Constipation 3. Renal insufficiency. 4. Metabolic alkalosis & belching are uncommon.

(Ref: K.

Nice to know

Drug interactions of antacids: All antacids may affect the absorption of other medications by either (reducing its absorption) or by increasing intragastric pH so that the drug's dissolution or solubility (for weakly basic or acidic drugs) is altered. Therefore, antacids should not be given within 2 hours of doses of **tetracyclines, fluoroquinolones, itraconazole, and iron**. Most drug interactions can be avoided by taking Antacids 2 hours before or after ingestion of other drugs.

(Ref: Katzung-13th)

Regulation of gastric HCl secretion

Q. Describe the mechanism of gastric HCl secretion from parietal cell and dictate the sites of drug intervention. (CU-15Ju)

Q. Draw a schematic diagram to show the regulation of acid secretion in parietal cells & the targets for pharmacologic modification. (CU-12J,11J,09Ju)

Ans.

Regulation of gastric HCl secretion

- The parietal cell contains receptors for gastrin, histamine (H_2), and acetylcholine (muscarinic, M_3) (See figure).
- When acetylcholine or gastrin bind to the parietal cell receptors, they increase cytosolic calcium.
- $\uparrow Ca^{2+}$ stimulates protein kinases that stimulate acid secretion from a H^+/K^+ ATPase (the proton pump) on the canalicular surface.
- In close proximity to the parietal cells are gut endocrine cells called **enterochromaffin-like (ECL) cells**.
- ECL cells have receptors for gastrin and acetylcholine and are the major source for histamine release. Histamine binds to the H_2 receptor on the parietal cell, resulting in activation of adenylyl cyclase, which increases intracellular cAMP. cAMP activates protein kinases that stimulate acid secretion by the H^+/K^+ ATPase.

(Ref: Katzung-13th)

Targets for pharmacologic modification

- H_2 receptor: Blocked by H_2 -blockers.
- H^+/K^+ ATPase (The proton pump): Blocked by proton pump inhibitors.
- M_3 muscarinic receptor: Blocked by anti-muscarinic drugs.

Schematic diagram to show the regulation of acid secretion in parietal cells:

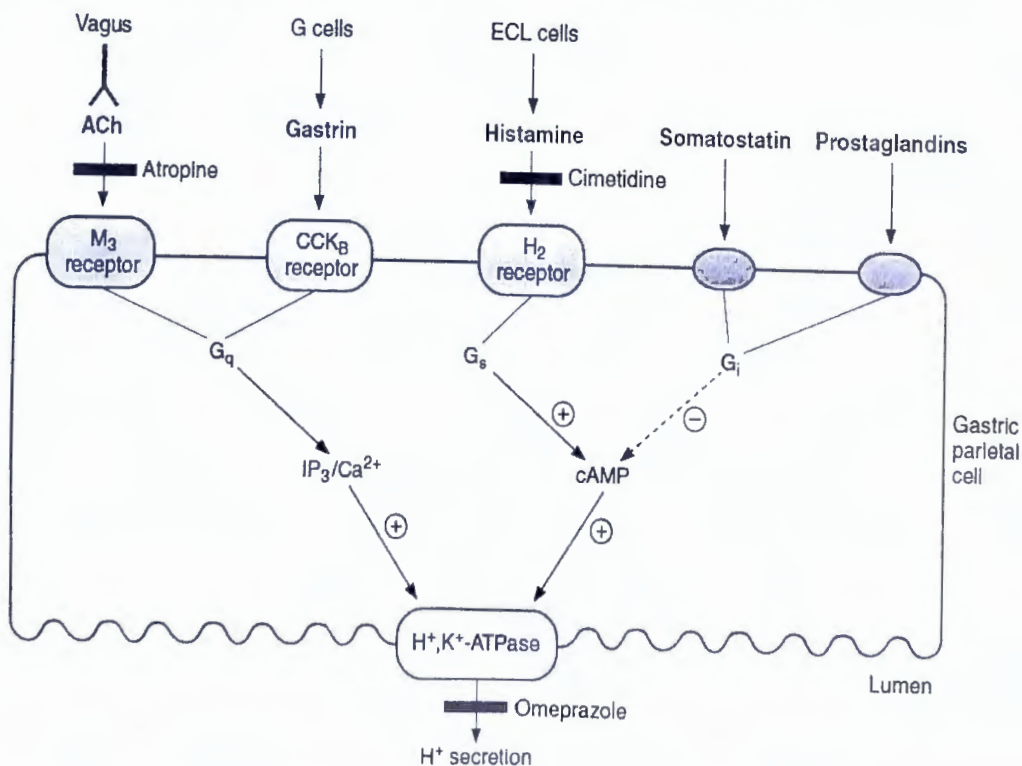


Fig. Schematic diagram of hydrogen ion secretion by the gastric parietal cell. ACh = acetylcholine; CCK = cholecystokinin; ECL = enterochromaffin-like; IP_3 = inositol triphosphate; M = muscarinic.

H₂-receptor blockers

Q. List the clinically useful H₂-receptor blockers. (CU-09J)

Ans.

H₂-receptor antagonists: Four H₂ antagonists are in clinical use:

1. Ranitidine
2. Famotidine
3. Nizatidine
4. Cimetidine

(Ref: Katzung-13th)

Nice to know

Important properties of H₂-blockers / Ranitidine:

1. Ranitidine exhibit competitive reversible inhibition of acid secretion at the parietal cell H₂ receptor.
2. Suppress 70% of 24 hour acid secretion, both basal & meal stimulated.
3. Predominantly inhibit basal acid secretion which is efficacious for suppression of nocturnal acid secretion. So, an evening dose is necessary in PUD, especially in duodenal ulcer.

(Ref: Goodman & Gilman's-11th/971)

Q. Mention the mechanism of action of H₂-receptor blockers drugs. (RU-17J)

Q. Explain the mechanism of action of Ranitidine in PUD. (RU-09J)

Q. Explain the mechanism of action of famotidine in PUD. (RU-15J)

Q. Explain the anti-ulcer role of ranitidine in peptic ulcer. (SU-17J,12Ju)

Q. Explain the anti-ulcer role of famotidine in peptic ulcer. (SU-13Ju)

Q. Explain the mechanism of action of cimetidine in PUD. (RU-13J)

Q. Mention the pharmacological action of clinically useful H₂-receptor blockers. (CU-09J)

Q. Discuss the role of Ranitidine in PUD. (SU-09J)

Ans.

Mechanism of action of H₂-receptor blockers / ranitidine / cimetidine: H₂ antagonists reduce acid secretion stimulated by histamine as well as by gastrin and cholinomimetic agents through two mechanisms.

1. **First**, H₂-receptor blockers/ Ranitidine /Famotidine competitively block H₂-receptors on parietal cell

↓

Histamine released from ECL cells by gastrin or vagal stimulation cannot bind to parietal cell H₂-receptors

↓

No acid secretion from the parietal cells.

↓

Healing of ulcer.

2. **Second**, direct stimulation of the parietal cell by gastrin or acetylcholine results in diminished acid secretion in the presence of H₂-receptor blockade.

(Ref: Katzung-13th)

Q. What are the indications of H₂-receptor blockers?

Q. Write down the indications of famotidine. (DU-02M)

Ans.

Indications of H₂-receptor blockers / famotidine:

1. Gastro-esophageal reflux disease (GERD).
2. Peptic ulcer diseases (PUD).
3. Non-ulcer dyspepsia
4. Prevention of bleeding from stress related gastritis.
5. Stress ulcer
6. Zollinger Ellison syndrome
7. Systemic mastocytosis

8. Pre-anesthetic use in emergency operation

(Ref: Katzung-13th)

Q. Mention the adverse effects of clinically useful H₂-receptor blockers. (CU-09J)

Q. Mention the adverse effects of cimetidine. (RU-13J)

Ans.

Adverse effects of H₂-receptor blockers: H₂-receptor blockers are extremely safe drugs. Adverse effects occur in fewer than 3% of patients. They are as follows —

1. Diarrhea & constipation
2. Headache
3. Myalgia
4. Fatigue

Other adverse effects include —

1. **CNS:** Mental status changes (confusion, hallucinations, agitation) may occur with administration of IV H₂ antagonists, especially in patients in the ICU who are elderly or who have renal or hepatic dysfunction.
2. **Endocrine:** Cimetidine causes-
 - a. Gynecomastia or impotence in men
 - b. Galactorrhea in women
3. **Pregnancy & nursing mothers:**
 - a. They should not be used in pregnancy
 - b. Secreted into breast milk & thus affects infants.
4. **CVS:** Rapid I/V infusion may cause bradycardia & hypotension due to blockade of cardiac H₂-receptors.
5. **Others:**
 - a. Rarely causes blood dyscrasias
 - b. Rarely cause reversible abnormalities in liver chemistry.

(Ref: Katzung-13th)

Q. What treatment will you prefer if Ranitidine fails? (RU-03M)

Ans. Ranitidine failed peptic ulcer is most probably due to *H. pylori* infection & treatment of choice is triple or quadruple therapy.

Q. Mention the drug interactions of cimetidine. (RU-04J)

Ans.

Drug interactions of cimetidine: Cimetidine inhibits cytochrome-P450 enzymes. So, it decreases the metabolism of other drugs & causes prolonged half life of other drugs. That's why, its use is restricted. As for example,

Warfarin + Cimetidine

In this drug interaction, cimetidine increases the plasma concentration of warfarin which results in warfarin toxicity, eg, bleeding.

(Ref: Katzung-13th)

Proton pump inhibitors (PPIs)

Q. Name the proton pump inhibitors. (DU-08J; RU-08J,06S; SU-07J)

Q. What are the PPIs used now-a-days?

Ans.

Proton pump inhibitors (PPI): Five proton pump inhibitors are available for clinical use:

1. Omeprazole
2. Esomeprazole
3. Pantoprazole
4. Lansoprazole
5. Rabeprazole

(Ref: Katzung-13th)

Nice to know

Proton pump inhibitors are administered as inactive **prodrugs**. To protect the acid-labile prodrug from rapid destruction within the gastric lumen, oral products are formulated for delayed release as acid-resistant, enteric-coated capsule or tablet formulations. After passing through the stomach into the alkaline intestinal lumen, the enteric coatings dissolve and the prodrug is absorbed.

After intestinal absorption, the PPIs diffuse readily across lipid membranes into acidified compartments such as the parietal cell canaliculus. There, it is rapidly converted into the active, reactive **thiophilic sulfonamide cation**.

(Ref: Katzung-13th)

Q. Explain the mechanism of action of proton pump inhibitors? (DU-08J, RU-09Ju,06S, SU-07J; CU-09J)

Q. Write down the mechanism of action Pantoprazole. (DU-14J)

Q. Write down the mechanism of action Lansoprazole. (DU-13J,12J,09Ju; RU-08J)

Q. Explain the role of omeprazole in the treatment of peptic ulcer. (SU-17J,13J,09J,06M)

Q. Explain the anti-ulcer role of pantoprazole in peptic ulcer. (SU-12Ju)

Q. Explain the anti-ulcer role of esomeprazole in peptic ulcer. (SU-13Ju)

Ans.

Mechanism of action of proton pump inhibitors (PPIs):

Proton pump inhibitors are administered as **inactive prodrugs**. Then they are converted into active form **thiophilic sulfonamide cation** in the parietal cell



The sulfonamide reacts with the H^+/K^+ ATPase (**the proton pump**), forms a covalent disulfide linkage



Irreversible inactivation of the proton pump



Counter-transport of H^+/K^+ ions via the proton pump is blocked



No secretion of H^+ by the parietal cell.

(Ref: Katzung-13th)

Q. Mention the clinical uses / indications of PPIs. (DU-09Ju,08J;RU-06S; SU-07J)

Q. Mention the clinical conditions where we can use omeprazole. (DU-06S)

Q. Write down the indications of pantoprazole/lansoprazole. (RU-09Ju,05M)

Ans.

Indications of PPIs/ omeprazole/ pantoprazole/ lansoprazole/ esomeprazole:

1. Peptic ulcer diseases (PUD).

- H. pylori associated PUD.
- NSAID associated PUD.
- Perforation of bleeding PUD.
- **Prevention of rebreeding from PUD:** Loading dose: 80 mg IV followed by maintenance dose: 8 mg/h in IV infusion for 3–5 days is commonly recommended.

2. Gastro-esophageal reflux disease (GERD).

3. Non-ulcer dyspepsia

4. Prevention of stress-related mucosal bleeding

5. Stress ulcer

6. **Zollinger Ellison syndrome:** Typical doses of omeprazole are 60–120 mg/d.

(Ref: Katzung-13th)

Q. What do you mean by triple therapy in the management of peptic ulcer? (DU-09Ju; CU-06S/I, RU-12Ju)

Q. Explain the pharmacological basis of using 'Triple Therapy' in peptic ulcer disease. (CU-07J)

Q. Discuss the principles of triple therapy. (CU-06S)

Q. Mention the treatment plans or drug regimens in a H. pylori induced PUD. (DU-16J, CU-07J, RU-07J)

Q. Explain the role of each component of "triple therapy" in PUD. (DU-09J; RU-12Ju,10J, SU-17M)

Q. Discuss the role of "triple therapy in peptic ulcer disease. (SU-09Ju)

- Q. How can you eradicate the *H. pylori*? (CU-17M, 14Ju, 13Ju)
 Q. Enlist the drugs used in *H. pylori* induced peptic ulcer. (DU-14J)
 Q. Short note: Triple therapy. (RU-16J, 14J, SU-16J, 15Ju, 15J)

Ans.

Management of *H. pylori* induced PUD: The aims of management are to relieve symptoms, induce healing and prevent recurrence. *H. pylori* eradication is the cornerstone of therapy for peptic ulcers, as this will successfully prevent relapse and eliminate the need for long-term therapy in the majority of patients.

***H. pylori* eradication:** All patients with proven acute or chronic duodenal ulcer disease and those with gastric ulcers who are *H. pylori*-positive should be offered eradication as primary therapy.

Triple therapy: Triple therapy is based upon a proton pump inhibitor taken simultaneously with two antibiotics (from amoxicillin, clarithromycin and metronidazole) for 7 days. *H. pylori* eradication is achieved in over 90% of patients. After completion of triple therapy, the proton pump inhibitor should be continued once daily for a total of 4–6 weeks to ensure complete ulcer healing.

Drugs for triple therapy

1. A proton pump inhibitor (12-hourly) for 7 days
2. Clarithromycin 500 mg 12-hourly for 7 days
3. Amoxicillin 1 g 12-hourly or metronidazole 400 mg 12-hourly, for 7 days.

(Ref: Davidson's- medicine-22nd)

Nice to know

Triple therapy: The best treatment regimen consists of a 14-day regimen of "triple therapy": a proton pump inhibitor twice daily; clarithromycin, 500 mg twice daily; and either amoxicillin, 1 g twice daily, or metronidazole, 500 mg twice daily. After completion of triple therapy, the proton pump inhibitor should be continued once daily for a total of 4–6 weeks to ensure complete ulcer healing.

(Ref: Katzung-13th)

Quadruple therapy: Quadruple therapy should be offered to those patients who remain infected after initial triple therapy once the reasons for failure of first-line therapy have been established.

Drugs for quadruple therapy

1. A proton pump inhibitor (12-hourly)
2. Bismuth 120 mg 6-hourly
3. Metronidazole 400 mg 12-hourly, and
4. Tetracycline 500 mg 6-hourly, for 7 days

For those who are still colonised with *H. pylori* after two treatments, the choice lies between a third attempt with quadruple therapy or long-term maintenance therapy with acid suppression.

(Ref: Davidson's- medicine-22nd)

Q. Discuss the role of clarithromycin in the management of peptic ulcer disease. (CU-13J)

Ans.

Role of clarithromycin in the management of peptic ulcer disease: Clarithromycin kills and eradicates *H. pylori* and thus helps in permanent healing of peptic ulcer disease.

Q. Discuss the role of amoxicillin in peptic ulcer disease. (SU-09J)

Ans.

Role of amoxicillin in peptic ulcer disease:

1. Amoxicillin kills *H. pylori* by inhibiting cell wall synthesis of the bacteria.
2. Amoxicillin potentiates the action of other antibiotics used in triple or quadruple therapy.

Q. A man aged 32 years had epigastric pain for few months. Endoscopy confirmed duodenal ulcer. Write his treatment with mechanism of drug used. (RU-11Ju)

Ans.

Treatment: Triple therapy

Mechanism of drugs used: Write from respective discussion.

Q. Mr. X suffers from upper abdominal discomfort with NSAIDs. How it can be overcome? (SU-13J)

Ans.

Treatment of NSAID induced PUD:

1. Antiulcerant:

a. H₂ blocker

b. PPI

c. To increase mucosal resistance: Sucralfate, Prostaglandins / colloidal bismuth compound.

2. Stop the offending NSAID. Use alternative analgesic such as opioid analgesic (eg, tramadol).

3. If NSAID therapy is mandatory, then it must be given at full stomach with PPI coverage 30 minutes before meal.

Q. Compare & contrast Ranitidine & omeprazole as anti-peptic ulcer drugs. (DU-6M; CU-07J)

Q. Compare & contrast H₂-receptor antagonists & PPIs as ulcer healing drugs. (CU-06M)

Q. Compare the status of PPIs and H₂-receptor antagonists as inhibitor of HCl secretion. (RU-15Ju)

Ans.

Comparison between H₂-receptor blockers & PPIs:

Traits	H ₂ -blockers /Ranitidine	PPIs / Omeprazole
1. Nature	Active drug	It is an inactive prodrug and requires activation.
2. Mechanism of action	Reversibly block the H ₂ receptor on parietal cell	Irreversibly block H ⁺ /K ⁺ ATPase (the proton pump) on the parietal cell
3. Duration of action	Relatively shorter	Longer
4. Development of tolerance	Yes	No
5. Suppression of 24 hrs HCl secretion	70%	90 - 98%
6. Efficacy	Less	More
7. Predominant inhibition	Suppress predominantly basal acid secretion	Suppress both basal + meal stimulated acid secretion
8. Drug interaction	No (Cimetidine inhibits Cyt-P450)	Significant drug interaction occurs
9. Dose	150 mg 12 hourly	20-40 mg 12 hourly

Q. Mention the adverse effects of proton pump inhibitors. (DU-08J; SU-07J)

Q. Explain the adverse effects of lansoprazole. (DU-09Ju; RU-08J)

Q. Mention the adverse effects of omeprazole. (RU-07Ju, CU-10/09J)

Ans.

Adverse effects of PPI / omeprazole / lansoprazole:

A. **General:** PPIs are extremely safe drug. In only 1-5% cases the following adverse effects are reported-

- Diarrhea
- Headache
- Abdominal pain
- Safety during pregnancy is not established.

B. **Nutritional:** Prolonged PPI therapy causes subnormal vitamin B₁₂ level.

C. **Respiratory & enteric infection:**

- Increased risk of enteric infection (*Clostridium difficile* infection)
- Increased risk of community acquired pneumonia & nosocomial pneumonia (unclear).

D. Potential problems due to increased serum gastrin level:

- Carcinoid tumor formation has not been documented.
- No risk of colonic carcinogenesis.
- So, at present routine serum gastrin level monitoring is not recommended in PPI taking patient.

(Ref: Katzung-13th)

Q. Short note: Pantoprazole. (DU-15Ju)

Ans. Write from above.

Long term use → Gastric
Adenocarcinoma

Sucralfate**Q. What is the mechanism of action of sucralfate? (CU-03J)****Q. List the role of sucralfate in peptic ulcer. (SU-16Ju, 13J)**

Ans.

Mechanism of action of Sucralfate:

1. Sucralfate is a salt of sucrose complexed to sulfated aluminium hydroxide, $\text{Al}(\text{OH})_3$. *Negatively charged sucrose sulfate binds to positively charged proteins* in the base of ulcers or erosion. In this way, it forms a physical barrier that restricts further caustic damage.
2. Sucralfate also stimulates mucosal PG & HCO_3^- secretion.

Indications of Sucralfate: At present its clinical uses are limited.

1. Peptic ulcer disease (PUD).
2. Prevention of stress related bleeding (As PPIs, H_2 -blockers, antacids may increase the risk of nosocomial pneumonia, many physician uses Sucralfate in stress related bleeding prevention).

Adverse effects of Sucralfate:

1. Constipation due to Al salt.
2. As small Al can be absorbed, it should be avoided in pts with renal failure.
3. The viscous layer, formed by Sucralfate may inhibit the absorption of phenytoin, digoxin and ketoconazole & fluoroquinolones.

(Ref: Katzung-13th)

Colloidal bismuth compounds

Mechanism of action of colloidal bismuth compounds: The precise mechanisms of action of bismuth are unknown. *Quadruple therapy*

1. Bismuth coats ulcers and erosions, creating a protective layer against acid and pepsin.
2. It may also stimulate prostaglandin, mucus, and bicarbonate secretion.
3. Bismuth subsalicylate reduces stool frequency and liquidity in acute infectious diarrhea, due to salicylate inhibition of intestinal prostaglandin and chloride secretion.
4. Bismuth has direct antimicrobial effects and binds enterotoxins, accounting for its benefit in preventing and treating traveler's diarrhea.
5. Bismuth compounds have direct antimicrobial activity against *H. pylori*.

Clinical uses of colloidal bismuth compounds:

1. Dyspepsia
2. Acute diarrhea
3. Prevention of Travelers' diarrhea.
4. *H. pylori* induced PUD.

Adverse effects: Have excellent safety profile.

1. Blackening of the stool (not altered black tarry stool).
2. Darkening of the tongue.
3. Prolong use may cause "encephalopathy" due to bismuth toxicity.
 - a. Ataxia
 - b. Headache
 - c. Confusion
 - d. Seizure
4. High dose may cause salicylate toxicity.
5. Should be avoided in patients with renal insufficiency.

(Ref: Katzung-13th)

PUD, GERD. management - 480

Misoprostol

Q. Explain the role of misoprostol in treatment of peptic ulcer. (SU-16Ju,06M)

Q. How does misoprostol protect gastric mucosa? (RU-12Ju)

Q. Write the mechanism of action of misoprostol? (CU-12Ju)

Q. Justify- use of misoprostol not the Antacid in the treatment of drug induced peptic ulcer. (CU-03J)

Q. Explain the pharmacological basis of using- Misoprostol in NSAID-induced peptic ulcer. (SU-14Ju)

Q. What are the advantages of misoprostol in the treatment of peptic ulcer? (CU-15Ju)

Ans.

Misoprostol: It is a synthetic PG. Misoprostol has both acid inhibitory and mucosal protective properties.

1. It stimulates mucus and bicarbonate secretion and enhances mucosal blood flow.
2. Reduces histamine-stimulated cAMP production in parietal cells and causing modest acid inhibition.
3. Prevents the luminal H^+ from diffusing into the mucosa.
4. Increases cell replication in mucosa.

(Thus, misoprostol prevents drug induced peptic ulcer. But antacid only relieves pain. It has no cytoprotective action.)

Nice to know**Clinical Uses:**

1. Prevention of NSAID-induced ulcers in high-risk patients. **Misoprostol reduces the incidence of NSAID-induced ulcers** to less than 3% and the incidence of **ulcer complications** by 50%.

(However, misoprostol has never achieved widespread use owing to its high adverse-effect profile and need for multiple daily dosing.)

Contraindication:

1. Pregnancy - *uterine contraction* *milk secretion*
2. Women of childbearing potential unless they have a negative serum pregnancy test and are compliant with effective contraceptive measures.

Q. Write down the adverse effects of misoprostol. (CU-12Ju)

Ans.

Adverse effects of misoprostol:

1. Diarrhoea, cramping abdominal pain.
2. Spotted bleeding, dysmenorrhea.

Q. What is the limitation of misoprostol? (RU-16Ju)

Ans.

Limitation of misoprostol

1. High adverse-effect profile
2. Need for multiple daily dosing.

Q. Give advice to a peptic ulcer pt.

Ans.

Advice to a peptic ulcer pt

1. Stop smoking
2. Stop NSAID
3. Stop alcohol
4. Take regular meals
5. Avoid oily, spicy food
6. No tension, no anxiety.

Q. Write down the treatment strategy of acute peptic ulcer. (SU-12J)

Ans.

Treatment strategy of acute peptic ulcer

1. **PPI in IV route:** Omeprazole, pantoprazole, esomeprazole.
2. **If bleeding PUD:** Nothing per oral, IV access, isotonic fluid infusion, blood transfusion.
3. After settlement / resuscitation of the patient, endoscopy should be done to detect the extent and severity of ulcer. Investigations to detect *H. pylori* infection should be done.

Q. Briefly discuss the management of GERD. (SU-16Ju)

Ans.

Gastro-esophageal reflux disease (GERD):

1. **Lifestyle advice, including-**
 - a. weight loss
 - b. avoidance of dietary items that the patient finds worsen symptoms.
 - c. elevation of the bed head in those who experience nocturnal symptoms.
 - d. avoidance of late meals.
 - e. giving up smoking.
2. **Drugs used for GERD:**
 - a. **PPIs:** Usually effective in resolving symptoms and healing oesophagitis.
 - b. When dysmotility features are prominent, **domperidone** can be helpful.
 - c. **Antacids and alginates:** Provide symptomatic benefit.
 - d. **H₂-receptor blockers:** Help symptoms without healing oesophagitis.
3. **Anti-reflux surgery:** If medical treatment fails or patients are unwilling to take long-term PPIs.

(Ref: Davidson's-22nd/867)

Nice to know

Gastroesophageal reflux disease (GERD) is a long-term condition where stomach contents come back up into the esophagus resulting in either symptoms or complications. Symptoms include the taste of acid in the back of the mouth, heartburn, bad breath, chest pain, vomiting, breathing problems, and wearing away of the teeth. Complications include esophagitis, esophageal strictures, and Barrett's esophagus.

Laxatives

Q. Define constipation.

Ans.

Constipation: Constipation is defined as infrequent passage of hard stools. Patients may also complain of straining, a sensation of incomplete evacuation and either perianal or abdominal discomfort. Constipation may be the end result of many gastrointestinal and other medical disorders.

Q. Classify laxatives. (RU-09Ju)

Q. Name the drugs used in constipation?

Ans.

Laxatives: The terms purgative, cathartic, laxative, aperients and evacuant are synonymous. They are medicines that promote defecation largely by reducing the viscosity of the contents of the lower colon.

(Ref: Bennett & Brown-11th)

Laxatives / drugs used in constipation:

A. Luminally active agents:

1. **Bulk forming laxatives:** Bulk-forming laxatives are indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis.

- Ispaghula husk
- Bran
- Psyllium
- Methylcellulose
- Polycarbophil (synthetic fibers)

2. **Osmotic laxatives:** The colon can neither concentrate nor dilute fecal fluid: fecal water is isotonic throughout the colon. Osmotic laxatives are soluble but nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.

- **Nonabsorbable Sugars or Salts**
 - Magnesium hydroxide (milk of magnesia)
 - Sorbitol.
 - Lactulose
 - Magnesium citrate
 - Sodium phosphate
- Balanced Polyethylene Glycol (PEG)

3. **Stool softeners (Emollients) / Stool Surfactant Agents:** These agents soften stool material, permitting water and lipids to penetrate. They may be administered orally or rectally.

- Glycerin suppository
- Docusate (oral / enema).
- Liquid paraffin (Mineral oil)

B. Stimulant Laxatives (cathartics): They induce bowel movements through direct stimulation of the enteric nervous system and colonic electrolyte and fluid secretion.

a. Anthraquinone derivatives:

- Aloe
- Senna
- Cascara

b. Diphenylmethane derivatives

- Bisacodyl
- Phenolphthalein (removed from the market owing to possible cardiac toxicity)

c. Castor oil

C. Chloride Channel Activator:

- Lubiprostone

D. Prokinetic agents: (acting primarily on motility) - *Prokin***a. Serotonin 5HT₄ receptor agonists:**

- Tegaserod
- Cisapride
- Prucalopride

b. Opioid receptor antagonists: act through intestinal mu (μ)-opioid receptors.

- Methylnaltrexone bromide
- Alvimopan

c. Misoprostol.

(Ref: Goodman & Gilman's-12th; Katzung-13th)

Q. Name some commonly used laxatives. (RU-10Ju)

Ans.

Some commonly used laxatives

1. Ispaghula husk
2. Lactulose
3. Magnesium hydroxide (milk of magnesia)
4. Glycerin suppository
5. Docusate (oral / enema).
6. Liquid paraffin (Mineral oil).

Q. How will you manage a case of constipation?

Ans.

Management of constipation:**A. Non-pharmacological approach:** The overwhelming majority of people do not need laxatives. For most of the people, intermittent constipation can be prevented by -

1. Fiber-rich diet (20-30 gm/day).
2. Adequate fluid intake.
3. Regular exercise.
4. The heeding of nature's call.
5. Avoidance of constipating drugs.

B. Pharmacological approach: Use of laxatives. Patients not responding to dietary changes or fiber supplements should undergo medical evaluation prior to the initiation of long-term laxative treatment.

(Ref: Katzung-13th)

Nice to know**General mechanism of action of laxatives:**

1. Laxatives increase retention of intra-luminal fluid by hydrophilic or osmotic mechanisms.
2. Laxatives cause net absorption of fluid by effects on small & large bowel fluid & electrolyte transport.
3. Laxatives alter motility by either inhibiting segmenting (non-propulsive) contractions or stimulating propulsive contractions.

(Ref: Goodman & Gilman's-12th)

Dietary fibres:**Sources:** Cell walls and supporting structures of vegetables and fruits.**Nature:** Most of the fibre in our diet is in the form of nonstarch polysaccharides (NSP), which are not digestible by human enzymes.**Types:**

1. Soluble (pectins, guar, ispaghula)
2. Insoluble (cellulose, hemicelluloses, lignin).

Insoluble fibre has less effect than soluble fibre on the viscosity of gut contents but is a stronger laxative because it resists digestion in the small bowel and so enters the colon intact.

Mechanism of action: They act by increasing the volume and lowering the viscosity of intestinal contents to produce a soft bulky stool, which encourages normal reflex bowel activity. They should be taken with liberal quantities of fluid (at least 2 litres daily).

Indication: Treatment of choice for simple constipation.

(Ref: Bennett & Brown-11th)

Q. Discuss the mechanism of action of ispaghula husk? (CU-04M)

Ans.

Mechanism of action of ispaghula husk: They are indigestible, hydrophilic colloids that absorb water and form a bulky, emollient gel that distend the colon & promote peristalsis.

Adverse effects of bulk forming laxatives:

1. Increased bloating
2. Flatus

Contraindications of bulk forming laxatives:

1. Intestinal obstruction.
2. Megacolon or megarectum.
3. Fecal impaction should be treated before fibre supplementation.

(Ref: Katzung-13th; Goodman & Gilman's-12th)

Q. Discuss the mechanism of action of lactulose. (CU-04M)

Q. Short note: Lactulose. (RU-16Ju)

Ans.

Mechanism of action of lactulose: Lactulose is a synthetic disaccharide. Taken orally, it is unaffected by small intestinal disaccharidases, is not absorbed and thus acts as an osmotic laxative. It increases fecal fluid & thus increase stool liquidity. Increased intestinal contents stimulate peristalsis and evacuation of stool.

(Ref: Bennett & Brown-11th, Katzung-13th)

Indications of lactulose:

1. Constipation: Treatment of acute constipation or the prevention of chronic constipation.
2. Hepatic encephalopathy
3. Frequently used to clear the colon for diagnostic procedures (eg, colonoscopy) or surgery.

Adverse effects of osmotic laxatives / lactulose:

1. **Hypermagnesemia** (So, lactulose should not be used for prolonged periods in patients with renal insufficiency due to risk of hypermagnesemia).
2. **Severe flatus and cramps.**
3. Risk of **intravascular volume depletion & electrolyte fluctuations.** (Hence they should not be used in patients who are frail, elderly, have renal insufficiency, or have significant cardiac disease.)

Contraindication

1. Renal failure
2. Severe cardiac disease

(Ref: Katzung-13th)

Q. Write down the mechanism of action of bisacodyl. Write the indications. (RU-10/09Ju)

Ans.

Mechanism of action of stimulant laxatives / bisacodyl: Stimulant laxatives induce bowel movement by—

1. Direct stimulation of the enteric nervous system
2. Increasing colonic electrolyte & fluid secretion by irritation.

Indications of stimulant laxatives / bisacodyl:

1. **Constipation:** Treatment of acute constipation or the prevention of chronic constipation.
2. **Long-term treatment of constipation**, especially in patients who are neurologically impaired and in bed-bound patients in long-term care facilities.

Adverse effect of stimulant laxatives / bisacodyl: More recent research suggests that long-term use of these agents probably is safe in most patients.

1. Abdominal cramps (*should be used only with caution in pregnancy, and never where intestinal obstruction is suspected.*)
2. Excessive fluid secretion → Diarrhea.
3. long-term use of cathartics → dependence and destruction of the myenteric plexus, resulting in colonic atony and dilation.

(Ref: Bennett & Brown-11th, Katzung-13th)

Nice to know**Stool softeners**

Mechanism of action of stool softeners (emollients): They decrease the surface tension of the stool to allow mixing of aqueous & fatty substance softening the stool & permitting easier defecation.

Adverse effects of stool softeners:

1. Long term use can impair absorption of fat soluble vitamins (A, D, E & K).
2. Aspiration can result in a severe lipid pneumonitis.

(Ref: Katzung-13th)

Enema

An **enema** is the procedure of introducing liquids into the rectum and colon via the anus. The increasing volume of the liquid causes rapid expansion of the lower intestinal tract, stimulates peristalsis and causes evacuation of stool. Enema is used for bowel preparation for-

1. GIT surgery
2. Radiological examination of gut, eg, barium enema
3. Colonoscopy
4. Sigmoidoscopy

Drugs stimulating GIT motility

Q. Write short notes on prokinetic agents. (SU-08J)

+ 669

Ans.

Prokinetic agents:

Definition: Drugs that selectively stimulate gut motor function are called prokinetic agents.

(Ref: Katzung-13th)

Prokinetic agents:

1. **D₂-receptor antagonists:**

- ✓ Metoclopramide
- ✓ Domperidone

2. **Cholinomimetic agents:**

- Bethanechol
- ✓ Neostigmine

3. **Macrolides:** Erythromycin, azithromycin

4. **Chloride channel activator:** Lubiprostone.

D₂ - antagonist
5HT₄ - agonist

(Ref: Katzung-13th)

Anti-emetic drugs

Causes of Vomiting / Emesis: Nausea and vomiting may be manifestations of a wide variety of conditions, including adverse effects from medications; systemic disorders or infections; pregnancy; vestibular dysfunction; central nervous system infection or increased pressure; peritonitis; hepatobiliary disorders; radiation or chemotherapy; and gastrointestinal obstruction, dysmotility, or infections.

Pathophysiology of emesis/vomiting

The brain stem "**vomiting center**" is a loosely organized neuronal region within the lateral medullary reticular formation and coordinates the complex act of vomiting through interactions with cranial nerves VIII and X and neural networks in the nucleus tractus solitarius that control respiratory, salivatory, and vasomotor centers. High concentrations of muscarinic M_1 , histamine H_1 , neurokinin 1 (NK_1), and serotonin $5-HT_3$ receptors have been identified in the vomiting center.

There are four important sources of afferent input to the vomiting center:

1. The "**chemoreceptor trigger zone (CTZ)**" or area postrema is located at the caudal end of the fourth ventricle. This is outside the blood-brain barrier but is accessible to emetogenic stimuli in the blood or cerebrospinal fluid. **The CTZ is rich in dopamine D_2 receptors and opioid receptors, and possibly serotonin $5-HT_3$ receptors and NK_1 receptors.**
2. The **vestibular system** is important in **motion sickness** via cranial nerve VIII. It is rich in **muscarinic M_1 and histamine H_1 receptors.**
3. **Vagal and spinal afferent nerves from the gastrointestinal tract are rich in $5-HT_3$ receptors.** Irritation of the gastrointestinal mucosa by chemotherapy, radiation therapy, distention, or acute infectious gastroenteritis leads to release of mucosal serotonin and activation of these receptors, which stimulate vagal afferent input to the vomiting center and chemoreceptor trigger zone.
4. The CNS plays a role in vomiting due to psychiatric disorders, stress, and anticipatory vomiting prior to cancer chemotherapy.

Identification of the different neurotransmitters involved with emesis has allowed development of a diverse group of antiemetic agents that have affinity for various receptors. Combinations of antiemetic agents with different mechanisms of action are often used, especially in patients with vomiting due to chemotherapeutic agents.

(Ref: Katzung-13th)

Q. Draw a schematic diagram to show the neuronal connections of the vomiting center and the targets for pharmacological intervention. (CU-14Ju)

Ans.

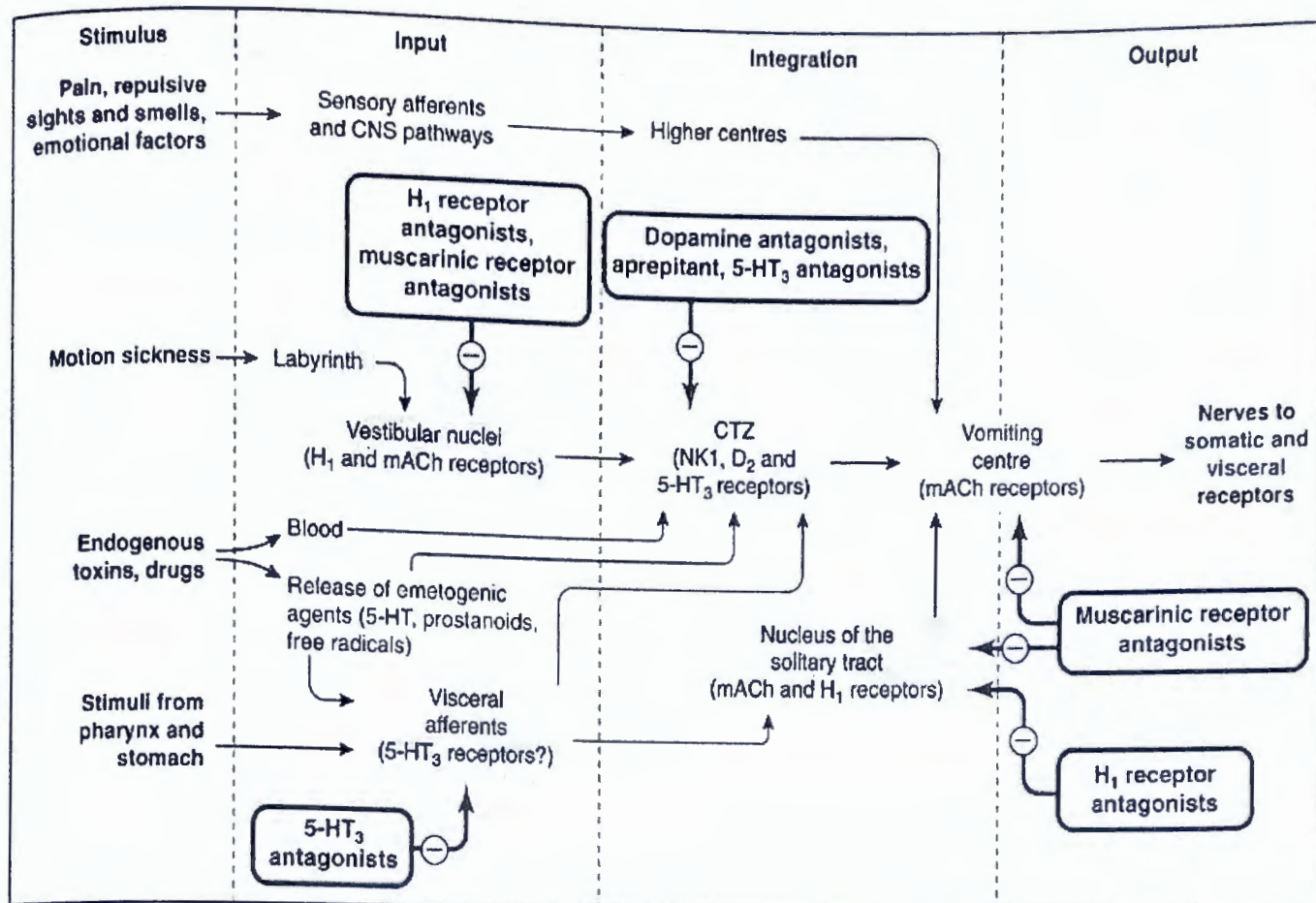


Figure. Schematic diagram of the factors involved in the control of vomiting, with the probable sites of action of antiemetic drugs. Chemoreceptor trigger zone (CTZ). 5-HT₃, 5-hydroxytryptamine type 3; D₂, dopamine D₂; H₁, histamine H₁; mACh, muscarinic acetylcholine; NK₁, neurokinin 1.

Q. Enumerate antiemetic drugs. (DU-09Ju; CU-15J, 13Ju, 11J, 09Ju; RU-14Ju, 13J)

Q. List the clinically useful anti emetic drugs. (CU-10J)

Ans.

Anti-emetic drugs:

1. Serotonin 5HT ₃ -receptor antagonists	- Ondansetron - Granisetron - Dolasetron - Palonosetron <i>3- chemotherapy induced</i>
2. Prokinetic agents (D ₂ -receptor blocker)	Domperidone <i>Metopramide</i>
3. Corticosteroids	- Dexamethasone - Methylprednisolone
4. Neurokinin receptor antagonists	- Aprepitant - Fosaprepitant <i>NK1</i>
5. Phenothiazines	- Prochlorperazine - Promethazine - Thiethylperazine
6. Butyrophenone	- Droperidol - Haloperidol <i>A.M.D. psychob.</i>

7. Substituted benzamides	• Metoclopramide • Trimethobenzamide
8. H ₁ -receptor antagonists	• Diphenhydramine • Dimenhydrinate • Meclizine • Cyclizine
9. Anticholinergic drugs	• Hyoscine
10. Benzodiazepines	• Lorazepam • Alprazolam • Diazepam
11. Cannabinoids	• Dronabinol • Nabilone

(Ref: Katzung-13th; Lippincott's-6th)

Prokinetic agents / D₂-receptor antagonists (Domperidone & Metoclopramide)

Q. Mention the mechanism of action of metoclopramide. (DU-15Ju, CU-05M)

Q. State the mechanism of domperidone. (CU-10J, SU-13J)

Q. Short notes: Metoclopramide. (DU-16J, CU-05J)

Ans.

Mechanism of action of metoclopramide & domperidone: Metoclopramide and domperidone are dopamine D₂ receptor antagonists. Within the GIT, activation of dopamine receptors inhibits cholinergic smooth muscle stimulation; blockade of this effect is believed to be the primary **prokinetic** mechanism of action of these agents. These agents increase esophageal peristaltic amplitude, increase lower esophageal sphincter pressure, and enhance gastric emptying but have no effect upon small intestine or colonic motility.

(Ref: Katzung-13th)

1. Metoclopramide / Domperidone **blocks dopamine D₂ receptor within the GIT**

↓
No suppression of dopamine mediated acetylcholine release from myenteric motor neurons

↓
↑ Acetylcholine is released from myenteric motor neurons

↓
Contraction of GIT smooth muscles by cholinergic stimulation

- ↓
- ↑ Esophageal peristaltic amplitude.
 - ↑ Lower esophageal sphincter pressure.
 - ↑ Gastric emptying.
 - No effect on small intestine or colonic motility

2. Metoclopramide and domperidone also **block dopamine D₂ receptors in the chemoreceptor trigger zone of the medulla (area postrema)**, resulting in potent antinausea and antiemetic action.

(Ref: Katzung-13th)

Q. Mention the indications of metoclopramide. (CU-05M)

Q. Mention the indications of domperidone. (RU-16J)

Ans.

Indications of metoclopramide & domperidone:

1. **Gastro-esophageal reflux disease (GERD):** Used mainly in combination with antisecretory agents, eg, proton pump inhibitor, in patients with regurgitation or refractory heartburn
2. **Impaired gastric emptying** due to postsurgical disorders (vagotomy, antrectomy) and diabetic gastroparesis
3. Non-ulcer dyspepsia.
4. **Prevention of vomiting (antiemetic):** Due to their potent antiemetic action, metoclopramide and domperidone are used for the prevention and treatment of emesis.
5. **Postpartum lactation stimulation:** Domperidone is sometimes recommended to promote postpartum lactation.

*(Ref: Katzung-13th)***Q. Mention the adverse effects of metoclopramide. (DU-15Ju, CU-05M)**

Ans.

Adverse effects of metoclopramide:

1. **CNS adverse effects:** As metoclopramide crosses BBB significantly, the most common adverse effects of it involve CNS.
 - Restlessness
 - Drowsiness
 - Insomnia
 - Anxiety
 - Agitation
2. **Extra pyramidal side effects:** Extrapyramidal effects due to central dopamine receptor blockade occur acutely in 25% of patients given high doses and in 5% of patients receiving long-term therapy.
 - Dystonias
 - Akathisia
 - Parkinsonian features
 - Tardive dyskinesia (after prolonged treatment with metoclopramide.)

For this reason, long-term use should be avoided unless absolutely necessary, especially in the elderly.
3. **Elevated prolactin levels** can cause-
 - Galactorrhea
 - Gynecomastia
 - Impotence
 - Menstrual disorders.

*(Ref: Katzung-13th)***Q. State the adverse effects of domperidone? (CU-10J,03J)**

Ans.

Adverse effects of domperidone: Domperidone is extremely well tolerated.

1. Because it does not cross the blood-brain barrier to a significant degree, neuropsychiatric and extrapyramidal effects are rare.
2. Elevated prolactin levels can cause-
 - Galactorrhea
 - Gynecomastia
 - Impotence
 - Menstrual disorders.

*(Ref: Katzung-13th)***Q. A patient aged 50 years of age, developed tremor & rigidity after a dose of Metoclopramide. Explain the causes & give the treatment. (SU-09J)**

Ans.

Explanation: Tremor & rigidity developed as a side effect of metoclopramide. As metoclopramide is a lipid soluble drug, it crosses the blood-brain barrier (BBB) readily. So CNS adverse effects are common in metoclopramide administration.

Treatment:

- Stop metoclopramide immediately.
- Muscle relaxant for rigidity: Baclofen, diazepam.

Q. Mention the advantages of domperidone over metoclopramide? (RU-14Ju)

Q. Why domperidone produces lesser adverse effects than metoclopramide? (CU-07J)

Ans.

Domperidone produces lesser adverse effects than metoclopramide:

- Metoclopramide can cross BBB. So its CNS adverse effects are common.
- Moreover, long term use or acute toxicity of metoclopramide can cause extrapyramidal effects.
- But, domperidone does not cross BBB & its neuro-psychiatric & extra-pyramidal adverse effects are rare. So, it is extremely well tolerated.

(Ref: Katzung-13th)

Q. How does prochlorperazine differ from metoclopramide? (DU-09Ju)

Ans.

Differences between Prochlorperazine & Metoclopramide:

Traits	Prochlorperazine	Metoclopramide
1. Chemistry	Phenothiazine	Substituted benzamide
2. Blockade of 5HT receptor	Yes	No
3. Anti-muscarinic action	Present	Absent
4. α -adrenergic blockade	Yes (reflex tachycardia, postural hypotension occurs)	No
5. Histaminergic blockade	Blocks (so strong sedation occurs)	No
6. Voltage gated Na^+ channel blockade	Blocks (arrhythmia occurs)	No
7. Peripheral conversion of androgen to estrogen	Yes (amenorrhea, galactorrhea, gynecomastia occur)	No
8. Prolactin level	No change	Increases
9. Use as antipsychotics	Yes	No

Q. Compare between domperidone and metoclopramide. (CU-17M)

Ans.

