Answers to University Question Papers

Model Question Paper as per MCI Regulations-1

As per recent MCI guidelines the examination pattern at the end of 3rd semester would be like this

1) 2 Theory papers of 100 marks each = 2×100

Consisting of structured essays, short assay questions, short answer questions

a) Short assay questions 2×10 = 20

b) Short assay answers 6×5 = 30

c) Short answer questions 10×3 = 30

Total = 80

MCQs and Quizzes = 20

Total = 100

2) Practicals = 100

3) Viva = 20

4) Practicals and Viva 80+20 = 120

5) Internal assessment – Theory =40 + Practicals 20=60

6) Grand Total for assessment = 420 marks

There might be variations in the updated notifications from NMC

Model Question Papers

PAPER I

Total Marks 100

1) Long Essay Questions 2 x 10 = 20

a) Mention the halogenated general anesthetics and mention the advantages and disadvantages of any two of them.

b) Explain the bioavailability of drugs and the factors modifying the same

2) Short Essay Questions 6 x 5 = 30

a) G-Protein couples' receptors.

b) Cardio-selective Beta receptor blockers

c) Selective serotonin reuptake inhibitors.

d) Non-depolarizing skeletal muscle relaxants.

e) Inhalational drugs used to treat bronchial asthma

f) Mechanism of action of bupivacaine and its clinical uses

3) Short Answer Questions 10 x 3 = 30

a) Explain therapeutic drug monitoring and give few examples

b) Cholinesterase Inhibitors and their uses

c) Drug addiction

d) Dobutamine

e) Tachyphylaxis

f) Verapamil

g) Phenylephrine

h) Uses of H1 Receptor blockers

i) Uses of Carbamazepine

j) Tremadol

PAPER II

Total Marks 100

1) Long Essay Questions 2 x 10 = 20

a) Classify Antidiabetic Drugs. Explain the mechanism of action of any two groups of the drugs and enumerate their adverse effects.

b) Classify the drugs used for acid peptic disease and discuss the mechanism of action of any two major groups and their indications.

2) Short Essay Questions 6 x 5 = 30

a) Explain the mechanism of action of high ceiling diuretics and their clinical indications.

b) Explain the mechanism of action of oral anticoagulants and their clinical uses.

c) Mention the drugs used to treat Herpes viral infections and their clinical uses.

d) Mention the drugs used to treat acne vulgaris.

e) Mention the selective estrogen receptor modulators and their clinical uses.

f) Explain the antiarrhythmic action and clinical uses of lidocaine.

3) Short Answer Questions 10 x 3 = 30

a) Levothyroxin

b) Methocobalamine

c) Enoxaparin

d) Indications of Sodium Nitropruside

e) Clinical uses of methotrexate

f) Indications of Fluconazole

g) Explain the rationale of combination of Sulfamethoxazole and Trimethorprim

h) Clinical uses of Artemether

i) Indications and adverse effects of INH

j) Domperidone

Answers to Model Question Paper I

1. Long Essay Questions:

(a) How do you classify general anesthetics? Mention their mechanism of action and anesthetic properties and disadvantages with suitable examples.

Ans: General anesthetics are classified as

a) Volatile inhalational anesthetics

i. Gases: - Nitrous oxide

ii. Liquids: - Halothane, euflurone, isoflurane, desflurane and sevoflurane

b) Non-volatile/ Non-inhalational anesthetics or IV anesthetics:

Thiopental, Thiamylol, propofol, methohexital, ketamine, etomidate.

Mechanism of Action

General anesthetics enhance the activity of inhibitory neurons, increase the levels of inhibitory neurotransmitters, and lower the actions of excitatory neurons and the levels of excitatory neurotransmitters glutamate and aspartate.

At the molecular level general anesthetics act at the GABA receptor enhancing the inhibitory neurotransmission which is also mediated by glycine. They act on GABA cl^- ion channel which acts as a receptor or augmenting cl^-conductance gated by cl^-channel. General anesthetics depress spontaneous and evoked activity in many areas of central nervous system, involving the synaptic processes inhibiting synaptic transmission. In addition, there is hyperpolarization of the neurons through activation of K^+ channels which leads to decreased production of action potentials. Ketamine and nitrous oxide do not act through GABA receptor.

Site of Action

General anesthetics cause generalized inhibition of central nervous system, and act primarily in areas like reticular activating system, central cortex, the cuneate nucleus, the obfactory cortex, hippocampus and dorsal horn of the spinal cord. Inhaled general anesthetics primarily act on the spinal cord to produce immobility.