Comparison between domperidone and metoclopramide

Traits	Domperidone	Metoclopramide
1. Used to promote postpartum lactation	Yes	No
2. Crosses BBB	No	Yes
3. CNS adverse effects	Rare	Common
4. Cause extrapyramidal effects	Rare	Common
5. Prolactin level	Increases	Increases
6. Patient compliance	Extremely well tolerated	Less well tolerated

Serotonin (5HT₃)-antagonists

Q. Mention the mechanism of action & adverse effects of ondansetron. (CU-15J, 13Ju, 11J, 09Ju; RU-13J)

Q. Short note: Ondansetron. (DU-17M, 16Ju)

Ans.

Ondansetron

Mechanism of action: Selective 5-HT₃-receptor antagonists have potent antiemetic properties that are mediated mainly through-

- Blockade of central 5-HT₃-receptor in the vomiting center and chemoreceptor trigger zone.
- Blockade of peripheral 5-HT₃ receptors on extrinsic intestinal vagal and spinal afferent nerves.

The antiemetic action of these agents is restricted to emesis attributable to vagal stimulation (eg, postoperative) and chemotherapy; other emetic stimuli such as motion sickness are poorly controlled.

(Ref: Katzung-13th)

Indications:

1. Chemotherapy induced nausea & vomiting.
2. Post-operative & post-radiation, nausea & vomiting.

(Ref: Katzung-13th)

Adverse effects: These 5-HT₃-receptor antagonists are well-tolerated agents with excellent safety profiles. The most common adverse effects are-

1. Headache
2. Dizziness
3. Constipation.
4. Prolongation of the QT interval (dolasetron)

(Ref: Katzung-13th)

Diarrhea and anti-diarrheal drugs

Diarrhea: WHO defines diarrhea as the passage of loose watery stools three or more times in 24 hours.

Classification: 3 types.

1. **Acute watery diarrhea:** Begins acutely & lasts for hours to days. No visible blood with stool. (Cause: Rotavirus, *V. cholerae*, *Salmonella*, Enterotoxigenic *E. coli*)
2. **Dysentery:** Passage of visible blood in the stool (Cause: *Shigella*, *C. jejuni*, enteroinvasive *E. coli*)
3. **Persistent diarrhea:** Lasts for more than 14 days. Stool may be mixed with blood.

Complications of diarrhea:

1. Dehydration & its complications.
2. Electrolyte imbalance
3. Malnutrition.

Q. Describe the principles of diarrheal management.

Q. Outline the treatment of a patient suffering from acute watery diarrhea. (DU-13Ju)

Ans.

Principles of management of diarrhea:

1. Correction of dehydration: by-
 - ORS
 - IV fluid
2. Treatment of associated problem & complications:
 - Correction of electrolyte imbalance
 - Improvement of general health status & treatment of PEM
 - Treatment of vomiting if present
 - Treatment of convulsion or vitamin A deficiency in children (if present).

3. Treatment of infective cause of diarrhea
 - Antibiotics
4. Further prevention of diarrhea.

(Ref: M.R. Khan, 3rd/152-161)

Q. How dehydration is corrected in diarrhea?

Ans.

Correction of dehydration in diarrhea:

A. Rehydration of body fluid:

1. Orally: By oral rehydration solution (ORS).
2. Parenterally: By infusion of IV fluids, eg,
 - Cholera Saline
 - Normal Saline
 - 5% Dextrose in aqua with normal saline (5% DNS)
 - Hartman's solution
 - Crystalloid solution

B. Prevention of further fluid loss:

1. Treatment of infection
2. Use of anti-diarrheal drugs

Q. Discuss the advantages of commonly used ORS. (RU-16J,12J)

Q. Discuss the role of rehydration therapy in the management of acute watery diarrhea. (CU-06S; SU-09Ju,06J)

Q. Mention the role of each constituent of ORS in the management of diarrhea. (SU-10J,08Ju, CU-07J)

Q. Discuss the role of ORS. (SU-17J)

Q. State the role of glucose of ORS in diarrhea. (DU-13Ju)

Ans.

Role of rehydration therapy in acute watery diarrhea / Role of each constituent of ORS in the management of diarrhea:

1. **Rehydration by water of the ORS:** Water of the ORS corrects fluid loss (dehydration). In acute watery diarrhea there is huge fluid loss in a short period of time & subsequently hypovolemia, shock & renal failure may develop. So ORS should be started & continued as far as possible. If possible an IV access should start & a normal saline should start.
2. **NaCl and KCl:** Corrects electrolyte loss and maintain electrolyte balance.
3. **Bicarbonate ion (HCO_3^-):** Corrects the acidosis.
4. **Citrate:** Increases the absorption of Na^+ and glucose and thus decreases stool output.
5. **Glucose:** Helps Na^+ absorption by Na^+ -glucose co-transport. Along with Na^+ , water is also absorbed. Thus glucose helps absorption of both Na^+ & water.

Viva Q. What is the role of glucose in ORS?

Ans. Na^+ is absorbed from the intestine by Na^+ -glucose co-transport. Thus, glucose helps in Na^+ absorption.

Q. What are the different types of ORS? Give the composition of them. (SU-10J, RU-16J,12J)

Q. Describe the new formulation ORS. (CU-07J)

Q. Write the composition of ORS with their objectives. (DU-13Ju, SU-07J)

Q. Short note: ORS. (RU-14J)

Q. Short note: Citrate based ORS. (RU-17J)

Ans.

ORS means oral rehydration salts. When ORS is dissolved in adequate amount of water, then the solution is called **Oral rehydration saline.**

Different types of ORS:

1. Citrate saline

2. Bicarbonate saline
3. Rice saline

Composition of ORS: The WHO/UNICEF recommended formulation is-

Constituents	Amount
1. NaCl	2.6 gm/L
2. KCl	1.5gm/L
3. Trisodium citrate dihydrate	2.5 gm/L
4. Anhydrous glucose	13.5 gm/L

(Ref: New formulation orsaline-N (WHO & UNICEF), SMC)

Composition of currently used oral rehydration saline in our country:

Bicarbonate Saline		Citrate Saline	
Constituents	Amount	Constituents	Amount
NaCl	3.5 g	NaCl	3.5 g
NaHCO ₃	2.5 g	Tri-Na-citrate	2.9 g
KCl	1.5 g	KCl	1.5 g
Glucose	20 g	Glucose	20 g
Water	1 L	Water	1 L

Q. Enumerate anti-diarrheal drugs. (SU-09Ju)

Q. Name some anti motility drugs. (CU-08J)

Ans.

Anti-diarrheal drugs/ anti motility drugs:

1. Opioid agonists	• Loperamide • Codeine • Diphenoxylate
2. Colloidal Bismuth compounds	• Bismuth subsalicylate • Bismuth subcitrate potassium
3. Kaolin & pectin	• Kaolin is a naturally occurring hydrated magnesium aluminum silicate (attapulgit). • Pectin is an indigestible carbohydrate derived from apples.
4. Bile salt binding resins	• Cholestyramine • Colestipol • Colesevelam
5. Somatostatin	• Octreotide

(Ref: Katzung-13th)

Q. Criticize indiscriminate uses of anti-motility drugs in watery diarrhea. (SU-17M,12/09Ju)

Q. Comment on use of anti-motility drugs on treatment of watery diarrhea. (SU-15J,13J)

Ans.

Indiscriminate use of anti-motility drugs:

1. Antimotility drugs reduce gastric motility. That's why it can be used in diarrhea. But its indiscriminate use in severe diarrhea can mask the clinical features, and there will be sequestration of fluid in the intestine, and thus patient may go to shock without any diarrhea.
2. These drugs may cause toxic megacolon, and should not be used in young children and patient with severe colitis.

Q. Name the anti-motility drugs. Justify the use of the named drugs in different diarrheal disease. (CU-08J)

Q. Briefly discuss the role of Loperamide in the treatment of acute diarrhea. (SU-15Ju,09Ju,06J,05S)
Ans.

Anti-motility drugs / Opioid agonists used in diarrhea:

1. Loperamide
2. Diphenoxylate
3. Codeine

infective diarrhea
to use opiate in
(Paralytic ileus)
Bacteria stops

Role of opioid agonists / Loperamide / Diphenoxylate in diarrhea:

1. Inhibition of pre-synaptic cholinergic nerves in the submucosal & myenteric plexuses

↓
Increase colonic phasic segmentation activity

↓
Increase colonic transit time and fecal water absorption.

2. They also decrease mass colonic movement & the gastro-colic reflex.

(Ref: Katzung-13th)

Q. What are the advantages of Loperamide than other opioid agonists?

Ans.

Advantages of Loperamide: Although all opioids have anti-diarrheal effects, loperamide is an ideal drug for diarrhea due to its following special properties-

1. It does not cross BBB.
2. It has no analgesic effect
3. It is not potential for addiction.
4. Tolerance to long term use has not been reported.

(Ref: Katzung-13th)

Q. Discuss the role of antimicrobials in the management of acute watery diarrhea. (CU-06S)

Q. Criticize indiscriminate uses of antimicrobials in acute diarrhea. (SU-17M,11Ju)

Ans.

Role of antimicrobials in the treatment of acute diarrhea: The main cause of acute watery diarrhea (especially in children) is Rota virus & 2nd most common cause is *V. cholerae*. Diarrhea is also caused by toxins and drugs such as antibiotics, cytotoxic drugs. Diarrhea caused by virus, toxins or drugs must not need any antibiotics. So routine use of antibiotics in acute watery diarrhea should be avoided & discouraged. Antibiotics should be used only where bacteria are responsible for diarrhea.

Antibiotic therapy in diarrhea:

- For viral diarrhea: No antibiotic
- Antibiotic is indicated in-
 1. Diagnosed case of cholera
 2. Dysentery
 3. Systemic manifestation of endotoxic shock
 4. Presence of fecal leukocytes (pus cells) for more than 10/HPF.

Q. What is the treatment of infective diarrhea?

Ans.

Treatment of infective diarrhea:

- Correction of dehydration
- Correction of electrolyte imbalance
- Use of appropriate antibiotics

Use of antibiotics in infective diarrhea

Cause of diarrhea	Drugs of 1 st choice	Alternative drugs
<i>V. cholerae</i>	Tetracyclines	• Quinolones • Aminoglycosides
<i>E. Coli</i>	Cephalosporin TMP-SMZ	• Quinolones • Aminoglycosides
<i>Shigella</i>	Quinolones	• TMP-SMZ • Ampicillin • Azithromycin • Ceftriaxone
<i>Campylobacter jejuni</i>	Azithromycin Erythromycin	• Tetracyclines • Quinolones

(Ref: Katzung-13th)

Q. Discuss the role of Tetracyclines in the treatment of acute diarrhea. (SU-10J,09Ju)

Ans.

V. cholerae is highly sensitive to Tetracyclines. Acute watery diarrhea caused by *V. cholerae* should be treated with tetracyclines.

Q. List the antimicrobials that may be used in infective diarrhea caused by *Shigella*. Select P drug in this case and justify your choice? (CU-06M)

Q. Outline the selection criteria for selection of P-drug in treatment of acute diarrhea. (SU-11Ju)

Ans.

Drugs for *Shigella* induced diarrhea:

1. Ciprofloxacin
2. Ampicillin
3. 3rd and 4th generation Cephalosporins
4. Co-trimoxazole

Ciprofloxacin is the P-drug of infective diarrhea caused by *Shigella* because of

1. Bactericidal effect
2. Rapid onset of action
3. Prolong duration of action
4. Short duration of therapy
5. Less prone to develop resistance
6. Less change of toxicity

Drugs used in cholera caused by *V. cholerae*:

1. Tetracycline
2. Ciprofloxacin

Drugs Used in of Irritable Bowel Syndrome (IBS)

IBS is an idiopathic chronic, relapsing disorder characterized by abdominal discomfort (pain, bloating, distention, or cramps) in association with alterations in bowel habits (diarrhea, constipation, or both). With episodes of abdominal pain or discomfort, patients note a change in the frequency or consistency of their bowel movements.

(Ref: Katzung-13th)

Drugs used in IBS: Pharmacologic therapies for IBS are directed at relieving abdominal pain and discomfort and improving bowel function.

A. For patients with predominant diarrhea	• Antidiarrheal agents, especially loperamide.
B. For patients with predominant constipation	• Dietary fiber • Osmotic laxatives, especially milk of magnesia. For women with IBS with predominant constipation: • 5-HT₄ partial agonist: Tegaserod (<i>no longer clinically available for cardiovascular risk</i>) • Chloride Channel Activator: Lubiprostone (<i>recently approved</i>)
C. For chronic abdominal pain	• Low doses of tricyclic antidepressants (eg, amitriptyline or desipramine, 10–50 mg/d) • Antispasmodics (Anticholinergics) • Dicyclomine • Hyoscyamine .
D. For nausea, bloating, and abdominal pain	• Serotonin 5-HT₃-Receptor Antagonists: • Alosetron • Ondansetron • Granisetron • Dolasetron • Palonosetron

(Ref: Katzung-13th)

Q. How tricyclic antidepressants help in IBS?

Ans.

At low doses, TCA may alter central processing of visceral afferent information. The anticholinergic properties of these agents also may have effects on gastrointestinal motility and secretion, reducing stool frequency and liquidity. Finally, tricyclic antidepressants may alter receptors for enteric neurotransmitters such as serotonin, affecting visceral afferent sensation.

(Ref: Katzung-13th)

Drugs Used to Treat Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) comprises two distinct disorders: ulcerative colitis and Crohn's disease. The etiology and pathogenesis of these disorders remains unknown. For this reason, pharmacologic treatment of inflammatory bowel disorders often involves drugs that belong to different therapeutic classes and have different but nonspecific mechanisms of anti-inflammatory action. Drugs used in inflammatory bowel disease are chosen on the basis of disease severity, responsiveness, and drug toxicity.

Drugs used in IBD:

1. Aminosalicylates:	• Sulfasalazine • Olsalazine • Balsalazide • Mesalamine
2. Glucocorticoids	• Prednisone • Prednisolone • Hydrocortisone (enemas, foam, or suppositories) • Budesonide
3. Purine Analogs:	• Azathioprine • 6-Mercaptopurine
4. Methotrexate	
5. Anti-TNF Therapy	• Infliximab • Adalimumab • Certolizumab

(Ref: Katzung-13th)

Drugs Used to Treat Variceal Hemorrhage

Portal hypertension most commonly occurs as a consequence of **chronic liver disease**. In portal hypertension **esophageal varices** can rupture, leading to massive upper gastrointestinal bleeding. Several drugs are available that reduce portal pressures.

1. Somatostatin & Octreotide
2. Vasopressin & Terlipressin
3. Beta-blocker: Propranolol and nadolol.

(Ref: Katzung-13th)

MCQ

- Q. Antisecretory drugs used in PUD are- (DU-17M)**
- misoprostol
 - ranitidine
 - omeprazole
 - bismuth compound
 - sucralfate
- a. F, b. T, c. T, d. F, e. F*
- Q. A 23-month-old boy has come with frequent loose motion for 3 days. You have assessed the child as having severe dehydration considering the present of- (DU-16J)**
- drinks eagerly
 - dry mouth and tongue
 - restless, irritable
 - skin pinch goes back very slowly
 - sunken eyes
- a. F, b. T, c. T, d. T, e. T*
- Q. Omeprazole- (DU-15Ju)**
- reduce gastric hydrochloric acid secretion
 - should be given an hour before meal
 - is a prodrug
 - produces achlorhydria
 - neutralizes gastric hydrochloric acid
- a. T, b. T, c. T, d. T, e. F*
- Q. Following drugs binds with bile acid in the intestine, thus preventing their return to the liver via the enterohepatic re-circulation: (CU-14Ju)**
- Niacin
 - Fenofibrate
 - Cholestyramine.
 - Fluvastatin
 - Colestipol.
- a. F, b. F, c. T, d. F, e. T*
- Q. Drugs produce anti-emetic effects are- (DU-14J)**
- metoclopramide
 - meclizine
 - imipramine
 - domperidone.
 - cimetidine
- a. T, b. T, c. F, d. T, e. F*
- Q. Antibiotics used for eradication of *helicobacter pylori* include- (DU-14J)**
- clarithromycin
 - amoxicillin
 - co-trimoxazole
 - ciprofloxacin
 - metronidazole.
- a. T, b. T, c. F, d. F, e. T*
- Q. Omeprazole- (DU-13Ju)**
- is a prodrug.
 - irreversibly inhibits Na^+/K^+ ATPase.
 - accelerates the gastric emptying.
 - blackens the tongue.
 - inhabits the cytochrome p-450 enzyme.
- a. T, b. F, c. F, d. F, e. F*
- Q. Drugs for eradicating *H. pylori* include- (DU-13J, 11Ju)**
- Clarithromycin
 - Tetracycline
 - Cotrimoxazole
 - Ciprofloxacin
 - Metronidazole
- a. T, b. T, c. F, d. F, e. T*
- Q. Omeprazole- (DU-12J)**
- Blocks H^+/K^+ ATPase pump. (T)
 - Is a synthetic analogue of prostaglandin. (F)
 - Blackens the tongue. (F)
 - Is indicated for reflux esophagitis. (T)
 - One of the triple drug therapy. (T)
- Q. Triple therapy for *H. pylori* eradication contains- (DU-11J)**
- Amoxicillin (T)
 - Flucloxacillin (F)
 - Lansoprazole (T)
 - Clarithromycin (T)
 - Erythromycin (F)
- Q. Pantoprazole- (DU-10J)**
- prevents Na^+/H^+ pump (F)
 - accelerates gastric emptying (F)
 - is indicated in reflux esophagitis (T)
 - one of the component of triple drug therapy (T)
 - decreases the pH without reducing the volume of gastric secretion (F)

Chapter 12

Respiratory pharmacology: Bronchial asthma

Drugs used in bronchial asthma

Bronchial asthma: Asthma is an inflammatory disease of the airways characterized by episodes of acute bronchoconstriction causing shortness of breath, cough, chest tightness, wheezing, and rapid respiration. Asthma is a chronic disease with an underlying inflammatory pathophysiology that, if untreated, may incur airway remodeling, resulting in increased severity and incidence of exacerbations and/or death. Deaths due to asthma are relatively infrequent, but significant morbidity results in high outpatient costs, numerous hospitalizations, and decreased quality of life.

(Ref: Lippincott's-6th)

Role of inflammation in asthma: Airflow obstruction in asthma is due to bronchoconstriction that results from contraction of bronchial smooth muscle, inflammation of the bronchial wall, and increased mucous secretion. Asthmatic attacks may be related to recent exposure to allergens or inhaled irritants, exercise leading to bronchial hyperactivity and inflammation of the airway mucosa. The symptoms of asthma may be effectively treated by several drugs, but no agent provides a cure for this obstructive lung disease.

(Ref: Lippincott's-6th)

Causes of airway narrowing in acute asthmatic attacks include-

1. Bronchoconstriction (contraction of airway smooth muscle)
2. Inspissation of thick, viscid mucus plugs in the airway lumen
3. Thickening of the bronchial mucosa from edema, cellular infiltration
4. Hyperplasia of secretory, vascular, and smooth muscle cells

Approach to treatment:

1. Prevention of exposure to allergen
2. **Bronchodilators:** To reverse acute bronchoconstriction. Short-term relief is thus most effectively achieved by bronchodilators, of which β -agonists are the most effective and most widely used. Theophylline and antimuscarinic agents are also used for reversal of airway constriction.
3. **Anti-inflammatory agents:** Long-term control is most effectively achieved with an anti-inflammatory agent such as an inhaled corticosteroid.

(Ref: Katzung-13th edition)

Q. Classify anti-asthmatic drugs. (DU-06S; CU-06S, SU-16Ju)

Q. Classify the drugs used in the management of bronchial asthma. (DU-12Ju, CU-17M, 15J, 14J, 13Ju/J, 11Ju, 08Ju, RU-09Ju; SU-17J, 15J, 09Ju)

Q. Classify anti-asthmatic drugs according to their mechanism of action. (CU-10J, 07J)

Q. Name the short-term reliever and long-term controller drugs used in bronchial asthma. (DU-11Ju)

Q. Outline antiinflammatory agents used in bronchial asthma. (RU-11J)

Q. Classify / Categorize / Name bronchodilators. (RU-16Ju, 15J, 13J, SU-16J, 11J)

Q. Lists the group wise important non-bronchodilator agents used in bronchial asthma. (CU-08J)

Q. Name clinically useful bronchodilators. (DU-10J, CU-06S; SU-07J)

Q. Enlist the antimuscarinic drugs used in bronchial asthma. (CU-15Ju)

Ans.

Anti-asthmatic Drugs:

A. Bronchodilator: Reverses bronchoconstriction and provides short-term relief (short-term reliever).

1. Selective β_2-agonists <i>non-selective // //</i> <i>→ adrenergic</i> <i>ephedrine</i>	a. Short acting (2-6 hours) <i>= SABA</i> • Salbutamol <i>(rebu)</i> • Albuterol • Terbutaline <i>(rebu)</i> • Metaproterenol • Pirbuterol b. Long acting (>12 hours) <i>LABA</i> • Salmeterol • Formoterol
2. Anti-muscarinic agent	• Ipratropium bromide <i>(rebu)</i> <i>→ old pt / COPD</i> • Tiotropium • Atropine

3. Methylxanthines	• Aminophylline • Theophylline • Doxophylline • Enprophylline • Pentoxifylline (used in intermittent claudication) • Theobromine (cocoa) • Caffeine
--------------------	---

B. Anti-inflammatory drugs: Suppress chronic inflammation of bronchial asthma (long-term controller).

1. Corticosteroids / Glucocorticoids	• Hydrocortisone (Inj) → 10 mg/day • Prednisolone (tablet) → 30 mg/day • Beclomethasone (inhaler) • Betamethasone (inhaler) • Triamcinolone (inhaler) • Budesonide • Ciclesonide • Flunisolide • Fluticasone • Mometasone <i>Acute (oral)</i> <i>Chronic (inhaler)</i>
2. Leukotriene receptor antagonists: These drugs also competitively prevent bronchoconstriction caused by leukotrienes (C4, D4 and E4) (cysteinyl LT)	• Zafirlukast • Montelukast
3. Leukotriene synthesis inhibitor	• Zileuton
4. Mast cell stabilizers: Prevents mast cell degranulation.	• Cromolyn sodium = Disodium chromoglycate • Nedocromil sodium
5. Anti-IgE monoclonal antibody: Inhibits the binding of IgE to mast cells & prevents mast cell degranulation.	• Omalizumab

6. Ca^{2+} channel blocker $\Rightarrow$ verapamil, diltiazem, nifedipine (Ref: Katzung-13th)
7. K^{+} channel opener $\Rightarrow$ cromakalim

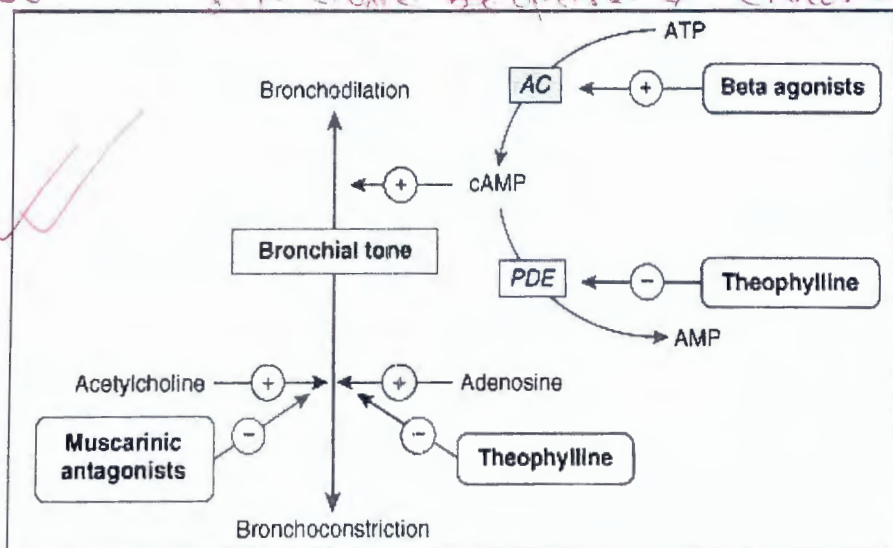


Fig. Bronchodilation is promoted by cAMP. Intracellular levels of cAMP can be increased by β -adrenoceptor agonists, which increase the rate of its synthesis by adenylyl cyclase (AC); or by phosphodiesterase (PDE) inhibitors such as theophylline, which slow the rate of its degradation. Bronchoconstriction can be inhibited by muscarinic antagonists and possibly by adenosine antagonists.

HF $\rightarrow$ isoprenaline + Diuretics
Q. Name the drugs used to decrease bronchial responsiveness to exogenous stimuli. Explain their action. (SU-12Ju)

HTN $\rightarrow$ CCB / MOCs + Salbutamol (X Steroid, X isoprenaline)
DM $\rightarrow$ Salbutamol + Insulin / LRA (X Steroid $\rightarrow$ $\uparrow$ Glucose)

Ans.

Drugs used to decrease bronchial responsiveness to exogenous stimuli

1. Corticosteroids
2. Leukotriene receptor antagonists
3. Leukotriene synthesis inhibitor
4. Mast cell stabilizers
5. Anti-IgE monoclonal antibody.

Write name of the individual class of drugs from above. Write their action from below.

- Q. Name the drugs used by *inhalation route* in the treatment of bronchial asthma. (DU-10Ju)
- Q. Name the inhalational drugs used to treat bronchial asthma. (DU-16Ju,14J, RU-15Ju)
- Q. Enumerate inhalers of different groups used in bronchial asthma. (RU-13J)
- Ans.

Drugs used by inhalation route in the treatment of bronchial asthma

1. **Selective β_2 -agonists:** Salbutamol, Salmeterol
2. **Anti-muscarinic agent:** Ipratropium bromide
3. **Corticosteroids:** Beclomethasone, betamethasone, triamcinolone
4. **Mast cell stabilizers:** Cromolyn sodium, nedocromil sodium.

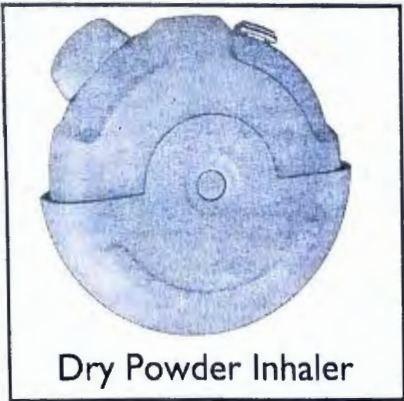
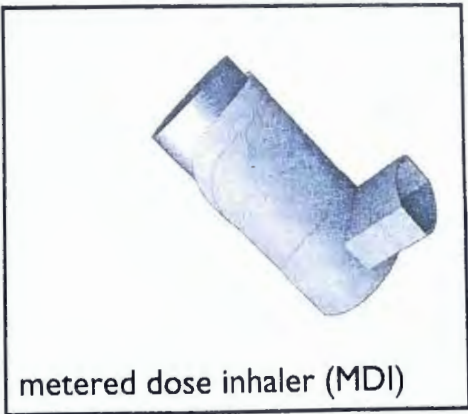
(Ref: Katzung-13th edition)

Q. How to differentiate meter dose and dry powder inhaler? (RU-15Ju)

Ans.

Differences between meter dose and dry powder inhaler:

Traits	Meter dose inhaler (MDI)	Dry powder inhaler (DPI)
1. Definition	A MDI is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is usually self-administered by the patient via inhalation.	A DPI is a device that delivers medication to the lungs in the form of a dry powder.
2. Propellant	Propellant based (HFA/CFC)	Non-propellant based.
3. Consistency	Solution / suspension	Solid particles
4. Other constituents	Contains surfactants and lubricants.	Might contain lactose.
5. Coordination of actuation-inhalation	Required.	Not required.
6. Cost	Less expensive.	More expensive.



Q. Name the drugs used in the treatment of acute bronchial asthma. (DU-07J, SU-13J)

Q. Name the drugs used in the treatment of status asthmaticus. (RU-09Ju/J)

Q. Enlist the drugs used in acute severe bronchial asthma. (RU-13Ju)

Q. Name 4 drugs used in the treatment of acute bronchial asthma. (DU-16J)

Ans.

Drugs used in acute severe bronchial asthma / status asthmaticus

A. Bronchodilator

1. Selective β_2 -agonists: Salbutamol, Terbutaline, Albuterol
2. Anti-muscarinic agent: Ipratropium bromide
3. Methylxanthines: Aminophylline, Theophylline

B. Anti-inflammatory drugs:

1. Corticosteroids: Hydrocortisone, Beclomethasone, betamethasone, triamcinolone

(Ref: Katzung-13th edition)

Q. State the management of severe acute bronchial asthma/ status asthmaticus. (SU-11Ju)

Q. Outline the pharmacological approach to treat status asthmaticus. (RU-15Ju)

Q. State the drug management of status asthmaticus. (RU-17J)

Ans.

Acute severe asthma/ status asthmaticus: This is a life-threatening emergency requiring rapid aggressive treatment. It is characterized by severe wheeze, breathlessness to such extent that the patient cannot complete sentences in 1 breath, tachycardia, central cyanosis and sometimes pulsus paradoxus.

(Ref: Davidson's-22nd edition)

Treatment of acute bronchial asthma:

1. Oxygen:

- Give high flow oxygen.
- Maintain oxygen saturation above 92%.

2. High doses of inhaled bronchodilators:

- Salbutamol by nebuliser in a dose of 2.5-5 mg over about 3 min, repeated in 15 min.
- Terbutaline 5-10 mg is an alternative.
- Ipratropium 0.5 mg may be added to the nebulised β_2 -agonist.

3. Systemic corticosteroids:

- Hydrocortisone 200 mg IV 4-6 hourly, then switch to-
- Prednisolone 30-60 mg orally (5-7 mg/kg)

4. Avoid sedation of any kind.

5. Chest x-ray to exclude pneumothorax.

Monitoring response to treatment: By-

1. Peak expiratory flow rate (PEFR)
2. Oxygen saturation: maintain $> 92\%$
3. Arterial blood gas (ABG) analysis: Maintain $\text{PaO}_2 > 8 \text{ kPa}$ (60 mm Hg).

(Ref: Bennett & Brown-11th; Davidson's-22nd)

Q. Enlist the receptors which after stimulation cause bronchoconstriction. (CU-17M)

Ans.

Receptors which after stimulation cause bronchoconstriction

1. β_2 adrenoceptors

Q. Outline the therapeutic approach to bronchial asthma. (SU-13Ju)

Q. Outline the therapeutic approach to chronic bronchial asthma. (SU-11Ju)

Ans.

A stepwise approach to the management of chronic bronchial asthma

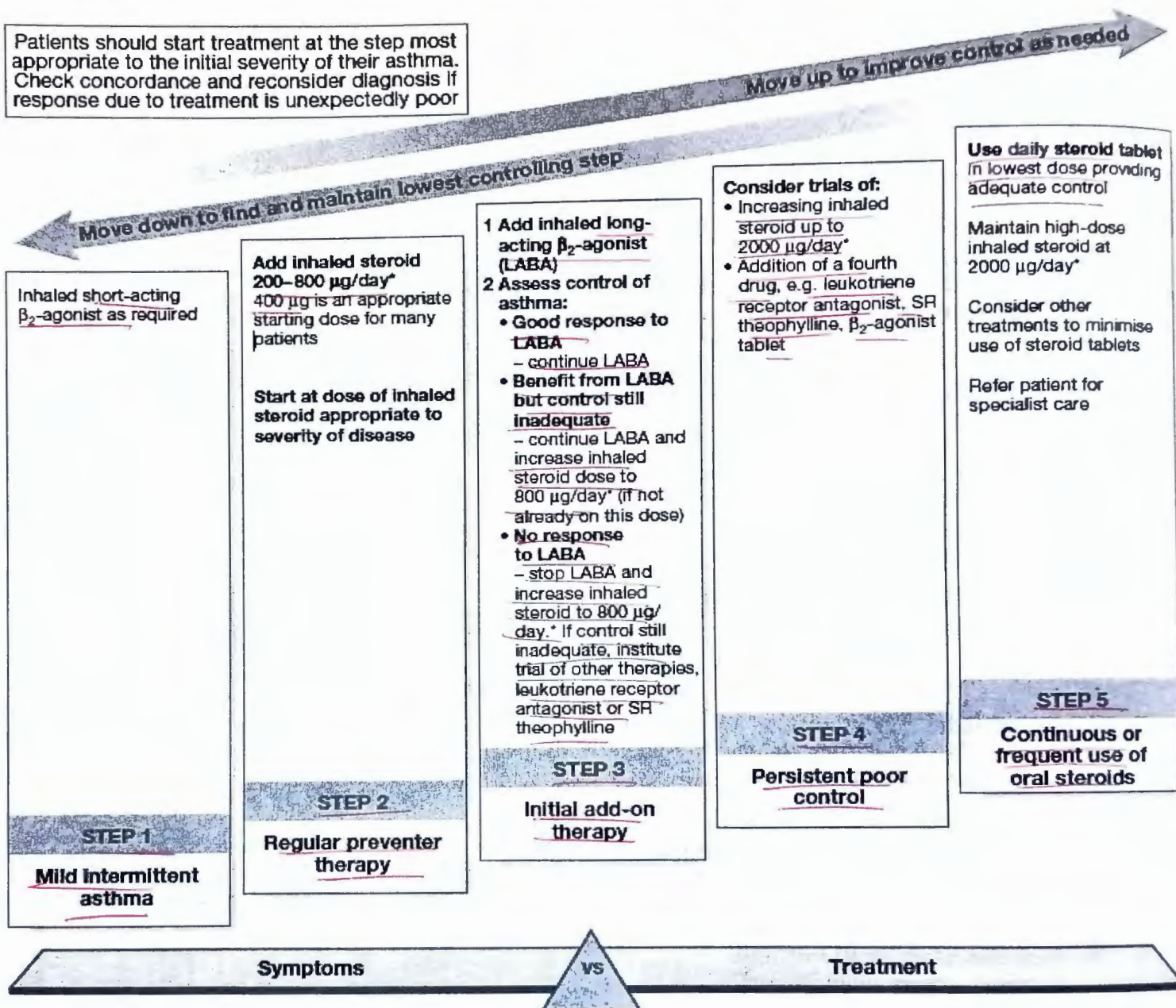


Figure. Management approach in adults based on asthma control. *Beclometasone dipropionate (BDP) or equivalent. From British Thoracic Society and SIGN.

(Ref: Davidson's-22nd)

Q. Name the drugs used for long-term control of bronchial asthma. (DU-17J)

Q. Enlist three drugs used in chronic bronchial asthma. (DU-17M)

Ans.

Drugs used for long-term control of bronchial asthma

1. Inhaled Short acting β_2 -agonists, eg, Salbutamol
2. Inhaled Long acting β_2 -agonists, eg, Salmetero

3. Inhaled Steroids, eg, Fluticasone
4. Leukotriene receptor antagonists, eg, Montelukast
5. Methylxanthines, eg, Doxophylline
6. Oral steroid, eg, prednisolone.

β_2 -agonist

Q. How β_2 selective agonists (salbutamol / salmeterol) act in bronchial asthma? (DU-16J, CU-17M, RU-06J)

Q. How salbutamol produces bronchodilatation? (CU-14J, RU-16J)

Q. Explain the role of salbutamol in bronchial asthma. (DU-17J, SU-17J)

Q. Write the M/A of salbutamol. (SU-16J)

Ans.

Mechanism of action (M/A) of β_2 selective agonists (salbutamol / salmeterol): Bronchial asthma is characterized by bronchoconstriction leading to severe respiratory distress.

β_2 agonist drugs (salbutamol / salmeterol) bind with β_2 receptor of bronchial smooth muscle

↓

Relaxation of bronchial smooth muscle (bronchodilatation)

↓

Quick relief of acute bronchoconstriction and asthma.

↑ cAMP
↑ adenylylation

(Ref: Katzung-13th)

Q. What are the advantages of inhaled β_2 -selective agonists?

Ans.

Advantages of inhaled β_2 -selective agonists/ salbutamol:

1. Selective action on β_2 -receptor of bronchial smooth muscle.
2. Rapid onset of action (within 1-5 minutes).
3. Very low systemic absorption and so less / no CVS & CNS (tremor) adverse effects.
4. Easy to use; even if can be used in office or during walking.
5. Topical delivery (anatomical selectivity).

(Ref: Goodman & Gilman's-12th)

Q. What is the role of salmeterol in bronchial asthma? (SU-08Ju,08J)

Q. Discuss the role of salmeterol in chronic bronchial asthma. (SU-17M,14J)

Ans.

Role of salmeterol in bronchial asthma: Salmeterol is a potent selective β_2 agonists that plays important role in long-term control of bronchial asthma. It is due to the fact that-

1. It has a long duration of action (12 hours or more) as a result of high lipid solubility.
2. It interacts with inhaled corticosteroids to improve asthma control.

However, it is not recommended as the sole therapy for asthma.

(Ref: Katzung-13th)

Q. What is the advantage of salmeterol over salbutamol?

Ans. Salbutamol has short duration of action (only 4 hours) whereas Salmeterol has long duration of action (12 hours).

Q. What are the toxicities of inhaled β_2 -selective agonists?

Ans.

Toxicities of inhaled β_2 -selective agonists / salbutamol: Chronic use of β_2 -selective agonists / salbutamol by inhaler cause-

1. Dryness of airway
2. Irritation of airway
3. Oropharyngeal candidiasis.

Q. What are adverse effects of systemic β_2 -selective agonists / salbutamol? (DU-16J, RU-06J, SU-16J)

Ans.

Adverse effects of systemic β_2 -selective agonists / salbutamol: (Due to sympathomimetic activity)

1. Tremor
2. Tachycardia
3. Arrhythmia
4. Palpitation
5. Hypokalaemia
6. Hyperglycemia

(Inhaled β_2 agonist)

Q. Ephedrine is no longer used in bronchial asthma- explain. (DU-03S)

Q. Briefly assign reasons why Salbutamol but not ephedrine is preferred as bronchodilator. (DU-05M)

Ans.

Ephedrine is no longer used in bronchial asthma, because-

1. Availability of new efficacious & β_2 -selective drugs such as salbutamol, salmeterol.
2. It has more duration of action than adrenaline.
3. It has more cardiovascular effect.
4. It is less potent.

Q. Compare the consequences between oral and inhalational salbutamol. (CU-16J)

Ans.

Comparison between oral and inhalational salbutamol

Traits	Oral salbutamol	Inhalational salbutamol
1. Onset of action	Slow	Rapid (within 1-5 minutes)
2. Selective action on β_2 -receptor of bronchial smooth muscle	No	Yes
3. Systemic absorption	High	Low
4. CVS & CNS (tremor) adverse effects	Present	Less or absent
5. Dryness of airway	No	Yes
6. Oropharyngeal candidiasis	No	Yes

Q. Discuss briefly the differences between salbutamol & aminophylline. (DU-09Ju)

Q. Compare salbutamol & theophylline as bronchodilator/anti asthmatic drug. (CU-15J,09Ju,05S)

Ans.

Differences between salbutamol & aminophylline

Traits	Salbutamol	Theophylline
1. Mechanism	Selectively stimulates β_2 receptors on bronchial tree	Inhibits phosphodiesterase enzyme
2. Onset of action	Slow	Rapid (due to IV route)
3. Duration of action	Relatively longer	Shorter
4. Route	Inhaled, Oral	IV, Oral
5. In acute asthma	Nebulized / inhaled form	IV route
6. Adverse effects	• Tremor • Tachycardia • Hypotension	• Arrhythmia (Tachycardia) • Palpitation • Insomnia
7. Therapeutic index	High	Narrow
8. Close observation during administration	Not needed	Needed
9. Cardiotoxic effect	Absent, because salbutamol has no β_1 effect	Present (Tachy-arrhythmia, tachycardia, hypertension, palpitation)
10. CNS toxicity	Less	More (insomnia, tremor, restlessness)

Q. Name the drugs used for nebulization. What are its advantages over inhalation? Mention the mechanism of action of any drug. (RU-14Ju)

Ans.

Drugs used for nebulization

1. Salbutamol
2. Terbutaline
3. Ipratropium

Advantages over inhalation

1. Rapid onset of action.
2. Suitable for acute severe asthma.
3. Less chance of dryness of airway.

Anti-muscarinic drugs in asthma

Q. Explain the action & role of Ipratropium bromide in bronchial asthma. (DU-16J, SU-09J)

Q. Justify the use of Ipratropium bromide in obstructive airway disease. (CU-15J)

Ans.

Role of ipratropium bromide in bronchial asthma: Antimuscarinic agents are effective bronchodilators.

Ipratropium bromide blocks M_3 -receptors on bronchial smooth muscles & glands

↓

↓IP3 & DAG

↓

Repolarization of muscles

↓

Relaxation of bronchial smooth muscles & decreased bronchial secretion

↓

Relief of bronchial asthma

(Ref: Katzung-13th)

Anticholinergic agents are generally less effective than β_2 -adrenergic agonists. Inhaled ipratropium is useful in patients who are unable to tolerate adrenergic agonists. Ipratropium is slow in onset and nearly free of side effects. These agents are not traditionally effective for patients with asthma unless COPD is also present.

Clinical use of inhaled muscarinic receptor antagonists (e.g. ipratropium)

1. Asthma, as an adjunct to β_2 -agonists and steroids.
2. COPD, especially long-acting drugs (e.g. **tiotropium**).
3. For bronchospasm precipitated by β_2 -blockers.

(Ref: Rang & Dale's-8th)

Methylxanthine drugs

Sources:

- Theophylline → tea
- Theobromine → cocoa
- Caffeine → coffee.

(Ref: Katzung-13th)

Q. Explain the mechanism of action & role of aminophylline in bronchial asthma. (DU-16J, RU-15J, SU-09J)

Phospholipase 2^{nm}
phosphodiesterase

Q. Outline the mechanism of action of theophylline. (CU-16J, RU-14J)

Q. Explain the role of theophylline in bronchial asthma. (RU-04J;SU-07J;06M)

Q. Write a short note on aminophylline. (SU-06S)

Ans.

Mechanism of action of Theophylline in bronchial asthma: Several mechanisms have been proposed for the actions of methylxanthines, but none has been firmly established.

1. Theophylline inhibits "phosphodiesterase (PDE)" enzyme $\rightarrow \uparrow$ cAMP $\rightarrow$ Relaxation of bronchial smooth muscle $\rightarrow$ Bronchodilation.
2. Theophylline inhibits 'phosphodiesterase enzyme 4' (PDE4) $\rightarrow \uparrow$ cAMP $\rightarrow$ Reduces the release of cytokines and chemokines from inflammatory cells $\rightarrow$ Decrease immune cell migration and activation.
3. Competitive inhibition of adenosine receptors $\rightarrow$ Prevents bronchoconstriction by adenosine and histamine release from airway mast cells.

(Ref: Katzung-13th)

Q. Discuss the pharmacological action of theophylline on respiratory system, CVS, CNS & kidney. (SU-07J)

Ans.

Pharmacological actions of theophylline

A. **CVS:** Directly stimulates the heart & dilates systemic blood vessels including coronary vessels & reduces peripheral resistance.

- Increase heart rate (tachycardia /tachyarrhythmia)
- Increase force of contraction
- Increase cardiac output
- Usually a rise in SBP & fall in DBP is observed with aminophylline.

B. **CNS:** Stimulatory effects including-

- Insomnia (most common adverse effects)
- Nervousness
- Restlessness
- Excitement
- Agitation
- Tremor
- Very high doses, from accidental or suicidal overdose, cause medullary stimulation and convulsions and may lead to death.

C. **Kidney:** Inhibits tubular reabsorption of Na^+ & water & thus causes mild diuresis.

(Ref: Katzung-13th)

Q. Mention the indications of aminophylline. (RU-04S/J)

Ans.

Indications of aminophylline:

1. Severe acute bronchial asthma
2. Chronic asthma
3. COPD
4. Apnea in preterm baby
5. Ordinary headache (caffeine + aspirin)
6. Migraine
7. Emergency treatment of left ventricular failure.

(Ref: Katzung-13th)

Q. Mention the adverse effects of aminophylline. (DU-16J, RU-14J)

Q. Mention the adverse effects of theophylline. (RU-14J)

Ans.

Adverse effects of theophylline / aminophylline:

1. **Cardio-vascular:** Tachycardia, palpitation, hypotension, precordial pain
2. **CNS (stimulatory):** Insomnia, headache, dizziness, severe restlessness, agitation.
3. **Overdose** may cause seizures or potentially fatal arrhythmias.
4. **Others:** Nausea, vomiting.

(Ref: Katzung-13th, Goodman & Gilman's-12th, Lippincott's-6th)

Q. Mention the advantage and disadvantages of theophylline

Ans.

Advantage of theophylline

1. Theophylline is an effective bronchodilator, and it has been shown repeatedly both to relieve airflow obstruction in acute asthma and to reduce the severity of symptoms and time lost from work or school in patients with chronic asthma.
2. Theophylline improves long-term control of asthma when taken as the sole maintenance treatment or when added to inhaled corticosteroids.
3. It is inexpensive.
4. It can be taken orally, by IV infusion and per-rectally.

(Ref: Katzung-13th)

Disadvantages of theophylline: Previously the mainstay of asthma therapy, theophylline has been largely replaced with β_2 agonists and corticosteroids due to-

1. Narrow therapeutic window.
2. High side-effect profile.
3. Potential for drug interactions.

(Ref: Katzung-13th)

Q. Why theophylline should be used with caution in I/V form?

Ans.

Theophylline should be used with caution in I/V form: Aminophylline/ theophylline has positive chronotropic & inotropic effect. Rapid IV administration of aminophylline/ theophylline sometimes causes **sudden death** due to **cardiac arrhythmia**. So, the drug should be injected slowly over 20-40 minutes or with infusion drip slowly to avoid severe toxic symptoms.

(Ref: Goodman & Gilman-12th)

Corticosteroids

Q. Name the glucocorticoids used in bronchial asthma. (DU-13Ju)**Q. Categorize glucocorticoids used in bronchial asthma with indication and routes in special situation. (SU-15Ju)****Q. Enlist inhalation Glucocorticoids. (CU-17J)**

Ans.

Glucocorticoids used in bronchial asthma

1. **IV**
 - a. Hydrocortisone
2. **Oral**
 - a. Prednisolone
3. **Inhalation Glucocorticoids**
 - a. Fluticasone
 - b. Budesonide
 - c. Beclomethasone
 - d. Ciclesonide

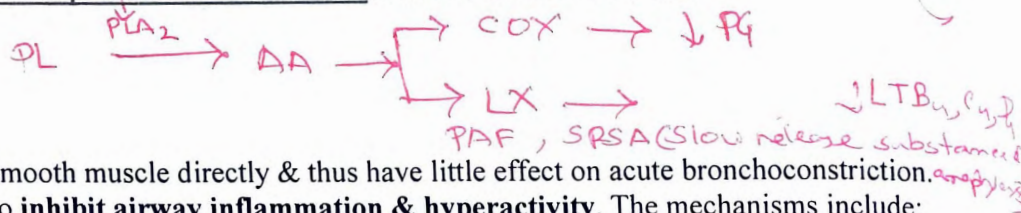
- e. Flunisolide
- f. Mometasone
- g. Triamcinolone

- Q. Explain the pharmacological rationale of using glucocorticoids in bronchial asthma. (CU-07J)
- Q. Explain the mechanism of action of beclomethasone in bronchial asthma. (DU-10Ju, RU-09Ju, 06M)
- Q. Discuss the role of glucocorticoids in bronchial asthma/chronic asthma. (DU-17M, 11Ju, CU-17J, 09Ju, RU-12Ju, SU-16Ju, 14Ju)
- Q. Discuss the beneficial effects of glucocorticoids in asthmatic patient. (DU-13Ju)
- Q. Explain the role of hydrocortisone in the management of bronchial asthma. (CU-13Ju)
- Q. How corticosteroids act in asthma? (DU-06S, CU-06M/S)
- Q. Discuss the role of steroids in bronchial asthma. (CU-13J, SU-09Ju; RU-10J)
- Q. Mention the role of fluticasone in the treatment of bronchial asthma. (SU-13J, 11J)

Ans.

Role of glucocorticoids / beclomethasone/prednisolone in asthma: Asthma is associated with -

- Airway inflammation
- Airway hyperactivity &
- Acute bronchoconstriction



Glucocorticoids do not relax airway smooth muscle directly & thus have little effect on acute bronchoconstriction. On the other hand they are effective to **inhibit airway inflammation & hyperactivity**. The mechanisms include:

- Inhibition of the influx of inflammatory cells into the lung after allergen exposure;
- Inhibition of the release of mediators from macrophages and eosinophils and reduction of the microvascular leakage which these mediators cause.

The glucocorticoids are effective in improving all indices of asthma control—severity of symptoms, tests of airway caliber and bronchial reactivity, frequency of exacerbations, and quality of life.

Inhaled corticosteroids (ICS) are the drugs of first choice in patients with any degree of persistent asthma (mild, moderate, or severe). No other medications are as effective as ICS in the long-term control of asthma. Severe persistent asthma may require the addition of a short course of **oral glucocorticoid** treatment.

(Ref: Katzung-13th + Bennett & Brown-11th; Lippincott's-6th)

- Q. Mention the role of glucocorticoids in acute bronchial asthma. (DU-07J, 06S; CU-04M; RU-05S)

Ans.

Role of glucocorticoids in acute bronchial asthma: Glucocorticoids do not relax airway smooth muscle directly & thus have little effect on acute bronchoconstriction.

But, Glucocorticoids potentiate the action of acute bronchodilators by their **antiinflammatory action** & thus used in acute asthma with the bronchodilator agents.

Urgent treatment is often begun with an oral prednisone (30–60 mg/day) or IV methylprednisolone (1 mg/kg 6 hourly); the daily dose is decreased after airway obstruction has improved. In most patients, systemic corticosteroid therapy can be discontinued after 7–10 days.

(Ref: Goodman & Gilman's-12th; Katzung-13th)

- Q. Discuss the role of fluticasone in bronchial asthma. (SU-17J)
- Q. Discuss the role of fluticasone in chronic bronchial asthma. (SU-17M, 14J)
- Q. Mention the role of fluticasone in acute bronchial asthma. (SU-09Ju)

Ans.

Role of fluticasone in chronic bronchial asthma: Fluticasone is effective in long-term control of chronic bronchial asthma. It is usually given in inhalation route along with a long-acting β_2 -agonist, eg, salmeterol. (write the actions of glucocorticoid in asthma from above.)

- Q. Why inhalational steroids are better than that of oral ones? (DU-12Ju)

Q. Mention the advantages of beclomethasone inhaler in treating bronchial asthma. (DU-10Ju)

Ans.

Inhalational steroids are better than oral steroids / Advantages of beclomethasone inhaler in treating bronchial asthma: To prevent bronchial asthma, long-term corticosteroid therapy is needed. If corticosteroids are given orally or parenterally, they produce severe adverse effects like Cushing's syndrome, adrenal suppression. But if they are given through inhalation, there is minimal systemic absorption and there will be few systemic effects. Thus aerosol treatment (inhalation) is the most effective way to avoid the systemic adverse effects of corticosteroid therapy. This is why some corticosteroids such as beclomethasone are given by inhalation to prevent asthma. An average daily dose of four puffs twice daily of beclomethasone (400 mcg/d) is equivalent to about 10–15 mg/d of oral prednisone for the control of asthma, with far fewer systemic effects.

(Ref: Katzung-13th)

Q. Mention the risks of inhaled corticosteroids? How do you avoid risk? (DU-09Ju)

Ans.

Risk of inhaled glucocorticoids:

1. Oropharyngeal candidiasis (most common)
2. Hoarseness of voice (direct local effect on vocal cords)
3. Dryness of airway
4. Irritation of airway
5. Long term complications: Osteoporosis, cataracts, slowing the rate of growth in children.

(Ref: Katzung-13th)

Prevention/ How to avoid risk:

1. The risk of oropharyngeal candidiasis can be reduced by having patients gargle water and spit after each inhaled treatment.
2. Counseling the patient about the user manual of the inhaler (e.g. correct positioning of the inhaler, inhaling the drug substance by deep inspiration during puffing).
3. The patient should shake well the inhaler before use

(Ref: Katzung-13th)

Mast cell stabilizers

Drugs that stabilize mast cells:

1. Cromolyn sodium (disodium cromoglycate)
2. Nedocromil sodium

Q. Explain the action & role of nedocromil sodium in bronchial asthma. (SU-09J)

Q. Discuss the role of cromolyn-Na in the management of bronchial asthma. (CU-08J;RU-02J;SU-06M)

Ans.

Mechanism of action of mast cell stabilizers:

Cromolyn and nedocromil



An alteration in the function of delayed chloride channels in the cell membrane of mast cells

Cl⁻ channel

Entry of Cl⁻ ions into the cells causes hyperpolarization of the cell

↓ Hyperpolarization of mast cell

No mast cell activation



No degranulation of mast cells → no histamine release.

No bronchoconstriction (as histamine causes bronchospasm)



Prevention of asthma

(Ref: Katzung-13th)

Clinical use of Cromolyn & Nedocromil

1. For prevention of bronchial asthma: To prevent bronchial asthma, cromolyn is taken shortly before exercise or before unavoidable exposure to an allergen.
2. Allergic rhinoconjunctivitis.

(Ref: Katzung-13th)

Q. Why cromolyn sodium is used prophylactically?

Ans.

Cromolyn sodium is used prophylactically: Cromolyn sodium (disodium cromoglycate) and nedocromil sodium have no effect on airway smooth muscle tone and are ineffective in reversing asthmatic bronchospasm; they are only of value when taken prophylactically. When used as aerosols (by nebulizer or metered-dose inhaler), they effectively inhibit both antigen- and exercise-induced asthma, and chronic use (four times daily) slightly reduces the overall level of bronchial reactivity.

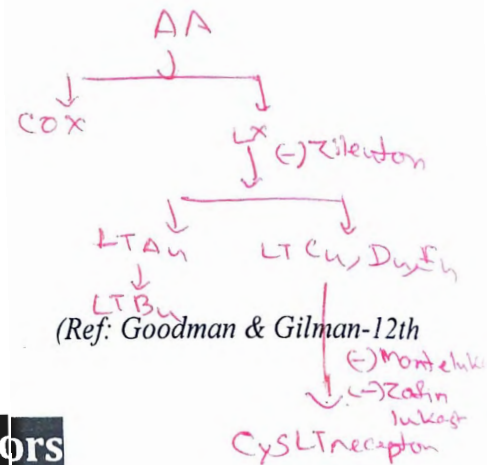
(Ref: Katzung-13th)

Q. Mention the adverse effects of mast cell stabilizers.

Ans.

Adverse effects of mast cell stabilizers: Because the drugs are so poorly absorbed, adverse effects of cromolyn and nedocromil are minor and are localized to the sites of deposition.

1. Bronchospasm
2. Cough or wheezing
3. Laryngeal edema
4. Joint pain & swelling
5. Angioedema
6. Headache
7. Nausea
8. Rash

**Leukotriene Pathway Inhibitors**

Leukotriene (LT) B₄ and the cysteinyl leukotrienes, LTC₄, LTD₄, and LTE₄, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade. 5-Lipoxygenase is found in cells of myeloid origin, such as mast cells, basophils, eosinophils, and neutrophils. LTB₄ is a potent chemoattractant for neutrophils and eosinophils, whereas the cysteinyl leukotrienes constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucous secretion.

Q. What do you know about the status of leukotriene inhibitor in asthma? (RU-13Ju, 12Ju, 11Ju)

Q. Short note: Montelukast. (SU-17J, 15J, 14Ju)

Ans.

Leukotriene receptor antagonists: These drugs also competitively prevent bronchoconstriction caused by leukotrienes (C₄, D₄ and E₄)

- **Zafirlukast**
- **Montelukast:** Of these two, montelukast is the most prescribed, probably because it can be taken without regard to meals and because of the convenience of once-daily treatment.

Leukotriene synthesis inhibitor

- **Zileuton**

Advantages:

1. Can be given to children 1 year of age and older
2. Available in chewable tablets and granule formulations.

Indication: All three drugs are approved for the prophylaxis of asthma but are not effective in situations where immediate bronchodilation is required.

(Long term therapy)

Adverse effects:

1. Liver toxicity (zileuton, so zileuton is the least prescribed of these agents)
2. Churg-Strauss syndrome (a systemic vasculitis accompanied by worsening asthma, pulmonary infiltrates, and eosinophilia)
3. Zafirlukast may interact with warfarin & increase prothrombin times.

(Ref: Goodman & Gilman's-12th)

Q. Explain the role of montelukast in the management of bronchial asthma. (DU-17J, 14Ju, CU-13Ju, SU-13J)

Q. Explain the pharmacological basis of using montelukast in bronchial asthma. (CU-14Ju)

Q. Discuss the role of Leukotriene inhibitor/ montelukast in chronic bronchial asthma. (DU-16Ju, SU-17M, 14J)

Q. Justify the use of Leukotriene receptor blockers in bronchial asthma. (CU-16J)

Ans.

Role of montelukast / Leukotriene receptor blockers in the management of bronchial asthma

1. Montelukast is indicated for the **prophylaxis of asthma** but are not effective in situations where immediate bronchodilation is required.
2. It can be taken without regard to meals and because of the convenience of once-daily treatment.
3. It reduces the frequency of exacerbation.
4. Very much effective in persistent asthma whether it is mild, moderate or severe.
5. It reduces inflammatory process and lacks of wide range of adverse effects compared to oral corticosteroids.
6. It is a steroid sparing agent.
7. Provides additional control of symptoms during exercise.
8. Available as tablet form; children and elderly people can easily take it for whom inhaler is not suitable.

(Ref: Goodman & Gillman-12th)

Omalizumab

Omalizumab is a recombinant DNA-derived monoclonal antibody that selectively binds to human immunoglobulin E (IgE). It is the 1st biological drug approved for the Rx of asthma. Due to the high cost of the drug (approximately \$600 for a 150-mg vial), limitations on dosage, and available clinical trial data, it is not presently used as first-line therapy.

Mechanism of action of omalizumab:

1. Omalizumab binds with IgE.

↓

IgE can't bind with IgE receptor on mast cell & basophil.

↓

No degranulation of mast cells and basophils and no release of mediators of allergic reaction.

↓

Prevention of asthma

2. **Omalizumab** may also inhibit IgE synthesis by B lymphocytes. (Ref: Katzung-13th)

Route: Parenteral route (intravenous or subcutaneous)

Clinical uses: As it is not a bronchodilator, it is used prophylactically. Omalizumab may be particularly useful for treatment of moderate to severe allergic asthma in patients who are poorly controlled with conventional therapy.

Importance of Omalizumab:

- 1. Omalizumab lessens asthma severity and reduces the corticosteroid requirement in patients with moderate to severe disease, especially those with a clear environmental antigen precipitating factor
- 2. It improves nasal and conjunctival symptoms in patients with perennial or seasonal allergic rhinitis.
- 3. Omalizumab's most important effect is reduction of the frequency and severity of asthma exacerbations, even while enabling a reduction in corticosteroid requirements.

Adverse effects of omalizumab:

- 1. Hypersensitivity reaction
- 2. Injection site reactions: Redness, stinging, bruising, induration.

(Ref: Goodman & Gilman's-12th)

Drugs used to treat Cough / Antitussives

Cough: Cough is a protective reflex that removes foreign material and secretions from the bronchi and bronchioles. Cough is the most frequent symptom of respiratory disease. It is caused by stimulation of sensory nerves in the mucosa of the pharynx, larynx, trachea and bronchi.

(Ref: Rang & Dale's-8th)

Causes of cough:

Origin	Common causes
Pharynx	• Post-nasal drip
Larynx	• Laryngitis, tumour, whooping cough, croup
Trachea	• Tracheitis
Bronchi	• Bronchitis (acute) and COPD • Asthma • Eosinophilic bronchitis • Bronchial carcinoma
Lung parenchyma	• Tuberculosis • Pneumonia • Bronchiectasis • Pulmonary oedema • Interstitial fibrosis
Drug side-effect	• ACE inhibitors

(Ref: Davidson's-22nd)

Antitussives: Antitussives are the drugs that cause suppression of cough.

A. Peripherally acting antitussives	1. Linctuses (demulsant preparations, lozenges) 2. Water aerosol inhalation 3. Benzoin inhalation 4. Methanol and eucalyptus inhalation
B. Centrally acting antitussives	• Opioids (addicting, powerful respiratory suppressant action): 1. Morphine 2. Diamorphine 3. Methadone • Opioids (less-addicting, less respiratory depression): 1. Codeine (methylmorphine) 2. Dextromethorphan a 3. Pholcodine
C. Sedative antihistamine: (Sedation reduces cough)	1. Diphenhydramine (Tusca syn) 2. Chlorpheniramine

Codeine

Codeine is the gold-standard treatment for cough suppression due to its long history of availability and use. Codeine decreases the sensitivity of cough centers in the central nervous system to peripheral stimuli and decreases mucosal secretion. These therapeutic effects occur at doses lower than those required for analgesia but still incur common side effects like constipation, dysphoria, and fatigue, in addition to its addictive potential.

(Ref: Lippincott's-6th)

Dextromethorphan

Dextromethorphan is a synthetic derivative of morphine that suppresses the response of the central cough center. It has no analgesic effects, has a low addictive profile, but may cause dysphoria at high doses, which may explain its status as a potential drug of abuse. Dextromethorphan has a significantly better side effect profile than codeine and has been demonstrated to be equally effective for cough suppression.

(Ref: Lippincott's-6th)

Expectorant

An expectorant (from the Latin *expectorare*, to expel from the chest) helps bring up mucus and other material from the lungs, bronchi, and trachea. An expectorant increases bronchial secretions and reduce the thickness or viscosity of bronchial secretions thus increasing mucus flow that can be removed more easily through coughing.

Expectorant are-

1. Iodide
2. Chloride
3. Bicarbonate
4. Acetates
5. Guaifenesin

Mucolytics

Mucolytics reduces the viscosity of the mucus (sputum). The mucus becomes thinner and can be removed more easily through coughing. Mucolytics are-

1. Acetylcysteine
2. Carbocysteine
3. Ambroxol.

MCQ

Q. Following are bronchodilators- (DU-17J)

- a. salmeterol
 - b. ipratropium bromide
 - c. hydrocortisone
 - d. nedocromil sodium
 - e. theophylline
- a. T, b. T, c. F, d. F, e. T*

Q. Following are bronchodilators- (DU-13J)

- a. salmeterol.
 - b. prednisolone.
 - c. chromoglycate.
 - d. ipratropium.
 - e. aminophylline.
- a. T, b. F, c. F, d. T, e. T*

Q. Role of drugs in bronchial asthma include- (SU-13J)

- a. Fluticasone decrease bronchial response
 - b. Montelukast is anti-inflammatory
 - c. Salmeterol inhibit bronchial secretion
 - d. Theophylline dilates muscle
 - e. Sodium cromoglycate is rapid acting
- a. T, b. T, c. T, d. T, e. F*
-

Chapter 13

Endocrine Pharmacology

Drugs for Diabetes Mellitus (DM)

Definition: Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin.

(Ref: Davidson's-22nd)

Classification: Most cases of DM can be separated into 2 types-

1. **Type-1 diabetes or Insulin dependent diabetes mellitus (IDDM) (Juvenile onset diabetes):** Occurs before age 20 yrs due to lack of insulin.
2. **Type-2 diabetes or Non-insulin-dependent diabetes mellitus (NIDDM) (Adult-onset diabetes):** occurs after age 40 yrs due to decreased sensitivity of tissue to insulin. It is more common.

Features	Type I DM	Type II DM
▪ Age at onset	Usually < 20 years	Usually > 40 years
▪ Body weight at time of disease onset	Normal or low	Obese
▪ Plasma insulin	Low or absent	Normal or high
▪ Insulin sensitivity	Normal	Reduced
▪ Therapy	Insulin	Weight loss, oral hypoglycemic agent
▪ Ketonuria	Yes	No
▪ Rapid death without insulin therapy	Yes	No
▪ Family history of diabetes	No	Yes
▪ Autoantibodies	Yes	No
▪ Diabetic complications at diagnosis	No	20%

(Ref: Guyton-12th; Davidson's-22nd)

Clinical features of DM

1. Polyuria (*frequent urination*)
2. Polydipsia (*excessive thirst*)
3. Polyphagia (*excessive hunger*)
4. Rapid weight loss
5. Nocturia (*abnormally excessive urination during the night.*)
6. Weakness

Insulin

Structure of insulin: Insulin is a polypeptide containing two chains of amino acids (A & B) linked by disulfide bridges (S-S). It contains 51 amino acids, 21 in A chain & 30 in B chain. When the two chains are split apart, the functional activity of the insulin is lost.

(Ref: Ganong-24th edition)

Biosynthesis & secretion:

- Gene → mRNA → Preproinsulin → Proinsulin → Insulin & C peptide
- **C peptide** can be measured by radioimmunoassay, and its level provides an index of B cell function in patients receiving exogenous insulin.

(Ref: Ganong-24th edition)

Storage of insulin: Granules within the B cells store the insulin in the form of crystals consisting of two atoms of zinc and six molecules of insulin.

Secretion of insulin: Insulin secretion stimulated by-

1. Glucose (main stimulus)
2. Other sugars (eg, mannose)
3. Certain amino acids (eg, leucine, arginine)
4. Hormones such as glucagon-like polypeptide-I
5. Vagal activity

*Antibody against C peptide
may cause ins. resistance*

Insulin degradation:

(Ref: Katzung-13th)

Endogenous insulin

- Liver- 60%
- Kidney- 35-40%

Exogenous insulin

- Kidney- 60%
- Liver- 30 -40%.

Half-life of insulin: The half-life of circulating insulin is 3–5 minutes.

(Ref: Katzung-13th)

Q. Give the mechanism of action of insulin. (CU-16J,10Ju,09J)

Ans.

Mechanism of action of insulin:

Insulin binds to the α -subunit of its receptor



Autophosphorylation of the β -subunit of the insulin receptor



Activation of tyrosine kinase activity of the intracellular portion of the β -subunit



Phosphorylation of some cytoplasmic enzymes & dephosphorylation of others



Activation of some of these enzymes & inactivation of others



Effects of insulin including:

- Translocation of glucose transporters (especially GLUT 4) to the cell membrane with a resultant increase in glucose uptake;
- Increased glycogen synthase activity and increased glycogen formation;
- Multiple effects on protein synthesis, lipolysis, and lipogenesis;
- Activation of transcription factors that enhance DNA synthesis and cell growth and division.

(Ref: Katzung-13th; Guyton-12th; Ganong-24th)

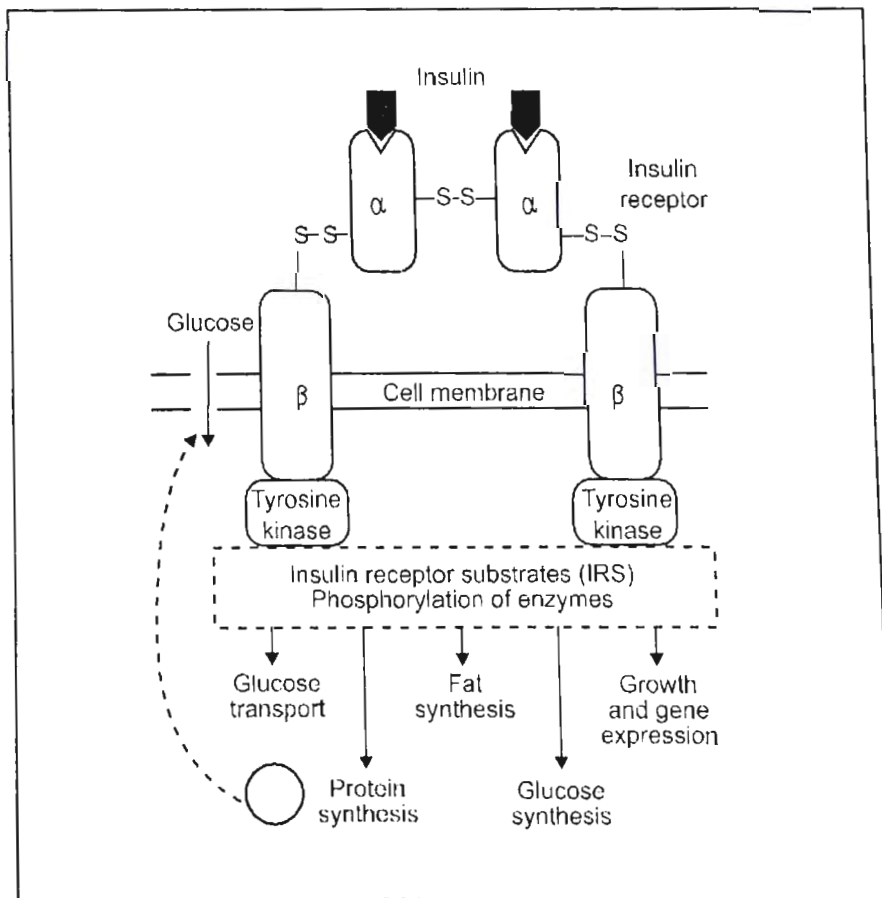


Figure: Mechanism of insulin action (Ref: Guyton)

Q. How does glucose stimulate insulin release? (CU-15Ju)

Ans.

How glucose stimulates insulin release:

Presence of glucose in the gut



Secretion of gut hormones, or incretins, eg. glucagon-like peptide (GLP-1)



Incretins stimulate insulin secretion in a glucose-dependent manner; thus hypoglycemia does not occur.

(Ref: Katzung-13th)

Q. What are the pharmacological actions of insulin? (RU-07Ju)

Ans:

Metabolic effects of insulin / Actions of insulin:

Type	Liver	Skeletal muscle	Adipose Tissue
• Carbohydrate metabolism	↑ Glycogenesis ↑ Glycolysis ↓ Glycogenolysis ↓ Gluconeogenesis	↑ Glucose uptake ↑ Glycolysis ↑ Glycogenesis ↓ Glycogenolysis	↑ Glucose uptake ↑ Lipogenesis from glucose
• Protein metabolism	↑ Protein synthesis ↑ Amino acid uptake	↑ Amino acid uptake ↑ Protein synthesis ↓ Protein catabolism ↓ Release of gluconeogenic amino acids	
• Fat metabolism	↑ Lipogenesis ↓ Ketogenesis	↑ Ketone uptake	↑ Fatty acid synthesis ↑ Glycerol phosphate synthesis ↑ Triglyceride deposition ⊕ Lipoprotein lipase (-) Hormone sensitive lipase
• K⁺ uptake		↑	↑
• General	↑ Cell growth		

(Ref: Ganong-24th; Guyton-12th)

Q. Mention how insulin lowers blood glucose level. (DU-13J,11J, CU-15J, RU-17J,15J,12Ju,11J, SU-17J,16Ju/J,13J,12Ju)

Q. Explain antidiabetic effects of insulin. (SU-13Ju,08Ju)

Q. Elaborate antidiabetic role of insulin glargine. (SU-14J)

Q. Explain hypoglycemic role of insulin. (SU-07Ju,06S)

Q. Explain the mechanism of action of insulin. (CU-14J,12J,10Ju)

Q. Explain blood glucose controlling action of insulin. (SU-12Ju)

Q. How do the insulin preparations lower elevated glucose level? (RU-14J)

Ans.

Antidiabetic effects of insulin / insulin glargine: Insulin lowers blood glucose level by the following mechanisms-

↑ Glycogenesis ↑ Glucose uptake ↑ Glycolysis ↓ Glycogenolysis ↓ Gluconeogenesis	}	Decreases blood glucose
---	---	-------------------------

Nice to know

Sources of insulin: According to source insulin is of 3 types.

1. **Bovine insulin**: Obtained from cow. It differs from human insulin by 3 amino acids & it is more antigenic.
2. **Porcine insulin**: Obtained from pork. It differs from human insulin by 1 amino acid & thus less immunogenic.
3. **Human insulin**: This is made either by enzyme modification of porcine insulin or by using recombinant DNA to synthesize the Proinsulin. This is done by introducing the DNA into either *E. coli* or yeast.

(Ref: Bennett & Brown-11th)

Q. Classify antidiabetic drugs. (SU-16Ju,16J)

Q. Categorize the drugs for DM? (DU-06M; CU-05J; RU-06S)

Q. Classify hypoglycemic agents. (SU-17J)

Ans.

Antidiabetic drugs according to mode of action:

A. Parenteral hypoglycemic agents: Insulin

B. Oral hypoglycemic agents (OHA): See below

Parenteral hypoglycemic agent / Insulin

Q. Enumerate different insulin preparations. (CU-06S; RU-14J,07Ju; SU-12J,06J)

Q. Name the different preparations of human insulin. (CU-06M)

Q. Classify insulin preparations according to duration of action. (DU-15Ju,14Ju,11Ju, CU-08Jan)

Q. Name the different insulin preparations on the basis of kinetic properties. (SU-15Ju)

Q. Mention the duration of action of different insulin preparations. (RU-07Ju,06M)

Q. What is lispro Insulin? (SU-06S)

Q. What are the insulin analogues? (CU-07Jan,06M)

Q. Enlist currently used insulin analogues? (RU-15J)

Ans.

Insulin preparations / insulin analogues: Insulin preparations are the only parenteral hypoglycemic agent. Four principal types of injected insulins are available:

1. Rapid-acting, with very fast onset and short duration;
2. Short-acting, with rapid onset of action;
3. Intermediate-acting; and
4. Long-acting, with slow onset of action

An inhaled form of rapid-acting insulin also is marketed.

Types	Preparation of insulin	Onset of action	Duration of action	Route of administration
1. Rapid acting or ultra short acting insulin	- Insulin Lispro - Insulin aspart - Insulin Glulisine - Human insulin recombinant inhaled	Within 15 min	3 -4 hours	IV
2. Short acting insulin	- Regular insulin - Natural insulin - Soluble insulin	Within ½ to 1½ hours	5 - 8 hours	IV
3. Intermediate acting insulin	- NPH (Neutral Protamine Hagedorn) or isophane insulin - Insulin zinc suspension (Lente insulin)	Within 1-2 hours	18-24 hours	Subcutaneous
4. Long acting insulin / Insulin Analogues	- Crystalline insulin zinc suspension (Ultralente insulin) - Protamine zinc insulin suspension - Insulin glargine - Insulin detemir	Within 3-4 hours	20-36 hours	Subcutaneous

Mixtures of insulin:

1. Mixture of regular & NPH Insulin	20% regular & 80% NPH insulin. 30% regular & 70% NPH insulin. 40% regular & 60% NPH insulin. 50% regular & 50% NPH insulin.
2. Mixture of lispro & NPH Insulin	25% Lispro & 75% NPH insulin. 50% Lispro & 50% NPH insulin.

(Ref: Katzung-13th; Goodman & Gilman's-12th)

Nice to know

Insulin analog: An insulin analog is an altered form of insulin, different from any occurring in nature, but still available to the human body for performing the same action as human insulin in terms of glycemic control. Through genetic engineering of the underlying DNA, the amino acid sequence of insulin can be changed to alter its ADME (absorption, distribution, metabolism, and excretion) characteristics.

These modifications have been used to create two types of insulin analogs:

1. **Rapid-acting injected insulin analog:** those that are more readily absorbed from the injection site and therefore act faster than natural insulin injected subcutaneously, intended to supply the bolus level of insulin needed at mealtime (**prandial insulin**).
2. **Long-acting injected insulin analogs:** those that are released slowly over a period of between 8 and 24 hours, intended to supply the basal level of insulin during the day and particularly at nighttime (**basal insulin**).

(Ref: Wikipedia)

Nice to know

- **Soluble and neutral insulin** are the same; the British National Formulary favours the former term, but neutral is the INN (internationally approved) name. Human, porcine and beef are available.
- **Isophane insulin** is the only approved name for suspensions of insulin with **protamine**. Human, porcine and beef are available; the latter is rarely used.
- **Biphasic insulins** are, with one exception, proprietary mixtures of soluble (neutral) insulin and isophane insulin, which provide soluble (neutral) insulin at concentrations between 10% and 50% of the total insulin concentration. These preparations remove the need for patients to mix soluble and isophane insulins, without losing the flexible administration of the right amount of soluble (neutral) insulin to cover the meal following the dose.
- **Mixed insulin zinc suspension** is proprietary mixtures of crystalline and amorphous zinc suspension.

(Ref: Bennett & Brown-11th)

Nice to know**Insulin delivery system:**

1. **Portable pen injectors:** To facilitate multiple S/C inj. of insulin, particularly during intensive insulin therapy, portable pen-size injectors have been developed. These contain cartridges of insulin & replaceable needles.
2. **Continuous insulin infusion devices (CSII) or insulin pumps:** The devices have a user-programmable pump that delivers individualized basal & bolus insulin replacement doses based on blood glucose self monitoring results.

(Ref: Katzung-13th)

Unit of Insulin: 1 IU of insulin is the biological equivalent of about 45.5 µg pure crystalline insulin (1/22 mg exactly). This corresponds to the amount of insulin required to reduce the concentration of blood glucose in a fasting rabbit to 0.045 per cent (45 mg/dL or 2.5 mmol/L) within 4 hours.

Strength of insulin: A vial of insulin is a combination of insulin hormone and a sterile liquid, called the diluent. The concentration of the insulin to the diluent determines its strength. The "U" value of insulin indicates its strength - the number reflects the number of active insulin units in each mL of liquid. U-100 will have 100 units per mL, and U-40 has 40 units per mL. Appropriate syringes are made for use with the respective insulin, marked with the correct measure for dosage.

Daily insulin secretion: Insulin production by a normal, thin, healthy person is between 18 and 40 units/day or about 0.2 to 0.5 units/kg of body weight per day. About half this amount is secreted in the basal state and about half in response to meals. Thus, basal secretion is about 0.5 to 1 units/h; after an oral glucose load, insulin secretion may increase to 6 units/h. In nondiabetic, obese, and insulin-resistant individuals, insulin secretion may be increased fourfold or more. Insulin is secreted into the portal circulation, and about 50% is destroyed by the liver before reaching the systemic circulation.

Daily insulin requirement:

- In type 1 DM patients, the average dose of insulin is usually 0.6 to 0.7 units/kg per day, with a range of 0.2 to 1 units/kg per day.
- Obese patients generally require more (2 units/kg per day) because of resistance of peripheral tissues to insulin.

Dose of insulin1. Split dose of intermediate-acting insulin

- 2/3rd of total daily dose: Before breakfast
- 1/3rd of total daily dose: Before dinner

Morning dose is adjusted according to the afternoon glucose level, and the evening dose is adjusted according to the fasting glucose level.

Conventional therapy presently consists of split-dose injections of mixture of rapid or short-acting and intermediate-acting insulins.

2. Multiple daily injection (MDI) therapy: Use long-acting or intermediate-acting insulins with multiple boluses of rapid-acting or short-acting insulin.

Dose: 0.5 unit/kg/day (subcutaneously in 3 divided doses).

Time: Just before meal (B- BLD)

- B - B: Before breakfast
- B - L: Before lunch
- B - D: Before dinner

Current regimen generally uses intermediate- or long-acting insulins with rapid-acting or short-acting insulin.

- Intermediate- or long-acting insulins provide basal or back-ground coverage.
- Rapid-acting or short-acting insulin meet the meal-time requirement.

Q. What are the routes of administration of insulin? (CU-08J)

Ans.

Routes of administration of insulin1. Subcutaneous injection: The standard mode of insulin therapy is subcutaneous (S/C) injection using conventional disposable needles & syringes.

Site: Abdomen, buttock, anterior thigh, dorsal arm.

Absorption is more rapid from the abdominal wall, followed by the arm, buttock and thigh. Rotation of insulin injection sites has traditionally been advocated to avoid lipohypertrophy and lipoatrophy.

2. Intramuscular or intravenous: In emergency situation (eg, diabetic ketoacidosis).3. Inhaled insulin: This is finely powdered & aerosolized human insulin & is readily absorbed into the bloodstream through alveolar walls. It has rapid onset & peak insulin levels (by 30 min) & peak effect (2-2.5 hrs) & duration of action (6 - 8 hours).**Q. What are the indications of insulin? (DU-14J, 11Ju, CU-12J, 19Ju, 09/07/06J, 05M; RU17J; SU-07J)****Q. Write down the absolute the indications of insulin. (CU-15JU)****Q. Write down the absolute indications of soluble Insulin. (CU-17J)**

Ans.

Indications of insulin:

1. Type-I DM (IDDM)
2. Uncontrolled type II DM
3. All diabetic complications:
 - Diabetic ketoacidosis
 - Diabetic nephropathy
 - Diabetic neuropathy
 - Diabetic retinopathy
 - Hyperglycemic hyperosmolar state
4. DM in pregnancy (*because insulin is not teratogenic but OHA are teratogenic*)
5. Per-operative & post-operative diabetic patient.
6. Diabetes with severe infection

7. Diabetic patient after RTA.

8. Hyperkalemia (as insulin increases K influx and thus decreases plasma K level).

Q. Short note: Insulin. (DU-17J)

Ans. Write in short from above.

Q. Write the pharmacological basis of using Insulin for type II diabetic patient in perioperative period. (CU-13Ju)

Ans.

Surgery and diabetes

Surgery, whether performed electively or in an emergency, causes catabolic stress and secretion of counter-regulatory hormones both in normal and in diabetic subjects. This results in increased glycogenolysis, gluconeogenesis, lipolysis, proteolysis and insulin resistance. In untreated or poorly controlled diabetes the uptake of metabolic substrate is significantly reduced, catabolism is increased and ultimately metabolic decompensation in the form of **diabetic ketoacidosis** may develop in both types of diabetes.

Thus surgery must be carefully planned and managed in the diabetic patient, with particular emphasis on good metabolic control and avoidance of hypoglycaemia, which is especially dangerous in the unconscious or semiconscious patient. To achieve this, insulin is used for type II diabetic patient in perioperative period.

(Ref: Davidson's-21st/816-817)

Q. A boy of 20 years has come to you with diabetes mellitus. What drug is suitable for him? (DU-09/08J; RU-10J)

Ans.

Drug of choice in a 20 years old diabetic boy: This is a case of type-I or juvenile or insulin dependent diabetes mellitus. In this case there is absolute deficiency of insulin. That's why my drug of choice is insulin.

Q. How will you manage a pregnant lady with postprandial blood glucose level of 13 mmol/L? Justify your choice of drug. What may be the risk of therapy? (DU-08/07Ju)

Ans.

Drug of choice in a pregnant lady with DM: Oral hypoglycemic agents (e.g. sulfonylureas) are teratogenic. That's why oral antidiabetic drugs are absolutely contraindicated in pregnancy. So **diabetes in pregnancy** is managed by **insulin**, not by oral hypoglycemic drugs.

Q. What are the adverse effects of insulin? (DU-14J,13J,12J, CU-14J,12J,10Ju,09/07J,06S; SU-07J)

Q. Mention the complications of insulin therapy. (DU-05M, SU-03M)

Q. Mention the long-term complications of insulin therapy. (SU-13J)

Q: Mention the cautions of soluble insulin. (CU-05M)

Ans.

Adverse effects / complications of insulin:

1. Hypoglycemia (most common)
2. Insulin hypersensitivity
3. Insulin resistance
4. Lipodystrophy: Lipoatrophy & lipohypertrophy
5. Insulin edema
6. Obesity
7. Hypokalemia
8. Alopecia
9. Increased Cancer Risk

(Ref: Goodman & Gilman's-12th; Katzung-13th)

Q. What is the management of insulin induced hypoglycemia? (DU-14Ju, CU-06M, RU-10Ju)

Q. Write the management of insulin induced hypoglycemic shock. (DU-15J)

Q. How will you manage a case of hypoglycemic shock? (DU-13J,12/11J, CU-04J; RU-13J)

Q. How will you manage a case of drug induced hypoglycemia? (CU-17J)

Ans.

Insulin induced hypoglycemia / hypoglycemic shock:

Mechanisms of hypoglycemia in a diabetic patient taking insulin: Hypoglycemic reactions are the most common complication of insulin therapy. They may result from-

1. A delay in taking a meal
2. Inadequate carbohydrate consumed
3. Unusual physical exertion
4. A dose of insulin that is too large for immediate needs.

Clinical features of hypoglycemia: Rapid development of hypoglycemia in individuals with intact hypoglycemic awareness causes signs of autonomic hyperactivity.

1. **Signs of sympathetic hyperactivity:** Tachycardia, palpitations, severe sweating, tremulousness
2. **Signs of parasympathetic hyperactivity:** Nausea, hunger.
3. Sudden unconsciousness
4. If untreated, convulsion & coma & ultimately death.

Treatment of Hypoglycemia: All the manifestations of hypoglycemia are relieved by **glucose** administration.

1. **Mild hypoglycemia in a patient who is conscious and able to swallow:**

- Simple sugar or glucose in a liquid form.
- Dextrose tablets, glucose gel, honey, sweet or any sugar containing beverage or food may be given.

2. **In case of unconscious patient:**

- 20–50 mL **50% glucose solution** by IV infusion over 2–3 minutes.
- If IV therapy is not available, **Inj. Glucagon (1 mg)** S/C or IM restores consciousness within 15 minutes.
- If glucagon is not available, small amounts of honey or syrup is given into the buccal pouch.

(Ref: Katzung-13th)

Q. What is insulin resistance? (RU-04M)

Q. Discuss about insulin resistance and its management. (DU-15Ju,07M)

Q. How Insulin resistance develops? (RU-04M)

Q. Short note: Insulin resistance. (RU-15Ju)

Ans.

Insulin resistance: Insulin resistance may be due to a decline in number and/or affinity of receptors or to defects in post-receptor mechanisms. A diabetic patient requiring more than 200 units/day is rare and regarded as insulin resistant.

Types of insulin resistance:

1. Immunogenic insulin resistance
2. Non-immunogenic insulin resistance

A. Immunogenic insulin resistance: In most cases, it is IgE mediated hypersensitivity reaction & Ab is formed against insulin. So, patient develops insulin resistance.

Diagnosis: Measuring the insulin specific IgG & IgE antibodies. Skin test is also useful.

Treatment:

- By changing the brand. If the patient has allergic reaction to porcine insulin, human insulin should be used.
- Antihistamine.
- Glucocorticoid.

B. Non-immunogenic insulin resistance: This is due to a decline in number &/or affinity of receptors or defects in post-receptor mechanisms.

Causes:

1. Inappropriate following of the prescription
2. Obesity.
3. Hyperinsulinemia.

Treatment:

- Good dieting.
- Use of **Sulfonylureas** along with **insulin** (as sulfonylureas increase insulin receptor synthesis)
- Physical exercise e.g. walking (it increases insulin sensitivity).

(Ref: Goodman & Gilman's-12th; Bennett & Brown-11th)

Q. What are the advantages and disadvantages of Insulin over the oral antidiabetic agents? (CU-16J,14J)

Ans.

Advantages of Insulin over the oral antidiabetic agents

1. Rapid onset of action
2. Can be used in pregnancy
3. Can be given in hepatic and renal insufficiency
4. Can be given in diabetic ketoacidosis.

Disadvantages of Insulin over the oral antidiabetic agents

1. Regular monitoring of blood glucose is necessary.
2. Risk of hypoglycemia is more.
3. Risk of hypersensitivity is more.
4. Needs regular injection.
5. Expensive

Oral hypoglycemic agents (OHA)

Q. Classify oral antidiabetic / hypoglycemic agents. (DU-12J, CU-17M, 13J, RU-05M/J, 04J; SU-07J)

Q. Enumerate important oral antidiabetic agents. (DU-15J, 14J)

Q. Name the euglycemic agents. (SU-09Ju; RU-08Ju)

Q. Enumerate the drugs used in type-II diabetes mellitus. (DU-06M)

Q. Name the insulin secretagogues. (DU-10Ju, RU-16Ju, 15Ju, 10Ju, 07J, SU-11, 10Ju)

Q. Name the drugs of Insulin independent DM. (CU-05J)

Q. What are the OHAs available in Bangladesh? (CU-04M)

Q. Short note: Insulin secretagogues. (DU-15Ju)

Ans.

Oral antidiabetic / hypoglycemic agents (OHA):

A. **Insulin secretagogues:** Increase insulin release.

1. Sulfonylureas	1 st generation sulfonylureas	• Tolbutamide • Chlorpropamide • Tolazamide
	2 nd generation sulfonylureas	• Glibenclamide (in USA) or Glyburide (outside USA) • Glipizide • Gliclazide • Glimepiride
2. Meglitinides	} <i>non-sulfonyl urease</i>	• Repaglinide
3. D-phenylalanine derivatives		• Nateglinide

B. **Biguanides:** (insulin sensitizer, euglycaemic agents) (E)

- Metformin
- Phenformin (*not used now a days*)

C. **Thiazolidinediones:** Insulin sensitizer. Two thiazolidinediones are currently available: (E)

- Pioglitazone
- Rosiglitazone

D. **α -glucosidase Inhibitors:** (E)

- 1. Acarbose
- 2. Miglitol

E. **Synthetic Amylin Analog:**

- Pramlintide

F. **Incretin-based therapies** (E)

1. **Incretin mimetics / Synthetic analog of glucagon-like-polypeptide 1 (GLP-1):**

- Exenatide

2. **Dipeptidyl Peptidase-IV (DPP-IV) Inhibitors:**

- Sitagliptin

Handwritten notes:
 Sitagliptin
 Saxagliptin
 Metformin
 Sitagliptin

(Ref: Katzung-13th; Lippincott's-6th)

Handwritten note:
 → Currently most used

Q. Define euglycemics and hypoglycemic with example. (RU-12Ju)

Ans.

Euglycemics: The drugs which reduce (control) or normalize blood glucose level without any potential hypoglycemic ability are called euglycemics anti-diabetic drugs. Eg, metformin, pioglitazone.

Hypoglycemic: The drugs that can cause hypoglycemia or have the potential risk of hypoglycemic incidence in addition to their anti-diabetic property are called hypoglycemic drugs. Eg, insulin, glipizide.

→ lactic acidosis etc

(Ref: Katzung-13th; Davidson's-22nd)

Nice to know

- The sulfonylureas and biguanides have been available the longest and are the traditional initial treatment choice for type 2 diabetes.
- Novel classes of rapidly acting insulin secretagogues, the meglitinides and D-phenylalanine derivatives, are alternatives to the short-acting sulfonylurea, tolbutamide.
- The thiazolidinediones, under development since the early 1980s, are very effective agents that reduce insulin resistance.
- Alpha-glucosidase inhibitors have a relatively weak antidiabetic effect and significant adverse effects, and they are used primarily as adjunctive therapy in individuals who cannot achieve their glycemic goals with other medications.

(Ref: Katzung-12th/754-758)

Sulfonylureas

Q. Write the mechanism of action of sulfonylureas. (DU-05J, CU-13J,09Ju, RU-12J, SU-10Ju,04M)

Q. Explain antidiabetic action of glimepiride / glipizide. (SU-15Ju,14J,08Ju)

Q. Explain blood glucose controlling action of glimepiride. (SU-13J,12Ju)

Q. Explain hypoglycemic effects of glipizide / glibenclamide. (CU-05M;RU-07J, SU-12J,09Ju,07J)

Q. How does glipizide influence K⁺ ion channel in pancreatic β cell? (CU-14Ju)

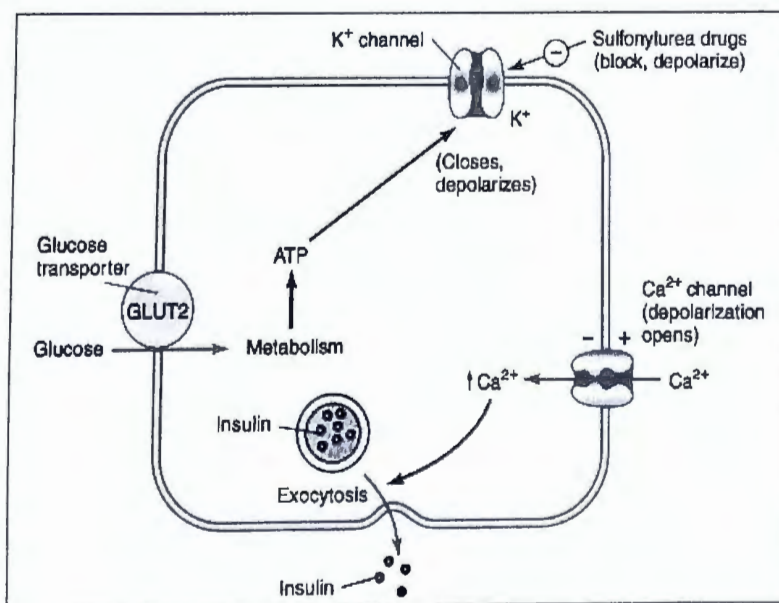
Ans.

Mechanism of action of sulfonylureas / glipizide / glibenclamide / glimepiride:

1. **Sulfonylureas increase insulin release from pancreatic β-cells by blocking ATP-sensitive K⁺ channels:**

Sulfonylureas → Block the ATP-sensitive K⁺ channels in pancreatic β-cells → Decreased outward potassium efflux → Depolarization of the B cell → opening of voltage-gated calcium channels → Increased intracellular calcium → Increased secretion of insulin.

(Ref: Katzung-13th edition)



*glucose → Insulin
β cell → K⁺ channel
close → ...*

Fig. One model of control of insulin release from the pancreatic B cell by glucose and by sulfonylurea drugs.

(Ref: Katzung-13th)

2. **Reduction of serum glucagon level:** Long-term administration of sulfonylureas to type 2 diabetics reduces serum glucagon levels, which may contribute to the hypoglycemic effect of the drugs. The mechanism for this

↑ insulin & somatostatin (β & δ cell) → ↓ α cell secretion → ↓ glucagon → hypoglycemia

suppressive effect of sulfonylureas on glucagon levels is unclear but appears to involve indirect inhibition due to enhanced release of both insulin and somatostatin, which inhibit A-cell secretion.

(Ref: Katzung-13th)

Q. What are the indications of sulfonylureas / glipizide? (CU-09/08Ju,05S; SU-07J)

Ans.

Indications of sulfonylureas / glipizide:

1. Type II DM in non-obese persons (*In obese persons metformin is used*)
2. In combination with insulin in some type I & II DM patient (especially in insulin resistant cases as sulfonylureas increase insulin receptor synthesis)

Q. Mention the adverse effects of sulfonylureas / glipizide/gliclazide? (DU-06S; CU-09/08Ju; SU-17J)

Ans.

Adverse effects of sulfonylureas / glipizide / glibenclamide:

1. Hypoglycemia
2. Weight gain
3. GIT upset: Nausea, vomiting.
4. Blood: Agranulocytosis, aplastic & hemolytic anemia, cholestatic jaundice.
5. Generalized hypersensitivity reaction.
6. Teratogenicity

Q. Will you recommend sulfonylureas in pregnancy or not? Justify your answer. (DU-06M)

Ans.

Gestational Diabetes Mellitus (GDM) / pregnancy induced DM is usually due to relative deficiency of insulin. So GDM can be managed by sulfonylureas. But **sulfonylureas are teratogenic**. That's why sulfonylureas are absolutely contraindicated in GDM. So DM in pregnancy is managed by insulin, not by oral hypoglycemic drugs.