1. Anesthetic properties and disadvantages of Enflurane.

Anesthetic Properties	Disadvantages
1. Blood-gas partition coefficient is 1.8. **2.** MAC 1.68% in pure oxygen and 0.5% in 70% nitrous oxide+ 30% oxygen. **3.** Provides rapid induction and rapid recovery. **4.** Has an adequate analgesic and skeletal muscle relaxation property?	**1.** Causes fall of blood pressures and reduced cardiac output. **2.** Causes respiratory depression. **3.** In higher doses it can cause spike and wave pattern in EEG causing generalized muscle twitching and contra indicated in patients with a history of epilepsy. **4.** Can cause postoperative shivering. **5.** Can cause mild simultaneous of tracheobronchial secretions

2. Anesthetic properties and disadvantage of Nitrousoxide.

Anesthetic Properties	Disadvantages
1. Blood-gas partition coefficient is 0.47; **2.** MAC 1.68% **3.** Because of poor solubility, it passes very quickly from the inspired gas mixture and quickly attains alveolar concentration and induces equilibrium in all compartments quickly thereby producing rapid onset and rapid recovery.	**1.** It is more an analgesic than a potent anesthetic because of its MAC of more than 100%. It is a less potent general anesthetic. **2.** It can increase cerebral blood flow but not to the extent produced by liquid general anesthetics. **3.** Not a skeletal muscle relaxant and muscle relaxants should be adequately supplemented with general anesthetic agent and used simultaneously. **4.** It gets exchanged with N_2 in any air-containing cavity in the body and enters the cavity faster and increases the volume or pressure inside it.

(b) Explain the drug-related factors modifying the drug action.

There are many factors that influence the drug action which may be a decrease or an increase or that produce an altogether different action or can even produce adverse effects.

The factors affecting the drug action may be broadly termed as – Drug related and patient related.

Drug related factors modifying the drug action:

a) Physical Properties

i. The poor solubility of procaine penicillin confers on it a longer duration of action compared to benzyl penicillin.

ii. Thiopental sodium is highly lipid soluble and gets distributed in the body compartments quickly and rapidly enters brain to produce general anesthesia.

b) Rate of Administration: The drug effects also depend upon the rates at which the drug is administrated.

i. Aminophyllin if given rapidly causes fall of blood pressure and respiratory distress and hence given over a period of 10 minutes.

ii. Thiopental if given rapidly causes respiratory depression but if given too slowly causes laryngospasm and cough.

c) Selective Distribution

i. Chloroquine is used in hepatic amebiasis mainly because it is selectively concentrated is the liver

ii. Aminoglycoside cause nephrotoxicity and ototoxicity because they get accumulated in the kidneys and perilymph and endolymph of the inner ear.

d) Biotransformation: Acetylcholine is rapidly hyrolized by acetylcholinesterage and has a very shorter duration of action. But carbachol and bethanechol can resist enzymatic destruction and can have longer duration of action.

e) Presence of Other Drugs: The effects of an individual drug may be affected by the concomitlant administration of another drug. The actions of warfarin can be affected by drugs like sulfonamides, aspirin (increased action) and barbiturates (decreased action).

f) **First-pass Metabolism:** Drugs such as propranolol, morphine, lidocaine and glyceryltrinitrate undergo varying degress of first-pass metabolism resulting in decreased bioavailability.

g) **Additive and Enhanced Effects:** When a drug is combined with another drug and if both the drugs have similar pharmacological responses, the total response or net response of the two drugs is equal to the arithmetic sum of their individual responses. Thus, a combination of aspirin and paracetamol provides a more qualitative response for the relief of pain.

On the other hand, when the combination of two drugs having different mechanisms of action produces a greater than the arithmetic sum of the individual effects of the drugs, the net effect is termed as synergism. It is a quantitative effect. For example, enalapril in combination with a thiazide diuretic yields a greater antihypertensive effect.

h) **Diminution of Effect:** when the effects of a drug are blocked or reduced in the presence of another drug, the feature is known as antagonism. A drug having affinity and efficacy for a receptor, is called an agonist. On the other hand, if a drug is having only affinity without efficacy the feature is know as antagonism. Here the antagonist simply occupies the receptor site and blocks the actions of agonist at the same site. For example, ach actions are blocked by atropine and D-tubocurarine working at two different sites (Ach M and Ach N receptor sites respectively).

i) **Chemical Antagonism:** In this case, one drug chemically reacts with and neutralizes the other drug. For example, an antacid or alkali will nullify the corrosive action of an acid. Similarly, protamine annuls the anticoagulant action of heparin, the former has a strong electropositive charge which antagonizes the electronegative charge of the later to which its action is due.

j) **Physiological Antagonism:** Here the two drugs have opposite effects but they are mediated through different mechanism or receptor systems. For example, adrenaline causes a rise in blood pressure, but nitrates cause a fall: therefore, the two are antagonistic to each one. While adrenaline causes vasoconstriction acting through α-receptors, nitrates cause vasodilatation acting on the smooth muscle of the blood vessel.