Q. What are the contraindications of sulfonylureas?

Ans.

Contraindications of sulfonylureas:

1. Type I DM
2. Pregnancy & lactation
3. Significant renal & hepatic insufficiency
4. In elderly patient especially with cardiac impairment.

(Ref: Goodman & Gilman's-12th)

Q. What are the drawbacks of sulfonylureas? (DU-07J)

Ans.

Drawbacks of sulfonylureas

1. To get hypoglycemic effect, 30% of the total β-cells of pancreas must be functioning.
2. Can only be given to NIDDM.
3. It cannot synthesize new insulins, but can release the stored insulin.
4. Cannot be given to pregnant women because of teratogenicity.
5. Cannot be given when more than 40 IU/day of insulin is needed.
6. These drugs are not adequate in diabetic complications.
7. Cannot be given in significant renal & hepatic insufficiency.
8. **Secondary failure**, ie, failure to maintain a good response to sulfonylurea therapy over the long term, remains a disconcerting problem in the management of type 2 diabetes. A progressive decrease in B-cell mass, reduction in physical activity, decline in lean body mass, or increase in ectopic fat deposition in chronic type 2 diabetes also may contribute to secondary failure.

Q. A 55 years old obese female diabetic patient suffered from severe MI. she has been receiving 15 mg Glipizide and her fasting blood sugar was estimated 220 mg/dl.

- Design pharmacological management for her.

- Explain the action of drugs used. (SU-10Ju)

Ans.

In elderly patient especially with cardiac impairment, Glipizide (sulfonylureas) is contraindicated. So, we should stop the drug immediately and should choose another, eg, insulin or metformin.

Meglitinides (Repaglinide, Nateglinide)

Mechanism of action of meglitinides: Same as sulfonylureas.

Indication of meglitinides: To reduce postprandial glycemic elevations in type II DM.

Adverse effect: Hypoglycemia

Precautions of using meglitinides:

1. As repaglinide & nateglinide are metabolized mainly (90%) by the liver, they should be used cautiously in hepatic insufficiency.
2. A small proportion is also metabolized by kidney & excreted through it, so they should also be used cautiously in renal insufficiency.

(Ref: Goodman & Gilman's-12th)

Biguanides: Metformin

Metformin is taken with or after meals. Its chief use is in the obese patient with Type 2 diabetes either alone or in combination with a sulfonylurea. It has a mild anorexic effect which helps to reduce weight in the obese.

(Ref: Bennett & Brown-11th/615)

Q. Explain how metformin reduces blood glucose level. (DU-10Ju,06S;CU-07J,RU-08Ju,06J,SU-06J)

Q. State the anti-diabetic action of metformin. (CU-17M,16Ju,14Ju, SU-15Ju,14J,13Ju)

Ans.

Mechanism of action of biguanides / metformin: Their blood glucose-lowering action does not depend on functioning pancreatic B cells. Patients with type 2 diabetes have considerably less fasting hyperglycemia as well as lower postprandial hyperglycemia after biguanides; however, hypoglycemia during biguanide therapy is essentially unknown. These agents are therefore more appropriately termed "euglycemic" agents.

Currently proposed mechanisms of action include-

1. reduced hepatic and renal gluconeogenesis;
2. slowing of glucose absorption from the gastrointestinal tract, with increased glucose to lactate conversion by enterocytes;
3. direct stimulation of glycolysis in tissues, with increased glucose removal from blood; and
4. reduction of plasma glucagon levels.

(correct insulin mechanism for glycogen partition)

↑ Insulin sensitivity

(Ref: Katzung-13th)

Q. Mention the indications of metformin / biguanides. (DU-06S; RU-16Ju,06J,05M, SU-07J)

Ans.

Indication of biguanides / metformin:

1. **Insulin resistance syndrome:** As Metformin is an insulin sparing agent & does not increase weight / provoke hypoglycemia, it is used in patients whose hyperglycemia is due to ineffective insulin action i.e. insulin resistance syndrome.
2. In type-II DM with insulin secretagogues or thiazolidinediones in whom oral monotherapy is inadequate.
3. NIDDM in **obese persons**.
4. Metformin is efficacious in preventing the new onset of type II DM in middle aged, obese person with impaired glucose tolerance & fasting hyperglycemia.

(Ref: Katzung-13th)

Q. Which drugs will be suitable for an obese diabetic lady aged 40 years? (RU-13Ju)
 Ans. Metformin

Q. Mention the adverse effects of metformin. (DU-10Ju, CU-06S; RU-08Ju; SU-07J)
 Ans.

Adverse effects of metformin:

1. GIT upset: Anorexia, nausea, vomiting, abdominal discomfort, diarrhea. They are dose related.
2. Decreased vitamin B₁₂ absorption in chronic use leads to megaloblastic anemia.
3. Metallic taste

(NB: Phenformin causes lactic acidosis. That's why it is not used now.)

(Ref: Katzung-13th)

Q. Mention the contraindications of metformin.

Ans.

Contraindications of metformin:

1. Patient with hepatic & renal insufficiency.
2. Alcoholism
3. Chronic cardio-pulmonary dysfunction, which causes tissue anoxia & increased risk of lactic acidosis.
4. Diabetic ketoacidosis.

(Ref: Katzung-13th)

Q. Short note: Metformin. (DU-13Ju, 12J)

Ans. Write in short from above.

Q. Enumerate 3 anti-diabetic drugs to be included in essential drug lists of Bangladesh. (CU-07J)

Ans.

3 anti-diabetic drugs that should be included in essential drug list:

1. Insulin
2. Glipizide
3. Metformin

Thiazolidinediones

Thiazolidinediones never produce hypoglycemia & hence it is called euglycaemic agents.

Q. Explain hypoglycemic action of pioglitazone. (SU-09/07Ju, 06S/M)

Q. Explain blood glucose controlling action of pioglitazone. (SU-12Ju)

Ans.

Hypoglycemic action of pioglitazone / rosiglitazone: Thiazolidinediones (Tzds) act to decrease insulin resistance by regulating genes involved in glucose and lipid metabolism and adipocyte differentiation.

Tzds binds with **peroxisome proliferator-activated receptor-gamma (PPAR-γ)** in muscle, fat, and liver.



PPAR-γ receptors modulate the expression of the genes involved in lipid and glucose metabolism, insulin signal transduction.



The drug promotes glucose uptake and utilization, especially in adipose tissue.

(Ref: Katzung-13th)

Indications of pioglitazone / rosiglitazone:

1. Type-II DM (especially in insulin resistance case)
2. Prevention of type II DM.

3. Monotherapy (along with diet & exercise) in mild degree DM.
3. In combination with biguanides & sulfonylureas in type II DM.
4. In glucose intolerance patients.
5. Prevention of recurrence of DM in high risk Hispanic women with a history of gestational DM.

(Ref: Katzung-13th & Tripathi-6th/270)

Adverse effects of pioglitazone

1. Dose related weight gain (average 1 - 3 kg)
2. Fluid retention (which presents as a mild anemia & peripheral edema) especially when used in combination with insulin & sulfonylureas.
3. Hepatotoxicity (especially with rosiglitazone)
4. Teratogenicity

(Ref: Katzung-13th)

Contraindications of pioglitazone

1. Obesity
2. Liver disease (CLD)
3. Heart failure
4. Pre existing edema
5. Pregnancy.

(Ref: Katzung-13th)

Acarbose / Miglitol / α -glucosidase inhibitors

Mechanism of action of acarbose:

Acarbose / miglitol



Competitive inhibition of 'intestinal α -glucosidase'



Reduce postprandial digestion & absorption of starch & disaccharides



Reduce blood glucose level

(Ref: Katzung-13th)

Adverse effects of acarbose / miglitol:

1. GIT adverse effects: Flatulence, diarrhea, abdominal pain.
2. Reversible hepatic enzyme elevation

(Ref: Katzung-13th)

Contraindications of acarbose:

1. Patients with inflammatory bowel disease (IBS)
2. Any intestinal condition that could be worsened by gas & distension
3. Should be used with cautions in patients with hepatic & renal impairment.

(Ref: Katzung-13th)

Incretin-based therapies

Q. How does glucose stimulate Insulin release? (CU-16Ju)

Ans.

How glucose stimulates Insulin release:

Presence of glucose in the gut



Glucose stimulates secretion of gut hormones, or **incretins**



Incretins (eg, glucagon-like peptide (GLP-1)) stimulates insulin secretion in a glucose-dependent manner.

Nice to know**Incretin:**

- Incretins are gut hormones, which potentiate glucose-induced insulin secretion.
- Glucagon-like peptide (GLP-1) is an incretin hormone which stimulates insulin secretion in a glucose-dependent manner; thus hypoglycemia does not occur.
- In addition, GLP-1 suppresses glucagon secretion, delays gastric emptying, reduces appetite and encourages weight loss.

Drugs used in incretin-based therapy: Incretin-based therapies are most useful in obese patients and can be used in combination with other oral anti-diabetic agents.

1. **Incretin mimetics / Synthetic analog of glucagon-like-polypeptide 1 (GLP-1):**

- Exenatide
- Liraglutide

2. **Dipeptidyl Peptidase-IV (DPP-IV) Inhibitors:**

- Sitagliptin,
- Vildagliptin
- Saxagliptin

Exenatide

It is a synthetic analog of glucagon-like-polypeptide 1 (GLP-1).

Indication: Adjunctive therapy in persons with type 2 diabetes treated with metformin or metformin plus sulfonylureas who still have suboptimal glycemic control.

Mechanism of action:

1. Potentiation of glucose-mediated insulin secretion. The increased insulin secretion is speculated to be due in part to an increase in beta-cell mass.
2. Suppression of postprandial glucagon release
3. Slowed gastric emptying, and
4. Central loss of appetite.

Route of administration: Exenatide is injected subcutaneously within 60 minutes before a meal.

Adverse effects:

1. Nausea (about 44% of users)
2. Vomiting
3. Diarrhea
4. Weight loss (in some users, presumably because of the nausea and anorectic effects.)
5. Necrotizing and hemorrhagic pancreatitis.

(Ref: Katzung-13th)

Sitagliptin

Q. Write how sitagliptin reduces blood sugar level. (RU-15Ju)

Q. State the anti-diabetic action of sitagliptin. (SU-15Ju, 13Ju)

Ans.

Mechanism of action of sitagliptin: Sitagliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4), the enzyme that degrades incretin and other GLP-1-like molecules. Its major action is to increase circulating levels of GLP-1 and GIP. This ultimately decreases postprandial glucose excursions by increasing glucose-mediated insulin secretion and decreasing glucagon levels.

(Ref: Katzung-13th)

Nice to know

Route of administration: Oral.

Dose: 100 mg orally once daily.

Clinical use: Sitagliptin can be given as monotherapy or combined with metformin or Tzds.

Adverse effects

1. Nasopharyngitis
2. Upper respiratory infections
3. Headaches
4. Rarely, severe allergic reactions

(Ref: Katzung-13th)

Adrenal Steroids & Adrenocortical antagonists

Q. Enlist adrenal steroids. (CU-14Ju)

Ans.

Adrenal steroids / Adrenocortical hormones

Layers of adrenal cortex	Hormones
1. Zona glomerulosa	1. Mineralocorticoids: • Aldosterone • Deoxycorticosterone
2. Zona fasciculata	2. Glucocorticoids: (Stress Hormone) • Cortisol • Corticosterone
3. Zona reticularis	3. Sex corticoids: • Adrenal androgens- ➤ Dehydroepiandrosterone ➤ Androstenedione • Estrogen

Glucocorticoids

Q. Classify glucocorticoids according to duration of action. (SU-09Ju;RU-10Ju,06J)

Q. Classify glucocorticoids according to potency. (RU-16J,12Ju,08J)

Q. Enumerate the glucocorticoids. (DU-16Ju)

Q. Classify glucocorticoids based on pharmacokinetic and pharmacodynamic properties. (SU-14Ju,13J)

Q. Name the long acting glucocorticoids. (SU-07J)

Q. Name the glucocorticoids according to route of administration. (SU-16J)

Q. List synthetic glucocorticoids. (SU-17J)

Ans.

Classification of glucocorticoids:

A. According to duration of action:

1. Short-to-medium-acting (< 12 hours)	• Hydrocortisone (Cortisol) • Cortisone • Prednisone. • Prednisolone • Methylprednisolone • Meprednisone
2. Intermediate-acting (12-36 hours)	• Triamcinolone • Paramethasone • Fluprednisolone
3. Long acting (>36 hours)	• Betamethasone • Dexamethasone

(Ref: Katzung-13th)

B. According to potency:

		Anti-Inflammatory activity (Potency relative to hydrocortisone)
High potency	Dexamethasone	30
	Betamethasone	25-40
	Fluprednisolone	15

Medium / intermediate potency	Paramethasone	10
	Triamcinolone	5
	Prednisolone	5
	Methylprednisolone	5
	Meprednisone	5
Low potency	Prednisone	4
	Hydrocortisone	1
	Cortisone	0.8

(Ref: Tripathi-6th/282)

C. According to route of administration:

IM	• Triamcinolone
IV, IM	• Betamethasone • Dexamethasone • Hydrocortisone — <i>Emergency Condition</i> • Prednisolone • Methylprednisolone
Inhaled and nasal sprays	• Beclomethasone • Budesonide • Ciclesonide • Flunisolide • Fluticasone • Mometasone • Triamcinolone (Aster Sin)
Oral	• Cortisone • Dexamethasone • Methylprednisolone • Prednisone
Topical	• Betamethasone • Hydrocortisone • Mometasone • Triamcinolone
Intra-articular	• Methylprednisolone • Triamcinolone

(Ref: Lippincott's-6th/369)

Q. Enumerate some clinically important synthetic glucocorticoids. (CU-08J; SU-06J)

Q. Name commonly used glucocorticoids. (RU-07J)

Ans. Commonly used glucocorticoids: Hydrocortisone, Prednisolone, Betamethasone, Dexamethasone, Methylprednisolone, and Triamcinolone.

Q. Classify anti-inflammatory drugs. (RU-09J)

Q. What are the drugs that affect prostaglandin synthesis? (SU-14J)

Ans.

Anti-inflammatory drugs / drugs that affect prostaglandin synthesis:

1. Steroid anti-inflammatory drugs (corticosteroids)
2. Non steroidal anti-inflammatory drugs (NSAIDs)

Q. Describe the mechanism of action of steroids. (CU-14Ju)

Q. Describe the mechanism of action of glucocorticoids. (CU-10J)

Q. How does glucocorticoid act at molecular level? (RU-08J)

Ans.

Mechanism of action of glucocorticoids / steroids / prednisolone:

Glucocorticoids enter into the cell & binds with the receptor in the cytoplasm.

Conformational change occurs in the receptor

The glucocorticoid-receptor complex is then actively transported into the nucleus & it interacts with DNA & nuclear proteins.

The complex binds with the glucocorticoid response element (GRE) on the gene.

After binding, it regulates the transcription by RNA polymerase-II & associated transcription factors.

mRNA synthesis

Protein synthesis

New proteins are responsible for glucocorticoid action.

(Ref: Katzung-13th)

Effects of glucocorticoids:

1. Physiological effects
2. Pharmacological effects

Q. Describe the effects of glucocorticoids on metabolism. (CU-11Ju, RU-06J)

Q. Enlist the important pharmacological effects of glucocorticoids. (DU-15J)

Q. Explain briefly the important pharmacological effects of glucocorticoids. (DU-13J, 10J, CU-12Ju)

Ans.

Effects of glucocorticoids on metabolism

1. On carbohydrate metabolism	• ↑Gluconeogenesis • ↑Glycogenesis • ↓Glucose utilization • ↑Blood glucose. <i>Glucose, Glycogen ↑</i>
2. On protein metabolism	In extrahepatic tissue- • ↓Amino acid uptake • ↓Protein synthesis • ↑Protein catabolism • ↑Amino acid mobilization from extrahepatic tissue into blood. <i>Protein ↓</i> In liver- • ↑Amino acid uptake • ↑Protein synthesis <i>Protein ↑</i> In plasma- • ↑Plasma protein • ↑Plasma amino acid.
3. On fat metabolism	• ↑Fatty acid mobilization from adipose tissue • ↑Fatty acid utilization for energy • ↑Ketone body formation • ↑Plasma fatty acid. <i>Fat ↑ storage & utilization</i>

(Ref: Guyton-12th; Ganong-24th)

Q. Describe the anti inflammatory effects of glucocorticoids. (DU-14Ju, 12J, CU-15J, 07J, RU-17J, 09Ju; SU-16Ju, 15Ju, 13Ju)

- Q. Explain the anti-inflammatory effects of corticosteroids. (RU-14J,09J, CU-11Ju)
 Q. Explain the anti inflammatory role of steroids. (SU-10J)
 Q. Explain the anti inflammatory effects of prednisolone. (RU-07Ju,06M, SU-14J,11Ju)
 Q. Explain anti inflammatory action of dexamethasone. (SU-17J,12Ju)
 Q. Explain the immunosuppressive effects of corticosteroids with uses exploiting this action. (RU-15J)
 Q. Explain the immunosuppressive effects of prednisolone. (RU-11Ju)

Ans.

Anti-inflammatory & immunosuppressive effects of corticosteroids/prednisolone: Glucocorticoids dramatically reduce the manifestations of inflammation. This is due to their profound effects on the concentration, distribution, and function of peripheral **leukocytes** and to their suppressive effects on the inflammatory **cytokines** and **chemokines** and on **other mediators** of inflammation.

Mechanism:

1. Increased influx of neutrophil into the blood from bone marrow → decreased migration from blood vessel → **Decreased neutrophil** number in the inflammatory site.
2. **Decreased circulatory lymphocytes, monocytes, eosinophils & basophils** due to their migration from the vascular bed to lymphoid tissue → Decreased number of these cells in the inflammatory site.
3. **Inhibit the functions of tissue macrophages** and other antigen-presenting cells. As a result,
 - a) Antigen presentation is reduced.
 - b) Phagocytosis is reduced.
 - c) Less production of IL-12 and interferon- γ , important inducers of TH1 cell activity, and cellular immunity.
4. **Inhibition of phospholipase-A₂ enzyme:** By this way-
 - a) Glucocorticoids inhibit the inflammatory response by reducing the prostaglandin, leukotriene, and platelet-activating factor synthesis.
 - b) Reduce COX-2 enzyme in inflammatory cells.

Phospholipid → Arachidonic Acid inhibition
5. Glucocorticoids cause **vasoconstriction** and **decrease capillary permeability** by **reducing histamine release** from basophils and mast cells.
6. **Complement** activation is unaltered, but its effects are inhibited.
7. **Antibody** production can be reduced by large doses of steroids, though it is unaffected by moderate dosages (eg, 20 mg/d of prednisone).

(Ref: Katzung-13th)

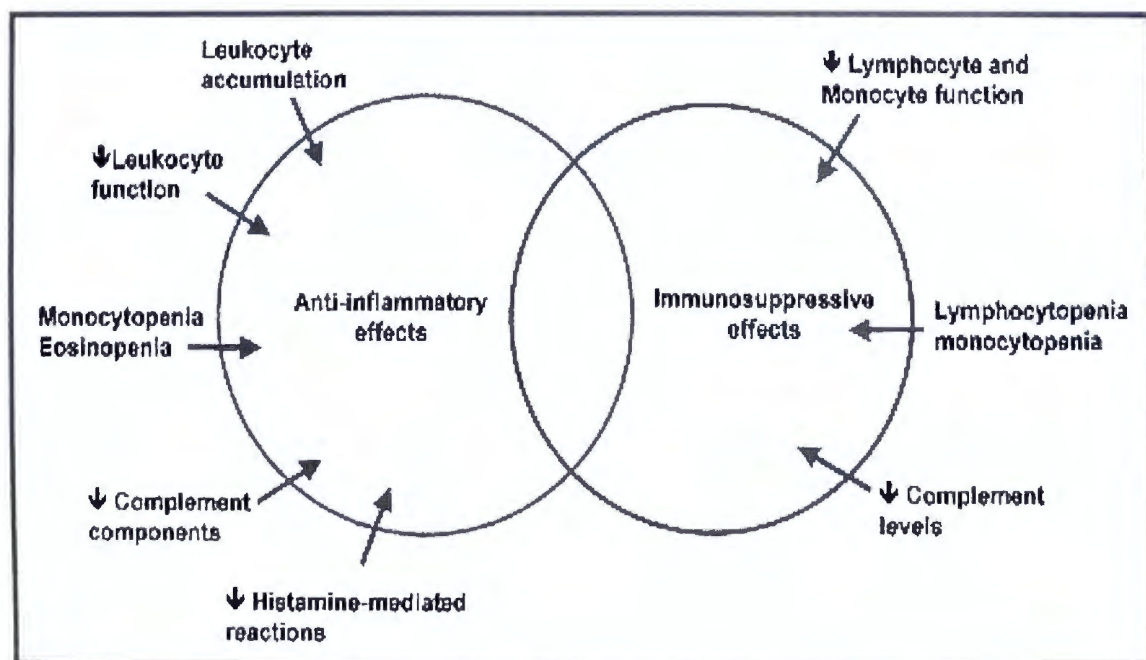


Fig. Anti inflammatory and immunosuppressive role of corticosteroids.

Q. Explain the permissive role of steroids / hydrocortisone. (SU-13Ju, 12Ju, 11J, 10J)

Q. Short note: Permissive effect of corticosteroids. (RU-16J)

Ans.

Permissive action of steroids: Small amounts of glucocorticoids must be present for a number of metabolic reactions to occur, although the glucocorticoids do not produce the reactions by themselves. This effect is called their **permissive action**. Permissive effects include the requirement for glucocorticoids to be present-

1. For glucagon and catecholamines to exert their calorogenic effects.
2. For catecholamines to exert their lipolytic effects.
3. For catecholamines to produce pressor responses and bronchodilation.

*Steroid → 3 3725m Adrenaline
20 205 202
(Ref: Ganong's-24th) 2TC*

Q. Mention the therapeutic principles of glucocorticoids. (RU-13J)

Ans.

Therapeutic principles of glucocorticoids

1. The decision to give glucocorticoids always requires a careful consideration of the relative risks and benefits in each patient.
2. For any disease and in any patient, the **lowest effective dose** should be given for the **shortest period** of time.
3. Abrupt cessation of glucocorticoids after prolonged therapy is associated with the risk of adrenal insufficiency, which may be fatal. So, dose of glucocorticoids should be **tapered slowly**.

(Ref: Goodman & Gilman's-12th)

Q. Mention the clinical uses of glucocorticoids. (DU-05M, CU-11J, 10J, RU-17J, SU-06J)

Q. What are the indications of glucocorticoids? (DU-15J, CU-05M; RU-14J, SU-11J)

Q. What are the indications of prednisolone? (CU-05M, SU-17J)

Q. Outline the immunosuppressive uses of glucocorticoids. (RU-16J)

Ans.

Indications of glucocorticoids

A. **Adrenal uses or replacement therapy:**

1. **Adrenocortical insufficiency:**

- Chronic (Addison's disease)
- Acute (Addisonian crisis)

2. **Adrenocortical hypo & hyper-function:**

- Congenital adrenal hyperplasia
- Cushing's syndrome
- Aldosteronism (primary & secondary)
- For diagnosis of Cushing's syndrome by the "dexamethasone suppression test"
- Iatrogenic adrenocortical insufficiency: Abrupt withdrawal.

(Ref: Katzung-13th; Bennett & Brown-11th)

B. **Some Nonadrenal Disorders:**

Disorder	Examples
Allergic reactions	• Angioneurotic edema • Asthma • Bee stings • Contact dermatitis • Drug reactions • Allergic rhinitis • Serum sickness • Urticaria

Collagen-vascular disorders	• Giant cell arteritis • Lupus erythematosus • Mixed connective tissue syndromes • Polymyositis • Polymyalgia rheumatic • Rheumatoid arthritis • Temporal arteritis
Eye diseases	• Acute uveitis • Allergic conjunctivitis • Choroiditis • Optic neuritis
Gastrointestinal diseases	• Inflammatory bowel disease • Nontropical sprue • Subacute hepatic necrosis
Hematologic disorders	• Acquired hemolytic anemia • Acute allergic purpura • Leukemia • Autoimmune hemolytic anemia • Idiopathic thrombocytopenic purpura • Multiple myeloma
Systemic inflammation	• Acute respiratory distress syndrome (ARDS)
Infections	• Acute respiratory distress syndrome (ARDS) • Sepsis
Inflammatory conditions of bones and joints	• Arthritis, • Bursitis • Tenosynovitis
Neurologic disorders	• Cerebral edema (<i>large doses of dexamethasone are given to patients following brain surgery to minimize cerebral edema in the postoperative period</i>) • Multiple sclerosis
Organ transplants	• Prevention and treatment of rejection (immunosuppression)
Pulmonary diseases	• Aspiration pneumonia • Bronchial asthma • Prevention of infant respiratory distress syndrome • Sarcoidosis
Renal disorders	• Nephrotic syndrome
Skin diseases	• Atopic dermatitis • Dermatoses • Lichen simplex chronicus (localized neurodermatitis) • Mycosis fungoides • Pemphigus • Seborrheic dermatitis • Xerosis
Thyroid diseases	• Malignant exophthalmos • Subacute thyroiditis
Miscellaneous	• Hypercalcemia • Mountain sickness

- Q. What are the adverse effects of long term use of glucocorticoids? (DU-15J,13J,08J, CU-13J,10J, RU-10Ju, SU-09Ju)
- Q. What are the major adverse effects of glucocorticoids? (SU-16Ju)
- Q. Write the GIT adverse effects of the synthetic glucocorticoids. (CU-08J)
- Q. Enumerate the potential adverse effects of prolonged oral corticosteroid therapy. (CU-07J)
- Q. What complications may occur with the long term use of dexamethasone? (CU-04M; SU-13J,12J,07J)
- Q. Mention the adverse effects of prednisolone after chronic use. (CU-05S)
- Q. What are the consequences of sudden withdrawal of glucocorticoids? (CU-13J,07Ju;RU-04J)

Ans. Adverse effects of long term use of glucocorticoids: Two categories of toxic effects results from the therapeutic use of corticosteroids.

- Due to rapid withdrawal of steroid therapy
- Due to continued therapy

A. Due to rapid / sudden withdrawal of corticosteroid therapy:

- Flare-up of the underlying diseases for which steroids were prescribed
- Acute adrenal suppression
- Other effects:
 - Fever, myalgia, arthralgia & malaise
 - Pseudo-tumor cerebri.

B. Due to continued / long term use of glucocorticoids: The major undesirable effects of glucocorticoids are the result of their hormonal actions, which lead to the clinical picture of **iatrogenic Cushing's syndrome**.

- Fluid & electrolyte disturbances:
 - Hypokalemic alkalosis
 - Edema
 - HTN
- Metabolic changes:
 - Hypokalemia with glycosuria
 - Iatrogenic Cushing's syndrome**
- Increased susceptibility to infection due to suppression of immunity
- GIT: Peptic ulcer diseases.
- Myopathy
- Osteoporosis & osteonecrosis
- Cataracts
- CNS & behavioral changes: Nervousness, insomnia, overt psychosis & changes in mood
- Regulation in growth & development: Growth retardation in children.

(Ref: Katzung-13th; Goodman & Gilman's-12th)

Biomedical Side Effects

DM → ↑ Glucocorticoids

Osteoporosis → Steroid → ↑ Osteoclastic activity (withdrawing or slow)

↑ BP - K^+ excretion, Na^+ reabs → ↑ BP

Hypokalemia - pt. lethargy

Aldosterone!

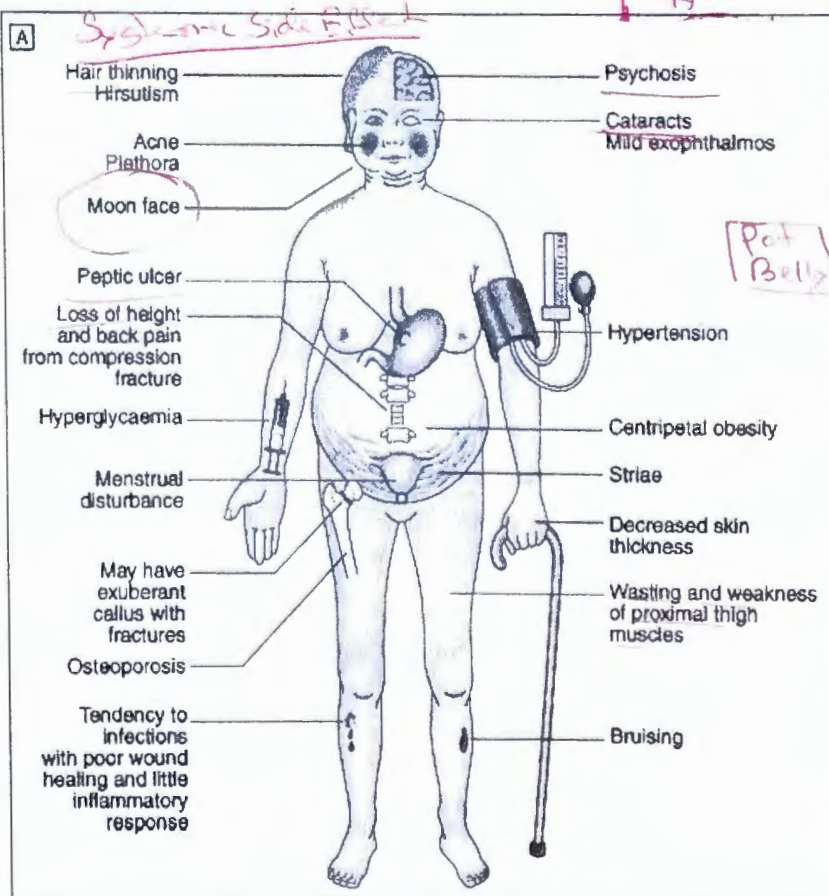
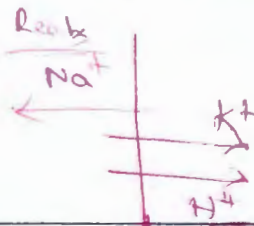


Fig. Cushing's syndrome

Q. Mention the rational management of the adverse effects caused by synthetic glucocorticoids. (CU-08J)
Ans.

Management of the adverse effects of corticosteroids:

1. Gradual withdrawal of the corticosteroids
2. Treatment of the developed problems:
 - a) Treatment of infection by appropriate antibiotics.
 - b) Treatment of PUD by anti-ulcer drugs.
 - c) Treatment of HTN by anti-hypertensive drugs.
 - d) Treatment of fluid & electrolyte imbalances etc.
3. Strict monitoring of the progress of the patient condition including vital signs
4. Prevention of the adverse effects:
 - a) Using short acting corticosteroids (hydrocortisone, prednisolone, methylprednisolone)
 - b) Using corticosteroids for the shortest period of time & gradual withdrawal after prolong use.

Q. Mention the contraindications for corticosteroid therapy. (DU-12J, RU-16J, CU-05M, SU-11J)

Q. Mention three important contraindications of glucocorticoid. (DU-08J)

Ans.
Contraindications of glucocorticoids: Glucocorticoids must be used with great caution in patients with-

1. Peptic ulcer
2. Heart disease or hypertension with heart failure
3. Certain infectious illnesses such as varicella and tuberculosis
4. Psychoses
5. Diabetes
6. Osteoporosis
7. Glaucoma.
8. Epilepsy

(Ref: Katzung-13th; Bennett & Brown-11th)

Q. What precautions are to be taken during prolonged steroid therapy? (DU-10J)

Q. What precautions are to be taken before glucocorticoid use? (CU-12J)

Q. Discuss the precautions that should be taken before prescribing steroid hormones. (DU-14Ju)

Ans.

Precautions to be taken during prolonged steroid therapy:

1. Patients receiving glucocorticoids must be monitored carefully for the development of-
 - a. Hyperglycemia
 - b. Glycosuria
 - c. Hypertension
 - d. Fluid retention (weight gain)
 - e. Hypokalemia (potassium supplement may be necessary)
 - f. Peptic ulcer
 - g. Osteoporosis (back pain)
 - h. Hidden infections.
 - i. Serious hazard of patient noncompliance.
2. **Mild withdrawal symptoms** (iatrogenic cortical insufficiency) include conjunctivitis, rhinitis, weight loss, arthralgia and itchy skin nodules.
3. **Patients must always**
 - carry a card giving details of therapy
 - be impressed with the importance of compliance
 - know what to do if they develop an intercurrent illness or other severe stress (eg, surgery): double their next dose and to tell their doctor. If a patient omits a dose then it should be made up as soon as possible so that the total daily intake is maintained, because every patient should be taking the minimum dose necessary to control the disease.

(Ref: Katzung-13th edition; Bennett & Brown-11th)

Q. Compare glucocorticoids & NSAIDs as anti inflammatory agents. (CU-17M, 14J, 12Ju, 09/08Ju, SU-10Ju)

Q. How glucocorticoids differ from NSAIDs? (SU-12J)

Ans.

Comparison between glucocorticoids & NSAIDs as anti inflammatory agents:

Traits	Glucocorticoids	NSAIDs
1. Mechanism of action	Inhibit phospholipase-A ₂ enzyme	Inhibit cyclooxygenase enzyme
2. Leukotrienes production	Inhibited	Not inhibited
3. Immune-suppressive effect	Present	Absent
4. Analgesic effect	Absent	Present
5. Antipyretic effect	Absent	Present
6. Antiplatelet effect	Absent	Present
7. Bronchoconstriction	No	Yes
8. Blood glucose level	Elevated	No change
9. Osteoporotic change	Occurs	No change
10. Opportunistic infection	Causes	No change
11. Iatrogenic Cushing syndrome	Can occur	No
12. Hypertension	Occurs	Does not occur

Q. Mention the principles of withdrawal of corticosteroids.

Ans.

Principles of withdrawal of corticosteroids: The longer the duration of therapy the slower must be the withdrawal. *Gradual withdrawal - Tapering*

- For use of less than 1 week (e.g. in severe asthma), although there is some hypothalamic suppression, withdrawal can be safely accomplished in a few steps.
- After use for 2 weeks, if rapid withdrawal is desired, a 50% reduction in dose may be made each day.
- If the patient has been treated for a longer period, reduction in dose is accompanied by the dual risk of a flare up of the disease and of iatrogenic hypoadrenalism; then withdrawal should be done very slowly, e.g. 2.5-5 mg prednisolone or equivalent at intervals of 3-7 days.

(Ref: Bennett & Brown-11th)

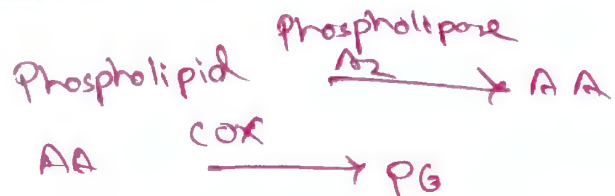
Adrenocortical antagonists

Glucocorticoid antagonist:

Glucocorticoid receptor antagonist: Mifepristone

Adrenal steroid synthesis inhibitors:

- Aminoglutethimide
- Metyrapone
- Ketoconazole
- Metyrapone
- Trilostane
- Abiraterone



(Ref: Katzung-13th)

Mineralocorticoid receptor antagonists / aldosterone antagonist

These drugs compete with aldosterone for its receptor and decrease its effect peripherally.

- Spironolactone
- Eplerenone
- Drospirenone

Gonadal hormones & Inhibitors

Q. Name the estrogens.

Ans.

Estrogens:

Steroidal	Natural	• Estradiol • Estrone • Estriol
	Synthetic	• Ethinyl estradiol • Mestranol • Quinestrol
Non-steroidal	Synthetic	• Dienestrol • Diethylstilbestrol • Benzestrol • Hexestrol • Methestrol • Methallenestril • Chlorotrianisene

(Ref: Katzung-13th)

Q. Write the clinical uses of estrogen.

Ans.

Clinical uses of estrogens:

A. Replacement therapy

1. **Primary Hypogonadism:** Estrogens have been used extensively for replacement therapy in estrogen-deficient patients. (*Treatment of primary hypogonadism is usually begun at 11–13 years of age and continued until the age of menopause*)
2. **Postmenopausal hormone replacement therapy (HRT)**

B. Pharmacotherapy:

1. **In combined OCP** along with progesterone
2. **In dysfunctional uterine bleeding (DUB)** in combination with progesterone.
3. **Intractable dysmenorrhea:** Estrogens combined with progestins can be used to suppress ovulation in patients with intractable dysmenorrhea.
4. **Hirsutism and amenorrhea** due to excessive secretion of androgens by the ovary: Estrogens combined with progestins is used to suppress ovarian function.

(Ref: Katzung-13th; Bennett & Brown-10th 645,647)

Q. Define HRT? (CU-06M)

Q. What is hormone replacement therapy? Name the hormone preparation used. Mention the indications & risks. (DU-08Ju)

Q. Describe the HRT in postmenopausal syndrome. (CU-06M)

Q. Short note: HRT. (DU-13Ju,12J, SU-06M; RU-15J,13Ju)

Ans.

Post-menopausal hormone replacement therapy (HRT): HRT refers to the use of estrogen treatment in order to reverse or prevent problems due to the loss of ovarian hormone secretion after the menopause, whether physiological or induced. The tissues sensitive to estrogen include brain, bone, skin, cardiovascular and genitourinary.

Indications of HRT:

1. To reduce the everyday symptoms of estrogen loss: hot flushes, sleeplessness, lethargy and depression, vaginal dryness.
2. To prevent the long-term complications associated with estrogen deficiency: osteoporotic fractures and coronary heart disease.

Risks of HRT:

1. Endometrial cancer.
2. Breast cancer.

These disorders may occur due to estrogen excess.

Preparations used for HRT. There are three types of regimen:

1. Women without a uterus take continuous estrogen alone.
2. Other women require estrogen combined with progestogen to prevent endometrial proliferation.
 - a. In the commonest, '**sequential**' regimen, women take estrogen without break, and add a progestogen from approximately the 14th to 28th day of each cycle. The first course is started on the 1st day of menstruation (if present), and 28-day cycles of treatment follow thereafter without interval.
 - b. In the '**continuous**' regimen, *appropriate only for women who have been amenorrheic for more than one year*, fixed dose combinations of estrogen and progestogen are taken without a break. Continuous combination HRT regimens will eventually induce amenorrhea in most women, thereby eliminating one of the major deterrents to HRT use, withdrawal bleeding.

(Ref: Bennett & Brown-11th)

Q. What are the adverse effects of estrogen therapy?

Ans.

Adverse effects of estrogen HRT:

- A. Common:
 1. Postmenopausal uterine bleeding
 2. Breast pain (mastalgia)
- B. Most serious complications:
 1. Venous thromboembolism
 2. Ca endometrium
 3. Ca breast
- C. Others:
 1. Nausea
 2. Hyper pigmentation
 3. Increased frequency of migraine headache

(Ref: Bennett & Brown-11th)

Q. Mention the contraindications of estrogen therapy.

Ans.

Contraindications of estrogen HRT:

1. Patient with estrogen dependent neoplasm; such as —
 - a. Ca endometrium &
 - b. Ca breast
2. Patient with undiagnosed genital bleeding.
3. History of thromboembolic disorders.
4. Liver diseases.
5. Relatively contraindicated in heavy smokers

(Ref: Katzung-13th)

Selective Estrogen-Receptor Modulators (SERMs)

Selective estrogen-receptor modulators (SERMs) are a new class of estrogen-related compounds. In the past, a number of these agents had been categorized as antiestrogens, and consequently, there is some confusion. The term SERM is now reserved for compounds that interact at estrogen receptors but have different effects on different tissues; that is, they display selective agonism or antagonism according to the tissue type. For example, tamoxifen is an estrogen antagonist in breast cancer tissue but can cause endometrial hyperplasia by acting as a partial agonist in the uterus.

(Ref: Lippincott's-6th)

Q. Name the selective estrogen-receptor modulators (SERMs).

Ans.

Selective estrogen-receptor modulators (SERMs)

1. Tamoxifen
2. Toremifene
3. Raloxifene
4. Clomiphene is also sometimes designated as a SERM.

(Ref: Lippincott's-6th)

Tamoxifen

Tamoxifen, a competitive partial agonist inhibitor of estradiol at the estrogen receptor in breast tissue, was the first selective estrogen receptor modulator (SERM) to be introduced.

Route of administration: Oral

Q. Enumerate the clinical use of Tamoxifen. (CU-16Ju)

(Ref: Katzung-13th)

Ans.

Indications / clinical use of Tamoxifen

1. Palliative treatment of metastatic **breast cancer** in postmenopausal women.
2. Used as adjuvant therapy following mastectomy or radiation and to reduce the risk of breast cancer in high-risk patients.

Adverse effects:

1. Hot flashes and nausea (most frequent)
2. Menstrual irregularities
3. Vaginal bleeding
4. Hyperplasia and malignancies of endometrium.

(Ref: Lippincott's-6th)

Clomiphene

Clomiphene is a partial estrogen agonist. It is an ovulation-inducing agent.

Route of administration: Oral

Mechanisms of Action

Clomiphene is a partial agonist at estrogen receptors. It interferes with the negative feedback of estrogens on the hypothalamus.

↓
Increases the secretion of gonadotropin-releasing hormone from hypothalamus.

↓
Increases the secretion of gonadotropins (FSH & LH) from anterior pituitary

↓
Stimulation of ovulation.

Clinical Use: The drug has been used successfully to treat **infertility associated with anovulatory cycles**. Clomiphene is used in the treatment of disorders of ovulation in patients who wish to become pregnant

Adverse Effects

1. Hot flushes (most common)
2. Headache
3. Constipation
4. Allergic skin reactions
5. Reversible hair loss
6. Visual disturbances
7. Ovarian enlargement

Contraindications & Cautions: Special precautions should be observed in patients with-

1. Enlarged ovaries. *(These women are thought to be more sensitive to this drug and should receive small doses.)*
2. Visual symptoms associated with clomiphene therapy.

(Ref: Katzung-13th)

Progesterone

Q. Classify progesterone.

Ans.

Progesterone

Natural	1. Progesterone
Synthetic	1. Norethindrone 2. L-Norgestrel 3. Hydroxyprogesterone 4. Medroxyprogesterone 5. Dimethisterone 6. Desogestrel 7. Lynestrenol

(Ref: Katzung-13th)

Q. What are the indications and adverse effects of progesterone? (CU-05J)

Ans.

Indications of progesterone:

1. **In contraception:** As combined OCP & as progesterone only pill (POP) / mini pill.
2. As postmenopausal HRT in combination with estrogen
3. Secondary amenorrhea
4. Abnormal uterine bleeding in patients without underlying organic pathology (fibroid or carcinoma).
5. Luteal-phase support to treat infertility
6. To decrease estrogen-induced endometrial hyperplasia
7. Premature labour
8. Anovulatory dysfunctional uterine bleeding (DUB)
9. Diagnostic use:
 - a. To test for estrogen secretion.
 - b. To test responsiveness of the endometrium.

Adverse effect of progesterone:

1. Irregular per vaginal bleeding.
2. Headache
3. Mood change
4. Weight gain
5. Other less frequently occurring:
 - ↓HDL
 - ↑LDL
 - ↓Bone density

(Ref: Goodman & Gilman's-12th)

Antiprogesterone

Antiprogesterone drugs:

1. Mifepristone
2. Lilopristone
3. Danazol

Mifepristone

Mifepristone is a progesterone antagonist with partial agonist activity. Mifepristone also has potent antigluccorticoid activity.

Route of administration: Oral

Mechanism of action:

- **Antiprogesterone action:** When administered in the early stages of pregnancy, mifepristone causes decidual breakdown by blockade of uterine progesterone receptors. This leads to detachment of the blastocyst, which decreases hCG production. Mifepristone also causes cervical softening, which facilitates expulsion of the detached blastocyst.
- Mifepristone also binds to glucocorticoid and androgen receptors and exerts anti-glucocorticoid and anti-androgenic actions.

(Ref: Goodman & Gilman-12th edition)

Indications:

1. **Termination of early pregnancy:** Administration of this drug to females early in pregnancy results, in most cases (up to 94 %), in abortion of the fetus due to the interference with progesterone and the decline in hCG.
2. Mifepristone is being investigated as an oral contraceptive and an emergency contraceptive agent.
3. Limited clinical studies suggest that mifepristone may be useful in the treatment of endometriosis, Cushing's syndrome, breast cancer, and possibly other neoplasms such as meningiomas that contain glucocorticoid or progesterone receptors.

(Ref: Katzung-13th; Lippincott's-6th)

Adverse effects:

1. Vaginal bleeding in females
2. Abdominal pain or pelvic pain
3. Vomiting
4. Diarrhea
5. Headache.

(Ref: Katzung-13th; Lippincott's-6th)

Danazol

Danazol, an isoxazole derivative of ethisterone with weak progestational, androgenic, and glucocorticoid activities, is used to suppress ovarian function. Danazol inhibits the midcycle surge of LH and FSH.

Indications: Danazol has been employed as an inhibitor of gonadal function and has found its major use in the treatment of

1. Endometriosis
2. Fibrocystic disease of the breast
3. Hematologic or allergic disorders, including hemophilia, Christmas disease, idiopathic thrombocytopenic purpura, and angioneurotic edema.

Adverse effects

1. Weight gain
2. Edema
3. Decreased breast size
4. Acne
5. Oily skin
6. Increased hair growth
7. Deepening of the voice
8. Headache
9. Hot flushes
10. Changes in libido, and
11. Muscle cramps.

Contraindications

1. Hepatic dysfunction
2. Pregnancy
3. Breast-feeding.

(Ref: Katzung-13th)

Hormonal contraceptives

Contraceptives: Drugs or devices which are used to prevent unwanted conception are called contraceptives.

Characteristics of ideal contraceptives: The following represent the ideal.

1. It must be extremely safe as well as highly effective
2. Its action must be quick in onset and quickly and completely reversible, even after years of continuous use
3. It must not affect libido.

(Ref: Bennett & Brown-11th)

Q. Mention various methods to prevent conception. (DU-05S)

Ans.

Different methods of contraception in clinical practice:

A. Spacing or temporary methods:

Methods		Examples
1. Barrier methods	Physical	• Condom • Vaginal diaphragm • Vaginal sponge • Cervical cap
	Chemical	• Foams • Creams, Jelly, Pastes • Suppositories • Soluble films
2. Intra-uterine devices (IUDs)	Non-medicated	• Lippes loop
	Medicated	• Copper T
3. Hormonal methods	Oral pills	• Combined pill- (Estrogen & progesterone) • Mini pill (Progesterone only pill, POP) • Sequential pill • Post-coital pill • Once-a-month pill • Male pill
	Depot (Slow release) formulations	• Injectables • Subcutaneous implants (eg, Norplant) • Vaginal rings
4. Post-conceptual methods		• Menstrual regulation (MR) • Menstrual induction (MI)
5. Miscellaneous	Behavioral methods	• Sexual abstinence • Coitus interruptus • Safe period (Rhythm method) • Birth control vaccine
	Natural methods	• Basal body temperature method • Cervical mucus method • Sympto-thermic method • Breast feeding

B. Terminal or permanent methods (Sterilization):

1. **Male sterilization:** Vasectomy

2. **Female sterilization:** Tubal ligation or tubectomy.

(Ref: Park's-Community medicine-20th)

Q. Enumerate the types of hormonal contraceptives with composition. (RU-16J)

Q. Name the hormonal contraceptive regimens. (CU-11Ju,05M; SU-14J,13J,09J,07J)

Q. Classify oral contraceptive pills. (DU-04S, CU-13Ju, RU-11J)

Q. Name the combined OCPs. (RU-12J, CU-10Ju)

Q. What are the compositions of OCPs? (CU-05J; RU-05S)

Q. Enumerate progesterone contraceptive preparations. (CU-05J)

Ans.