2. Short Essay Questions:

a) **G-Protein Coupled Receptors:** They are transmembrane receptors, also called metabotropic receptors coupled to intracellular effective systems/ second messengers like cAMP, cGMP, Ca^{+}, IP_3 and DAG through G-Proteins (guanine nucleotide binding protein). Example of G-Protein coupled receptors include muscarinic acetylcholine(mAch), α_2, opioid, β – adrenergic, 5 – HT and histamine receptors and also receptors for several hormones, including glucagon. G – Proteins are of three types namely G_S, G_I, and G_q. $G_s$mediates the actions of adrenergic, histaminergic, and 5 – HT (serotonin) receptors, glucagon receptors and receptors of several other hormones. G_I mediates the actions of α_2, mAch and opioid receptors. $G_q$mediates the actions of mAch, $5\text{-}HT_{1c}$, vasopressin type1 redeptors and angiotensin 11 receptors.

b) **Cardioselective Beta-blockers:** β_1 – blockers are also known as cardio-selective blockers as they exclusively block β1 receptor – by virtue of B1 receptor blockade located in the heart (SA nodal, AV nodal and Ventricular tissues). Examples include metoprolol, atenolol, esmolol, acebutolol, bisoprolol and nebiolol.

By virtue of their β_1 –blockade on the myocardium, they reduce heart rate, force of contraction, and sympathetic activity such as seen during exercise. They have an antihypertensive action due to the reduction of heart rate, cardiac output, inhibition of release of renin from GJ apparatus, inhibition of presynaptic nor-adrenaline release. They also elicit antiarrhythmic effect predominantly because of their action on phase-4 depolarization of cardiac action potential.

They are clinically useful to treat hypertension, angina prophylaxis (chronic stable angina) and early phase of acute myocardial infarction, supraventricular arrhythmias, and chronic congestive heart

failure. Their use is associated with decreased morbidity and mortality post MI. Treatment with β_o-blockers reduces the risk of stroke, coronary artery disease and congestive heart failure.

c) **Selective Serotonin Reuptake Inhibitors:** Citalopram, venlafaxine, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, and fluvoxamine are the selective serotonin reuptake inhibitors. They act by preventing the reuptake of 5-HT into the tryptaminergic nerve terminal thereby increasing the 5-HT levels. They are used as antidepressants is anxiety disorders (velnafaxine, duloxetine) and used to treat panic, generalized anxiety disorder, phobia and obsessive-compulsive disorder. They are also effective to treat posttraumatic stress disorder.

d) **Non-depolarizing Muscle Relaxants:** D – tubocurarine, atracurium, cisatracurium, mivacurium, doxacurium, metocurium are the non-depolarizing skeletal muscle relaxants that are in clinical use. They act on the $\mathbf{N_m}$ type of cholinergic receptors and block the actions of Ach and prevent the muscle contraction. As the action is a total blockade of the end plate potential, a type of faccid paralysis occurs in comparison to depolarizing agents which produce initial spasticity followed by flaccidity.

They are used as adjuvant to general anesthesia, in intensive care units to facilitate mechanical ventilation, or endotracheal intubation and in acute respiratory distress syndrome to assist normal or assisted ventilation; Neostigmine is the antagonist for non-depolarizing skeletal muscle relaxants.

e) **Inhalational drugs used to treat bronchial asthma:** Terbutaline, metaproterenol, salbutamol, fenoterol, formoterol, and salmeterol are used by inhalation, and act as β_2 agonists to cause relaxation of bronchial smooth muscle. They are used to treat acute and chronic bronchial asthma. Ipratropium is a $\mathbf{M_3}$ receptor antagonist used to treat acute episodes of bronchial asthma. Budesonide, fluticasone, beclomethasone, flunisolide, mometasone are the cortiostemids used to treat acute episodes of chronic bronchial asthma. Steroids do not have any bronchodilatory effects. They suppress the airway inflammation which is responsible for bronchoconstriction. This is brought about by suppression of inflammatory mediators, including cytokines, chemokines adhesion molecules, leukotreins, prostaglandins. Both ipratropium and $\beta_2$agonists cause bronchodilation releiving the symptoms.

f) **Mechanism of action of bupivacaine:** Bupivacaine is a local anesthetic and acts by blocking the voltage-gated Na+ channels which contain the receptor site for the agents located at its cytoplasmic (inner portion) thereby preventing the permeability of or flux of Na+ into the excitable membrane. It blocks the generation of action potentials in the nerve cells by increasing the threshold for electrical excitation.

It is used to provide spinal, epidural, regional, local, and infiltration anesthesia. Its onset of action is slow but has a longer duration of action of nearby 2 to 9 hours. Bupivacaine is more cardiotoxic than other local anesthetics as its duration of the cardiac action potentials is longer than that of the rest of local anesthetics. This is because of its slow diassaociation from the binding sites.

3. Short Answer Questions:

a) **Explain therapeutic drug monitoring and give few examples:** when a drug is administered it is likely to give not only the desired pharmacological and clinical responses but also the undesirable adverse effects. These adverse effects may be mild, moderate, and severe depending upon the dose given, the patient's response and duration of action of the drug.

Therapeutic drug monitoring is a process by which it becomes necessary sometimes to monitor the drug response with the corresponding dose given and the incidence of adverse effects it produces. The monitoring is necessary for a drug that is being administered over extended periods and those with narrow margin of safety. Therapeutic drug monitoring facilitates mainly to know plasma levels of the drug and the corresponding therapeutic response, adverse effects observed and adjust the dose

accordingly. The drugs which require therapeutic dry monitoring include lithium, digoxin, antimalignancy drugs and anticonvulsants.

b) **Cholinesterase inhibitors and their uses:** These drugs act by inhibiting acetylcholinesterase thereby increasing the actions of endogenous acetylcholine levels and inducing cholinomimetic effects. Edrophonium, neostigmine, physostigmine, demecarium are the reversible cholinesterase inhibitors. Organophosphorus compounds like ecothiophate, diisopropyl flurophosphate, parathion is some of examples of irreversible cholinesterase inhibitors. They are used mainly to treat myasthenia gravis, glaucoma, atropine poisoning, paralyticus ileus and atony of the urinary bladder.

c) **Drug addiction:** when a drug or non-therapeutic agent is used for extended periods it is likely to produce a state of tolerance which is a feature of reduced pharmacological response and that may lead to an increase in dose or over consumption to get the same response. Initially there would be physical dependance followed by psychic dependence as in the case of non-prescriptional and non-therapeutic agents like alcohol, opioids, LSD, phencyclidine, anabolic steroids. Addiction is the term used to include the development of either physical or psychic dependence or both.

d) **Dobutamine:** It is a direct acting inotropic drug; the action being mediated through cardiac β_1– receptors increasing cardiac contractility and cardiac output. Dobutamine is mainly used in cardiac decompensation that occurs after cardiac surgery or in patients with congestive heart failure or myocardial infarction. It increases cardiac output without any significant effect on heart rate or blood pressure.

e) **Tachyphylaxis:** It is a term used to denote acute tolerance observed usually in experimental procedures. It develops very quickly with successive doses with reduced pharmacological responses, and it cannot be overcome immediately by increasing the dose. Indirectly acting sympathomimetic drugs such as ephedrine, tyramine and amphetamine are the examples which show tachyphylaxis. The phenomenon of tachyphylaxis is due to exhaustion of the stores of sympathetic amines or may be due to metabolic degradation of the agent by the corresponding enzymes.

f) **Verapamil:** It is a calcium channel blocker and acts by blocking the voltage gated calcium channels in the blood vessels and heart. It causes relaxation of the vascular smooth muscle followed by vasodilation, decreased cardiac contractility producing negative inotropic and chronotropic effects. It is mainly used in hypertension, variant or prinzmetal angina, exertional angina, and cardiac arrhythmias.

g) **Phenylephrine:** It is α_1– receptor agonist. It is not a catecholamine and hence not inactivated by COMT and has much longer duration of action. It is mainly used as vasopressor to raise the blood pressure in conditions of hypotension, and along with local anesthetics to produce local vasoconstriction and slow its absorption and to provide longer duration of action. It is also used as a mydriatic drug (10% solution) without any effect on intraocular pressure. It is also used as nasal decongestant.