Hormonal contraceptive regimens/ oral pills/ OCPs:

Types of OCPs	Compositions
1. Combined OCP	Estrogen: Ethinyl estradiol (mostly used), mestranol Progesterone: Levonorgestrel, Norethindrone
2. Minipills / Progestin only pills (POP)	Norgestrel
3. Post coital or emergency pill	Ethinyl estradiol: 2.5 mg twice daily for 5 days Combined pill: 2 tabs as early as possible within 72 hours & then 2 tabs 12 hours after the first dose.
4. Sequential pills	1 st 2 weeks → Ethinyl estradiol Next 1 week → Norethindrone
5. Male pills	Gossypol

The combination agents are further divided into-

- **Monophasic** forms (constant dosage of both components during the cycle).
- **Biphasic** or **triphasic** forms (dosage of one or both components is changed once or twice during the cycle).

(Ref: Katzung-13th)

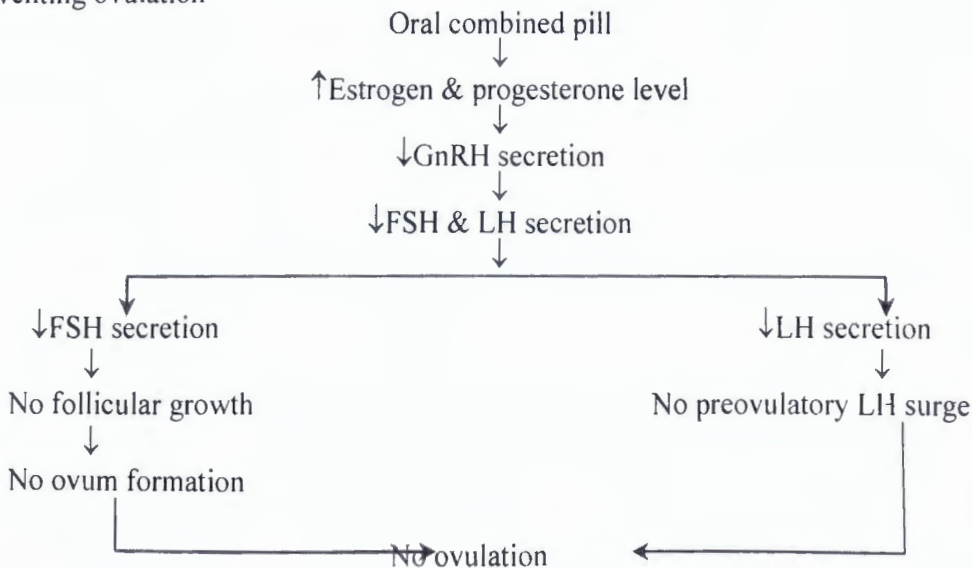
Q. Mention the mechanism of action of OCPs. (DU-17M,16J, SU-05M, RU-12J,11J, CU-11J)

Q. How does combined preparation produce contraception? (RU-16J)

Ans.

Mechanism of action of oral contraceptive pill:

1. By preventing ovulation-



2. Progesterone makes the endometrium unfavorable for implantation.
3. Progesterone makes cervical mucus thick & unfavorable to sperm migration.

4. Both estrogen & progesterone cause abnormal motility of fallopian tube and uterus. So the sperm is expelled out.

Q. What are the mechanisms of action of progesterone only contraceptives / mini pill?

Ans.

Mechanisms of action of progesterone only contraceptives / mini pill:

1. Progesterone makes the endometrium unfavorable for implantation.
2. Progesterone makes cervical mucus thick & unfavorable to sperm migration.

Q. What are the indications of OCPs? (DU-17J, CU-11J, SU-15J)

Q. What are the non-contraceptive uses of OCPs? (CU-13Ju)

Ans.

Indications of OCPs:

1. Contraception.
2. **Non-contraceptive uses**
 - a. Endometriosis
 - b. Irregular menstruation
 - c. In "holy Hajj festival" to prevent menstruation.
 - d. Abnormal menstrual bleeding
 - e. Dysfunctional uterine bleeding (DUB)
 - f. Functional ovarian cyst

Estrogen - milk suppress

CV risk, Cancer risk

Q. What are the indications of mini pill? (CU-05J; RU-04M/S)

Ans.

Indications of progesterone only pill (POP) / mini Pill / micro Pill:

1. Contraception in lactating mother.
2. Women for whom combined OCPs are contraindicated because of cardiovascular risks.
3. Young women with risk factors for neoplasia.

Q. Which oral pill could be prescribed to a lactating mother and why? Mention its mechanism of action and adverse effects. (RU-14J)

Ans.

Progesterone only pill (POP) / mini Pill could be prescribed to a lactating mother, because it does not suppress lactation.

Q. Compare estrogen-progesterone combined pill & progesterone only pill as contraceptives. (CU-17M, 09Ju)

Q. How do combined oral contraceptives differ from mini pill? (SU-12Ju)

Ans.

Comparison of estrogen-progesterone combined pill & progesterone only pill as contraceptives:

Traits	Combined pill	Progesterone only pill
1. Composition	Progesterone + Estrogen.	Only progesterone.
2. Effect on follicular development	Has negative effect.	No effect.
3. Efficacy	100% effective	Not 100% effective
4. Reliability	More	Less
5. Causes thromboembolism	Yes	No
6. Effect on lactation	Estrogen suppresses lactation	It does not suppress lactation. So lactating mother should prefer it.
7. Use in lactating mother	Not used.	Used.

Q. What is rationale of using combination of estrogen & progesterone? (SU-14Ju)

Q. Mention rationale of combination of Ethinyl estradiol and norgestrol as contraceptive. (SU-17M)

Ans.

Rationale of using combination of estrogen & progesterone-

1. Combined OCP is 100% effective.
2. It is more reliable.
3. It has negative effect on follicular development.

Q. What are the adverse effects of OCP? (DU-17J, CU-13J, 11Ju/J, 10Ju, RU-05S, SU-07J, 06S)

Q. Mention 4 adverse effects of OCP in prolong use. (DU-16J)

Ans.

Adverse effects of OCPs: The incidence of serious known toxicities associated with the use of these drugs is low—far lower than the risks associated with pregnancy. Minor adverse effects are frequent, but most are mild and many are transient.

A. Mild adverse effects: *vertigo*

1. Nausea; mastalgia (breast pain); breakthrough bleeding & edema.
2. Changes in the serum protein & other effects on endocrine function.
3. Mild & transient headache
4. Withdrawal bleeding

B. Moderate adverse effects: Any of the following may require discontinuance of oral contraceptives: *mid cycle bleeding*

1. Breakthrough bleeding (*most common problem in using progestational agents alone for contraception.*)
2. Weight gain (*controlled by shifting to preparations with less progestin effect or by dieting.*)
3. Increased skin pigmentation.
4. Acne (*exacerbated by agents containing androgen-like progestins, whereas agents containing large amounts of estrogen usually cause marked improvement in acne.*)
5. Hirsutism
6. Ureteral dilation and bacteriuria.
7. Vaginal infections
8. Amenorrhea occurs in some patients.

Severe adverse effects:

1. Vascular Disorders

- Venous thromboembolic disease
- Myocardial infarction
- Cerebrovascular diseases: >35 yrs of age

2. Gastrointestinal Disorders

- cholestatic jaundice
- cholecystitis
- cholangitis

3. Depression

4. Other

- Alopecia
- erythema multiforme
- erythema nodosum
- Other skin disorders.

(Ref: Katzung-13th edition)

Q. What are the contraindications of oral pills/combined OCP? (CU-17M, 07J, SU-05M)

Ans.

Contraindications of oral pills *TTLM*

A. Absolute contraindications include:

1. History of thromboembolic venous, arterial or cardiac disease.
2. Transient cerebral ischemic attacks without headache
3. Liver diseases: Infective hepatitis, cholestatic jaundice, Dubin-Johnson and Rotor syndromes

4. Migraine.
5. Carcinoma of the breast or of the genital tract, past or present
6. Other conditions including: SLE, porphyria, following evacuation of a hydatidiform mole (until urine and plasma gonadotrophin concentrations are normal),
7. Undiagnosed vaginal bleeding.

B. Relative contraindications or uses with caution, include:

1. Family history of venous thromboembolism, arterial disease or a known prothrombotic condition, e.g. factor Leiden.
2. Diabetes mellitus.
3. Hypertension (avoid if blood pressure exceeds 160/100)
4. Smoking > 40 cigarettes per day.
5. Age over 35 years (avoid if > 50 years)
6. Obesity (avoid if body mass index exceeds 39 kg/m²)
7. Long-term immobility, e.g. due to leg plaster, confinement to bed
8. Breast feeding (until weaning or for 6 months after birth).

(Ref: Bennett & Brown-11th)

Q. What factors will you consider before prescribing OCP? (SU-14J,09J)

Q. How do you select a client for combined OCP? (CU-04M)

Q. What are the precautions to be taken to advice oral contraceptives? (DU-04M)

Q. Describe the principles of prescribing OCP to a newly married woman. (CU-15Ju)

Ans.

Selection of an ideal client for combined OCP: To select a patient for prescribing OCP, thorough history, physical examination, and some investigations are needed to exclude contraindications.

1. **Age** of the patient is important. If she is more than 35 yrs of age, she should be prescribed with caution & regular checkup is needed.
2. **Personal history:** In smokers, it is to be prescribed with caution as it is associated with increased incidence of thromboembolism.
3. **Menstrual history** is to be taken to exclude pregnancy, undiagnosed uterine diseases etc.
4. **Family history** of cerebro-vascular diseases including hypertension, breast cancer and hyperlipidemia should be excluded.
5. **Medical history** regarding thromboembolic episodes, jaundice, epilepsy, DM, allergic condition, migraine should be excluded.
6. **Examination of breast** should be done for any nodule. Blood pressure and weight should be noted.
7. **Pelvic examination** to exclude fibroid or cervical pathology is mandatory.
8. **Investigation:** Vaginal cytology if facilities are available.

From the above mentioned examination to screen, if it reveals that the woman is free from any systemic diseases and contraindication, she is suitable candidate for OCP therapy.

Q. Why combined oral pills are not wise to use after 35 years of age? (DU-07J)

Ans.

Rationale of using combined OCPs after 35 years of age: Combined OCPs has some serious adverse effects such as venous thromboembolism, MI, cerebrovascular diseases, increased chance of breast carcinoma etc. Moreover the chance of development of hypertension, diabetes mellitus, obesity, heart failure (which are relative contraindication of OCP) is increased after 35 years age. So use of OCP should be limited or should use with caution & after appropriate advice of a doctor or educated health personals.

Q. Give 3 important causes of contraceptive therapy failure. (DU-07J)

Ans.

Causes of contraceptive failure:

1. Concomitant use of enzyme inducing drugs (e.g. Rifampicin, Phenytoin) → Increased concentration of OCP metabolizing enzymes → Increased Metabolism of OCP → Contraceptive failure.
2. Concomitant use of broad spectrum antibiotic → Decreased normal intestinal flora → Decreased enterohepatic circulation → ↓Bioavailability of OCP → Contraception failure.
3. Irregular using of the pills (e.g. missing of pill in one or two consecutive days)

Q. Write short note on: Injectable contraceptives. (CU-06J)

Ans.

Injectable contraceptives:

1. **Depot medroxyprogesterone acetate (DMPA):** IM 150 mg in every 3 months.
2. **Norethisterone enanthate (NET-EN):** IM 200 mg in every 2 months.

Depot medroxyprogesterone acetate (DMPA): It is a 3-month depot injection of *intramuscular progestogen*. It is equal in efficacy to the combined pill and is an alternative.

M/A: It works by inhibiting ovulation, and also renders cervical mucus impenetrable to sperm. After a 150 mg dose, ovulation is inhibited for at least 14 weeks.

Side effects:

1. Unpredictable spotting and bleeding, particularly during the first year of use. Spotting and bleeding decrease with time.
2. Amenorrhea
3. Not desirable for women planning a pregnancy soon after cessation of therapy because ovulation suppression can sometimes persist for as long as 18 months after the last injection.
4. Reversible reduction in bone density.
5. Changes in plasma lipids with increased risk of atherosclerosis.

Advantage:

1. Long-term DMPA use reduces menstrual blood loss.
2. Decreased risk of endometrial cancer.

(Ref: Katzung-13th)

Q. Short note: Postcoital Contraceptives.

Ans.

Postcoital Contraceptives: Pregnancy can be prevented following unprotected coitus by the administration of estrogens alone or in combination with progestins ("**morning after**" contraception). When treatment is begun within 72 hours, it is effective 99% of the time.

Postcoital Contraceptives
• Conjugated estrogens: 10 mg three times daily for 5 days • Ethinyl estradiol: 2.5 mg twice daily for 5 days • Diethylstilbestrol: 50 mg daily for 5 days • Mifepristone: 600 mg once with misoprostol, 400 mcg once • L-Norgestrel: 0.75 mg twice daily for 1 day • Combined pill: Norgestrel, 0.5 mg, with ethinyl estradiol, 0.05 mg (eg, Emcon): 2 tabs as early as possible within 72 hours & then 2 tabs 12 hours after the first dose.

Adverse effects

1. Nausea or vomiting (relieved by antiemetics)

2. Other include headache, dizziness, breast tenderness, and abdominal and leg cramps.

(Ref: Katzung-13th)

Q. Short note: Norplant. (DU-05/04J)

Ans.

Norplant:

It is an implant of levonorgesterol, a progesterone preparation. Norplant implant consists of 6 sialistic capsules, non-bio-degradable, 3.5 x 2.4 mm. Each contains 36 mg of levonorgesterol closed at both ends.

Site of insertion: Flexor surface of upper left arm sub-dermally.

Duration of action: Norplant is effective for 5–6 years. The implant must be removed when its effective period has elapsed.

Advantages:

1. Extremely effective.
2. Low levels of hormone have little effect on lipoprotein and carbohydrate metabolism or blood pressure.

Disadvantages

1. Surgical procedure for insertion and removal of capsules.
2. Some **irregular bleeding** rather than predictable menses.
3. **Intracranial hypertension** in some women.

(Ref: Katzung-13th)

Q. Mention the non-contraceptive health benefits of combined OCPs. (DU-17M, CU-10Ju)

Ans.

Contraceptive health benefits of combined OCPs: Contraception

Non-contraceptive health benefits of combined OCPs:

1. Decreased incidence of ovarian & endometrial carcinoma significantly:
 - They significantly reduce the incidence within 6 months of use
 - The incidence is decreased 50% after 2 years of use
 - The protective effects persists up to 15 years after OCP use is discontinued
2. Decrease incidence of ovarian cysts & benign fibrocystic breast disease
3. OCP has important beneficial effect on menstruation:
 - a. More regular menstruation
 - b. Decreased menstrual blood loss & Fe deficiency anemia
 - c. Decreased incidence of dysmenorrhea
4. Decreased incidence of PID (pelvic inflammatory disease)
5. Decreased incidence of ectopic pregnancies & endometriosis.

Combined OCP prevents thousands of deaths, episodes of various diseases & cases of hospitalization each year.

(Ref: Goodman & Gilman's-12th)

Androgens & Anabolic Steroids

Androgens: The androgens are a group of steroids that have anabolic and/or masculinizing effects in both males and females.

Testosterone is the most important androgen in humans.

- In men, approximately 8 mg of testosterone is produced daily.
- About 95% is produced by the Leydig cells and only 5% by the adrenals.
- Small amount of testosterone is also produced in female by the ovaries and adrenals and by the peripheral conversion of other hormones.

Anabolic steroid: Androgen receptor agonists used for anabolic effects (eg, weight gain, increased muscle mass) are called anabolic steroids.

Androgens	
Natural	• Testosterone • Dihydrotestosterone • Androstenedione • Dehydroepiandrosterone
Synthetic	• Testosterone cypionate • Testosterone enanthate • Methyltestosterone • Fluoxymesterone • Oxymetholone • Oxandrolone • Nandrolone decanoate

(Ref: Katzung-13th)

Physiologic Effects of Androgens

1. Development of secondary sexual characteristics in male at puberty.
2. Stimulation and maintenance of sexual function in men.
3. Increase lean body mass and stimulate body hair growth and sebum secretion.
4. Metabolic effects include the reduction of hormone binding and other carrier proteins and increased liver synthesis of clotting factors, triglyceride lipase, α_1 -antitrypsin, haptoglobin, and sialic acid. They also stimulate renal erythropoietin secretion and decrease HDL levels.

Clinical Uses of Androgens

1. **Androgen replacement therapy** in hypogonadal men.
2. **Gynecologic Disorders**
 - To reduce breast engorgement during the postpartum period, along with estrogens.
 - Endometriosis (Danazol)
 - Hormone replacement therapy in the postmenopausal period in an attempt to eliminate the endometrial bleeding and to enhance libido.
 - Used for chemotherapy of breast tumors in premenopausal women.
3. **Use as Protein Anabolic Agents:** Androgens and anabolic steroids are used in an attempt to reverse protein loss after trauma, surgery, or prolonged immobilization and in patients with debilitating diseases.
4. **Refractory anemias such as aplastic anemia.** (Now recombinant erythropoietin is used).
5. **Osteoporosis** (now bisphosphonates replaced androgen use for this purpose.)
6. **Use as Growth Stimulators:** These agents have been used to stimulate growth in boys with delayed puberty. If the drugs are used carefully, these children will probably achieve their expected adult height.
7. **Anabolic Steroid and Androgen Abuse in Sports:** Many athletes and their coaches believe that anabolic steroids—in doses 10–200 times larger than the daily normal production—increase strength and aggressiveness, thereby improving competitive performance. Such effects have been unequivocally demonstrated only in women. Furthermore, the adverse effects of these drugs clearly make their use inadvisable.
8. **Aging.**

(Ref: Katzung-13th)

Adverse Effects: The adverse effects are due largely to their masculinizing actions and are most noticeable in women and prepubertal children.

1. In women,

- a. Hirsutism
 - b. Acne
 - c. Amenorrhea
 - d. Clitoral enlargement
 - e. Deepening of the voice.
 - f. Endometrial bleeding upon discontinuation
 - g. Atherosclerotic disease in women.
2. In older males, prostatic hyperplasia, causing urinary retention.
 3. Replacement therapy in men may cause acne, sleep apnea, erythrocytosis, gynecomastia, and azoospermia.
 4. Hepatic dysfunction.
 5. Alkylated androgens in high doses can produce peliosis hepatica, cholestasis, and hepatic failure. They lower plasma HDL₂ and may increase LDL.
 6. Hepatic adenomas and carcinomas.
 7. Behavioral effects include psychologic dependence, increased aggressiveness, and psychotic symptoms.

(Ref: Katzung-13th)

Contraindications & Cautions

1. Pregnant women or women who may become pregnant during the course of therapy.
2. They should be avoided in infants and young children.
3. Carcinoma of the prostate or breast.
4. Patients with renal or cardiac disease predisposed to edema.

(Ref: Katzung-13th)

Q. Short note: Gynaecomastia.

Ans.

Gynaecomastia: Gynaecomastia is the presence of glandular breast tissue in males. Normal breast development in women is estrogen-dependent, while androgens oppose this effect. Gynaecomastia results from an imbalance between androgen and estrogen activity, which may reflect androgen deficiency or estrogen excess.

Causes of gynaecomastia

1. Idiopathic
2. Physiological
3. Drug-induced
 - a. Cimetidine
 - b. Digoxin
 - c. Anti-androgens (cyproterone acetate, spironolactone)
 - d. Some exogenous anabolic steroids (diethylstilbestrol)
4. Hypogonadism
5. Androgen resistance syndromes
6. Estrogen excess
 - a. Liver failure (impaired steroid metabolism)
 - b. Estrogen-secreting tumour (for example, of testis)
 - c. hCG-secreting tumour (for example, of testis or lung)

(Ref: Davidson's-21st/759)

Androgen Suppression & Antiandrogens

Antiandrogens: Antiandrogens counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors.

Steroid Synthesis Inhibitors	• Ketoconazole
Inhibitor of Conversion of Steroid Precursors to Androgens	• Abiraterone • Finasteride • Dutasteride
Androgenic Receptor Inhibitors	• Cyproterone • Cyproterone acetate • Flutamide • Bicalutamide • Nilutamide • Spironolactone

(Ref: Katzung-13th)

Indication:

1. Benign prostatic hypertrophy (Finasteride and dutasteride)
2. Prostatic carcinoma (Flutamide)
3. Metastatic carcinoma of the prostate (Bicalutamide and nilutamide)
4. Hirsutism in women (Cyproterone, spironolactone, finasteride, flutamide)
5. To decrease excessive sexual drive in men (Cyproterone)

(Ref: Katzung-13th)

Q. Enumerate the clinical use of Finasteride. (CU-16Ju)

Ans.

Clinical use of Finasteride

1. Benign prostatic hyperplasia
2. Hirsutism in women
3. Early male pattern baldness in men

(Ref: Katzung-13th)

Chemical Contraception in Men

Gossypol: Extensive trials of this cottonseed derivative have been conducted in China. This compound destroys elements of the seminiferous epithelium but does not significantly alter the endocrine function of the testis.

In Chinese studies, large numbers of men were treated with 20 mg/d of gossypol for 2 months, followed by a maintenance dosage of 60 mg/wk. On this regimen, 99% of men developed sperm counts below 4 million/mL. Hypokalemia is the major adverse effect and may lead to transient paralysis. Because of low efficacy and significant toxicity, gossypol has been abandoned as a candidate male contraceptive.

(Ref: Katzung-13th)

Thyroid hormones & anti-thyroid drugs

Thyroid hormones:

1. Tetraiodothyronine / Thyroxine (T_4) } Follicular cell
2. Triiodothyronine (T_3) }
3. Calcitonin → Parafollicular cell

Drugs used in treatment of Hypothyroidism

Q. Mention the thyroid preparations. (RU-14Ju)

Ans.

Thyroid preparations:

A. Synthetic: The synthetic preparations of the sodium salts of the natural isomers of the thyroid hormones are available and widely used for thyroid hormone therapy.

1. Levothyroxine
2. Liothyronine
3. Liotrix

B. Animal origin: Desiccated thyroid.

(Ref: Katzung-13th)

Levothyroxine (T_4)

Q. Explain the role of thyroxine in hypothyroidism. (DU-14Ju, 13Ju)

Q. Why synthetic Levothyroxine is the preparation of choice for thyroid replacement? (RU-14Ju)

Ans.

Synthetic levothyroxine is the preparation of choice for thyroid replacement and suppression therapy because of its stability, content uniformity, low cost, lack of allergenic foreign protein, easy laboratory measurement of serum levels, and long half-life (7 days), which permits once-daily administration. In addition, T_4 is converted to T_3 intracellularly; thus, administration of T_4 produces both hormones. Generic levothyroxine preparations provide comparable efficacy and are more cost-effective than branded preparations.

(Ref: Katzung-13th)

Liothyronine (T_3)

Q. Liothyronine is not recommended for routine replacement therapy- Explain.

Ans.

Liothyronine is not recommended for routine replacement therapy: Although liothyronine (T_3) is three to four times more potent than levothyroxine, it is not recommended for routine replacement therapy because of its-

1. Shorter half-life (24 hours), which requires multiple daily doses.
2. Higher cost.
3. Greater difficulty of monitoring its adequacy of replacement by conventional laboratory tests.
4. Greater risk of cardiotoxicity.

(Ref: Katzung-13th)

Nice to know

Desiccated thyroid: The use of desiccated thyroid rather than synthetic preparations is never justified, since the disadvantages of protein antigenicity, product instability, variable hormone concentrations, and difficulty in laboratory monitoring far outweigh the advantage of lower cost.

(Ref: Katzung-13th)

Drugs used in treatment of hyperthyroidism (thyrotoxicosis)

Antithyroid drugs: A large number of compounds are capable of interfering, directly or indirectly, with the synthesis, release, or action of thyroid hormones.

(Ref: Goodman & Gilman-12th edition)

Q. Enlist antithyroid drugs. (DU-13Ju; SU-13Ju)

Ans.

Antithyroid drugs:

1. Thioamides: They inhibit the thyroid peroxidase-catalyzed reactions and block iodine organification. In addition, they block coupling of the iodotyrosines.	- Carbimazole - Methimazole - Propylthiouracil - <i>Phenytoin</i>
2. Anion inhibitors: All are monovalent anions & can block uptake of iodide by the gland through competitive inhibition of the iodide transport mechanism.	- Perchlorate (ClO_4^-) - Pertechnetate (TcO_4^-) - Thiocyanate (SCN^-)
3. Hormone release inhibitor	- Lithium salts - Iodide
4. Iodotyrosine deiodination inhibitor	Nitrotyrosines
5. Peripheral iodothyronine deiodination inhibitor (PID ^o)	- Thiouracil derivatives - Oral cholecystographic agents - Amiodarone
6. Radioactive iodine (^{131}I): It is selectively taken up by the thyroid gland → emits β particles → damage thyroid cells → Decreases thyroid hormone synthesis.	^{131}I

(Ref: Katzung-13th; Goodman & Gilman-12th edition)

Adjuvant therapy with drugs that have no specific effects on thyroid gland hormonogenesis is useful in controlling the peripheral manifestations of thyrotoxicosis. These drugs include-

1. inhibitors of the peripheral deiodination of thyroxine to the active hormone, triiodothyronine;
2. β -blockers: Propranolol, Metoprolol, Atenolol.
3. Ca^{2+} channel blockers.

(Ref: Goodman & Gilman-12th edition)

Common Adv Effect

*Aplastic anemia
Thrombocytopenia
Neutropenia*

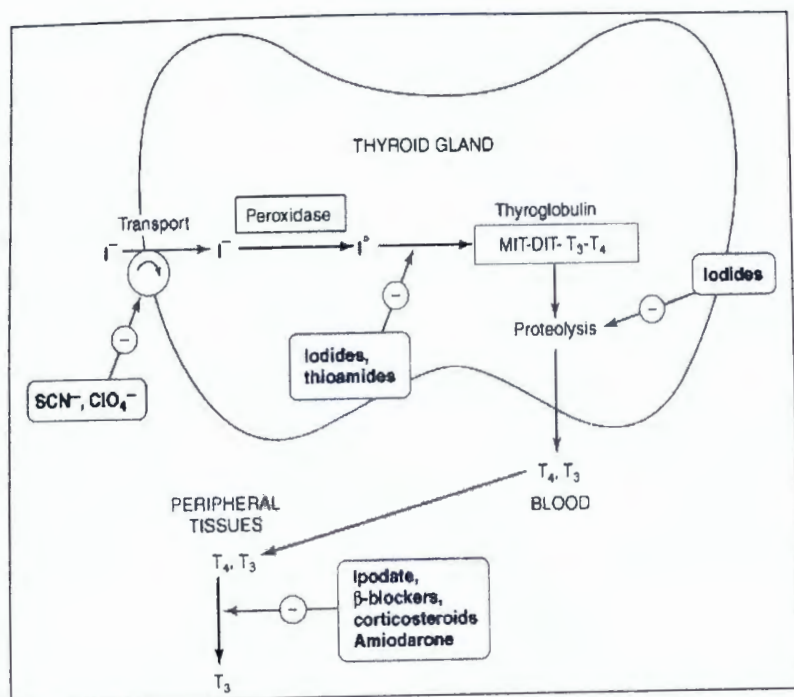


Fig: Biosynthesis of thyroid hormones. The sites of action of various drugs that interfere with thyroid hormone biosynthesis are shown

(Ref: Katzung-13th)

Thioamides

The thioamides **methimazole** and **propylthiouracil** are major drugs for treatment of thyrotoxicosis. Methimazole is about ten times more potent than propylthiouracil.

Mechanism of action: The thioamides act by multiple mechanisms.

1. Prevent hormone synthesis by inhibiting the thyroid peroxidase-catalyzed reactions and blocking iodine organification.
2. Block coupling of the iodotyrosines. They do not block uptake of iodide by the gland.
3. Inhibit the peripheral deiodination of T₄ and T₃.

Since the synthesis rather than the release of hormones is affected, the onset of these agents is slow, often requiring 3–4 weeks before stores of T₄ are depleted.

(Ref: Katzung-13th)

Indications:

1. Hyperthyroidism (thyrotoxicosis)

Macule → Small, flat discolored spot

Papule → Small, raised bump, red

Pruritic → Unpleasant sensation

that provokes urge to scratch

Toxicity: Adverse reactions to the thioamides occur in 3–12% of treated patients.

1. Nausea and GI distress.
2. An altered sense of taste or smell (methimazole)
3. Most common adverse effect: Maculopapular pruritic rash (4–6%).
4. Rare adverse effects include an urticarial rash, vasculitis, a lupus-like reaction, lymphadenopathy, hypoprothrombinemia, exfoliative dermatitis, polyserositis, and acute arthralgia.
5. Hepatitis (more common with propylthiouracil) and cholestatic jaundice (more common with methimazole) can be fatal.
6. Most dangerous complication: Agranulocytosis (granulocyte count < 500 cells/mm³). The reaction is usually rapidly reversible when the drug is discontinued.

(Ref: Katzung-13th)

IODIDES

Prior to the introduction of the thioamides in the 1940s, iodides were the major antithyroid agents; today they are rarely used as sole therapy.

Mechanism of action: They inhibit organification and hormone release and decrease the size and vascularity of the hyperplastic gland.

Clinical Use of Iodide

1. Preparation for surgical thyroidectomy in hyperthyroid patient
2. Thyrotoxic crisis (in conjunction with antithyroid drugs and propranolol)
3. to protect the thyroid from radioactive iodine fallout following a nuclear accident.
4. Strong iodine solution (Lugol's solution) is widely used and consists of 5% iodine and 10% potassium iodide, which yields a dose of 6.3 mg of iodine per drop.

(Ref: Goodman & Gilman-12th edition)

Toxicity: Adverse reactions to iodine (iodism) are uncommon and in most cases reversible upon discontinuance. They include-

1. Acneiform rash
2. Swollen salivary glands
3. Mucous membrane ulcerations
4. Conjunctivitis
5. Rhinorrhoea
6. Drug fever
7. Metallic taste
8. Bleeding disorders

9. Rarely, anaphylactoid reactions.

(Ref: Katzung-13th)

Adrenoceptor-Blocking Agents

Q. Explain the role of propranolol in hyperthyroidism. (SU-12Ju)

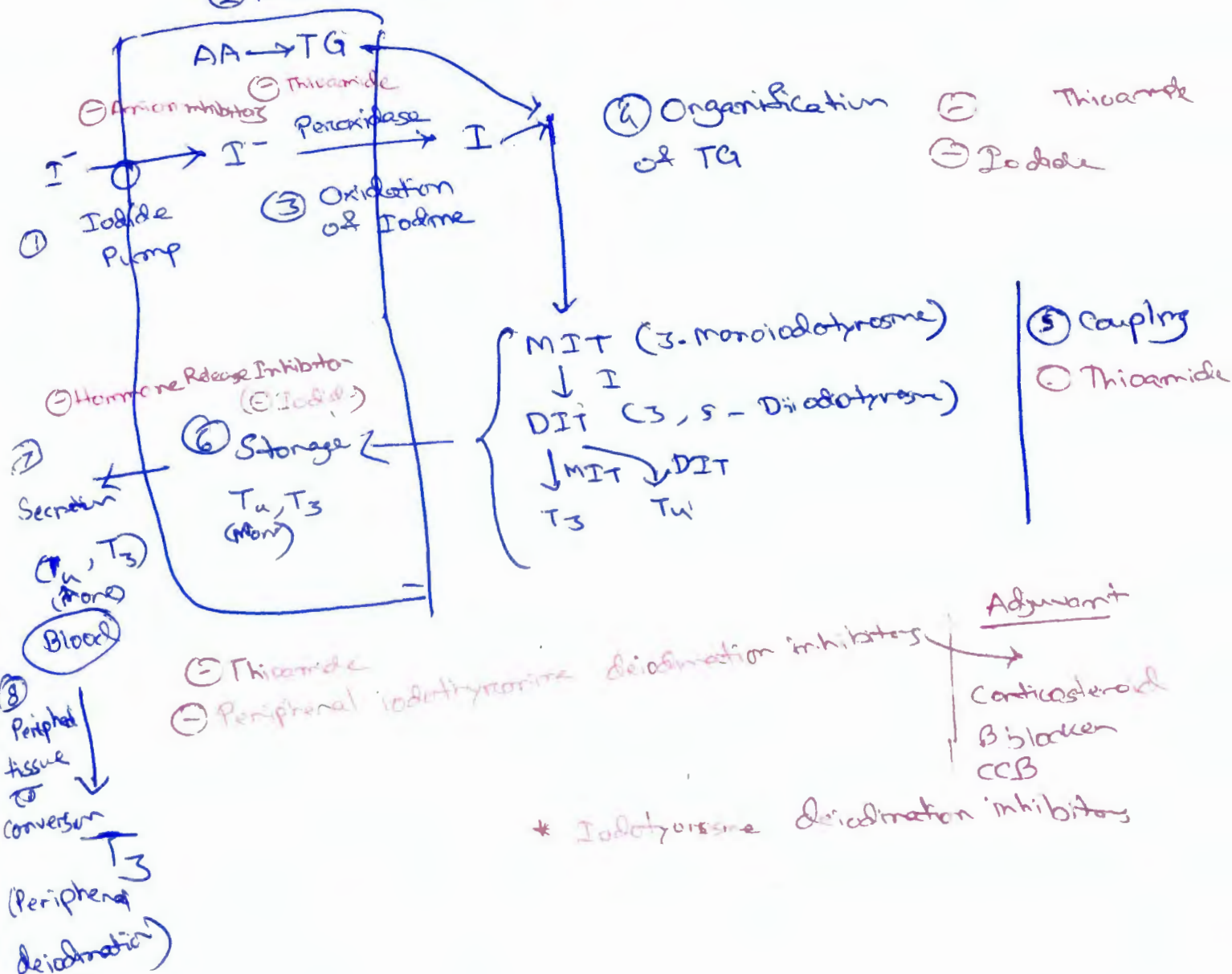
Ans.

Role of β -blocker (eg, propranolol) in hyperthyroidism: Beta blockers without intrinsic sympathomimetic activity (eg, metoprolol, propranolol, atenolol) are effective therapeutic adjuncts in the management of thyrotoxicosis since many of these symptoms mimic those associated with sympathetic stimulation. **Propranolol** has been the β -blocker most widely studied and used in the therapy of thyrotoxicosis. Beta blockers cause clinical improvement of hyperthyroid symptoms but do not typically alter thyroid hormone levels. Propranolol at doses greater than 160 mg/d may also reduce T_3 levels approximately 20% by inhibiting the peripheral conversion of T_4 to T_3 .

40 mg/dose

① Thyroid Cell ^{Radioactive iodine, ^{131}I (iodine)} Lumen (Ref: Katzung-13th)

② Formation & secretion of Thyroglobulin



MCQ

Q. Long acting glucocorticoids are- (DU-17M)

- a) prednisolone
- b) fludrocortisone
- c) betamethasone
- d) dexamethasone
- e) triamcinolone

a. F, b. F, c. T, d. T, e. F

Q. Euglycaemic antidiabetic drugs are- (DU-17J)

- a. tolbutamide
- b. glipizide
- c. metformin
- d. pioglitazone
- e. insulin

a. F, b. F, c. T, d. T, e. F

Q. Ovulation is induced by- (DU-15Ju)

- a. clomifene
- b. mifepristone
- c. tamoxifen
- d. cylofenil
- e. gestrinone

a. T, b. F, c. F, d. F, e. F

Q. Insulin- (DU-15Ju)

- a. is a polypeptide
- b. may cause antibody production
- c. causes reduction of protein synthesis
- d. decreases glucose transport into the cell
- e. is preferred in gestational diabetes mellitus

a. T, b. F, c. F, d. F, e. T

Q. Euglycaemic anti-diabetic drugs include- (DU-14Ju)

- a. chlorpropamide
- b. glyburide
- c. metformin
- d. rosiglitazone
- e. insulin

a. F, b. F, c. T, d. T, e. F

Q. Oral contraceptive preparations: (CU-14Ju)

- a) Containing estrogen and progesterone are the most effective
- b) Containing progesterone only may be advantageous after child birth.
- c) May lead to iron-deficiency anemia.
- d) May lead to hypertension

e) May be used to treat excessive menstrual bleeding.

a. T, b. T, c. F, d. T, e. T

Q. Following classes of antidiabetic agents have the ability to reduce Insulin resistance: (CU-14Ju)

- a) Alpha-Glucosidase inhibitors
- b) Dipeptidyl peptidase- 4 inhibitors.
- c) Meglitinides
- d) Biguanides
- e) Thiazolidinediones

a. F, b. F, c. F, d. F, e. T

Q. Absolute indications of insulin are- (DU-13Ju)

- a. type I diabetes mellitus.
- b. gestational diabetes mellitus.
- c. first line therapy in type II diabetic mellitus.
- d. diabetic ketoacidosis.
- e. hypoglycemic shock.

a. T, b. T, c. F, d. T, e. F

Q. Drug used in hypothyroidism are- (DU-13Ju)

- a. levothyroxine.
- b. propylthiouracil.
- c. propranolol.
- d. liothyronine.
- e. radioactive iodine.

a. T, b. F, c. F, d. T, e. F

Q. Insulin enhances- (DU-13J)

- a. glycogenolysis.
- b. glycogenesis.
- c. glycolysis.
- d. gluconeogenesis.
- e. potassium transit into the cell.

a. F, b. T, c. T, d. F, e. T

Q. Anti-diabetic action of drug involve: (SU-13J)

- a. Glipizide release insulin
- b. Pioglitazone increases insulin sensitivity
- c. Metformin promotes glycogenesis
- d. Insulin increases glucose uptake
- e. Repaglinide inhibits glucose transporters

a. T, b. T, c. F, d. T, e. F

Q. Following drugs can cause gynaecomastia- (SU-13J)

- a. Cimetidine
- b. Chlorpromazine

- c. Digoxin
 - d. Ranitidine
 - e. Fluoxetine
- a. T, b. F, c. T, d. F, e. F*

Q. Hyperthyroidism can be treated by- (DU-12Ju)

- a. Tri-iodothyronine (F)
- b. Iodide (T)
- c. Methimazole (T)
- d. Propylthiouracil (T)
- e. Levothyroxine (F)

Q. Short acting insulin preparations are- (DU-12Ju)

- a. Insulin glargine (F)
- b. Soluble insulin (T)
- c. Insulin lispro (F)
- d. Insulin aspart (F)
- e. NPH insulin (F)

Q. Metformin- (DU-12Ju)

- a. Causes hypoglycemia.
 - b. Increases peripheral glucose uptake and utilization in target tissues.
 - c. Causes weight loss.
 - d. Is contraindicated in renal failure.
 - e. Increases the sensitivity of insulin receptor.
- a. F, b. T, c. T, d. T, e. F*

Q. Long acting glucocorticoids are- (DU-12Ju)

- a. Prednisolone (F)
- b. Betamethasone (T)
- c. Fludrocortisone (F)
- d. Dexamethasone (T)
- e. Triamcinolone (F)

Q. Side effects of metformin are- (DU-12J)

- a. Weight gain. (F)
- b. Gastrointestinal upset. (T)
- c. Lactic acidosis. (F)
- d. Hypoglycemia (F)
- e. Impaired kidney function. (?)

Q. Insulin- (DU-11Ju)

- a. Decreases the conversion of amino acid to glucose. (T)
- b. Increases gluconeogenesis (F)
- c. Increases glucose transport into cells (T)
- d. Induces lipoprotein lipase. (T)
- e. Stimulates glycogenesis. (T)

Q. Glucocorticoids are used for the treatment of- (DU-11Ju)

- a. Chronic dermatitis (T)
- b. Asthma (T)
- c. Osteoporosis (F)
- d. Nephrotic syndrome (T)
- e. Glaucoma (F)

Q. Adverse effects of combined oral contraceptives include- (DU-11Ju)

- a. Breakthrough bleeding (T)
- b. Increased risk of endometrial cancer (F)
- c. Increased risk of ovarian cancer (F)
- d. Nausea (T)
- e. Reduced risk of ischemic stroke (F)

Q. Long-acting glucocorticoids- (DU-11J)

- a. Prednisolone (F)
- b. Fludrocortisone (F)
- c. Betamethasone (T)
- d. Dexamethasone (T)
- e. Triamcinolone (T)

Q. Metformin- (DU-11J)

- a. enhances peripheral utilization of glucose (T)
- b. causes hypoglycemia (F)
- c. increases insulin release from beta cells (F)
- d. is contraindicated in renal failure (T)
- e. causes weight loss (T)

Q. Glucocorticoids- (DU-10J)

- a. inhibit production of lipoprotein (F)
- b. inhibit phospholipase A₂ (T)
- c. have got permissive effect (T)
- d. increase circulatory no. of neutrophils (T)
- e. increase circulatory no. of T cells (F)

Q. Beclomethasone- (DU-10Ju)

- a. is an anti-inflammatory drug (T)
- b. is a natural glucocorticoid (F)
- c. is given by inhalation (T)
- d. is a bronchodilator (F)
- e. inhibits phospholipase A₂ enzyme (T)

Q. Regarding aldosterone- (DU-10Ju)

- a. It is a glucocorticoid (F)
- b. It is released from zona glomerulosa (T)
- c. It can cause hyperkalaemia (F)
- d. Its action can be antagonized by triamterene (?)
- e. Its release can be inhibited by losartan (T)

Q. Glibenclamide- (DU-10Ju)

- a. is an insulin secretagogue (T)
- b. blocks ATP dependent K^+ channel in beta-cells (T)
- c. inhibits glucose absorption from GIT (F)
- d. is clinically useful in treating obese DM (F)
- e. does not cause hypoglycemia (F)

Q. Metformin- (DU-10J)

- a. is a biguanide preparation (T)
- b. enhances peripheral utilization of glucose (T)
- c. causes hypoglycemia (F)
- d. increases insulin release from beta cells (F)
- e. increase insulin sensitivity (F)

Thyroid Status: Extreme symptom of hyperthyroidism

Normal Lab

- TSH $\rightarrow$ 0.15 - 3.5 mU/L
- FT₄ $\rightarrow$ 10-27 pmol/L
- FT₃ $\rightarrow$ 3 ng/L
- TT₄ $\rightarrow$ 60-150 nmol/L
- TT₃ $\rightarrow$ 1-2.6 nmol/L

Effect of T₃ & T₄

CHO metabolism $\rightarrow$ $\uparrow$ Glucose absorption from GIT
 $\uparrow$ " uptake in all
 $\uparrow$ Insulin secretion
 $\uparrow$ Gluconeogenesis
 $\uparrow$ Glycolysis

Fat " $\rightarrow$ $\uparrow$ Fatty acid mobilization from adipose tissue
 $\uparrow$ Plasma FFA
 $\downarrow$ Plasma cholest. est., TAG, PL

Protein " $\rightarrow$ $\uparrow$ Protein synthesis

$\uparrow$ BMR

$\downarrow$ Body wt

$\uparrow$ O₂ consumption

CVS $\rightarrow$ $\uparrow$ HR, $\uparrow$ Force, $\uparrow$ CO, $\uparrow$ Blood Flow

CNS $\rightarrow$ $\uparrow$ Brain development

Res $\rightarrow$ $\uparrow$ RR

Endocrine $\rightarrow$ $\uparrow$ Secretion
 Normal sexual func

GIT $\rightarrow$ $\uparrow$ Appetite
 $\uparrow$ Food intake
 $\uparrow$ motility
 $\uparrow$ Digestion
 $\uparrow$ excretion

Muscle $\rightarrow$ $\uparrow$ Protein breakdown

$\uparrow$ Growth

Sleep $\rightarrow$ Hypo $\downarrow$
 Hypo $\uparrow$

Chapter 14

Special topics

Hyperthyroidism → wt loss, Tachycardia (>100 bpm),
Palpitation, tremor, sweating, menstrual pattern change,
↑ sensitivity to heat, ↑ bowel movement, Nervousness,
Anxiety, irritability, fatigue, muscle weakness

Hypothyroidism → Fatigue, Feeling cold, Poor memory,
constipation, bradycardia, dyspepsia, hoarse voice,
poor healing, heavy menstrual period,

Dry, coarse skin, cold extremities, myxoedema, hair loss,
slow pulse, Carpal tunnel syndrome, pleural effusion,
ascites, pericardial effusion

Low iodine diet → hyperthyroidism & → myxoedema

Rational use of drugs

- Q. What do you mean by rational use of drugs (RUD)? (DU-16Ju,11/10J,09J, RU-15Ju,13/09J, SU-09/07Ju)
 Q. Define rational use of medicine (RUM). What are the criteria to fulfill the rational use of medicine? What are the objectives and uses of it? (DU-14Ju, RU-07/06J, SU-08Ju,CU-06M)
 Q. What are the selection criteria of rational use of drugs? (RU-07J,04J,06S, SU-08Ju)
 Q. What factors should be considered to ensure rational use of drugs? (RU-13J)
 Q. Outline the principles that govern rational use of drugs. (CU-09J, SU-14Ju)
 Q. Short note: Rational use of drugs. (RU-16Ju)
 Q. Short note: RUD. (SU-13Ju,12J)

Ans.

Rational use of medicine (RUM) / Rational use of drug (RUD): Appropriate drug in appropriate indication with proper dosage regimen is called rational use of medicine.

According to WHO, rational use of medicines requires that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community".

Selection criteria of RUM / RUD:

1. Safety profile.
2. Efficacy
3. Suitability/individualization
4. Affordability
5. Need
6. Cost

(Rule of right: Right drug, given to the right patient, at the right time, at right doses at a right interval for a right duration of time.)

Objectives of RUM / RUD:

1. To identify the magnitude and nature of inappropriate medicine utilization.
2. To describe factors which influence the decision making processes.
3. To identify the factors which influence the behaviour of the prescribers.
4. To relate issues to specific medicine use problem.
5. To assess which prescribers and patients factors might be addressed in a program to reduce irrational use of medicine.

(Ref- Misbahuddin-5th/17)

Uses of RUM /RUD:

1. Prescription
2. Purchase / availability
3. Intake

(Note: **Rational use of drug** has been replaced by **rational use of medicine** based on the fact that the prescriber when prescribes a medicine must know the adverse effects of the active components of the medicine as well as the adverse effects of the excipient.)

Q. Outline the principles that govern rational use of drugs. (CU-09J)

Q. Outlines the guidelines for rational use of drugs (RUD). (SU-07J)

Ans.

Guidelines for RUD / Educational intervention:

To fix the target of the drug:

1. Target may be the cure of the disease / infection
2. Target may be the control of the disease (controlling HTN, DM)
3. Prevention of disease (prophylactic drugs for TB, malaria)
4. Diagnosis of the disease

B. To select out the therapy:

a. **No drug therapy:** For example, diastolic blood pressure 90 or 95 mm of Hg. Therapy should be without drug, only restricting this or that.

b. **Drug therapy:**

1. Selection of the drug: Based on **Risk: Benefit ratio** by

➤ Knowing pharmacological profile of the drug for assessment of benefit & risk:

- Seriousness of the problem to be treated
- Efficacy of the drug to be used
- Seriousness and frequency of possible adverse reactions of the drug to be used
- Safety and efficacy of other drugs that might be used instead

➤ Knowing patient profile for assessing benefit by drug's suitability/individualization of dosage regimen:

- Age
- Renal function
- Hepatic function
- Immune status (hypersensitivity)
- Pregnancy
- concomitant drugs
- Severity of the disease

➤ Knowing cost profile for assessing benefit and cost:

- Assessing seriousness of the problem
- Assessing cost of medication
- Assessing cost of administration
- Assessing cost of monitoring
- Assessing cost of pretreatment in case of treatment failure.