h) **Use of H_1 receptor blockers:** H_1 blockers are mainly used in allergic conditions like urticaria, dermatosis, conjunctivitis, seasonal rhinitis and common cold to relieve sneezing, rhinorrhea, itching of the eyes, nose, and throat. They are often combined with nasal decongestants like pseudoephedrine, phenylephrine; and with acetaminophen (paracetamol) for better relief of symptoms.

i) **Uses of carbamazepine:** It is an antiepileptic drug. It acts by blocking Na^+ channels and limits repetitive firing of action potentials evoked by sustained depolarizations in the cortical areas. It abolishes maximum electroshock – induced convulsions. It has no GABA like action. It is mainly used in generalized tonic – clonic contractions, simple and partial complex seizures (Temporal lobe

epilepsy), trigeminal and glossopharyngeal neuralgia, pain disorders like multiple sclerosis, and postherpetic neuralgia.

j) **Tremadol:** It is a synthetic codeine analog with a weak opioid receptor agonist activity. It is mainly effective in relieving mild-to-moderate pain such as labor pain, pain due to injuries, toothache, neurological pain, and many other not so severe types of pain. It is not effective to relieve pain of musculoskeletal origin. It is not effective to relieve pain due to malignancy. It is available in combination of paracetamol for a better therapeutic effect. It is available as immediate release and sustained release dosage forms, while the immediate release preparation is useful for acute pain and the the sustained preparation is useful for chronic pain.

Answers to Model Question Paper II

1. Long Essay Questions:

(a) What are Aminoglycosides? Give examples and mention their clinical uses and adverse effects.

Ans: Aminoglycosides are the antibiotics effective against many Gram-negative organisms such as E. coli, salmonella, shigella, enterobacter, citrobacter, klebsiella, morganella, pseudomonas and mycobacterium tuberculosis. They also have efficacy against enterococci and streptococci in combination with betalactams and vancomycin to produce synergistic effect. Aminoglycosides consist of streptomycin, gentamicin, tobramycin, amikacin, netilmicin and kanamycin.

The common properties of aminoglycosides include:

- They contain amino sugars linked to a hexose through a glycosidic bridge.
- They are effective against Gram negative infections with the exception of amikacin which has remarkable activity against methicillin – resistant S. aureus (MRSA).
- They are administered mainly parenterally (IM/IV).
- They are usually given in once daily doses and also as twice daily doses.
- The exhibit concentration dependent bactericidal activity with an increase of action with corresponding increase of the dose of the drug.
- They possess post antibiotic effect and they continue to kill the bacteria even after their plasma levels fall below the minimum inhibitory concentration (MIC).
- They cause ototoxicity and nephrotoxicity with slight variability among the compounds.
- All of them are useful in fulminating conditions like bacterial endocarditis, urinary tract infections, septicemias and pulmonary tuberculosis (Streptomycin, Kanamycin and amikacin).

Clinical uses of Aminoglycosides

1) Streptomycin is useful in bacterial endocarditis caused by enterococci, D streptococci, viridans sfreptococi in combination with penicillin or vancomycin. It is used to treat mycobacterium tuberculosis in combination with other anti TB drugs like pyrazinamide, INH, rifampicin, ethambutol). It is also effective to treat plague, tularemia, and brucellosis.
2) Gentamicin is the most preferred drug to treat serious, life – threatening Gram – negative infections such as septicemia, systemic bacteremia, infected burns, osteomyelitis, pneumonia and peritonitis caused by P aeruginosa, enterobacter, klebsiella, serratia, proteus and acinobacter. It is usually combined with extended spectrum penicillin or a cephalosporin which provides a synergistic effect.

   The other uses of gentamiain include urinary tract infections, bacterial endocarditis caused by enterococci, streptococci, strepococcus pneumoniae; nosocomial pneumonia and sepsis. Topically it can be used for infected burns, wounds or skin infections and external ocular infections (eye drops).
3) Tobramycin is used mainly for infections caused by P. aeruginosa
4) Amikacin has the same uses as gentamicin and tobramycin and particularly if the bacterial strains are not sensitive and resistant to the earlier drugs.

Adverse effects of Aminoglycosides:

All aminoglycosides produce potential dangerous reversible and irreversible adverse effects such as ototoxicity, nephrotoxicity and neuromuscular effects. Ototoxicity produced by aminoglycoside is

irreversible (both cochlear and vestibular dysfunction). Nephrotoxicity is manifested as increased excretion of brush border enzymes, proteinuria, and appearance of casts in the urine, and decrease of GFR. Neomycin is the most nephrotoxic because of its high accumulation in the renal cortex and streptomycin is beast nephrotoxic.

(b) Classify Antithyroid Drugs. Explain the mechanism of action of the principal group, and their uses.

Ans: Antithyroid drugs can be classified as

1) Thioamides – Propylthiouracil, methimazole, carbimazole
2) Anion inhibitors – Potassium perchlorate, thiocyanate, pertechnetate
3) Iodine and iodates – Lugol's iodine, potassium iodide
4) Iodinated contrast media – Diatrizoate, iohexol
5) Radioactive iodine – ^{131}**i**

Mechanism of Action Thioamides: They decrease thyroid hormone production. They interfere with peroxidase –catalyzed reactions and prevent the iodination of tyrosine to form mono and diiodotyrosin residues, coupling of iodotyrosine residues to form T4 and T3 and prevent the conversion of T4 to T3 (Propylthiouracil) peripherally by inhibiting 5' – deiodinase. Due to this additional property, propylthiouracil is often used to provide rapid relief from severe thyrotoxicosis. Thioamides also inhibit thyroid release. Propylthiouracil provides rapid reversal of symptoms compared to methimazole and has a short half-life of 1.5hr compared to 6 hrs with methimazole. Propylthiouracil is also the drug of choice during 1st trimester of pregnancy and also the drug of choice during the recovery phase of thyrotoxic crisis.

Uses of Antithyroid Drugs

1) Thioamides are used in the management of hyperthyroidism and thyrotoxic crisis and in the preparation of patients for surgical subtotal thyroidectomy.
2) Anion inhibitors act as competitive inhibitors of thyroid transport mechanism and prevent the uptake of iodide by the gland. They are effective in treating iodine – induced hyperthyroidism which may occur in patients treated with antiarrhythmic compound amiodarone.
3) Lugol's iodine inhibits the uptake and incorporation of iodine into the thyroid gland and inhibits TSH control over the thyroid gland and decreases the levels of T4 and T3. It also inhibits the release of thyroid hormones. Lugol's iodine is used in combination with propylthiouracil in the management of thyrotoxic crisis to rapidly inhibit thyroid secretion. Most commonly it is used in the preoperative preparation of patients about to go for thyroid surgery to decrease the vascularity and turgescence of the thyroid gland.
4) Iodinated contrast media are used in the treatment of hyperthyroidism as they rapidly inhibit the peripheral conversion of T4 to T3.
5) Radiolabeled iodine (^{131}I) is used in the treatment of hyperthyroidism while other isotopes of radioactive iodine are used for thyroid ablation by emitting β – particle emission.
6) B – adrenergic blockers (propranolol) are used to control the sympathetic effects associated with hyperthyroidism, particularly cardiovascular sympathetic effects (increased here rate, blood pressure). It is also used in thyrotoxic crisis for the similar effects.

(c) Write about the following.

a. Mechanism of action of clomifene and its adverse effects.

Ans: clomifene is an ovulation inducing agent and has partial agonist and antagonist actions. It binds to the estrogen receptors (ERα and ERβ) because of its antagonistic action and blocks the negative

feedback inhibition of release pituitary gonadotropins (FSH, LH) by estrogen and facilitates their release. The FSH and LH release during midcycle facilitates ovulation. Women who are infertile suffer from polycystic ovary syndrome (poly follicular syndrome) which is characterized by amenorrhea, anovulation, dysfunctional uterine bleeding (DUB), and infertility. Hence clomifene is used in the treatment of ovulatory dysfunction.

The adverse effects of clomifene include hot flushes similar to those seen in menopausal syndrome. It can cause enlargement of ovaries, increased incidence of multiple births, ovarian cysts, and GI side effects like nausea and vomiting.

b. Mechanism of action of methotrexate, its uses and important adverse effects.

Ans: Methotrexate is an antimetabolite and inhibits the enzyme dihydrofolate reductase thereby preventing the conversion of dihydrofolate to tetrahydrofolate (antifolate action). This blocks regeneration of tetrahydrofolate and prevents synthesis of purines and pyrimidines which in effect results in interfering with the formation of DNA, RNA, and key cellular proteins. Formation of methotrexate polyglutamate derivatives is essential for its antitumor activity.