2. Selection of proper dosage regimen:

- Dose
- Formulation
- Route of administration
- Dosage interval
- Duration of treatment

3. Monitoring drug therapy: Monitoring of

- Beneficial & harmful effect by clinical markers and surrogate markers
- Patients compliance by—
 - Treatment cost
 - Patient understands about the R_x of the disease.
 - Frequency of drug administration
 - Adverse drug reactions (ADRs)
 - Taste of the drug → applicable for infants and children.

4. Programming patient education:

- Benefit and risk
- Dosage regimen
- Prognosis.

Q. Define compliance. (DU-12Ju, 11J, 10J)

Q. How can you improve the compliance of drug therapy? (DU-14Ju, 12Ju, 11J, 10J)

Ans.

Compliance of drug therapy: Compliance may be defined as the extent to which the patient follows a regimen prescribed by a healthcare professional.

Patient compliance is the extent to which the actual behaviour of the patient coincides with medical advice and instructions: it may be complete, partial, erratic, nil, or there may be overcompliance.

(Ref: Bennet & Brown-11th)

Suggestions for Improving Patient Compliance

1. Provide respectful communication; ask patient how they take medicine.
2. Develop satisfactory, collaborative relationship between doctor and patient; encourage pharmacist involvement.
3. Provide and encourage use of medication counseling.
4. Give precise, clear instructions, with most important information given first.
5. Support oral instructions with easy-to-read written information.
6. Simplify whenever possible.
7. Use mechanical compliance aids as needed (sectioned pill boxes or trays, compliance packaging, color-coding).
8. Use optimal dosage form and schedule for the individual patient.
9. Assess patient's literacy and comprehension and modify educational counseling as needed. Don't rely on patient knowledge about his or her disease, alone, to improve compliance.
10. Find solutions when physical or sensory disabilities are present (use nonsafety caps on bottles, use large type on labels and written material, place tape marks on syringes).
11. Enlist support and assistance from family or caregivers.
12. Use behavioral techniques such as goal setting, self-monitoring, cognitive restructuring, skills training, contracts, and positive reinforcement.

(Ref: Goodman & Gilman-12th edition)

Nice to know

Patient noncompliance is manifest in drug therapy as accidental or intentional errors in dosage or schedule, overuse, underuse, early termination of therapy or not having a prescription filled. Therapeutic failure can result from patient noncompliance.

Noncompliance may occur because:

1. *the patient has not understood the instructions, so cannot comply, or*
2. *understands the instructions, but fails to carry them out.*

(Ref: Bennet & Brown-11th)

Q. Write down the prime factors responsible for poor patient compliance.

Ans.

Prime factors for poor patient compliance are:

1. *Frequency and complexity of drug regimen.* More than three drugs to be taken concurrently or more than three drug taking occasions in the day (the ideal of one occasion only is often unattainable).
2. *Unintentional noncompliance* or forgetfulness.
3. *'Intelligent' or wilful noncompliance.* Patients decide they do not need the drug or they do not like the drug, or take 2-3-day drug holidays.
4. *Lack of information.* Oral instructions alone are not enough. Lucid and legible labelling of containers is essential, as well as patient-friendly information leaflets.
5. *Poor patient-doctor relationship and lack of motivation* to take medicines as instructed offer a major challenge to the prescriber whose diagnosis and prescription may be perfect, but yet loses efficacy by patient noncompliance.

(Ref: Bennet & Brown-11th)

Nice to know**Doctor compliance**

Doctor compliance is the extent to which the behaviour of doctors fulfils their professional duty:

1. *not to be ignorant*
2. *to adopt new advances when they are sufficiently proved (which doctors are often slow to do)*
3. *to prescribe accurately*
4. *to tell patients what they need to know to warn, i.e. to recognize the importance of the act of prescribing.*
5. *to warn, i.e. to recognize the importance of the act of prescribing.*

(Ref: Bennet & Brown-11th)

Rational prescribing

Q. Define prescription. (SU-13Ju)

Q. Define prescription. What are the types of prescribing?

Ans.

Prescription: A prescription is a written order or advice given by a registered physician, dentist or veterinarian to prepare and or to dispense medicine for diagnosis, prevention, control or cure of a disease.

Types of prescribing:

According to rational use:

1. Rational prescribing
2. Irrational prescribing.

According to clinical practice:

1. Outdoor patient prescription
2. Chart order prescription
3. General / ethical prescription

Q. What do you mean by rational prescribing? (DU-05M, RU-06M; SU-08J)

Q. What are the factors that should be considered for rational prescribing? (DU-09/08J; RU-10J)

Q. Enumerate & discuss the principles of rational prescribing. (DU-12Ju, CU-17J, 15J, 13Ju, 10Ju, SU-07J)

Q. What steps should be taken for rational prescribing? (RU-14J, 07J)

Ans.

Rational prescribing:

Definition: Rational prescribing means prescribing the drugs by considering their therapeutic efficacy & suitability.

Criteria / steps / factors / principles of rational prescribing:

1. Appropriate diagnosis- based on clinical features and laboratory diagnosis.
2. Appropriate indication- whether the drug is actually necessary or not.
3. Appropriate medicine- based on safety, efficacy, affordability, availability and need.
4. Appropriate patient
5. Appropriate dosage
6. Appropriate duration
7. Appropriate route of administration
8. Appropriate information to the patient
9. Appropriate monitoring must be done.

(Ref- Misbahuddin-5th/171,172)

Necessity of rational prescribing: It is necessary —

1. To improve treatment outcome.
2. To decrease adverse drug reactions (ADRs)
3. To decrease financial loss of patient.

Q. Define irrational prescribing. (CU-06M)

Q. Discuss the underlying causes of irrational prescribing. (DU-06M; CU-06M; RU-07Ju)

Ans.

Irrational prescribing:

Definition: It is the prescription of inappropriate, ineffective and economically inefficient drugs where cost-benefit ratio is unfavorable to the recipient.

Causes of irrational prescribing:

➔ **Factors related to the prescribers:**

1. Use of medicine when no medicine is indicated.
2. Lack of objective drug information.

3. Misleading belief about drug efficacy
4. Heavy patient load
5. Tendency to prescribe latest and expensive brand of particular drug.
6. Use of wrong medicine for the specific condition requiring drug therapy.
7. Misleading belief.

☛ **Factors related to the patient:**

1. Lack of education and information regarding hazards of inappropriate medication.
2. Patient's demand or expectation, eg, irrational prescription of vitamins.
3. Easy to purchase any drug from the drug store without any prescription.
4. Use of traditional medicine.

☛ **Factors related to the dispenser:**

1. Wrong interpretation of prescription.
2. Supply of wrong drug from stock.
3. Wrong dosage.
4. Inadequate package of labeling.
5. Inaccurate compounding.
6. Insufficient knowledge of the disease process.
7. Insufficient time to take with patient about their drugs.
8. Inability to communicate to patient about therapy.

☛ **Factors related to the drug suppliers:**

1. For making more money sometimes manufacturers and distributors create an artificial shortage of essential drugs.
2. Sometimes expired drugs are available in market due to lack of proper supervision.

☛ **Factors related to the legal authorities:**

1. Lack of proper supervision and monitoring.
2. No restriction of prescribing vital medicines and antibiotics by nonformal prescribers.
3. Poor regulation enforcement.
4. Quality assurance of the drug is not properly maintained.

(Ref- Misbahuddin-5th/173,174)

Q. Mention the common irrational prescribing practices. (DU-06M)

Q. Give some examples of irrational use of drugs. (RU-15Ju,09J)

Ans.

Common irrational prescribing practices / irrationalities in prescribing:

1. Use of drug when none is needed; e.g. antibiotics for viral fevers & nonspecific diarrhea.
2. Compulsive co-prescription of vitamins & tonics.
3. Use of drugs not related to the diagnosis; e.g. chloroquine / ciprofloxacin for any fever, proton pump inhibitor (PPI) for any abdominal symptoms.
1. Selection of a wrong drug; e.g. tetracycline / ciprofloxacin for pharyngitis, β -blockers as antihypertensive drug for asthmatic patient.
2. Prescribing ineffective / doubtful efficacy drugs; e.g. serratiopeptidase for injuries / swellings, antioxidants, cough mixtures, memory enhancers etc.
3. Incorrect route of administration; e.g. injection when the drug can be given orally.
4. Incorrect dose either under-dosing or overdosing especially occurs in children.
5. Incorrect duration of treatment; e.g. prolong post-surgical use of antibiotics, stoppage of antitubercular drugs or other antibiotics as soon as relief of symptoms is obtained.
6. Unnecessary use of drug combinations; e.g. ciprofloxacin + tinidazole for diarrhea, ampicillin + cloxacillin for staphylococcal infection, ibuprofen + paracetamol as analgesic.
7. Unnecessary use of expensive medicines when cheaper drugs are equally effective.
8. Craze for latest drugs; e.g. routine use newer antibiotics & other drugs.

9. Unsafe use of drugs; e.g. use of single anti-tubercular drug, corticosteroids for fever, anabolic steroids in children.
10. Polypharmacy without regard to drug interaction.

Q. Lists the hazards/disadvantages of irrational prescribing. (RU-15Ju,14J,10J)

Q. Discuss the consequences of irrational use of drugs. (SU-09/08Ju)

Ans.

Hazards / consequences of irrational prescribing: Irrational use of drugs may lead to some bad effects on the patient as well as on the community.

1. Delay / no relief of symptoms or disease.
2. Drug resistance
3. Drug dependence
4. Addiction
5. Tolerance
6. More adverse drug reactions
7. Drug toxicity
8. Prolong hospitalizations & loss of working hours.
9. Ultimately increase morbidity & mortality.
10. Financial loss of the person & the community.

Q. How irrational prescribing can be avoided? (DU-06M)

Q. How can we ensure the rational use of drugs? (RU-09J)

Q. Write down about regulatory strategies to manage irrational prescribing. (CU-06M)

Ans.

Regulatory strategies for managing / preventing irrational prescribing

A. Prescriptions

- Division of prescription medicines → Specific medicine are selected by doctors of specific categories
- Prescription demarcation → Specially categorized drugs are prescribed over especially supplied prescription

B. Professional competence

- Qualifying
- Continuous assessment of performance

C. Medicines at market

- Medicine policy or health policy
- Concept of essential medicines (drugs).

Q. Outline the principles of pharmacotherapy. (CU-08Ju)

Ans.

Pharmacotherapy / pharmacotherapeutics: Definite area in the subject of pharmacology that deals with the principles (rules) of using the drugs used for diagnosis, prevention & curative treatment of the diseases is called pharmacotherapy.

Principles of rational prescribing / pharmacotherapy:

1. **Fixation of therapeutic target:** To fix the therapeutic target, knowledge about pathophysiology & prognosis of the disease is required. The target may be —
 - ***Cure of the disease:*** Antibiotic therapy in infectious diseases.
 - ***Control of the disease:*** Antihypertensive drugs & Antidiabetic drugs in HTN & DM respectively.
 - ***Prevention of the disease:*** Prophylaxis of malaria, TB & other communicable diseases.

- **Alteration of the normal physiological function:** Oral Contraceptive pills for contraception.
 - **Diagnosis of the disease:** Dexamethasone suppression test to diagnose Cushing's syndrome.
 - **Reduce the symptoms & severity of the disease in case of chronic / malignant diseases:** Analgesic in chronic pain, radiotherapy & chemotherapy in non-curable malignant disease reduces the symptoms & severity of the diseases (i.e. palliative care).
2. **Selection of therapy:** Therapy may be —
- Non-drug therapy (e.g. restriction of diet, advising physical exercise)
 - Drug therapy:
3. **Selection of drugs & dosage regimen** (if it's a drug therapy):
- Selection of the drug on the basis of knowing the disease profile, pharmacological profile of the drug & cost profile.
 - Designation of proper dosage regimen which includes —
 - Dose of the drug
 - Formulation of the drug
 - Route of administration
 - Frequency & time interval of the drug
 - Duration of the treatment
4. **Monitoring of therapy:**
- Monitoring of beneficial & harmful effects by chemical & surrogate markers.
 - Monitoring of the patient's compliance. The determinants of patient's compliance include treatment cost, patient's understanding about the treatment of the disease, frequency of drug administration, ADRs, taste of the drug etc.
5. **Education of the patient about the therapy:**
- Counseling with the patient & his attendants about risks & benefits of the drug therapy or avoiding the treatment & related behavior of both the patient & the attendants.
 - Accurate direction about the dosage regimen, duration of the therapy & follow up of the patient.
 - Advising the patient about the treatment complications & the further disease complication.

Q. A 30 years old bus driver, sufferings from common cold was managed by a general practitioner with Tab. Paracetamol, Cap. Amoxicillin & Tab. Chlorpheniramine. He recovered after a week. Was the case rationally treated? Criticize. (CU-06M)

Ans.

No, the patient was not rationally treated.

Criticism of the prescription:

- **Paracetamol:** As the patient may have some fever and headache, prescribing paracetamol is appropriate in this case.
- **Amoxicillin:** As common cold is usually a viral disease, antibiotics such as amoxicillin are unnecessary in this case. Rather there is chance of developing drug resistance & extra cost burden to the bus driver.
- **Chlorpheniramine:** As the profession of the patient was driving, treatment with chlorpheniramine was a dangerous one. Because Chlorpheniramine is a 1st generation & strongly sedative anti-histamine, so there will be drowsiness & lack of concentration during driving & there may occur a serious accident. So, this type of irrational prescribing should be strongly inhibited.

Rational prescribing in this patient: Only fexofenadine / loratadine / desloratadine (non sedative anti-histamine) at bed time is enough to treat the bus driver in this case. If chlorpheniramine is used, driving should be prohibited at least 10-12 hours after the drug administration.

Essential drug concept

Q. Define essential drug. (DU-15Ju,07Ju; CU-17J,15J,12Ju,07Ju/J; SU-10J,06S; RU-16J,14Ju,13Ju,12J)

Q. What do you mean by essential drugs/ essential drug concept? (DU-06S,SU-09J, CU-05/04M)

Q. What do you mean by essential drug list (EDL)? (DU-09Ju)

Q. Mention the criteria for selecting essential drugs. (DU-07Ju; RU-13Ju)

Q. Write down the selection criteria of essential drugs. (RU-16J,12J)

Q. Short note: Essential Drug. (DU-13J,10/08Ju; RU-17J, SU-13Ju,11J)

Q. Short note: Essential Drug concept. (DU-05J,RU-07Ju)

Q. Short note: Essential drug list (EDL). (DU-11J)

Ans.

Essential drug: WHO defines essential drugs as the drugs (or representatives of classes of drugs) 'that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage forms'.

Essential drug concept: This is the concept about the drugs that make the differentiation about the drug requirements.

Example: Neostigmine is the essential drug for neuromuscular junction blocker.

WHO criteria of selecting an essential drug:

1. Adequate data on its efficacy & safety should be available from clinical studies.
2. It should be available in a form in which quality, including bioavailability & stability on storage can be assured.
3. Its choice should be dependent upon pattern of prevalent diseases; availability of facilities & trained personnel; financial resources; genetic, demographic & environmental factors.
4. In case of two or more similar drugs, choice should be made on the basis of their relative efficacy, safety, quality, price & availability. Cost-benefit ratio should be a major consideration.
5. Choice may also be influenced by comparative pharmacokinetic properties & local facilities for manufacture & storage.
6. Most essential drugs should be single compounds.
7. Selection of essential drugs should be a continuous process which should take into account the changing priorities for public health action, epidemiological condition as well as availability of better drugs / formulations & progress in pharmacological knowledge.
8. Recently, it has been emphasized to select essential drugs based on rationally developed treatment guidelines.

Essential drug list: Countries needing essential drug list can use the list as a basis for their own choices (WHO also publishes model prescribing information). The list is updated every few years and contains about 300 items.

1. **Core list:** 117 drugs in Bangladesh. The drugs that are included here are for all the licensed prescriber. Any graduate doctor can prescribe.
2. **Complementary list:** Drugs included here are for the specialists. Prescribing needs special techniques, institution, e.g. antiarrhythmic drugs cannot be given to ambulatory patient. It requires cardiac monitoring (hospitalized patient). That is why antiarrhythmic drugs are in complementary list.

Criteria included into national essential drug list (in short):

1. Safety profile
2. Efficacy
3. Low cost
4. Availability

Basis of selection (in short):

1. Disease that is prevalent in the community.
2. Safety of the drug

3. Efficacy of the drug
4. Cost-effectiveness of the drug.

Q. What is the importance of essential drug list in promoting rational use of drugs? (DU-09Ju, RU-14Ju)

Q. What are the advantages of having a national list of ED? (RU-13Ju)

Q. What is the importance of essential drug concept? (RU-07J)

Q. Give the necessity/advantage of essential drugs. (RU-16J)

Ans.

Importance of essential drug concept

1. Essential drug concept allows reduction in the number of pharmaceutical products to be manufactured, imported, stored, analyzed & distributed from among the thousands.
2. Improvement of the quality of the drug utilization, management, information & monitoring.
3. Stimulation of local pharmaceutical industries.
4. Solution of the primary health care problems by providing high priority safe and cost-effective drugs.
5. Facilitating the use of drugs more economically and rationally.

Q. Describe the essential drug list (EDL) in Bangladesh.

Q. Mention the total number of ED in our country with the number at different levels. (RU-14Ju)

Ans.

Essential drug list (EDL) in Bangladesh: The total number of EDS in Bangladesh is 150. EDS have been recommended to be used by various levels of health care personnel. These include-

1. **List of 12 essential drugs for use by the village level health workers**, eg, aspirin tablet, chloroquine tab / syrup, aluminium hydroxide gel/tab/susp, ORS, etc.
2. **List of additional 33 essential drugs for primary health care (PHC) up to the Thana health complex level**, eg, paracetamol tab, metronidazole, atropine, omeprazole etc.
3. **List of additional 105 essential drugs for use in tertiary level**, eg, indomethacin cap/suppository, metronidazole tab, thiopental sodium, griseofulvin etc.
4. **Supplementary list: 100 items of specialized drugs**, eg, beclomethasone inhaler, sodium valproate, Mitomycin tab/inj, etc.

(Ref: Lecture SOMC)

Q. Enumerate 3 anti-diabetic drugs to be included in “Essential Drug Lists” of Bangladesh. (CU-07J)

Q. Enumerate 3 anti-hypertensive drugs to be included in “Essential Drug Lists” of Bangladesh. Justify your selection. (CU-05M)

Q. Enumerate 5 anti-microbial drugs to be included in “Essential Drug Lists” of Bangladesh. Justify your selection. (CU-04M)

Ans.

3 anti-hypertensive drugs that should be included in essential drug list:

1. Atenolol
2. Losartan
3. Amlodipine

5 anti-microbial drugs that should be included in essential drug list:

1. Flucloxacillin
2. Ciprofloxacin
3. Metronidazole
4. Rifampicin
5. Isoniazid

3 anti-diabetic drugs that should be included in essential drug list:

1. Insulin
2. Glipizide
3. Metformin

Q. Short note: Polypharmacy. (DU-13Ju)

Q. Write down the advantages of polypharmacy. (RU-11J)

Ans.

Polypharmacy:

Definition: Polypharmacy is the use of multiple medications by a patient, generally older adults.

Indications

1. **To treat chronic diseases**, eg, diabetes mellitus, hypertension, ischemic heart disease, etc.
2. **Treatment of infections where there is chance of development of drug resistance**, eg, TB.
3. **To treat severe infection**, eg, contaminated RTA, tetanus, septicemia, etc.
4. **Balanced anesthesia:** It consists of-
 - a. Intravenous anesthetic
 - b. Inhaled anesthetics
 - c. Analgesic
 - d. Skeletal muscle relaxant.

Example:

1. **Treatment of myocardial infarction:** A statin, an ACEI inhibitor, a beta-blocker, aspirin, paracetamol and an antidepressant.
2. **Treatment of TB:** 4 drugs (INH, rifampicin, pyrazinamide, ethambutol).
3. **Treatment of hypertension:** Losartan & hydrochlorothiazide.

Advantages

1. Dose requirement for individual drugs become less.
2. Well control of the disease.
3. Good patient compliance.

Disadvantages

1. More drugs → wide range of side-effects.
2. More drugs → more risk of drug-drug interactions.
3. Higher costs.
4. Polypharmacy is often associated with a decreased quality of life, decreased mobility and cognition.

Q. What do you mean by P-drug? (DU-07M,05/04M; RU-06M; SU-09J,07Ju)

Q. What factors should be considered for selection of P-drug? (DU-10J,07M)

Q. Mention the criteria for selecting P-drug. (DU-15Ju,12J, RU-15Ju)

Q. Short note: P-drug concept. (DU-11Ju, CU-08J, SU-13Ju,12Ju)

Q. Short note: P-drug. (CU-16Ju, RU-15J, SU-17J,15Ju,15J,14Ju)

Ans.

P-drug:

P-drug means:

1. Priority drug
2. Prefer drug
3. Personal drug
4. Primary drug

Criteria of P-drug / factors for selection:

1. Efficacy (E)
2. Safety (S)
3. Cost-effectiveness (C)
4. Availability (A)
5. Suitability (S)

Remember: ES CAS

The sequence may be altered for some drugs, eg, thiacetazone is a 2nd line drug for treatment of TB. But as it is very cheap, it is a 1st line drug in 3rd world countries.

Example: In case of antihypertensive drugs—

Drugs	Efficacy (E)	Safety (S)	Cost-effectiveness (C)	Availability (A)	Suitability (S)
1. Propranolol	++	++	++	++	++
2. Thiazide	++	+	++	++	++
3. Amlodipine	+++	+	+	+	+
4. α -Methyl dopa	++	+	+	+	+
5. Prazosin	++	$\pm$	+	+	+
6. Captopril	+++	+	+	+	+

Q. Discuss shortly the steps of selecting essential & P-drugs. (SU-12J,09J)

Ans.

Steps of selecting essential & P-drugs: The selection of a P-drug consists of the following 5 steps-

1. To define the diagnosis.
2. To specify the therapeutic objective.
3. To make an inventory of effective groups of drugs.
4. To choose an effective group according to criteria.
5. To choose a P-drug.

Q. Select a P-drug for a case of acute respiratory infection in 10 years old boy. (SU-10J)

Ans.

P-drug for a case of acute respiratory infection: Amoxicillin

Reasons for selection

1. Good efficacy against organisms causing RTI.
2. Well-tolerability
3. Relatively cheap
4. Good availability
5. Broad spectrum of activity

MCQ

Q. Drugs included in essential drug list are- (DU-17M)

- a) paracetamol
- b) antacid
- c) methotrexate
- d) zidovudine
- e) folic acid

a. T, b. T, c. F, d. F, e. T

Q. P-drug selection depends on- (DU-15Ju)

- a. efficacy of drug
- b. safety of drug
- c. patient behavior
- d. latest drugs
- e. cost effectiveness

a. T, b. T, c. F, d. F, e. T

Q. Advantages of an essential drug include- (DU-15Ju)

- a. safety
- b. limited use
- c. availability
- d. cost-effectiveness
- e. cannot be used by health workers

a. T, b. F, c. T, d. T, e. F

Q. Irrational use of drug may occur by- (DU-14Ju)

- a. the use of appropriate drug
- b. indiscriminate use of antibiotics
- c. administration of drug in right dose
- d. using drugs without proper indication
- e. the use of new expensive drugs

a. F, b. T, c. F, d. T, e. T

Q. P-drug selection depends on- (DU-13J)

- a. efficacy.
- b. safety.
- c. patient behavior.
- d. latest drug.
- e. cost effectiveness.

a. T, b. T, c. F, d. F, e. T

Q. P drug selection depends on- (DU-11Ju)

- a. Efficacy (T)
- b. Safety (T)
- c. Cost-effectiveness (T)
- d. Patient behavior (F)
- e. Latest drug (F)

Chapter 15

Cancer chemotherapy & Gene therapy

Cancer chemotherapy

Definition of cancer: Cancer is a disease characterized by uncontrolled multiplication and spread of abnormal forms of the body's own cells. The terms *cancer*, *malignant neoplasm* (neoplasm simply means 'new growth') and *malignant tumour* are synonymous.

(Ref: Rang & Dale's-8th)

Cancer cells have four characteristics that distinguish them from normal cells:

1. uncontrolled proliferation
2. loss of function because of lack of capacity to differentiate
3. invasiveness
4. the ability to metastasise.

(Ref: Rang & Dale's-8th)

Treatment of cancer: There are three main approaches to treating established cancer- **surgical excision**, **irradiation (radiotherapy)** and **chemotherapy**- and the role of each of these depends on the type of tumour and the stage of its development.

(Ref: Rang & Dale's-8th)

Principles of Cancer Chemotherapy: Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cell that can arrest a tumor's progression. The attack is generally directed toward DNA or against metabolic sites essential to cell replication- for example, the availability of purines and pyrimidines that are the building blocks for DNA or RNA synthesis. Ideally, these anticancer drugs should interfere only with cellular processes that are unique to malignant cells. Unfortunately, most currently available anticancer drugs do not specifically recognize neoplastic cells but, rather, affect all kinds of proliferating cells- both normal and abnormal. Therefore, almost all antitumor agents have a steep dose-response curve for both toxic and therapeutic effects.

(Ref: Lippincott's-6th)

Goal of treatment: The ultimate goal of chemotherapy is a cure (that is, long-term, disease-free survival). A true cure requires the eradication of every neoplastic cell. If a cure is not attainable, then the goal becomes control of the disease (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life. In advanced stages of cancer, the likelihood of controlling the cancer is far from reality and the goal is palliation (that is, alleviation of symptoms and avoidance of life-threatening toxicity). This means that chemotherapeutic drugs may be used to relieve symptoms caused by the cancer and improve the quality of life, even though the drugs may not lengthen life.

(Ref: Lippincott's-6th)

Indications for treatment: Chemotherapy is indicated when neoplasms are disseminated and are not amenable to surgery. Chemotherapy is also used as a supplemental treatment, to attack micrometastases following surgery and radiation treatment in which case it is called adjuvant chemotherapy. Chemotherapy given prior to the surgical procedure in an attempt to shrink the cancer is referred as neoadjuvant chemotherapy, and chemotherapy given in lower doses to assist in prolonging a remission is known as maintenance chemotherapy.

(Ref: Lippincott's-6th)

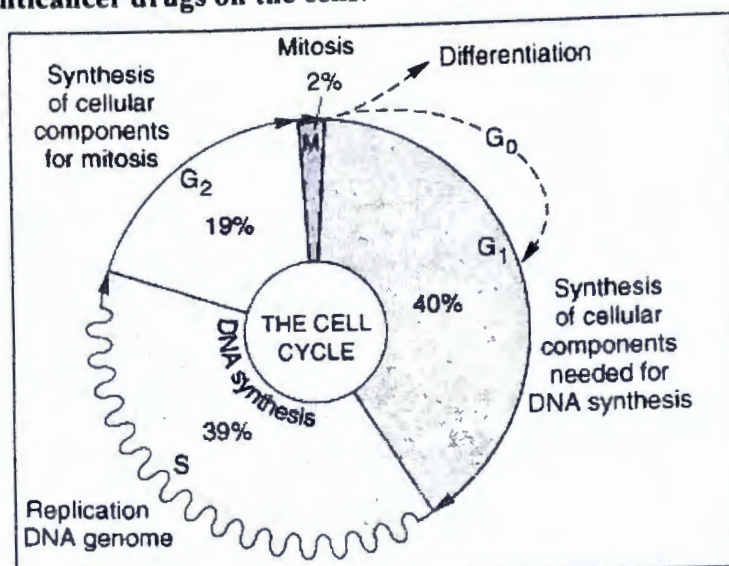
Cell cycle and action of anticancer drugs on the cells:

Figure: The cell cycle and cancer. A conceptual depiction of the cell cycle phases that all cells—normal and neoplastic—must traverse before and during cell division. The percentages given represent the approximate percentage of time spent in each phase by a typical malignant cell; the duration of G₁, however, can vary markedly.

On the basis of cell cycle, anticancer drugs are grouped into —

1. Cell cycle specific (CCS) drugs &
2. Cell cycle nonspecific (CCNS) drugs.

Cell cycle specific drugs: Anticancer drugs which exert their action on cells by traversing the cell cycle are called cycle specific drugs. In general, CCS drugs are most effective in hematologic malignancies and in solid tumors in which a relatively large proportion of the cells are proliferating or are in the growth fraction.

Cell cycle nonspecific drugs: Anticancer drugs which can sterilize or kill tumour cells both resting in the G₀ phase & cycling are called cell cycle nonspecific drugs. CCNS drugs (many of which bind to cellular DNA and damage these macromolecules) are particularly useful in low growth fraction solid tumors as well as in high growth fraction tumors.

(Ref: Katzung-13th)

Q. Classify anticancer drugs. (DU-17M)

Q. Classify the drugs used in cancer chemotherapy. (RU-06M)

Q. Name the structural analogs used in cancer chemotherapy. (SU-99M, CU-99M)

Ans.

Classification of anticancer drugs:

Cell Cycle-Specific (CCS) Agents	Cell Cycle-Nonspecific (CCNS) Agents
Antimetabolites (S phase) • Capecitabine • Cladribine • Clofarabine • Cytarabine (ara-C) • Fludarabine • 5-Fluorouracil (5-FU) • Gemcitabine • 6-Mercaptopurine (6-MP) • Methotrexate (MTX) • 6-Thioguanine (6-TG)	Alkylating agents • Altretamine • Bendamustine • Busulfan • Carmustine • Chlorambucil • Cyclophosphamide • Dacarbazine • Lomustine • Mechlorethamine • Melphalan • Temozolomide • Thiotepa
Epipodophyllotoxin (topoisomerase II inhibitor) (G₁-S phase) • Etoposide	Anthracyclines • Daunorubicin • Doxorubicin • Epirubicin • Idarubicin • Mitoxantrone
Taxanes (M phase) • Albumin-bound paclitaxel • Docetaxel • Paclitaxel	Antitumor antibiotics • Dactinomycin • Mitomycin
Vinca alkaloids (M phase) • Vinblastine • Vincristine • Vinorelbine	Camptothecins (topoisomerase I inhibitors) • Irinotecan • Topotecan
Antimicrotubule inhibitor (M phase) • Ixabepilone	Platinum analogs • Carboplatin • Cisplatin • Oxaliplatin
Antitumor antibiotics (G₂-M phase) • Bleomycin	

(Ref: Katzung-13th)

Q. Outline the principles of combining cytotoxic drugs in the treatment of malignancy. (RU-16Ju)

Ans.

Principles of combining cytotoxic drugs in the treatment of malignancy: The selection of drugs in combination chemotherapy is influenced by:

1. **Choosing drugs that act at different biochemical sites in the cell.**
2. **Using drugs that attack cells at different phases of the growth cycle.** 'CHOP' is a standard combination chemotherapy regimen for non-Hodgkin's lymphoma. The acronym stands for cyclophosphamide, doxorubicin (previously known as hydroxydoxyrubicin), vincristine (previously

called oncovin) and prednisolone. The first three cytotoxic drugs exert their antitumour effect on different aspects of cell proliferation. The antitumour effect of corticosteroid remains unclear.

3. **The desirability of attaining synchronisation of cell cycling to achieve maximum cell kill.** Cells are killed or are arrested in mitosis by vincristine, which is then withdrawn. Cells then enter a new reproductive cycle more or less synchronously, and when most are judged to be in a phase sensitive to a particular phase-specific drug, e.g. methotrexate or cytarabine, it is given.
4. **Avoidance of cross-resistance between drugs.** In some instances, use of one drug regimen followed by another rather than using them simultaneously in combination avoids drug resistance and improves therapeutic efficacy. For example, epirubicin given for four cycles followed by CMF (concomitant cyclophosphamide, methotrexate and 5-fluorouracil) for four cycles has largely replaced CMF alone as standard adjuvant chemotherapy for breast cancer, because the outcome is better.
5. **Non-overlapping toxicity profiles.** Before establishing a combination regimen, phase I trials are undertaken, frequently fixing the dose of one drug while escalating the dose of another, in small cohorts of carefully monitored patients, so that toxicity and patient safety can be monitored.
6. **Empirical evidence of efficacy against a particular tumour type.** The antitumour activity of platinum complexes was a chance finding.
7. **Enhanced cell killing in preclinical models when drugs are combined.** Oxaliplatin on its own has limited cytotoxicity against colorectal cancer cell lines in vitro and in mouse xenograft models, but its combination with 5FU confers a more than additive, i.e. synergistic, killing effect on tumour cells.

Considerations of pharmacokinetics in relation to cell kinetics are of great importance, as drug treatment alters the behaviour of both malignant and normal cells.

(Ref: Bennet & Brown-12th/516)

Q. Lists the common adverse effects of anticancer drugs. (DU-17M,07Ju; RU-10/07J,06M)

Q. Mention the general hazards of cancer chemotherapy. (RU-16Ju)

Q. Discuss the common adverse effects of cancer chemotherapy. (RU-08J)

Ans.

Common adverse effects of anticancer drugs: Because their main effect is on cell division, anticancer drugs will affect all rapidly dividing normal tissues and thus they are likely to produce, to a greater or lesser extent, the following general toxic effects:

1. Nausea and vomiting
2. Bone marrow toxicity (myelosuppression) with decreased leukocyte production and thus decreased resistance to infection
3. Impaired wound healing
4. Loss of hair (alopecia)
5. Damage to gastrointestinal epithelium
6. Depression of growth in children
7. Sterility
8. Teratogenicity.

(Ref: Rang & Dale's-8th)

Q. Short note: Anti-cancer induced nausea and vomiting (emesis).

Q. How will you manage anti-cancer induced nausea and vomiting (emesis)?

Q. Discuss the management of drug induced vomiting. (DU-17M)

Ans.

Anti-cancer induced emesis: Nausea and vomiting is the principle side effects of anti-cancer chemotherapy. Chemoreceptor trigger zone (CTZ) is directly stimulated by toxins or drugs. Neurotransmitters (e.g. dopamine) also stimulate the vomiting center. There is variation of emetic effect among chemotherapeutic drugs—

Mild emetics	▪ Methotrexate ▪ Fluorouracil
Severe emetics	▪ Doxorubicin (adriamycin) ▪ Dacarbazine ▪ Mechlorethamine
Very severe emetics	▪ Cisplatin

Prevention of anti-cancer induced emesis: Use of antiemetics as a component of regular chemotherapeutic regimen. The drugs are —

1. **Serotonin antagonists:** Ondansetron, granisetron.
2. **Dopamine antagonists:** Metoclopramide.
3. **Major tranquilizers:** Phenothiazines.
4. **Cannabinoids:** Dronabinol.
5. **Others:** High dose glucocorticoids (dexamethasone), benzodiazepines (sedatives) and antihistamines.

Q. Why 5HT₃ receptor blockade is so important in cancer chemotherapy induced vomiting? (CU-17M)

Ans.

5HT₃ receptor blockade is important in cancer chemotherapy induced vomiting: 5-HT₃ receptor antagonists Granisetron, ondansetron and palonosetron are of particular value in preventing and treating the vomiting and, to a lesser extent the nausea, commonly encountered during administration of cytotoxic drugs such as cisplatin. The primary site of action of these drugs is the CTZ.

(Ref: Rang & Dales-8th/375)

Nice to know:

Mechanism of action of alkylating anticancer drugs:

Alkylating anticancer drugs
 ↓
 Transfer alkyl group to DNA
 ↓
 Alkylation of DNA
 ↓
 Intra-strand linking and cross linking of DNA strands
 ↓
 Blocks replication and transcription of DNA
 ↓
 Blocks production of undifferentiated cells
 ↓
 Anticancer effect.

(Ref: Katzung-13th)

Mechanism of action of 5-fluorouracil (5-FU): 5-Fluorouracil (5-FU) is a prodrug requiring activation via a complex series of biotransformation reactions to ribosyl and deoxyribosyl nucleotide metabolites.

1. 5-FU is converted to 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP) → FdUMP inhibits the enzyme thymidylate synthase → inhibits synthesis of thymidylate → inhibition of DNA synthesis through "thymineless death."
2. 5-FU is converted to 5-fluorouridine-5'-triphosphate (FUTP) → FUTP is then incorporated into RNA → interferes with RNA processing and mRNA translation.
3. In addition, 5-FU is converted to 5-fluorodeoxyuridine-5'-triphosphate (FdUTP) → FdUTP can be incorporated into cellular DNA, resulting in inhibition of DNA synthesis and function.

Thus, the cytotoxicity of 5-FU is thought to be the result of the combined effects on both DNA- and RNA-mediated events.

(Ref: Katzung-13th)

Mechanism of action of vincristine: Vincristine → Tubulin inhibitor → Inhibits polymerization of the microtubules of the cytoskeleton and mitotic spindle → Mitotic arrest at metaphase → Dissolution of the mitotic spindle → Inhibits chromosomal segregation at the pole of dividing cell → Blocks uncontrolled cell division → Anticancer effect.

(Ref: Katzung-13th)

Malignancies responsive to chemotherapy:

1. Acute lymphocytic leukemia (ALL)
2. Acute myelocytic & myelomonocytic leukemia
3. Chronic lymphocytic leukemia (CLL)
4. Chronic myelogenous leukemia (CML)
5. Hodgkin's disease (stages III & IV)
6. Non-Hodgkin's lymphoma
7. Multiple myeloma
8. Macroglobulinemia
9. Polycythaemia vera
10. Carcinoma of different organs: Adrenal, breast, cervix, colon, endometrium, lung, ovary, pancreas, prostate, stomach, testis, thyroid, head & neck, choriocarcinoma (trophoblastic neoplasm).
11. Wilm's tumor
12. Neuroblastoma
13. Carcinoid
14. Insulinoma
15. Estrogenic sarcoma
16. Miscellaneous sarcomas
17. Melanoma

Gene therapy

Gene therapy: Gene therapy is the genetic modification of cells to prevent, alleviate or cure disease.

(Ref: Rang & Dale's-8th)

Potential applications:

1. radical cure of monogenic diseases (e.g. cystic fibrosis, haemoglobinopathies)
2. amelioration of diseases with or without a genetic component, including many malignant, neurodegenerative and infectious diseases.

(Ref: Rang & Dale's-8th)

Steps of gene therapy: Two steps —

1. Gene identification and cloning
2. Gene transfer and expression

(Ref: Misbahuddin-5th/198,199)

Transfer of recombinant gene into target cells: The transfer of recombinant nucleic acid into target cells is critical to the success of gene therapy. Target genes must cross the plasma and nuclear membranes, and it must then bind to the chromosomes of target cells.

There are two main strategies for delivering genes into patients: the in vivo and ex vivo approach.

1. **In vivo strategy:** The *vector* containing the therapeutic gene is injected into the patient, either intravenously or directly into the target tissue (e.g. a malignant tumour).
2. **Ex vivo strategy:** The ex vivo strategy is to remove cells from the patient (e.g. stem cells from marrow or circulating blood, or myoblasts from a biopsy of striated muscle), treat them with the vector and inject the genetically altered cells back into the patient.

Criteria of an ideal vector

1. *Safe*
2. *Highly efficient* (i.e. insert the therapeutic gene into a high proportion of target cells.)

3. *Selective* (i.e. it would lead to expression of the therapeutic protein in the target cells but not to the expression of viral proteins.)

(Ref: Rang & Dale's-8th)

Table: Delivery systems for gene therapy

Vector	Advantages	Disadvantages
1. Liposomes	Virus-free	Low efficiency, sometimes cytotoxic
2. DNA cassettes	Virus-free	Low efficiency, expression temporary
3. Herpes simplex virus type I	Highly infective, persistent expression	No integration with host DNA, cytotoxic, difficult to handle
4. Adenovirus	Highly infective in epithelia	Immunogenic and temporary
5. Adeno-associated virus	Stable	Low capacity, requires a helper virus
6. Retrovirus	Efficient, permanent	Low capacity, unstable, must integrate into host DNA

(Ref: Rang & Dale's-8th)

MCQ

- Q. Following medications would be effective to counteract the emesis in patient with ovarian cancer taking cisplatin: (CU-14Ju)**
- Droperidol.
 - dolasetron
 - prochlorperazine.
 - Dronabinol
 - Ondansetron
- a. T, b. T, c. T, d. T, e. T

Chapter 16

Dermatology

Topical Antibacterial Preparations

Indications: Topical antibacterial agents may be useful in

1. Preventing infections in clean wounds
2. early treatment of infected dermatoses and wounds
3. reducing colonization of the nares by staphylococci
4. Axillary deodorization, and
5. the management of acne vulgaris.

(Ref: Katzung-13th edition)

Antibiotic-corticosteroid combinations: Some topical anti-infectives contain corticosteroids in addition to antibiotics. There is no convincing evidence that topical corticosteroids inhibit the antibacterial effect of antibiotics when the two are incorporated in the same preparation. In the treatment of secondarily infected dermatoses, which are usually colonized with streptococci, staphylococci, or both, combination therapy may prove superior to corticosteroid therapy alone. Antibiotic-corticosteroid combinations may be useful in treating diaper dermatitis, otitis externa, and impetiginized eczema.

(Ref: Katzung-13th edition)

Topical Antibacterial	Indication
Bacitracin (Ointment base alone or in combination with neomycin, polymyxin B, or both.)	• Gram-positive organisms such as streptococci, pneumococci, and staphylococci. • Most anaerobic cocci, neisseriae, tetanus bacilli, and diphtheria bacilli are sensitive.
Mupirocin (ointment)	• Most gram-positive aerobic bacteria, including methicillin-resistant <i>S aureus</i> (MRSA). • Impetigo caused by <i>S aureus</i> and group A β-hemolytic streptococci.
Retapamulin	• Group A β-hemolytic streptococci and <i>S aureus</i>, excluding MRSA.
Polymyxin B (solution or ointment)	• Gram-negative organisms, including <i>Pseudomonas aeruginosa</i>, <i>Escherichia coli</i>, enterobacter, and klebsiella.
Neomycin & Gentamicin (Powder, ointment or cream)	• Gram-negative organisms, including <i>E coli</i>, proteus, klebsiella, <i>P aeruginosa</i> and enterobacter. • Staphylococci and group A β-hemolytic streptococci.
Clindamycin (water-based gel and lotion)	• Acne
Erythromycin (water-based gel)	• Acne
Metronidazole (water-based gel)	• Rosacea

Sodium Sulfacetamide (10% lotion and as a 10% wash)	• Acne vulgaris and acne rosacea
---	--

(Ref: Katzung-13th edition)

Topical Antifungal Preparations

Topical Antifungal Agents	Topical formulation	Indications / Antifungal spectrum
Topical Azole Derivatives: Clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sulconazole, and sertaconazole	Cream or lotion and as vaginal cream or suppositories	• Dermatophytes (epidermophyton, microsporum, and trichophyton) • Yeasts (<i>Candida albicans</i> and <i>Pityrosporum orbiculare</i>)
Ciclopirox olamine	1% cream and lotion	• Inhibitory activity against dermatophytes, candida species, and <i>P orbiculare</i>.
Allylamines: Naftifine & Terbinafine	1% creams and other forms	• Highly active against dermatophytes but less active against yeasts.
Butenafine	1% cream	• superficial dermatophytosis
Tolnaftate	Cream, solution, powder, or powder aerosol	• Dermatophyte infections caused by epidermophyton, microsporum, and trichophyton. It is also active against <i>P orbiculare</i> but not against candida.
Nystatin	Oral suspension, vaginal tablet,	• Effective against <i>C albicans</i> infections but ineffective against dermatophytes.
Amphotericin B	Cream and lotion form	• Effective against <i>C albicans</i> infections but ineffective against dermatophytes.

(Ref: Katzung-13th edition)

Topical Antiviral Agents

Topical antiviral agents	Indication
1. Acyclovir (Zovirax) (5% ointment) 2. Penciclovir (1% cream) 3. Valacyclovir 4. Famciclovir	Herpes virus family, including herpes simplex types 1 and 2

Adverse effects: Adverse local reactions to acyclovir and penciclovir may include pruritus and mild pain with transient stinging or burning.

(Ref: Katzung-13th edition)

Ectoparasiticides

Ectoparasiticides	Indications
1. Permethrin (Cream)	• Pediculosis (1% cream) • Scabies (5% cream)
2. Lindane (Hexachlorocyclohexane) (shampoo or lotion)	• Pediculosis capitis or pubis
3. Crotamiton (cream or lotion)	• Scabies • Antipruritic
4. Sulfur	• Scabies <i>Although it is nonirritating, it has an unpleasant odor, is staining, and is thus disagreeable to use. It has been replaced by more aesthetic and effective scabicides in recent years, but it remains a possible alternative drug for use in infants and pregnant women.</i>
5. Malathion (0.5% lotion)	• Pediculosis

(Ref: Katzung-13th edition)

Treatment of Scabies

Scabies: Scabies is an infectious disease of the skin caused by the itch mite characterized by pruritic papular lesions along the burrows containing the mites and their eggs.

(Ref: Rashid, Khabir, Hyder-4th/264)

Causative agent: Female *Sarcoptes scabiei hominis*.

Site of lesion:

1. Around the finger webs, wrists, extensor aspect of elbows and axilla
2. Nipples in women & genitals in men
3. Around the umbilicus, lower abdomen, thighs and buttock
4. Feet and ankles
5. Palms in infants

Q. Outline the pharmacotherapy of scabies. (RU-15Ju)

Ans.

Treatment of scabies:

- a. Children should be excluded from the school until the day after treatment.
- b. All affected persons of a family should be treated simultaneously.
- c. Before treatment, all patients should have a good soap and warm water bath.
- d. **Scabicides:** The drugs used are-
 1. **Permethrin (Cream):** Single application of 5% cream is applied to the body from the neck down, left on for 8–14 hours, and then washed off.
 2. **Benzyl benzoate (25%) emulsion.**
 3. **Tetraethyl Monosulfiram (Tetmosol)**
 4. **Lindane (Hexachlorocyclohexane) (shampoo or lotion):** Single application to the entire body from the neck down, left on for 8–12 hours, and then washed off.
 5. **Crotamiton (10%) cream or lotion:** Two applications to the entire body from the chin down at 24-hour intervals, with a cleansing bath 48 hours after the last application.
 6. **Sulfur ointment (0.5 - 1 %)** in vaseline
- e. **Antipruritic agent:** Antihistamine
- f. A cleaning bath is taken two days after the last application, and changed to fresh cloths.

(Ref: Rashid, Khabir, Hyder-4th/264,265)

Chapter 17

Immunopharmacology

Immunization: It is defined as a technique by which immunizing agents are introduced into the body for the production of antibody to prevent disease.

Active Immunization: Active immunization consists of the administration of **antigen** to the host to induce formation of antibodies and cell-mediated immunity. Immunization is practiced to induce protection against many infectious agents and may utilize either inactivated (killed) materials or live attenuated agents.

(Ref: Katzung-13th edition)

Q. Active immunization is generally preferable to passive immunization- Explain.

Ans.

Active immunization is generally preferable to passive immunization—in most cases because higher antibody levels are sustained for longer periods of time, requiring less frequent immunization, and in some cases because of the development of concurrent cell-mediated immunity. However, active immunization requires time to develop and is therefore generally inactive at the time of a specific exposure (eg, for parenteral exposure to hepatitis B, concurrent hepatitis B IgG [passive antibodies] and active immunization are given to prevent illness).

(Ref: Katzung-13th edition)

Vaccine: Vaccine is an immune-biological substance designed to produce specific protection against a given disease.