Methotrexate is used in the treatment of childhood leukemias with reasonable periods of remissions. It is also effective for choriocarcinoma, hydatiform mole, breast cancer, and solid tumors such as osteogenic sarcoma, psoriasis and rheumatoid arthritis.

The adverse effects of methotrexate include anorexia, nausea, vomiting, progressive weight loss, bloody diarrhea, and leucopenia. It causes maximum damage to bone marrow and GI mucosa. **Leucovorin** (5-fromyl derivative folic acid) is indicated to diminish toxicity and counteract the effects of impaired methotrexate elimination or inadvertent overdosage of methotrexate.

c. Clinical uses of corticosteroids

Ans: Corticosteroids (glucocorticoids) can be used for hormonal and non- hormonal uses.

Hormonal indications mainly are related to replacement therapy, and the non-hormonal uses are by virtue of their antiinflammatory and immunosuppressant actions.

Hormonal uses include acute adrenal insufficiency (Addison's disease), chronic adrenal insufficiency, congenital adrenal hyperplasia, Cushing syndrome secondary to an ACTH secretary pituitary adenoma after surgical removal of the tumor.

Non- hormonal uses include

1) Rheumatic fever and rheumatic arthritis.
2) As adjuvant with other drugs to treat psoriatic arthritis, ankylosing spondylitis, post traumatic osteoarthritis, acute and subacute bursitis, synovitis, osteoarthritis (OA), tenosynovitis and acute gout and chronic rheumatoid arthritis.
3) Renal diseases (nephrotic syndrome).
4) Allergic conditions like angioneurotic edema, hay fever, serum sickness, urticaria (including for topical use), contact dermatitis, drug reactions, including anaphylactic shock.
5) Bronchial asthma, both for acute and chronic episodes.
6) Dermatological conditions like psoriasis eczema, atopic dermatitis seborrheic dermatitis, acne vulgaris, and acne rosacea and in bacterial infections along with topical antibiotics.
7) GI diseases like inflammatory bowel syndrome.
8) Immuno suppression after organ transplantation, tissue grafting and several graft rejections.

9) Autoimmune diseases like Guillain – Barre syndrome, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, autoimmune hemolytic anemia, polymyositis, autoimmune uveitis, scleroderma and Sjogren syndrome.
10) Cerebral edema due to space occupying lesions.
11) Ocular diseases like allergic conjunctivitis, keratitis and Kerato conjunctivitis.

(d) Drugs for Nosocomial Infections.

Ans: Nosocomial infections are hospital acquired infections during the process of receiving health care that were not present during the time of admission. They can be acquired by the patients, hospital staff (doctors, nursing sisters, and paramedical staff) and can occur anywhere (area) in the hospital from person to person, or by the use of invasive procedures, surgery, indwelling catheters, prosthetic devices, all of which are infected with microorganisms. They are more likely to occur in closed areas such as ICUs, surgical theatres and isolated hospital wards. The most common forms of nosocomial infections include pneumonia, skin and soft tissue infections, GI infections, blood stream infections, and urinary tract infections. Both Gram positive and Gram-negative bacteria can be the source of infection apart from opportunistic fungal and viral infections in immunocompromised patients.

Treatment is usually started with ceftriaxone 1 – 2g IM/IV twice daily or levofloxacin 750mg (PO) once daily or moxifloxacin 400mg (PO)once daily all being empirical drugs to begin with keeping in view that the pathogens for the infections might be or proven to be streptococcus pneumoniae, H. influenzae, methicillin – sensitive staphylococcus aureus. The other important drug for use is vancomycin 15-20mg/kg IV 8^{th} hourly, or linezolid 600mg/orally, 12^{th} hrly for 10 -14 days or Ertapenem 1g once daily IV/IM for 14 days to cover Gram negative infections caused by E. coli, Klebsiella pneumoniae, enterobactor, proteus and serratia. Similarly, antiviral and antifungals may also be added in immunocompromised patients.

(e) Fibrinolytic Drugs.

Ans: Fibrinolytics (fibrinolytic agents) are the agents used to facilitate lysis of already formed clots and thereby restore the patency of the obstructed blood vessel. Fibrinolytic drugs are life saving in acute thrombotic disordered like MI, pulmonary embolism, deep vein thrombosis and cerebrovascular thrombotic stroke. The following drugs are used as fibrinolytic agents.