(Ref: Park-20th/98)

Vaccines may be prepared from-

1. Live modified organisms
2. Inactivated or killed organisms
3. Extracted cellular fractions
4. Toxoids or
5. Combination of these

More recent preparations are-

1. Sub-unit vaccines
2. Recombinant vaccines.

(Ref: Park-20th/98)

Types of vaccines:

Live attenuated vaccines	Inactivated or killed vaccines	Toxoids	Cellular fractions	Combinations
Bacterial: • BCG • Typhoid oral • Plague Viral: • Oral polio • Yellow fever • Measles • Rubella • Mumps • Influenza Rickettsial: • Epi. typhus	Bacterial: • Typhoid • Cholera • Pertussis • C.S. meningitis • Plague Viral: • Rabies • Salk (polio) • Influenza • Hepatitis B • Japanese encephalitis • KFD	Bacterial: • Diphtheria • Tetanus	• Meningococcal vaccine • Pneumococcal vaccine	• Pentavalent vaccine (Diphtheria-pertussis-tetanus-hepatitis B-haemophilus influenza type b) • DT (Diphtheria- tetanus) • DP (Diphtheria- pertussis) • DPT and typhoid vaccine • MR (Measles and rubella) • DPTP (DPT plus inactivated polio)

(Ref: Park/20th/98,99)

Q. Define toxoid with example.

Ans.

Toxoid: These are vaccines prepared from toxin by inactivation (combining formaldehyde with toxin) which have no toxigenicity but retain antigenicity.

Example: Tetanus toxoid (TT), Diphtheria toxoid (DT).

(Ref: Park/20th/100)

Q. Discuss about EPI in Bangladesh.

Ans.

EPI: It means Expanded Programme of Immunization. It is a global programme on immunization launched in May 1974, by the WHO to protect all children of the World against six vaccine preventable diseases namely- Tuberculosis, Diphtheria, Whooping cough, Tetanus, Poliomyelitis & Measles. EPI in Bangladesh was formally launched on 7th April, 1979.

Now, hepatitis B vaccine to prevent hepatitis B, and haemophilus influenza type b (Hib) vaccine to prevent childhood meningitis and pneumonia have been added in EPI.

(Ref: Rashid, Khabir, Hyder-4th/408)

Vaccines used in EPI:

1. BCG vaccine
2. Pentavalent vaccine (Diphtheria-pertussis-tetanus-hepatitis B-haemophilus influenzae type b (Hib))
3. Oral polio vaccine (OPV)
4. Measles vaccine

EPI schedule in Bangladesh:

Vaccine	Dose	Age of Starting	No. of Dose	Interval between doses	Site of Vaccination	Route of Administration
BCG	0.05 ml	After birth	1	-	Upper & outer part of left arm (Deltoid region)	Intradermal
Pentavalent vaccine (Diphtheria-Pertussis-Tetanus-Hepatitis B-Haemophilus influenzae type b (Hib))	0.5 ml	6 weeks	3	4 weeks	Antero-lateral part of mid thigh	Intramuscular (IM)
Oral polio vaccine (OPV)	2-3 drops	6 weeks	4	4 weeks	Oral	Oral
MR (Measles-rubella)	0.5 ml	9 months	1	-	Antero-lateral part of mid thigh	Subcutaneous
Measles	0.5 ml	15 months	1	-	Antero-lateral part of mid thigh	Subcutaneous

Passive Immunization: Passive immunization consists of transfer of immunity to a host using preformed immunoglobulins. Passive immunization is useful for-

1. individuals unable to form antibodies (eg, congenital agammaglobulinemia);
2. prevention of disease when time does not permit active immunization (eg, postexposure);
3. for treatment of certain diseases normally prevented by immunization (eg, tetanus); and
4. for treatment of conditions for which active immunization is unavailable or impractical (eg, snakebite).

(Ref: Katzung-13th edition)

Examples of passive immunization

Indication	Product
Botulism	Botulism antitoxin, equine
Cytomegalovirus (CMV)	Cytomegalovirus immune globulin (IV)
Diphtheria	Diphtheria antitoxin, equine
Hepatitis A	Immune globulin (intramuscular, IM)
Hepatitis B	Hepatitis B immune globulin (HBIG)
HIV-infected children	Immune globulin (IV)
Measles	Immune globulin (IM)
Idiopathic thrombocytopenic purpura (ITP)	Immune globulin (IV)
Primary immunodeficiency disorders	Immune globulin (IV)
Rabies	Rabies immune globulin
Respiratory syncytial virus (RSV)	Palivizumab
Rubella	Immune globulin (IM)
Snake bite (coral snake)	Antivenin (<i>Micrurus fulvius</i>), equine
Snake bite (pit vipers)	Antivenin (Crotalidae) polyvalent, equine
	Antivenin (Crotalidae) polyvalent immune Fab, ovine
Tetanus	Tetanus immune globulin (TIG)
Varicella	Varicella-zoster immune globulin

(Ref: Katzung-13th edition)

Antisera / antitoxins: Antisera is the human or animal (eg, horse) serum containing one or more antibodies that are specific for one or more antigens and are administered to confer immunity. The antibodies in an antiserum result from previous immunization or exposure to an agent of disease.

Examples of antisera:

1. ATS: Anti-tetanus serum
2. ADS: Anti-diphtheria serum
3. ARS: Anti-rabies serum
4. AGS: Anti-gas gangrene serum

Adverse effects of antisera: Hypersensitivity reactions ranging from anaphylaxis to serum sickness may occur.

Chapter 18

PRACTICAL PHARMACOLOGY

**Abbreviations used in Prescription
Prescription Writing
Tracing
Case history writing
Drug interaction
Dosage formulation
OSPE**

Abbreviations used in Prescription

Abbreviation	Latin Elaboration	English meaning
Rx	Recipe	Take thou
a	Ante	Before
p	Post	After
d	Dies	Daily
bd	bis in die	twice a day
tds / tid	ter die sumendus	3 times a day
qid / qd / qds	quarter die sumendus	4 times a day
stat	statim	immediately
sos	Si opus sit	if necessary
Ag	Aqua	Water
AC	ante cibum	before meal
PC	post cibum	after meal
Syr	Syrupus	Syrup
Cap	Capsula	Capsule
Ad	Add/Ad	Upto
CM	Cas-mane	Next morning
Ft	Fiat	Let it be made
od	omni die	everyday
om	omni mane	every morning
on	omni nocte	every night
po	per os	by mouth
Gtt	Guttae	Drops
HS / hs	Hora somne	At bed time
lb	Librium	Pound
oz	Ozium	Ounce
dr	Drum	A drum (1 gin)
Mist	Misture	Mixture
Tab	Tabula	Tablet
M	Misce	Mix
Mft	Misce & fiat	Mix & let it be made
Gr	Granum	Grain
H or h	Hora	Hour
Sig	Siga	Leveling
Spt	Spiritus	Spirit
Tr	Tintura	Tincture
Pulv	Pulvis	Powder
Ung	Unguentum	Amount
USP	-	United state pharmacopoeia
BP	-	British pharmacopoeia
IU	-	International unit
USAN	-	United state approved name
BAN	-	British approved name
BNF	-	British national formulary
IV	-	Intravenous
IM	-	Intramuscular
S/C	-	Subcutaneous

Prescription Writing

Prescription: A prescription is a written order by a registered medical practitioner or a dentist to a pharmacist containing name of some drugs with their amount, doses & direction to the patient.

The prescription is the means by which medicines and efficacy and to prevent fraudulent misuse; full that are not considered safe for sale directly to the details will be found in national formularies and public are delivered to patients. Its format is officially prescribers have a responsibility to comply with regulated to ensure precision in the interests of safety these.

(Ref: Bennett & Brown-11th)

Types: There are two types of prescription:

1. **Precompounding prescription:** Prescription of already prepared drugs (by pharmaceutical companies).
Eg, Tab. Ciprofloxacin (500 mg), Cap. Omeprazole (20 mg), Inj. Ceftriaxone (1 g).
2. **Extemporaneous prescription:** The pharmacist prepares the medication according to the drugs, doses and dosage forms designated by the physician. Eg, dispense 10% unguentum sulpharis.

Another classification:

1. Outdoor patient prescription
2. Chart order prescription
3. General / ethical prescription

Parts of a prescription: An ideal prescription should have the following parts:

1. Superscription
2. Inscription
3. Subscription
4. Transcription
5. Signature

1. **Superscription:** It includes-
 - a) Information about the prescriber
 - b) Information about the patient
 - c) Rx (it means- take thou!)
2. **Inscription:** It includes-
 - a) Name of the drug (generic or trade name), eg, Ciprofloxacin.
 - b) Dosage formulation, eg, tablet, capsule, injection etc.
 - c) Unit dosage: Amount of drug per tablet, per capsule etc.
3. **Subscription:** It provides information to the pharmacist about the quantity and dosage formulation of the drug to be dispensed.
4. **Transcription:** It includes direction to the patient containing instruction about the amount of drug, time and frequency of doses to be taken.
5. **Signature:** Prescription should be signed by the prescriber.

Model of an ideal prescription

Dr. X..... MBBS, MD (Neuromedicine) Address:..... Phone no.....	Date:.....
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	
History: 1... 2... 3... Clinical features: 1... 2... 3... Investigations: 1... 2... 3... Diagnosis: Advice: 1... 2... 3...	Rx. Tab. Ciprofloxacin (500mg).....(total 14 tablets) 1 + 0 + 1 (7 days) Tab. Paracetamol (500 mg) 1 + 1 + 1 (After meal, if fever) Tab. Domperidone (10 mg) 1 + 1 + 1 (1/2 hour before meal, if vomiting)
Prescriber's signature:	

Superscription Dr. X..... Date:..... MBBS, MD (Neuromedicine) Address:..... Phone no.....	
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	

Inscription Tab. Ciprofloxacin (500mg)	Subscription Total 14 tablets
Transcription 1 + 0 + 1 (for 7 days)	
Signature	

Prescription for Tuberculosis (TB)

Dr. X..... MBBS, FCPS (Medicine) Address:..... Phone no.....	Date:.....
Patient's name:..... Age:..... Sex:..... Weight:..... 50 kg Address:..... Phone no.....	
Diagnosis: Pulmonary TB Advice: 1. Take drug regularly 2. Take high protein diet 3. Isolation of the patient until sputum is AFB negative. 4. Follow up monthly by Hb%, ESR, CXR, P/A view & sputum for AFB, liver function tests 5. If skin rash, yellow coloration of urine, please contact with the physician without omitting drugs. 6. Don't worry for orange coloration of urine.	Rx. Tab. 4-FDC 3 + 0 + 0 daily 1/2 hour before breakfast- 2 months. Tab. 2-FDC 3 + 0 + 0 daily 1/2 hour before breakfast- 4 months. Tab. Pyridoxine (20 mg)- 180 1 tab daily for 6 months. Prescriber's signature

Q. Justify combination therapy in tuberculosis:

Ans.

Combination therapy in tuberculosis

1. **To broaden the spectrum.**
2. **To prevent development of resistance:** Mycobacteria are notorious for their ability to develop resistance against drugs. Combinations of two or more drugs are required to overcome these obstacles and to prevent emergence of resistance during the course of therapy.
3. **To shorten duration of treatment:** Combination therapy reduces the total duration of treatment.
4. **To reduce individual toxic effect of a large dose of a single drug.** Eg, retrobulbar neuritis is a dose-related adverse effect of ethambutol. This dose-related side effect is more likely to occur at doses of 25 mg/kg/d continued for several months. At 15 mg/kg/d or less, visual disturbances are very rare.
5. **To increase chemotherapeutic potentiation:** One drug potentiates the other drug. Eg,
 - Ethambutol enhances the activity of rifampicin.
 - Pyrazinamide enhances the sterilizing ability of rifampicin.

(Ref: Katzung-13th)

Q. Tell one side effect of each drug.

Ans.

Isoniazid	1. Hepatitis 2. Peripheral neuropathy
Rifampicin	1. Causes harmless orange/red coloration of saliva, urine, sweat, tears, and contact lenses. 2. Liver damage- cholestatic jaundice and hepatitis
Pyrazinamide	1. Hepatotoxicity 2. Hyperuricemia leading to acute gouty arthritis
Ethambutol	1. Retrobulbar neuritis, resulting in loss of visual acuity and red-green color blindness.
Streptomycin	1. Ototoxicity 2. Nephrotoxicity

Prescription for acute bronchial asthma

Dr. X..... Date:..... MBBS, FCPS (medicine) Address:..... Phone no.....	
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	
Diagnosis: Acute bronchial asthma Advice: 1. Immediate hospitalization 2. Bed rest in propped up position 3. High flow O₂ (4-6 L/min) stat & SOS	Rx. Nebulization of 0.5 ml Sulbutamol respiratory solution + 0.5 ml Ipratropium bromide solution + 1-2 ml distilled water for 10 minutes. If not improved, repeat this every 30 min. Inj. Hydrocortisone (100 mg/vial) 1-2 vial IV stat and then 1 vial IV 6-8 hourly Inj. Aminophylline (125mg/amp) 2 amp in 500 ml 5% DA @ 10-15 drops/min Prescriber's signature

When the patient is stable, start treatment of chronic persistent asthma

Prescription for Chronic bronchial asthma

Dr. X..... Date:..... MBBS, FCPS (medicine) Address:..... Phone no.....	
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	
Diagnosis: Chronic bronchial asthma Advice: 1. Avoid dust, cold, pollen grains and other allergens. 2. Avoid smoking	Rx. Sulbutamol inhaler 2 puffs whenever dyspnea Ticamet inhaler (Salmeterol + Fluticasone) 2 puffs twice daily Continue Tab. Montelukast 10 mg 1 + 0 + 0 2 months Prescriber's signature

Prescription for enteric fever

Dr. X.....	Date:
MBBS, FCPS (medicine)	
Address:.....	
Phone no.....	
Patient's name:.....	Age: Sex: Weight:
Address:.....	
Phone no.....	
Diagnosis: Enteric fever Advice: - Bed rest till fever subsides. - Low residual diet and plenty of fluid by month. - Tepid sponging if temp high. - Hand should be washed with soap water before meal and after defecation. - Safe disposal of excreta should be ensured.	Rx. Tab. Ciprofloxacin (500mg).....(total 20 tablets) 1 + 0 + 1 <i>(10 days)</i> Tab. Paracetamol (500 mg) 1 + 1 + 1 <i>(After meal, if fever)</i> Tab. Domperidone (10 mg) 1 + 1 + 1 <i>(1/2 hour before meal, if vomiting)</i>
Prescriber's signature	

Drug of choice for enteric fever: Ciprofloxacin is the drug of choice now-a-days in the treatment of enteric fever, because-

1. It is bactericidal against *Salmonella typhi* and *paratyphi*.
2. Fewer side effects than Chloramphenicol, Co-trimoxazole.
3. Less rapid development of bacterial resistance.
4. Shorter duration of treatment with ciprofloxacin.
5. It also shows promise in reducing incidence of typhoid carrier states.

Prescription for Pneumonia

Dr. X..... Date:..... MBBS, FCPS (medicine) Address:..... Phone no.....	
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	
Diagnosis: Pneumonia Advice: 1. Tepid sponging if temp. is high 2. Chest X-ray P/A view after 10 days 3. Normal diet	Rx. Inj. Ceftriaxone 1 g/vial 1 vial IV daily for 14 days Tab. Clarithromycin (500 mg) 1+0+1 for 14 days Tab. Paracetamol (500 mg) 1+1+1 after meal until fever subsides Suppository paracetamol (500 mg) 1 stick per rectal if temp. > 102°F Prescriber's signature

Prescription for Urinary tract infection

Dr. X..... Date:..... MBBS, MD (Nephrology) Address:..... Phone no.....	
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	
Diagnosis: UTI Advice: 1. Plenty of fluid should be taken (at least 2 liters) 2. Take drug regularly 3. Urine culture. 4. Urine analysis, microscopy & culture should be repeated 5 days after therapy.	Rx. Tab. Ciprofloxacin (500 mg) 1 + 0 + 1 for 14 days Tab. Timonium methyl sulphate 1 + 1 + 1 If there is pain Prescriber's signature

Prescription for angina pectoris

Dr. X..... MBBS, MD (cardiology) Address:..... Phone no.....	Date:.....
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	
Diagnosis: Angina Pectoris Advice: 1. Immediate hospitalization 2. Complete bed rest. 3. Salt restricted diet. 4. Record Pulse, BP, Temp, RR every 30 minutes. 5. Avoid smoking, alcohol, fatty food.	Rx. Glyceryl trinitrate spray (Nitromint spray) 1-2 puffs sublingually stat & SOS Oxygen inhalation (4-6 L/min) Stat & SOS Tab. Aspirin (75 mg) 4 tab stat and then 0+1+0 (after meal) Cap. Omeprazole (20 mg) 1+0+1 (1/2 hr before meal) Tab. Isosorbide mono-nitrates (20 mg) 1 + 1 + 0 Inj. Pethidine (100mg) 1/2 amp I/V stat Inj. Prochlorperazine 1/2 amp I/V stat Syp. Lactulose 2-3 tsf tds Tab. Bromazepam (3mg) 0 + 0 + 1
Prescriber's signature	

Viva Q. Tell the role of GTN in angina pectoris.

Ans.

Glyceryl trinitrate (GTN) rapidly relieves chest pain of angina pectoris. It is widely used in anginal pain, because-

1. *Rapid onset of action when given sublingually (within 1-3 min)*
2. *Reduce cardiac O₂ consumption.*
3. *Dilates collateral vessels. So, improved perfusion to ischemic area.*
4. *Highly effective in acute anginal pain.*

Viva Q. Tell one side effect of GTN.

Ans.

Headache

Prescription for Myocardial infarction

Dr. X.....
 MBBS, MD (cardiology)
 Address:.....
 Phone no.....

Date:.....

Patient's name:..... Age:..... Sex:..... Weight:.....
 Address:.....
 Phone no.....

Diagnosis: Myocardial infarction

Advice:

1. Immediate hospitalization in the coronary care unit (CCU)
2. Complete bed rest.
3. Open IV access
4. Continuous cardiac monitoring of Pulse, BP, ECG.
5. Diet: Liquid & salt restricted.
6. Avoid smoking, alcohol, fatty food.

Rx.

Glyceryl trinitrate spray (Nitromint spray)
 1-2 puffs sublingually stat & SOS

Oxygen inhalation (4-6 L/min) Stat & SOS

Inj. Streptokinase (1.5 million unit)
 1 vial in 100 ml of 5% DA @ 100 microdrops/min over 1 hour

Inj. Hydrocortisone (100 mg)
 1-2 vial IV stat

Tab. Aspirin (75 mg)
 4 tab stat and then 0+1+0 (after meal)

Inj. Pethidine (100mg)
 $\frac{1}{2}$ - $\frac{2}{3}$ amp I/V stat

Inj. Prochlorperazine (12.5 mg)
 1 amp I/V stat

Cap. Omeprazole (20 mg)
 1+0+1 (1/2 hr before meal)

Tab. Isosorbide mono-nitrates (20 mg)
 1 + 1 + 0

Syp. Lactulose
 2-3 tsf tds

Tab. Bromazepam (3mg)
 0 + 0 + 1

Prescriber's signature

Prescription for peptic ulcer disease

Dr. X..... MBBS, MD (Gastroenterology) Address:..... Phone no.....	Date:.....
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	
Diagnosis: Peptic ulcer disease (<i>H. pylori</i> induced)	Rx. Tab. Clarithromycin 500 mg (7 days) 1 + 0 + 1 Cap. Amoxicillin 1 gm (7 days) 1 + 0 + 1 Cap. Omeprazole (20 mg) 1 + 0 + 1 (<i>1/2 hr before meal for 7 days</i>) After 7 days, Cap. Omeprazole (20 mg) 1 + 0 + 0 (<i>1/2 hr before meal for 30 days</i>)
Advice: 1. Physical rest till pain subsides 2. Avoid anxiety, tension. 3. Avoid smoking, alcohol, excess tea, and spicy foods. 4. Don't take NSAIDs and steroid tablet in empty stomach. 5. Take nutritious food regularly without spices.	Prescriber's signature

Drug of choice for peptic ulcer disease: Omeprazole is the drug of choice in peptic ulcer disease.

Mechanism of action of Omeprazole: It inhibits proton pump by inhibiting H^+-K^+ ATPase.

Prescription for Scabies

Dr. X..... MBBS Address:..... Phone no.....	Date:.....
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	
Diagnosis: Scabies	Rx. Permethrine 5% cream Apply once over the whole body except face and wash off after 24 hours
Advice: 1. All cloths should be boiled. 2. All other family members should be treated properly & simultaneously	Prescriber's signature

Prescription for chronic heart failure

Dr. X..... Date:..... MBBS, MD (Cardiology) Address:..... Phone no.....	
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	
Diagnosis: Chronic heart failure Advice: 1. Reduction of physical activity but encourage low level of stamina building exercise 2. Salt restricted diet.	Rx. Tab. Frusemide (40 mg) Till edema subsides 1 + 1 + 0 Syp. KT (Potassium) 2 tsf tds after meal Tab. Captopril (25 mg) 1/2 + 0 + 1/2 Continue Tab. Spironolactone (25 mg) Till edema subsides 1 + 1 + 0 Tab. Carvedilol (6.25 mg) Continue ½ + 0 + ½ for 2 weeks then 1 + 0 + 0 Tab. Digoxin (0.25 µg) Continue (except Friday) 2 + 0 + 2 for 2 days, then 1 + 0 + 0 Prescriber's signature

Prescription for Malaria

Dr. X..... Date:..... MBBS Address:..... Phone no.....	
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	
Diagnosis: Malaria (Uncomplicated falciparum malaria) Advice: 1. Tepid sponging regularly 2. Take normal diet 3. Drink plenty of water 4. Sleep under mosquito net	Rx. Tab. Coartem (Artemether + Lumefantrine) 1 st dose: 0 hour 2 nd dose: 8 hour 3 rd dose: 24 hour 4 th dose: 36 hour 5 th dose: 48 hour 6 th dose: 60 hour (Total 6 doses in 3 days) Tab. Primaquine (15 mg) 3 tabs single dose on day 4 Tab. Paracetamol (500 mg) 1+1+1 After meal until fever subsides Prescriber's signature

Prescription for Diabetes mellitus

Dr. X..... Date:..... MBBS, FCPS Address:..... Phone no.....	
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	
Diagnosis: DM Advice: 1. Diabetic diet 2. Regular exercise 3. Avoid excess sugar, sweetmeat. 4. Take more vegetable 5. Testing urine glucose for follow-up	Rx. Inj. Soluble Insulin HM 100 6 units S/C by insulin syringe just before breakfast 6 units S/C by insulin syringe just before lunch 6 units S/C by insulin syringe just before dinner Prescriber's signature

NB: The dose of insulin mentioned above is just an example. It should be adjusted by monitoring blood glucose.

Prescription for iron deficiency anemia

Dr. X..... Date:..... MBBS, FCPS Address:..... Phone no.....	
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....	
Diagnosis: Iron deficiency anemia Advice: Take iron containing foods 1. Meat 2. Egg 3. Liver 4. Green banana 5. Vegetables	Rx. Tab. Ferrous sulphate (200mg) 1+1+1 (Continue for 3 months after correction of anemia) Tab. Albendazole (400 mg) 1 tab at night on 1 st day to be chewed 1 tab at night on 14 th day to be chewed Tab. Vitamin B complex 0 + 1 + 0 ---- 6 months Signature.

Prescription for ascariasis

Dr. X..... MBBS Address:..... Phone no.....		Date:.....
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....		
Diagnosis: Ascariasis Advice: 1. Hand washing with soap water before meal & after defecation 2. Proper disposal of excreta 3. Other family members should be treated at the same time.	Rx. Tab. Albendazole (400 mg) 1 tab at night on 1 st day to be chewed 1 tab at night on 14 th day to be chewed Signature.	

Prescription for bacillary dysentery

Dr. X..... MBBS Address:..... Phone no.....		Date:.....
Patient's name:..... Age:..... Sex:..... Weight:..... Address:..... Phone no.....		
Diagnosis: Bacillary dysentery Advice: 1. Maintain personal hygiene 2. Hand washing with soap water before meal & after defecation 3. Proper disposal of excreta 4. Take non-residual diet, eg, dhai and chira 5. Adequate intake of fluid	Rx. Tab. Ciprofloxacin (500mg) 06 1 + 0 + 1 --- for 3 days Oral rehydration saline (ORS)- Take frequently by mouth if loose motion Tab. Timonium methyl sulphate (50 mg) 1 + 1 + 1 If there is abdominal cramp or pain Prescriber's signature	

Prescription for amebic dysentery

Dr. X.....		Date:.....	
MBBS			
Address:.....			
Phone no.....			
Patient's name:.....		Age:.....	Sex:..... Weight:.....
Address:.....			
Phone no.....			
Diagnosis: Amebic dysentery		Rx.	
Advice: 1. Maintain personal hygiene 2. Hand washing with soap water before meal & after defecation 3. Proper disposal of excreta 4. Take non-residual diet, eg, dhai and chira 5. Adequate intake of fluid		Tab. Metronidazole (400mg) 21	
		1 + 1 + 1 for 7 days	
		Oral rehydration saline (ORS)- Take frequently by mouth if loose motion	
		Tab. Timonium methyl sulphate (50 mg)	
		1 + 1 + 1 If there is abdominal cramp or pain	
		Prescriber's signature	

Tracing

Tracing no: 01

Name of the tracing: Effects of adrenaline and noradrenalin on BP.

Observation:

- This is a Brodie's kymographic tracing of BP from the common carotid artery of a Pentobarbitone anaesthetized cat showing the effect of Adrenaline and noradrenalin on BP.
- At first, we recorded the baseline BP. Then we administered Adrenaline and there was a sharp rise of BP & immediate return of BP to baseline. We again administered same dose of Adrenaline, which showed the same effect.
- Then we administered noradrenalin and there was a sharp rise of BP that is greater than that of adrenaline and immediate return of BP to baseline.

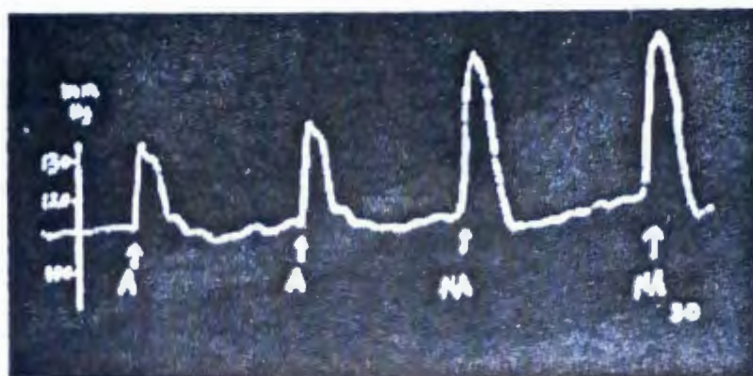


Figure 01. Kymographic tracing showing the effects of Adrenaline & Noradrenalin on blood pressure of a pentobarbitone anaesthetized cat.

Interpretation:

1. At first when we administered Adrenaline, there was a sharp rise of BP. This is because adrenaline acted on α_1 receptor causing vasoconstriction and β_1 receptor increasing heart rate & force of contraction. Both effects increased BP. But it also activates β_2 receptors in the blood vessels supplying skeletal muscles resulting in vasodilation in skeletal muscles and some decrease in BP. But the net effect is increased BP.
2. BP sharply came back to baseline due to the reuptake of Adrenaline by uptake-II mainly & some portion by uptake-I and by circulating MAO and COMT enzymes.
3. When we administered noradrenalin, it caused sharp rise of blood pressure which is greater than that of Adrenaline. This is because it has prominent α_1 and β_1 effect but no β_2 effect.
4. BP sharply came back to baseline because of the reuptake of noradrenalin by Reuptake-I mainly (80%) & by Reuptake-II (20%) & by circulating enzyme MAO and COMT.

Tracing no: 02

Name of the tracing: Effects of Histamine and Acetylcholine on BP.

Observation:

- This is a Brodie's kymographic tracing of BP, recorded from the common carotid artery of a Pentobarbitone anaesthetized cat showing the effects of Histamine and Acetylcholine on BP.
- At first, we recorded the baseline BP. Then we administered 5µg/kg Histamine that caused sharp fall of blood pressure and immediate return of BP to baseline. We again administered same dose of Histamine, which showed the same effect.
- Then we administered 5µg/kg Acetylcholine and there was a sharp fall of blood pressure and immediate return of BP to baseline. We did the same experiment, which showed the same effect.

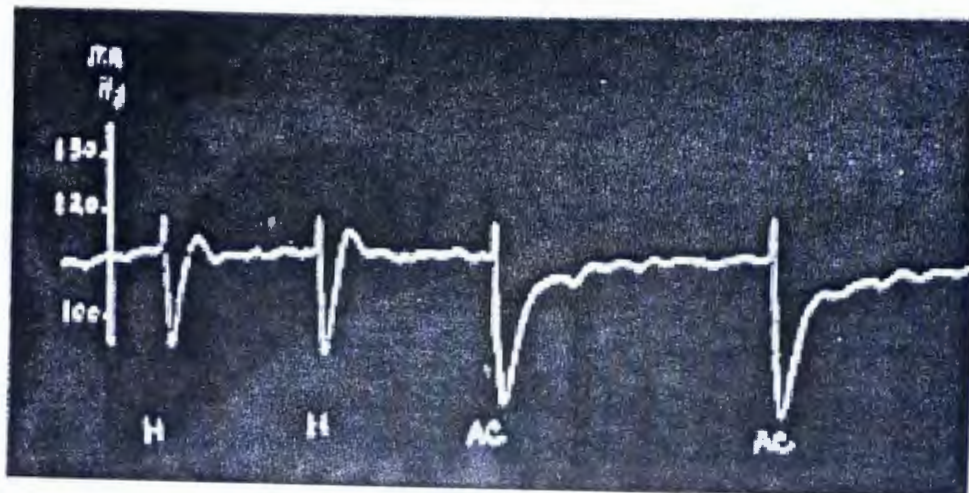


Figure 02. Kymographic tracing of the blood pressure record from the common carotid artery of a pentobarbitone anaesthetized cat.

Drug injected intravenously at:

H- 5µg/kg Histamine;

AC- 5µg/kg Acetylcholine

Interpretation:

1. When we administered Histamine, it caused sharp fall of blood pressure because it acted on H₁ receptor of arterioles and met-arterioles & caused vasodilatation & fall in PR and BP.
2. BP sharply came back to normal, because of the metabolism of histamine.
3. When we administered ACh, there was a sharp fall of BP due to its direct vasodilatory effect by releasing NO from intact blood vessel and negative inotropic and chronotropic effect.
4. BP sharply came back to normal, because of the metabolism of acetylcholine by cholinesterase.

Tracing no: 03

Name of the tracing: Effects of Acetylcholine and Atropine on blood pressure.
Or,
Effects of Cholinergic and Anti-cholinergic drug on blood pressure.

Observation:

- This is a Brodie's kymographic tracing of BP, recorded from the common carotid artery of a Pentobarbitone anaesthetized cat showing the effect of Acetylcholine on blood pressure before and after Atropine administration.
- Drugs were administered by the way of cannulated external jugular vein. At first we recorded baseline BP. Then we administered $5\mu\text{g/kg}$ Acetylcholine IV and there was sharp fall of BP and immediate return to baseline BP. We again administered same dose of ACh, which shows the same effect.
- Then we administered $10\mu\text{g/kg}$ Atropine. There is no change in BP. After this we administered $5\mu\text{g/kg}$ ACh, which showed gradual rise of BP & gradually it comes back to baseline.

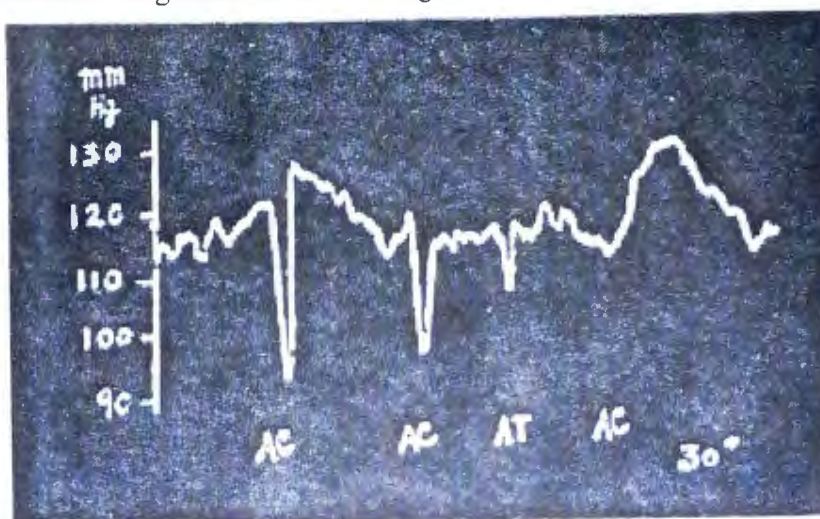


Figure: 03. Kymographic tracing of the blood pressure recorded from the common carotid artery of a pentobarbitone anaesthetized cat.

Drug injected intravenously at:

AC- $5\mu\text{g/kg}$ Acetylcholine and

AT- $10\mu\text{g/kg}$ Atropine

Interpretation:

1. At first we administered ACh. There was sharp fall of blood pressure due to direct vasodilatory effects of ACh by releasing NO from intact blood vessels and negative inotropic and chronotropic effect.
2. There was immediate return of BP to baseline BP due to hydrolysis of ACh by cholinesterase.
3. When we administered atropine; it blocked muscarinic receptors and didn't stimulate it. So there was no change in BP.
4. After this when we administered ACh, it acted on nicotinic receptors & caused release of noradrenaline and adrenaline from the sympathetic nerve endings & adrenaline from the adrenal medulla. They increased BP by increasing heart rate, force of contraction and vasoconstriction. During this time, ACh could not act on muscarinic receptors, because they were blocked by atropine.
5. There was slow return of BP to normal due to uptake of noradrenalin by uptake-1.

Tracing no: 04

Name of the tracing: Effects of Histamine and Anti-histamine (promethazine) on BP.
Or,
Effects of Histamine and promethazine on BP.

Observation:

- This is a Brodie's kymographic tracing of BP recorded from common carotid artery of a Pentobarbitone anaesthetized cat showing the effect of Histamine and Anti-histamine on BP.
- At first we recorded baseline BP & then administered 3 µg/kg Histamine which caused sharp fall of BP and immediate return of BP to baseline. Then we administered same dose of Histamine, which showed the same effect.
- Then we administered 1 µg/kg Antihistamine (promethazine). After this we administered 5 µg/kg Histamine which showed no change in BP.

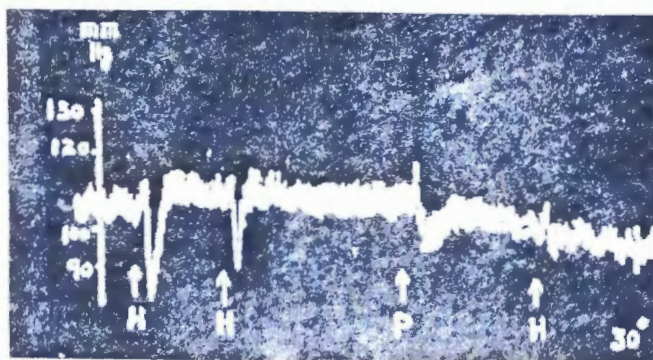


Figure 04: Kymographic tracing of the blood pressure record from the common carotid artery of a pentobarbitone anaesthetized cat.

Drugs were administered by way of cannulated external jugular vein, at H- 3 µg/kg Histamine; P- 1 µg/kg promethazine.

Interpretation:

1. When we administered Histamine, there is sharp fall of BP. This was because, histamine acted on H₁-receptor causing vasodilatation of arterioles and met-arterioles and decreased peripheral resistance and BP.
2. When we administered anti-histamine, it has blocked H₁-receptor.
3. After this when we administered histamine again, there is no effect. This was because H₁-receptors were already blocked by antihistamine.

Tracing no: 05

Name of the tracing: Effects of adrenalin, phenoxybenzamine and propranolol on blood pressure.
Or,
Effects of adrenergic and anti-adrenergic drugs on blood pressure.

Observation:

- This is a Brodie's kymographic tracing of blood pressure recorded from the common carotid artery of a Pentobarbitone anaesthetized dog showing the effect of adrenaline on blood pressure before and after phenoxybenzamine and after propranolol without phenoxybenzamine.
- At first, we recorded baseline BP. Then we administered 5 µg/kg of adrenaline I/V and there was a sharp rise of BP recorded and immediate return of BP to baseline. We again administered same dose of adrenaline, which showed the same effect.
- Then we administered 3 µg/kg of phenoxybenzamine and there was no change in BP. After this we administered 5 µg/kg adrenaline again. There was gradual fall of BP and gradually it came back to baseline. We again administered the same dose of adrenaline that shows the same effect.

- Then we administered 50 $\mu\text{g/kg}$ of propranolol and there was no change in BP. After this we administered 5 $\mu\text{g/kg}$ of adrenaline that showed no effect.



Figure 05: Kymographic tracing of the blood pressure recorded from the common carotid artery of a pentobarbitone anaesthetized dog.

Drug injected intravenously, at A- 5 $\mu\text{g/kg}$ of adrenaline; P- 3 $\mu\text{g/kg}$ of phenoxybenzamine, I- 50 $\mu\text{g/kg}$ of propranolol (Inderal).

Interpretation:

1. At first when we administered Adrenaline, there was a sharp rise of BP. This is because adrenaline acted on α_1 receptor causing vasoconstriction and β_1 receptor increasing heart rate & force of contraction. Both effects increased BP. But it also activates β_2 receptors in the blood vessels supplying skeletal muscles resulting in vasodilation in skeletal muscles and some decrease in BP. But the net effect is increased BP.
2. BP sharply came back to baseline due to the reuptake of Adrenaline by uptake-II mainly & some portion by uptake-I and by circulating MAO and COMT enzymes.
3. When we administered phenoxybenzamine, it caused no change, because it irreversibly blocked α receptors without causing vasoconstriction. So it is a α receptor antagonist.
4. We again administered same dose of adrenaline and there was gradual fall of BP. This time adrenaline stimulated β_2 -receptors situated in blood vessels of skeletal muscles causing vasodilatation that resulted in fall in PR and BP. Gradually BP came back to baseline due to the metabolism of adrenaline by MAO and COMT. This time adrenaline could not bind to α receptors, because they were already blocked by phenoxybenzamine.
5. With the same dose of adrenaline without phenoxybenzamine, the effect was observed. This proved that phenoxybenzamine irreversibly blocked α receptors.
6. When we administered propranolol, it blocked β -receptors. After this, when we administered same dose of adrenaline, there is no change in kymograph. This is because at this time adrenaline could not bind to α receptor or β receptor. So there was no rise or no fall of BP.

Tracing no: 06

Name of the tracing: Effects of adrenaline, noradrenalin & ephedrine on blood pressure.

Observation:

- This is a Brodie's kymographic tracing of blood pressure recorded from the common carotid artery of a Pentobarbitone anaesthetized cat showing the effect of Adrenaline, Nor-adrenaline & Ephedrine on BP.
- At first, we recorded the baseline BP. Then we administered Adrenaline and there was sharp rise of BP & immediate return of BP back to baseline.
- Then we administered Noradrenalin which also increased BP and there was immediate return of BP back to baseline. Noradrenalin increased BP more than adrenaline.
- Then we administered Ephedrine. BP increased slowly and came back slowly to normal.

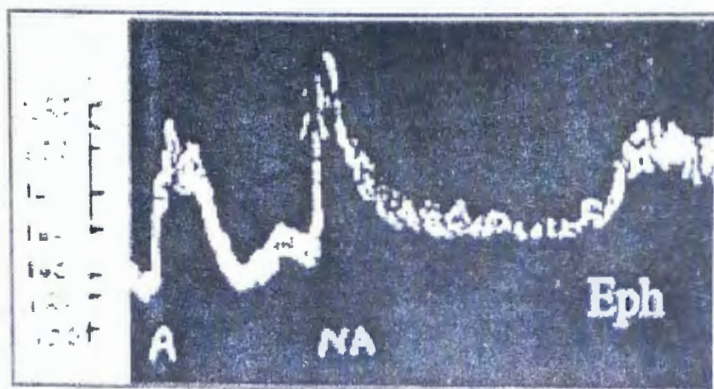


Figure 06. Kymographic tracing showing the effects of Adrenaline, Noradrenalin & Ephedrine on blood pressure of a pentobarbitone anaesthetized cat.

Drug injected intravenously, at

A- 10 µg/kg of adrenaline

NA- 10 µg/kg of noradrenalin

Eph- 10 µg/kg of Ephedrine

Interpretation:

1. At first when we administered Adrenaline, there was a sharp rise of BP. This is because adrenaline acted on α_1 receptor causing vasoconstriction and β_1 receptor increasing heart rate & force of contraction. Both effects increased BP. But it also activates β_2 receptors in the blood vessels supplying skeletal muscles resulting in vasodilation in skeletal muscles and some decrease in BP. But the net effect is increased BP.
2. BP sharply came back to baseline due to the reuptake of Adrenaline by uptake-II mainly & some portion by uptake-I and by circulating MAO and COMT enzymes.
3. When we administered noradrenalin, it caused sharp rise of blood pressure which is greater than that of Adrenaline. This is because it has prominent α_1 and β_1 effect but no β_2 effect.
4. BP sharply came back to baseline because of the reuptake of noradrenalin by Reuptake-I mainly (80%) & by Reuptake-II (20%) & by circulating enzyme MAO and COMT.
5. When we administered Ephedrine, it causes slow rise of BP by direct & indirect (causes release of catecholamines) effects.

Tracing no: 07

Name of the tracing: Effects of adrenaline and phenoxybenzamine on blood pressure

Observation:

- This is a Brodie's kymographic tracing of BP recorded from the common carotid artery of a pentobarbitone anaesthetized dog showing the effect of adrenaline on BP before and after phenoxybenzamine.
- At first, we recorded baseline BP. Then we administered 5 $\mu\text{g}/\text{kg}$ of adrenaline I/V and there was sharp rise of BP recorded and sharply it came back to baseline.
- Then we administered 1 mg/kg of phenoxybenzamine and there was no change. After this we administered 5 $\mu\text{g}/\text{kg}$ of adrenaline again. There is gradual fall of BP and gradually it came back to baseline.

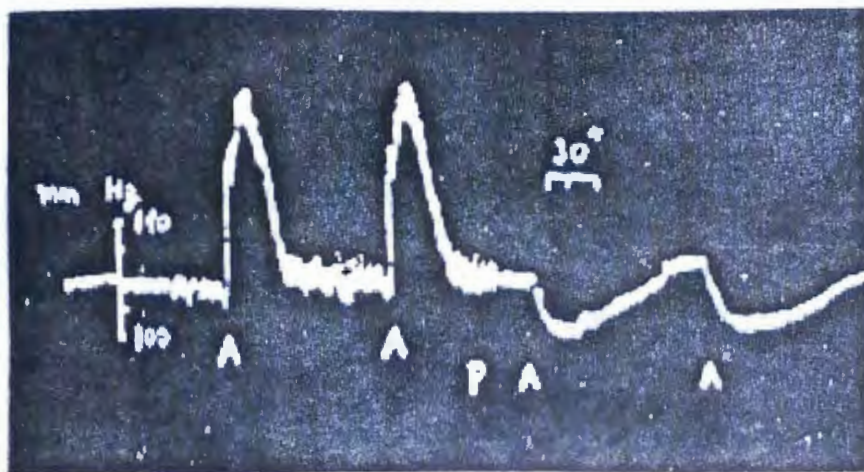


Figure 07. Kymographic tracing of the blood pressure recorded from the common carotid artery of a pentobarbitone anaesthetized dog.

Drug injected intravenously, at A— 5 $\mu\text{g}/\text{kg}$ of adrenaline; P— 1 mg/kg of phenoxybenzamine

Interpretation:

1. At first when we administered Adrenaline, there was a sharp rise of BP. This is because adrenaline acted on α_1 receptor causing vasoconstriction and β_1 receptor increasing heart rate & force of contraction. Both effects increased BP. But it also activates β_2 receptors in the blood vessels supplying skeletal muscles resulting in vasodilation in skeletal muscles and some decrease in BP. But the net effect is increased BP.
2. BP sharply came back to baseline due to the reuptake of Adrenaline by uptake-II mainly & some portion by uptake-I and by circulating MAO and COMT enzymes.
3. When we administered phenoxybenzamine, it caused no change, because it irreversibly blocked α receptors without causing vasoconstriction. So it is a α receptor antagonist.
4. We again administered same dose of adrenaline and there was gradual fall of BP. This time adrenaline stimulated β_2 -receptors situated in blood vessels of skeletal muscles causing vasodilatation that resulted in fall in PR and BP. Gradually BP came back to baseline due to the metabolism of adrenaline by MAO and COMT. This time adrenaline could not bind to α receptors, because they were already blocked by phenoxybenzamine.
5. With the same dose of adrenaline without phenoxybenzamine, the effect was observed. This proved that phenoxybenzamine irreversibly blocked α receptors.

Case History Writing

Case no- 01: Clinical diagnosis: Acute exacerbation of Bronchial Asthma

Name: Mr. Elias Molla

Age: 35 years

Sex: Male

Religion: Islam

Marital status: Married

Occupation: Service holder

Address: Bakshibazar, Dhaka

Ward no. 4

Bed no. 10

Date of admission: 05.11.2010

Date of discharge: 08.11.2010

Chief complaints:

1. Severe respiratory distress for 3 hours.
2. Cough for the same duration

History of present illness: According to the statement of the patient he was reasonably well 3 hours back. Then he developed severe respiratory distress which was so severe that he could not complete one sentence in one breath. He gave history of the same attack in the past, especially during cold climate and exposure to dust. Breathlessness was associated with cough productive of thick, tenacious sputum. With these complaints he got admitted into DMCH for proper management.

History of past illness: Recurrent attack of bronchial asthma

Drug history: He has been taking salbutamol inhaler when there was attack.

Family history: Nothing contributory

Personal history: He is a smoker and takes 10 sticks per day for the last 10 years.

General examination:

Appearance: Ill looking, dyspneic

Body built: Average

Co-operation: Co-operative

Decubitus: Propped up position

Nutrition: Average

Cyanosis: Present

Edema: Absent

Clubbing: Absent

Neck vein: Not engorged

Pulse: 100 beats/mm

BP: 120/80 mmHg

Respiratory rate: 30/min

Temperature: 98°F

Systemic examination:

A. Respiratory system:

Inspection:

1. Signs of dyspnea are present
2. Rate of respiration is increased, rhythm is normal
3. Movement of the chest wall is bilaterally restricted

Palpation:

1. Position of trachea: Central
2. Position of apex beat: In left 5th intercostal space

Auscultation:

1. Rhonchi found during expiration & it is high pitched.

B. **Cardiovascular system:** No abnormality detected

C. **Alimentary system:** No abnormality detected

Investigations:

- a) Chest X-ray P/A view: Hyper-inflated lung fields.
- b) Pulmonary function test:
 - Peak expiratory flow rate: Reduced
 - FEV1: 60%
 - Vital capacity: Decreased.

Confirmatory diagnosis: Acute exacerbation of Bronchial Asthma.

Treatment:**A. General:**

1. Bed rest in propped up position
2. O₂ inhalation
3. Avoidance of allergens

B. Specific:

1. Nebulization with 0.5 ml salbutamol respiratory solution + 0.5 ml ipratropium bromide + 1.5 ml distilled water- stat and sos
2. Inj. Hydrocortisone (100mg)
2 vial IV stat and then 1 vial IV 8 hourly
3. Inj. Aminophylline: IV or IM
Loading dose —5 mg/kg over 20 minutes, followed by slow infusion with 5% DA.
4. Salbutamol inhalation: 2 puffs tds
5. Budesonide inhalation: 2 puffs bid

Drug discussion:**Aminophylline:**

- **Group:** Bronchodilator
- **Mechanism of action:** Aminophylline → (-) Phosphodiesterase → ↑cAMP or cGMP → Relaxation of bronchial smooth muscle → Bronchodilation.
- **Adverse effects:**
 - a. Headache
 - b. Dizziness
 - c. Tachycardia
 - d. Palpitation

Salbutamol:

- **Group:** Bronchodilator
- **Pharmacological effect:**
 1. Stimulates β_2 receptors and causes relaxation of bronchial smooth muscle → Bronchodilation.
 2. Stabilizes mast cell membrane → ↓Histamine release.
- **Adverse effects:**
 - a. Nervousness
 - b. Tachycardia
 - c. Headache

- d. Tremor
- e. Dizziness

Conclusion: After 3 days of treatment he become comparatively well without any marked toxicity. Patient was discharged from the hospital with the treatment of chronic persistent asthma and advice to be on regular check up at outdoor patient department.

Case no 2: Clinical diagnosis: Urinary tract infection with pregnancy

Name: Farhana Yasmin

Age: 25 years

Sex: Female

Religion: Islam

Marital status: Married

Occupation: College teacher

Address: Mirpur, Dhaka

Ward no. 19

Bed no. 10

Date of admission: 05.07.2010

Date of discharge: 10.07.2010

Chief complaints (C/C):

1. Burning sensation on micturition for 5 days
2. Fever & lower abdominal pain for 6 days
3. Amenorrhea for 8 months

History of present illness: According to the statement of the patient she was reasonably well 6 days back. Then she developed low grade intermittent fever & colicky lower abdominal pain with no radiation. For the last 5 days she has been suffering from burning sensation on micturition and incomplete voiding. With these complaints she got admitted into DMCH for proper management. She has been also amenorrheic for last 8 months.

History of past illness: Nothing contributory

Drug history: She had taken some analgesic but got little improvement.

Family history: Nothing contributory.

General examination:

Appearance: Anxious

Body built: Below average

Co-operation: Co-operative

Decubitus: On choice

Nutrition: Average

Intelligence: Average

Edema: Absent

Pulse: 100 beats/min

BP: 120/80 mmHg

Respiratory rate: 15 breaths/min

Temperature: 98°F

Systemic examination:

A. Abdomen:

Inspection:

- Abdomen is uniformly enlarged.
- Stria gravidarum is present.

Palpation:

- Height of uterus: Corresponding to 32 weeks
- Fetal movement: Present
- Tenderness at loin & renal angle: Absent

Percussion:

- Percussion note is resonant on both flanks; dull centrally over the uterus.

Auscultation:

- Fetal heart sound: Present; 142 beats/min

B. Cardiovascular system: No abnormality detected

C. Respiratory system: No abnormality detected

Clinical diagnosis: Urinary tract infection with 32 week of pregnancy.

Investigations:**a. Routine blood examination:**

Hb%: 12 gm/dl

ESR: 22 mm in 1st hour

TC of WBC: 13000/mm³ of blood

DC of WBC:

Neutrophil: 80%

Lymphocyte: 30%

Eosinophil: 03%

Monocyte: 02%

Basophil: 00%

b. Urine for routine & microscopic examination (R/M/E): Pus cell: 20/HPF

c. Urine culture: Growth of E. coli 10⁶/ml.

d. Blood urea: 18 mg/ml

e. Serum creatinine: 0.8 mg/dl

f. Ultrasonography of abdomen: 32 weeks of pregnancy with live fetus

Confirmatory diagnosis: Urinary tract infection with 32 weeks of pregnancy.

Treatment:**General measure:**

1. Bed rest
2. Plenty of fluid
3. Frequent bladder emptying
4. Tab. Paracetamol 500 mg 3 times daily till the fever subsides
5. Tab. Timonium methyl sulphate 3 times daily for lower abdominal pain

Special management: Cap. Cephalexin 500 mg 6 hourly for 7 days

Advice:

1. Adequate intake of fluid, at least 2 L/min
2. Frequent bladder emptying
3. Antibiotic should be taken in proper time and full course should be completed
4. Urine should be collected for culture 2 weeks after stoppage of antibiotic course.

Drug discussion:**Pharmacokinetics:**

- **Paracetamol:** Tablet is well-absorbed from gut, small volume of distribution, half life 2 hours, metabolized in liver and excreted through kidney.

- **Cephalexin:** Oral capsule, variable absorption from gut, wide volume of distribution, half life 1 hour, metabolized in liver and 88% excreted through kidney.

Pharmacodynamics:

- **Paracetamol:** Inhibits PG synthesis in the brain, potent anti-pyretic
- **Cephalexin:** A first generation cephalosporin, broad spectrum, bactericidal by inhibiting cell wall synthesis and safe in pregnancy.

Drug interaction: No drug interaction

Rational criticism of management of the patient:

1. Proper and rational drug was chosen for the patient.
2. Antibiotic was given for 7 days which would be sufficient to eliminate bacteria.
3. Regular follow-up thorough the rest of the pregnancy.

Case no 3: A case record on Diabetes Mellitus (DM) with peripheral neuropathy

Name: Mr. Zahir

Age: 45 years

Sex: Male

Religion: Islam

Marital status: Married

Occupation: Service holder

Address: Faridganj, Chandpur

Ward no. 4

Bed no. 10

Date of admission: 05.08.2010

Date of discharge: 10.08.2010

Chief complaints (C/C):

1. Increased frequency of micturition for 3 years.
2. Increased thirst and hunger for 2 years.
3. Ulcer in the right leg for 1 year.

History of present illness: According to the statement of the patient he was reasonably well 3 years back. Then he gradually developed a state of frequency of micturition for 3 years. There is increased thirst and hunger for 2 years and generalized weakness for 1 year. He also complains a large ulcer in the right leg for 1 year. With these above complaints he got admitted into DMCH for proper management.

History of past illness: Nothing contributory

Drug history: He had taken medicine but unable to mention the name.

Family history: His father had same complaints.

General examination:

Appearance: Anxious

Body built: Below average

Co-operation: Co-operative

Decubitus: On choice

Nutrition: Average

Intelligence: Average

Anemia: Absent

Jaundice: Absent

Cyanosis: Absent

Edema: Absent

Clubbing: Absent

Dehydration: Absent

Koilonychia: Absent

Lymph node: Not enlarged

Neck vein: Not engorged
Pulse: 100 beats/min
BP: 120/80 mmHg
Respiratory rate: 15 breaths/min
Temperature: 98°F
Others: There is a large ulcer in the right leg

Systemic examination:

A. Nervous system:

- **Higher psychic function:** Intact
- **Motor function test:** Intact
- **Tendon reflex:** Diminished
- **Plantar & ankle jerks:** Normal
- **Clonus:** Absent
- **Sensory function:** Diminished

B. Cardiovascular system: No abnormality detected

C. Alimentary system: No abnormality detected

D. Respiratory system: No abnormality detected

E. Ophthalmoscopic examination: Normal

Salient features: Mr. Zahir, 45 years old, coming from Faridganj, Chandpur, was admitted in the DMCH with the complaints of increased frequency of micturition for 3 years, increased thirst and hunger for 2 years, and a large ulcer in his right leg for 1 year. On examination, the vital signs of the patient are stable and there was a large ulcer in right leg and there was sensory impairment.

Clinical diagnosis: Diabetes mellitus with peripheral neuropathy

Investigations:

a. Routine blood examination:

Hb%: 12 gm/dl
 ESR: 12 mm in 1st hour
 TC of WBC: 7000/mm³ of blood
 DC of WBC:
 Neutrophil: 70%
 Lymphocyte: 30%
 Eosinophil: 03%
 Monocyte: 02%
 Basophil: 00%

b. Urine for routine & microscopic examination (R/M/E):

Colour: Orange
 Sugar: Present (+++)
 Ketone bodies: Present
 Pus cell: 3/HPF
 Epithelial cells: 1-2/HPF
 Albumin: Nil

c. Special investigation:

Fasting blood sugar level: 9 mmol/L
 Blood sugar 2 hours after meal: 16 mmol/L
 Oral glucose tolerance test (OGTT): Cross renal threshold level.
 Estimation of HbA_{1c}: 9%
 Serum creatinine: 1 mg/dl

Confirmatory diagnosis: Diabetes mellitus with peripheral neuropathy

Treatment:**General measure:**

1. Diabetic diet: Reduce carbohydrate diet consumption
2. Take mild aerobic exercise

Special management: Inj. Insulin

Drug discussion:

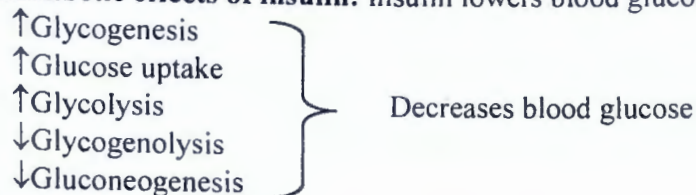
Drug name: Insulin

Pharmacological name: Soluble/regular insulin.

Trade name: Inj. Insul-R (Popular pharma), Inj. Maxulin-R (Incepta pharma)

Group: Parenteral hypoglycemic agent.

Antidiabetic effects of insulin: Insulin lowers blood glucose level by the following mechanisms-



Dose: Dose is adjusted according to blood glucose level or color of urine on Benedict test

Urine color	Insulin dose (IU)
Brick red	20
Red	16
Orange	12
Yellow	08
Green	04
Blue	02

Time: 15 minutes before meal.

Frequency of dose: TDS

Adverse effects:

1. Hypoglycemia (most common)
2. Insulin hypersensitivity
3. Insulin resistance
4. Lipodystrophy: Lipoatrophy & lipohypertrophy
5. Insulin edema
6. Obesity
7. Hypokalemia
8. Alopecia

Drug interaction: With

1. Phenobarbitone
2. Phenytoin

Conclusion: The patient Mr. Zahir, 45 years old, came to DMCH with complaints of polyuria, polyphagia & polydipsia. After proper treatment he improved very rapidly and was discharged from the hospital with controlled blood sugar. He was advised to be on regular check up at outdoor patient department.

Case no 4: Clinical diagnosis: Kala-azar

Name: Mr. Maruf
Age: 30 years
Sex: Male
Religion: Islam
Marital status: Unmarried
Occupation: Unemployed

Address: Trishal, Mymensingh
Ward no. 4
Bed no. 5
Date of admission: 05.07.2010
Date of discharge: 10.07.2010

Chief complaints (C/C):

1. Fever & cough for 3 months
2. Swelling of abdomen for 2 months
3. Yellow discoloration of skin & sclera for 2 months

History of present illness: According to the statement of the patient he was reasonably well 3 months back. Then he developed intermittent fever which appeared in the evening and subsided with sweating in the next morning. Then he developed swelling of the left side of his abdomen along with yellow discoloration of skin & sclera for 2 months. With these complaints she got admitted into DMCH for proper management.

History of past illness: Nothing contributory

Drug history: He has taken some anti-pyretic but got no improvement.

Family history: Nothing contributory.

General examination:

Appearance: Anxious
Body built: Below average
Co-operation: Co-operative
Decubitus: On choice
Nutrition: Average
Intelligence: Average
Anemia: Present
Jaundice: Present
Clubbing: Present
Edema: Absent
Pulse: 90 beats/min
BP: 120/80 mmHg
Respiratory rate: 15 breaths/min
Temperature: 98°F

Systemic examination:**A. Abdomen:****Inspection:**

- Abdomen is distended.

Palpation:

- Live: Enlarged
- Spleen: Enlarged
- Abdomen: Tender
- Axillary & inguinal lymph nodes: Enlarged.

Percussion:

- Percussion note is dull over enlarged liver & spleen.
-

Auscultation:

- Bowel sound: Present
- No bruits over enlarged viscera

B. Cardiovascular system: No abnormality detected

C. Respiratory system: No abnormality detected

Clinical diagnosis: Kala-azar

Investigations:**a. Routine blood examination:**

Hb%: 8 gm/dl

ESR: 50 mm in 1st hour

TC of WBC: 15000/mm³ of blood

DC of WBC:

Neutrophil: 55%

Lymphocyte: 35%

Eosinophil: 04%

Monocyte: 06%

Basophil: 00%

b. Peripheral blood film: Normocytic normochromic anemia

c. Ultrasonography of abdomen: Hepatomegaly & splenomegaly

d. ICT for kala-azar: Positive

e. Bone marrow aspiration: LD bodies of kala-azar parasites

f. Serum bilirubin: 8 mg/dl

Confirmatory diagnosis: Kala-azar

Treatment:**General measure:**

1. Bed rest
2. Regular & normal intake of diet
3. Tab. Paracetamol 500 mg 3 times daily till the fever subsides

Special management: Sodium antimony gluconate 20mg/kg body weight IM for 20 days.

Advice:

1. Adequate intake of fluid, at least 2 L/min
2. Frequent bladder emptying
3. Antibiotic should be taken in proper time and full course should be completed
4. Urine should be collected for culture 2 weeks after stoppage of antibiotic course.

Drug discussion:**Pharmacokinetics:**

- **Paracetamol:** Tablet is well-absorbed from gut, small volume of distribution, half life 2 hours, metabolized in liver and excreted through kidney.
- **Sodium antimony gluconate:** Given parenterally, eliminate the parasite. Short half life (2 hours) and longer half life (>24 hours) phase.

Pharmacodynamics:

- **Paracetamol:** Inhibits PG synthesis in the brain, potent anti-pyretic

- **Sodium antimony gluconate:** First line drug for cutaneous & visceral leishmaniasis. The exact mechanism of action is unknown.

Drug interaction: No drug interaction

Rational criticism of management of the patient:

1. Proper and rational drug was chosen for the patient.
2. Patient should be informed of the complication of treatment and relapse of symptoms.

Case-05: A case record on Congestive cardiac failure (CCF)

Name: Mr. Zafar Uddin
Age: 55 years
Sex: Male
Religion: Islam
Marital status: Married
Occupation: Service holder

Address: Faridganj, Chandpur
Ward no. 4
Bed no. 10
Date of admission: 05.09.2010
Date of discharge: 10.09.2010

Chief complaints:

1. Difficulty in breathing for 3 years.
2. Swelling of both legs for 25 days.
3. Abdominal distension for 8 days.

History of present illness: According to the statement of the patient he was reasonably well 3 years back. Then he gradually developed mild dyspnea, which occurs at the time of working and increased during exertion and gradually relieved by taking rest. He also complains of swelling of both legs for 25 days which is increased during walking or standing for long time and decreased on lying. He also developed abdominal distension for 8 days. It was mild initially and gradually increased and becomes severe in last 3 days. With these above complaints he got admitted into DMCH for proper management.

History of past illness: The pt. had MI 3½ yrs back.

Drug history: He has been taking anti-ischemic drugs since the attack of MI.

Family history: His father died of MI.

General examination:

Appearance: Ill looking
Body built: Average
Co-operation: Co-operative
Decubitus: Propped up position
Nutrition: Average
Intelligence: Average
Anaemia: Absent
Jaundice: Absent
Cyanosis: Present
Edema: Present (+++)
Clubbing: Absent
Dehydration: Absent
Koilonychia: Absent
Lymph node: Not enlarged

Thyroid gland: Not enlarged
Neck vein: Engorged
Pulse: 120 beats/mm
BP: 100/80 mmHg
Respiratory rate: 28/min
Temperature: 98.6°F

Systemic examination:

A. Cardiovascular system:

Pulse:

1. Pulse rate: 120 beats/min
2. Rhythm: Irregular
3. Volume: Low
4. Character: Pulsus alternans
5. Condition of vessel wall: Firm

Examination of venous system:

1. Neck vein: Engorged, pulsatile
2. Abdomino-jugular reflux: Present

Examination of precordium:

1. Inspection: Apex beat visible
2. Palpation:
 - Apex beat shifted downwards and laterally
 - Low and weak in character
3. Percussion: Area of cardiac dullness increased.
4. Auscultation: Heart sound diminished.

B. Respiratory system:

1. Respiratory rate: Increased
2. Basal crepitation: Present

C. Alimentary system:

1. Abdominal distension: Present
2. Fluid thrill: Present
3. Shifting dullness: Present
4. Liver: Enlarged and tender

Salient features: Mr. Zafar Uddin, 55 years old, coming from Faridganj, Chandpur, was admitted in the DMCH with the complaints of breathlessness, leg edema and distended abdomen. On examination, patients pulse was 120 beats/mm, low volume, BP 100/80 mmHg, apex beat shifted downwards and laterally. Cardiac dullness was increased; there were engorged neck vein and palpable tender liver. Ascites was also present.

Clinical diagnosis: Congestive cardiac failure.

Investigations:

1. Blood for routine examination: Normal
2. Urine examination: Normal
3. Fasting lipid profile: Increased LDL-cholesterol
4. Chest X-ray P/A view: There was cardiomegaly. Lung field was hazy.
5. ECG: Showed signs of old MI (pathological Q wave)
6. Echocardiography: Showed features of Congestive cardiac failure due to ischemic cardio-myopathy.

Confirmatory diagnosis: Congestive cardiac failure due to ischemic cardio-myopathy

Treatment:

A. General measure:

1. Reduction of workload of heart
 - Reduce physical activity
 - Weight reduction
 - Salt restriction

2. **Drugs:**

To decrease Preload:

- Diuretics: Tab. Frusemide 40 mg bd at morning & afternoon
- Vasodilator: Nitrates, prazosin, hydralazine.
- ACE inhibitor.
- Glyceryl trinitrate.

To decrease Afterload: Hydralazine, diazoxide

To decrease both preload & afterload & prevent remodeling of heart: ACE inhibitors.

Anti-ischemic drugs: Aspirin (75 mg daily), atorvastatin (20 mg daily)

B. Digitalis

• ***Slow digitalization:***

1st day: Tab. Digoxin 0.5 µg 3 times a day

2nd day: Tab. Digoxin 0.25 µg 4 times a day

3rd day: Tab. Digoxin 0.25 µg 3 times a day

Then, maintenance dose: Tab. Digoxin 0.25 - 0.5 µg once daily.

• ***Rapid digitalization:***

1.5 µg immediately, then 0.5 µg 6 hourly to a total dose of 3 µg. Then, maintenance dose 0.25 - 0.5 µg once daily.

Drug discussion:

Digitalis:

Generic name: Digoxin

Group: Cardiac glycoside (Cardiotonic agent)

Mechanism of action: Increase force of contraction of heart and decrease heart rate

Objective of use:

1. To increase cardiac output
2. To increase myocardial contractility
3. To decrease heart rate
4. To reduce end diastolic volume

Adverse effects:

A. GIT adverse effects: (*Most frequent*)

1. Anorexia
2. Nausea
3. Vomiting
4. Diarrhea

B. Cardiac adverse effects:

1. Bradycardia (earliest adverse effect.)

C. CNS adverse effects:

1. Insomnia
2. Disorientation
3. Visual hallucination leading to colour blindness (due to increased depolarization in rods and cones)

4. Convulsion

D. Miscellaneous:

1. Hypokalemia
2. Gynecomastia in male (due to steroid nucleus)
3. Galactorrhea in female

Frusemide:

Pharmacological effect: Prevention of reabsorption of Na and Cl⁻ ion from ascending limb of loop of Henle. Thus causes diuresis and relieves edema. When pulmonary edema is relieved, breathlessness is improved.

Objective of use:

1. To reduce extracellular fluid
2. To reduce workload of heart

Adverse effects:

1. Hypovolemia
2. Hypokalemia
3. Hypocalcemia

Conclusion: After proper treatment the pt. improved well and was discharged from the hospital with advice to be on regular check up at outdoor patient department.

Drug Interactions

Amlodipine + Atenolol

Result: Potentiation of anti-hypertensive effect

Explanation: Amlodipine is a Ca^{2+} channel blocker and it acts on both heart muscle and blood vessels to exert its anti-hypertensive action. On the other hand, Atenolol selectively blocks the β_1 receptor of the heart muscle to produce antihypertensive action. Combination of them potentiates the anti-hypertensive effect.

Alcohol + Benzodiazepine

Result: Additive or synergistic CNS depression.

Explanation: Both of the drugs are CNS depressant. On the top of that, alcohol increases benzodiazepine absorption leading to increased benzodiazepine conc. in plasma. The resulting effect is more CNS depression.

Erythromycin + Fexofenadine

Result: Fexofenadine toxicity.

Explanation: Erythromycin is a hepatic microsomal enzyme inhibitor and it inhibits the metabolism of fexofenadine leading to increased fexofenadine conc. in plasma.

NSAID + Propranolol

Result: Antihypertensive effect of propranolol is decreased.

Explanation: NSAID inhibits renal vasodilator prostaglandin (PG). This leads to renal vasoconstriction. So renal perfusion is reduced leading to decreased renal blood flow and activation of rennin angiotensin mechanism. As propranolol acts by this mechanism, its effect is hampered and anti-hypertensive effect is decreased.

Amoxicillin + Clavulanic acid

Result: Potentiation of antibiotic effect of amoxicillin.

Explanation: Amoxicillin is a β -lactam drug which can be degraded by β lactamase enzyme produced by some bacteria. Clavulanic acid is also a β lactam drug and has more affinity for β -lactamase enzyme. It competitively binds with β lactamase and prevents the degradation of amoxicillin by β lactamase.

Iron + tetracycline

Result: Decreased bioavailability of both Iron (Fe^{2+}) and tetracycline.

Explanation: Interaction takes place at the level of absorption. Tetracycline is chelated by iron (Fe^{2+}) as divalent cation and if they are simultaneously present in the gut, absorption of tetracycline & iron will be impaired and bioavailability of both of them will be decreased.

Iron + Antacid

Result: Decreased bioavailability of Iron only.

Explanation: Interaction takes place at the level of absorption. Aluminium (Al^{3+}) of Antacid forms insoluble complex with Iron. Thus absorption of Iron from GIT is impaired reducing its bioavailability.

Sulfamethoxazole + Trimethoprim

Result: Potentiation of anti-folate effect.

Explanation: Individually sulfamethoxazole and trimethoprim both are bacteriostatic drug. But when used in combination, they become bactericidal by inhibiting sequential steps in bacterial nucleic acid synthesis. Combination of these two drugs leads to-

1. Potentiation of action.
2. Broadening of spectrum
3. Decreased dose thereby less adverse effects.
4. Decreased development of resistance.

Theophyllin + Salbutamol**Result:**

1. Potentiation of bronchodilator effect
2. Potentiation of cardiac muscle stimulatory effect leading to cardiac arrhythmia.

Explanation: Theophyllin and salbutamol both are bronchodilator. Combination of them potentiates the bronchodilator effect. Theophyllin has a direct positive inotropic and chronotropic effect on heart. At low conc., it appears to result from increased catecholamine release that is caused by inhibition of presynaptic adenosine receptors.

At higher conc. Ca^{2+} influx may be increased directly through the increase in cAMP that results from inhibition of phosphodiesterase. Salbutamol, on the other hand acts on β_1 receptors of the heart muscle leading to muscle contraction. Combination of these two drugs thereby leads to cardiac arrhythmia.

Phenytoin + Sodium valproate**Result:** Phenytoin toxicity

Explanation: Na valproate is a hepatic microsomal enzyme inhibitor. So it inhibits the metabolism of phenytoin. It also displaces phenytoin from plasma protein binding site thereby increasing the conc. of phenytoin in plasma leading to phenytoin toxicity

Rifampicin + oral contraceptive pill (OCP)**Result:** Contraception failure

Explanation: Interaction takes place at the level of metabolism. Rifampicin is a hepatic microsomal enzyme inducer and it induces the metabolism of estrogen content of OCP thus causing unwanted pregnancy.

Isoniazid + Phenytoin**Result:** Phenytoin toxicity

Explanation: Isoniazid is a hepatic microsomal enzyme inhibitor. It inhibits the metabolism of phenytoin thereby increasing phenytoin conc. in plasma leading to toxicity.

Aminoglycosides + Cephalosporins**Result:** Severe nephrotoxicity

Explanation: Both are nephrotoxic drug. So combination of them produces severe nephrotoxicity.

Aminoglycosides + Loop diuretics**Result:** Irreversible ototoxicity

Explanation: Both are ototoxic drug. Combination of them produces severe ototoxicity. Loop diuretics (Frusemide) is a high ceiling diuretic which causes excretion of fluid from endolymph and perilymph of inner ear and helps in more deposition of ototoxic aminoglycosides on hair cells. This destroys hair cells permanently and produce ototoxicity.

Aspirin + NaHCO_3 **Result:** Increased excretion of Aspirin through urine.

Explanation: NaHCO_3 is a systemic alkalizer which alkalinizes the urine. Aspirin becomes acidic in pH after acetylation in the liver. Acidic aspirin becomes ionized in the alkaline urine which decreases its reabsorption to the renal tubules thereby increasing the excretion of aspirin in urine.

Cimetidine + Propranolol**Result:** Increased plasma conc. of propranolol leading to hypotension.

Explanation: Cimetidine is a hepatic microsomal enzyme inhibitor and it inhibits the metabolism of propranolol. This leads to increased plasma conc. of propranolol leading to hypotension.

Heparin + Protamin sulphate**Result:** Action of heparin is lost.

Explanation: Heparin is negatively charged and protamin sulphate is positively charged. So a direct chemical reaction takes place neutralizing the effect of heparin. Protamin sulphate is an antidote for heparin.

Ticarcillin + Tazobactam

Result: Potentiation of antibiotic effect of ticarcillin.

Explanation: Ticarcillin is a β lactam drug which is degraded by β -lactamase enzyme produced by some bacteria. Tazobactam is also a β lactam and has more affinity for β lactamase. Tazobactam binds competitively with β lactamase thereby preventing the degradation of ticarcillin by β -lactamase.

Antacid + Ciprofloxacin

Result: Decreased bioavailability of ciprofloxacin.

Explanation: Aluminium (Al^{3+}) and magnesium (Mg^{2+}) of antacid form insoluble complex with ciprofloxacin and impairs its absorption from GIT thereby reducing bioavailability of ciprofloxacin.

Digoxin + Thiazide

Result: Digoxin toxicity leading to cardiac arrhythmia and death.

Explanation: Digoxin competes with K^+ to bind to the ATPase pump of cardiac muscle. Hypokalemia caused by thiazide diuretic leads to increased Digoxin binding to the cardiac muscle leading to toxicity, cardiac arrhythmia and death.

Phenobarbitone + Oral contraceptive pill (OCP)

Result: Contraception failure.

Explanation: Phenobarbitone is a hepatic microsomal enzyme inducer and it induces the metabolism of estrogen content of OCP leading to unwanted pregnancy.

Antihistamine + Steroid

Result: Synergistic anti-inflammatory effect.

Explanation: Steroid acts as an anti inflammatory drug by stabilizing mast cell membrane. It prevents further release of Histamine. Antihistamine blocks the histamine receptors and antagonizes the action of Histamine released from mast cell. So combination of anti-histamine with steroid potentiates anti-inflammatory action of steroid.

Tetracycline + Penicillin

Result: Antibiotic antagonism. Antibiotic action of penicillin is lost.

Explanation: Tetracycline is a bacteriostatic drug which inhibit the growth of microorganisms whereas penicillin is a bactericidal drug which kills rapidly multiplying organisms. When bacterial growth is inhibited by tetracycline, penicillin cannot kill the bacteria. Thus tetracycline protects the microorganisms by antagonizing the action of penicillin.

Insulin + Propranolol

Result: Masking of signs and symptoms of hypoglycemia

Explanation: Insulin is a hypoglycemic agent. Propranolol also causes hypoglycemia by inhibiting gluconeogenesis and glycogenolysis. Combination of them causes more hypoglycemia. In addition to this, Propranolol masks the S/S of hypoglycemia except sweating by its β_2 blocking effect. So without S/S, hypoglycemia can't be detected and patient may die.

Isoniazid + Rifampicin

Result: Potentiation of anti-mycobacterial action.

Explanation: Isoniazid acts on rapidly multiplying organism both extra & intracellularly. Rifampicin acts on both slowly & rapidly multiplying organism extra and intracellularly. Combinations of these 2 drugs thereby are able to eradicate both dormant and actively multiplying organism.

Salicylate + Tolbutamide

Result: Hypoglycemic shock.

Explanation: Salicylate displaces tolbutamide from plasma protein binding site. So there is increased plasma conc. of tolbutamide which is a hypoglycemic agent. The result is hypoglycemic shock.

Ceftriaxone + Vancomycin

Result:

1. Potentiation of action.
2. Broadening of spectrum.

Explanation: Combination of these two antibiotics leads to potentiation of antimicrobial effect. In addition, Ceftriaxone acts against mainly gram negative organism and vancomycin against gram positive organisms. This leads to broadening of spectrum.

Rifampicin + Vancomycin

Result:

1. Potentiation of action.
2. Broadening of spectrum.

Explanation: Vancomycin inhibits cell wall synthesis thereby potentiating the entry of rifampicin into the cell which then acts on bacterial RNA synthesis. Thus potentiation of action occurs. Vancomycin acts on Gram positive organism.

Digoxin + Erythromycin

Result: Increased bio-availability of digoxin leading to cardiac arrhythmia and death.

Explanation: Erythromycin is a broad spectrum antibiotic which destroys the normal flora of gut which normally impairs 10% absorption of digoxin. So combination of them will lead to increased digoxin absorption → Increased digoxin bioavailability leading to cardiac arrhythmia.

Penicillin + Gentamicin

Result:

1. Potentiation of action.
2. Broadening of spectrum.

Explanation: Penicillin inhibits cell wall synthesis thus facilitate the penetration of gentamicin which then inhibits protein synthesis. Thus potentiation of action occurs. Penicillin acts against gram positive organism and gentamicin against gram negative one thereby broadening of spectrum occurs.

Penicillin + Probenecid

Result: Bioavailability of penicillin is increased.

Explanation: Both are organic acids. They compete for binding with carrier protein in PCT for renal tubular secretion. But probenecid has more affinity for the carrier protein and binds with it. So renal tubular secretion of penicillin doesn't occur and its bioavailability is increased.

Metronidazole + Alcohol

Result: Disulfiram like reaction (Headache, dizziness, convulsion) occurs.

Explanation: Metronidazole inhibits the enzyme alcohol dehydrogenase thereby inhibiting the metabolism of alcohol. As a result plasma conc. of alcohol is increased leading to disulfiram like reaction.

Verapamil + Propranolol

Result: Heart block and death.

Explanation: Verapamil acts as a potent cardio-depressant by acting on the Ca^{2+} channel of both the conductive tissue and muscle of heart. It decreases heart rate and cardiac contractility. On the other hand propranolol also decreases cardiac contractility and heart rate by blocking the receptor of heart. Combination of these two cardio-depressants leads to heart lock and death.

Clonidine + Tricyclic antidepressant (TCA)

Result: Hypertensive crisis.

Explanation: Clonidine has an α_2 agonistic action and facilitates the re-uptake of NA in the synaptic membrane. But TCA blocks the α_2 receptors thereby preventing the reuptake of NA leading to increased sympathetic discharge. This results in hypertensive crisis.

Levodopa + Carbidopa

Result: Increased bioavailability of levodopa.

Explanation: Carbidopa prevents the peripheral metabolism of levodopa by dopa decarboxylase in the intestine thereby increasing the bioavailability of levodopa. Carbidopa also increases the penetration of brain by levodopa. In addition to this, carbidopa has an anti-emetic effect.

Insecticide (OPC) + Atropine

Result: Antagonism of the effects of insecticide (OPC)

Explanation: Insecticide is an organophosphorus compound (OPC). OPC is an inhibitor of cholinesterase enzyme thereby increasing the conc. of acetylcholine (Ach) resulting in increased effects of Ach e.g. hypotension, secretion, CNS effects. Atropine, an anti-muscarinic drug inhibits the action of Ach by blocking muscarinic receptor. Atropine thus antagonizes the effects of OPC.

Potassium sparing diuretic + Angiotensin converting enzyme (ACE) inhibitor

Result: Dangerous hyperkalaemia.

Explanation: Potassium sparing diuretic causes hyperkalemia. ACE inhibitor blocks the rennin-angiotensin aldosterone axis thereby decreasing the conc. of aldosterone. Decreased aldosterone leads to hyperkalemia by decreasing the excretion of potassium. Combination of these two leads to severe hyperkalemia.

Sulfonamide + Bilirubin

Result: Hyperbilirubinemia

Explanation: Sulfonamide has more affinity for plasma protein binding site than bilirubin, so it displaces bilirubin from plasma protein binding site, increases conc. of bilirubin in blood and causes hyperbilirubinemia. As phase II metabolism is not properly developed in infant, bilirubin can't be metabolized in blood. Then it crosses BBB and is deposited in basal ganglia of brain leading to kernicterus in infant.

Morphine + Naloxone

Result: In morphine poisoning, Naloxone antagonizes the action of morphine.

Explanation: Morphine is an opioid receptor agonist and Naloxone is an antagonist of opioid receptor. In acute morphine poisoning, when naloxone is given it antagonizes the action of morphine by binding to opioid receptor.

Chlorpromazine + Procyclidine

Result: Prevention of Parkinsonism effect.

Explanation: Procyclidine blocks muscarinic receptor. Increased Ach caused by chlorpromazine can't act on muscarinic receptor. So manifestation of Parkinsonism does not appear.

Dosage formulations

Dosage forms: Dosage form is the preparation of a drug for delivering or applying into the body through a particular route.

Formulation- 01: Tablets.

Q. What is this?

Ans. An aluminium blister containing tablets (*mention the name of the drug with its strength, eg, paracetamol 500 mg*).

Q. What type of formulation is this?

Ans. Tablet

Q. What is tablet?

Ans. Tablet is a solid dosage form in which powder, crystalline, or granular form of drug is compressed in a disk or molded with pharmacologically inert substances (excipients).



Q. By which route is it taken?

Ans. Mainly oral. Also sublingual (eg, aspirin, nitroglycerine tablet)

Q. What is the composition of a tablet?

Ans. Tablet is composed of active ingredient plus excipient.

Q. How is a tablet absorbed from the GIT?

Ans. After disintegration, dissolution, a tablet is absorbed.

Q. Is it suitable for unconscious patients or emergency situations?

Ans. No.

Formulation- 02: Capsules.

Q. What is this?

Ans. An aluminium blister containing capsules (*mention the name of the drug with its strength, eg, omeprazole 20 mg or amoxicillin 500 mg*).

Q. What type of formulation is this?

Ans. Capsule

Q. What is capsule?

Ans. Capsule is a solid dosage form in which one or more active ingredients with or without inert substances are enclosed within a small shell or container generally prepared from gelatin.



Q. By which route is it taken?

Ans. Oral

Q. What is the composition of a capsule?

Ans. Capsule is composed of active ingredient plus excipient.

Q. How is a capsule absorbed from the GIT?

Ans. After dissolution, a capsule is absorbed.

Q. Is it suitable for unconscious patients or emergency situations?

Ans. No.

Formulation- 03: Injections.

Q. What is this?

Ans. It is an ampoule containing injectable drugs (mention the name, eg, diazepam 10 mg or gentamicin 80 mg or ketorolac 30 mg).

Q. By which route is it taken?

Ans. Injections (intravenous, intramuscular, subcutaneous, intra-articular, intrathecal injection, etc.)

Q. Is it suitable for unconscious patients or emergency situations?

Ans. Yes.



Figure: Ampoule

Formulation- 03: Suppository.

Q. What is this?

Ans. Aluminium foil containing suppository.

Q. What is suppository?

Ans. It is a solid medicated preparation designed for insertion into the rectum (or vagina, when it may be called a *pessary*); it may be designed to dissolve or it may melt at body temperature; the vehicle in which the drug is carried may be fat, glycerol with gelatin, or macrogols (polycondensation products of ethylene oxide) with gelatin.

Q. By which route is it taken?

Ans.

Rectum.

Vagina (when it is called a *pessary*).



Figure: Suppository

OSPE

Q. Name 5 drugs causing teratogenicity.

Ans.

Drugs that produce teratogenicity:

Drugs	Teratogenic effects
• Aspirin / Indomethacin	Premature closure of ductus arteriosus
• Androgens	Virilization; Limb, esophageal & cardiac defect
• Methotrexate	Cleft palate, Hydrocephalus, Fetal death
• Thalidomide	Phocomelia
• Tetracyclines	Discolored & deformed teeth, Retarded bone growth
• Warfarin	Depressed nose, Eye & hand defect, Growth retardation
• Phenytoin	Cleft lip, Cleft palate, Microcephaly, Hypoplastic phalanges
• Carbamazepine	Neural tube defects
• Valproic acid	Spina bifida, & other neural tube defect
• ACE inhibitors	Growth retardation, Hypoplastic organs
• Anti-thyroid drugs	Fetal goiter & Hypothyroidism
• Progestins	Virilization of female fetus
• Isotretinoin	Craniofacial, cardiac & CNS defect.

Q. Name 5 enzyme inducers.

Ans.

Enzyme inducing drugs:

1. Rifampicin
2. Barbiturates (eg, phenobarbitone)
3. Phenytoin
4. Phenylbutazone
5. Carbamazepine
6. Griseofulvin
7. Testosterone
8. Hydrocarbon

Q. Name 5 enzyme inhibitors.

Ans.

Enzyme inhibitors

1. Cimetidine
2. Chloramphenicol
3. Metronidazole
4. Allopurinol

Q. Name 5 drugs causing addiction.

Ans.

Drugs causing addiction: Write 5 from below

1. Morphine
2. Heroine
3. Pethidine
4. Barbiturates
5. Amphetamine
6. Alcohols
7. Cocaine
8. LSD
9. Marijuana

Q. Name 5 drugs that produce dependence.

Ans.

Drugs producing dependence

1. Morphine
2. Heroine
3. Pethidine
4. Barbiturates
5. Amphetamine
6. Alcohols
7. Cocaine
8. LSD
9. Marijuana
10. Diazepam
11. Tobacco
12. Cannabis

(Ref: Bennett & Brown-11th)

Q. Name the drugs causing the following adverse effects...

Ans.

Drugs causing postural hypotension:

1. α -blocking drugs:
 - Prazosin
 - Terazosin
2. Ganglion blockers:
 - Guanabenz
 - Guanafacin
3. TCAs:
 - Amitriptyline
 - Nortriptyline
4. Anti-psychotics: Chlorpromazine

Drugs causing hypotension:

1. α 1-blocking drugs: Prazosin, Terazosin
2. β -blocking drugs: Propranolol, Atenolol
3. Parasympathomimetic: ACh, Physostigmine
4. Ca^{2+} -channel blockers: Diltiazem, Verapamil
5. ACE inhibitors: Lisinopril
6. Angiotensin-II receptor blockers: Losartan
7. Direct vasodilators: Diazoxide, Minoxidil, Na-Nitroprusside
8. Nitroglycerine: GTN
9. Anti-depressant: TCAs
10. Diuretics: Frusemide
11. Anti-parkinsonism drugs: Levodopa

Drugs causing reflex tachycardia:

1. Non-selective α -blockers:
Phenoxybenzamine
2. Selective α 1-blockers: Prazosin, Terazosin
3. Ganglion blockers: Guanabenz, Guanafacin
4. TCAs: Amitriptyline, Nortriptyline
5. Anti-psychotics: Chlorpromazine
6. Ca^{2+} -channel blockers: Verapamil, Diltiazem (vessel-selective)

Drugs causing bradycardia:

1. β -blockers: Propranolol, Atenolol
2. Digitalis
3. Parasympathomimetic: ACh, Physostigmine
4. Ca^{2+} -channel blockers: Diltiazem, Verapamil (vessel-selective)
5. Adrenaline (Reflex bradycardia)

Drugs increasing blood pressure:

1. Adrenaline
2. Glucocorticoids
3. Oral contraceptive pills (OCPs)
4. Cyclosporine
5. Leflunomide
6. Clonidine withdrawal
7. MAO inhibitors
8. TCAs

Drugs causing prolong QT interval:

1. Sotalol
2. Amiodarone
3. Amitriptyline
4. Chlorpromazine
5. Erythromycin
6. Halofantrine

(Ref: Davidson's medicine-22nd)

Drugs causing complete heart block:

1. Digoxin
2. β -blocker

(Ref: Davidson's medicine-22nd)

Drugs inhibiting platelet function:

1. NSAIDs:
 - Aspirin
 - Phenylbutazone
 - Indomethacin
2. Heparin
3. Dextran
4. Antibiotics:
 - Penicillins
 - Cephalosporins

(Ref: Davidson's medicine-22nd)

Drugs causing neutropenia:

1. Anti-inflammatory drugs:
 - Phenylbutazone
 - Penicillamine
 - Naproxen
2. Anti-arrhythmic:
 - Quinidine
 - Procainamide
3. Anti-hypertensive:
 - ACE inhibitors: Captopril, Enalapril.
 - Ca^{2+} -channel blockers: Nifedipine
5. Anti-depressant: Amitriptyline
6. Anti-convulsants:
 - Phenytoin
 - Na-valproate
 - Carbamazepine
7. Antibiotics:
 - Penicillins
 - Sulfonamides
 - Cephalosporins
8. Anti-malarial:
 - Chloroquine
 - Sulfadoxine
 - Pyrimethamine
9. Miscellaneous:
 - Anti-thyroid drugs
 - Metoclopramide
 - Ranitidine
 - Cyclophosphamide
 - Azathioprine
 - Sulfasalazine

(Ref: Davidson's medicine-22nd)

Drugs causing lymphadenopathy: Phenytoin*(Ref: Davidson's medicine-22nd)***Drugs causing thrombocytopenia:**

1. Cytotoxic drugs
2. Thiazide diuretics
3. Anti-metabolites

*(Ref: Davidson's medicine-22nd)***Drugs causing aplastic anemia:**

1. Cytotoxic drugs
2. Antibiotics:
 - Chloramphenicol
 - Sulfonamide
3. Anti-rheumatic agents:
 - Phenylbutazone
 - Penicillamine
 - Indomethacin
 - Oxyphenbutazone
4. Anti-thyroid drugs
5. Anti-convulsants
6. Immune-suppressive drug: Azathioprine

Drugs causing hepatotoxicity:

1. NSAIDs:
 - Paracetamol toxicity
 - Diclofenac
 - Aspirin
2. Anti-TB drugs:
 - Rifampicin
 - Pyrazinamide
 - INH
3. Antibiotics:
 - Oxacillin
 - Ketoconazole
 - Erythromycin (cholestatic jaundice)
4. Azathioprine
5. Leflunomide
6. Chlorambucil
7. Anti-cancer drugs
8. Halothane
9. Griseofulvin

Nephrotoxic drugs:

1. NSAIDs
2. Aminoglycosides
3. Cephalosporins (except ceftriaxone, cefoperazone)
4. ACE inhibitors
5. Angiotensin-II receptor blockers
6. Cyclosporine
7. Methicillin

Neurotoxic drugs:

1. Isoniazid (peripheral neuropathy)
2. Aminoglycosides
3. Ethambutol
4. Quinolones
5. Acyclovir
6. Polymyxin

Ototoxic drugs:

1. Irreversible ototoxicity: Aminoglycosides, Chloroquine
2. Reversible ototoxicity: Frusemide

Drugs causing superinfection:

1. Amoxicillin
2. Ampicillin
3. Cephalosporins
4. Chloramphenicol
5. Tetracyclines

Drugs causing severe GIT upset (nausea, vomiting diarrhea):

1. Methotrexate
2. Azathioprine
3. Digoxin
4. Fluoroquinolones (e.g. ciprofloxacin)
5. Tetracyclines
6. Sulfasalazine
7. Leflunomide
8. Cyclophosphamide
9. Cyclosporine

Drugs causing hyperuricemia:

1. Pyrazinamide
2. Thiazide diuretics
3. Loop diuretics
4. Cyclosporine

*(Ref: Davidson's medicine-22nd)***Drugs causing gynecomastia:**

1. Digoxin
2. Spironolactone
3. Cimetidine
4. Exogenous anabolic steroids: Diethylstilbestrol
5. Antiandrogen: Cyproterone acetate

Drugs causing osteoporosis

1. Corticosteroids
2. GnRH agonists
3. Over replacement of Thyroxin (T3)
4. Sedatives
5. Anticonvulsants (eg, Phenytoin)
6. Alcohol excess

7. Heparin

(Ref: Davidson's medicine-22nd)

Drugs causing hyperprolactinemia:

1. Chlorpromazine (Anti psychotic)
2. Metoclopramide (Anti emetic)
3. α -Methyl Dopa (Anti hypertensive)
4. Reserpine
5. Anti depressant drugs

(Ref: Dutta Gynaecology-4th/427)**Drugs causing hypokalemia:**

1. Loop Diuretics
2. Thiazide diuretics
3. Carbonic Anhydrase Inhibitors (Acetazolamide)
4. Corticosteroids
5. Carbenoxolone
6. Liquorice

(Ref: Davidson's medicine-22nd)

Drugs causing hyperkalemia:

1. K^+ -sparing diuretics:
 - Amiloride
 - Spironolactone
 - Triamterene

2. ACE inhibitors

3. NSAIDs

4. β -blockers

5. Cyclosporine

6. Prolonged heparin therapy

(Ref: Davidson's medicine-22nd)

Drugs causing urticaria:

1. Salicylates
2. Codeine
3. Antibiotics
4. ACE inhibitors
5. Fe-dextran

Drugs producing metallic taste:

1. Metronidazole
2. Tetracycline
3. Rifampicin

Drugs causing alopecia:

1. Cytotoxic drugs
2. Anti-coagulant drugs
3. Fe-dextran
4. OCPs
5. Anti-thyroid drugs

(Ref: Burton's undergraduate medicine, Page: 154)

Drugs causing hyperpigmentation:

1. Busulfan

2. Chlorpromazine

3. OCPs

4. Chloroquine

(Ref: Burton's undergraduate medicine, Page: 152)

Drugs that increase histamine release:

1. Almost all drugs (as all drugs are foreign body to our body & can cause immunological reactions e.g. anaphylaxis)
2. Morphine
3. D-tubocurarine
4. Succinylcholine

(Ref: Goodman & Gilman's-12th)

Drugs causing anaphylactic shock:

1. Penicillins (mainly IV route)
2. Cephalosporins
3. Sulfur containing drugs- Sulfonamides, Thiazide diuretics etc.
4. Insulin preparations
5. Streptokinase
6. Heparin
7. NSAIDs
8. Histamine

Drugs causing erythema nodosum (tender nodules on leg):

1. Sulfonamide

(Ref: Burton's undergraduate medicine)

Drugs causing toxic epidermal necrolysis (TEN):

1. Penicillins
2. Barbiturates
3. Phenytoin
4. Phenylbutazone

(Ref: Burton's undergraduate medicine)

Drugs causing peripheral neuropathy:

1. Isoniazid
2. Methotrexate
3. Phenytoin
4. Vincristine
5. Metronidazole
6. Aminoglycosides
7. Vitamin-B₁₂ in a folate-deficit patient

Drugs causing Steven Johnson syndrome (SJS):

1. Penicillin
2. Sulfonamides
3. Aminoglycosides
4. Carbamazepine
5. Phenytoin
6. Barbiturates
7. Allopurinol.

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COMING SOON OSPE on MICROBIOLOGY

- In Prof. exams of Microbiology, OSPE covers **50 marks** out of total 300 marks.
- There are no guidelines or books for taking preparation for OSPE.
- Students usually take preparation for Written & Viva.
- When they face the OSPE exams, they are usually quite unprepared. And they usually answer from common sense and residual knowledge.
- As a result, OSPE marks are not usually satisfactory. This affects the total marks and result.
- A good guideline and proper preparation will make you 100% confident to gain high scores in OSPE.
- **So, Blueprint Microbiology OSPE is coming soon In-Sha-Allah to fill this big gap in the preparation of exams.**