1) Streptokinase though exerts most striking and potentially beneficial effects in fresh thrombi,

   its action is limited by two factors. It is capable of producing antigenic reactions and likely to cause anaphylactic reaction if reused when it was given once earlier. It is relatively nonspecific and can result in systemic fibrinolysis causing bleeding episodes.

2) Urokinase

   It lacks antigenecity unlike streptokinase. It directly vonverts plasminogen to active plasmin which in turn leads to the breakdown of fibrin mesh structure in the clot. It is mainly used for restoration of blood flow in peripheral blood vessels, occluded catheters used in dialysis, and also for other embolic disorders such as MI, stroke, pulmonary embolism and deep vein thrombosis.

3) Tissue plasminogen activators like alteplase, reteplase, tenectiplase and anistreplase are the most preferred agents used in acute MI and cerebrovascular stroke. They are the recombinant derivatives of naturally occurring tissue plasminogen activator and have the same indications as the rest of the fibrinolytic drugs.

   All the fibrinolytic drugs act by converting of the inactive zymogen, plasminogen to the active protease plasmin. Plasmin is a relatively nonspecific protease that digests fibrin to fibrin degradation products with dissolution of the clot.

(f) Prophylactic use of antibiotics with examples.

Ans: Antibiotics are not only effective in acute bacterial infections but also serve as prophylactic agents for the prevention of a possible infection by microorganisms (chemoprophylaxis).

a. Rifampin is administered to prevent meningococcal meningitis in people who are in close contact with an infected person.

b. Prevention of gonorrhea and syphilis soon after contact with an infected person.

c. Chemoprophylaxis is recommended in patients with valvular lesions of the heart who are likely to be predisposed to endocarditis, and those undergoing dental, surgical or other procedures which are likely to produce bacteremia. Similarly, patients with valvular heart disease undergoing tonsillectomy are recommend chemoprophylaxis

d. Travellers visiting endemic areas of malaria can be protected by prior administration of sulfadoxine and pyrimethamine or mefloquine.

e. Chemoprophylaxis can prevent cardiac valvular disease at a later age in patients with childhood rheumatic arthritis. Long – acting penicillin like benzathine penicillin is given for the purpose.

f. Prior administration of a broad-spectrum antibiotic can prevent wound infection or any other abdominal/thoracic infection is a person to undergo surgery.

Model Question Papers

PAPER III

1. Long Essay Questions:

1. Classify non – insulin antidiabetic drugs. Explain the mechanism of action of any two groups and enumerate their adverse effects.

Ans:

a) Insulin secretagogues
   i) Sulfonylureas – glibenclamide, glimepiride, gliclazide, glipizide
   ii) Non – sulfonylurea derivatives – Nateglinide Repaglinide

b) Biguanides – Metformin

c) Thiazolidinediones – Rosiglitazone, Pioglitazone

d) α – glucosidase inhibitors – Acarabose, Volgibose, Miglitol

e) GLP – 1 analogue – Exenatide, liraglutide, semaglutide

f) Dipeptidyl peptidase inhibitors – Sitagliptin, saxagliptine, alogliptin

g) Sodium – glucose Co – transporter – 2 (SGLT – 2) inhibitor – Dapagliflozin empagliflozin canagliflozin

h) Amylinomimetics – Pramlintide

i) Bile acide Sequestrants – Colesevelam

j) Dopamine agonists – Bromocriptine

a) Insulin secretagogues

i) Sulfonylurea's derivatives: Glibenclamide, glimepiride, gliclazide, glipizide is the second-generation sulfonylurea derivative. Chlorpropamide and tolbutamide belong to the first – generation drugs of the same class. Because of undue hypoglycemia and other unsuitable administrative procedures, caused by first generation drugs, the second-generation group of drugs is the most commonly prescribed oral antidiabetic drugs.

Mechanism of Action: Sulfonylurea drugs act by liberating insulin from the pancreatic β – cells. This is brought about by binding of sulfonylureas to a 140 KD sulfonylurea receptor (SUR1) which is an integral part of the ATP – sensitive potassium channel (KATP) that is present on the β – cell membrane surface. Closure of the KATP channel prevents the outflow of potassium with an increase in the intracellular K^+ levels that triggers the opening of voltage gated Ca^+ channels (inward flux of Ca+) leading to depolarization of the cell membrane followed by degranulation and release of insulin. Sulfonylureas may further facilitate increased insulin levels by reducing hepatic clearance of the hormone.

Adverse effects: The most common adverse effect associated with sulfonylureas administration is hypoglycemia which may be substantiated by inadequate calorie intake. The chances of hypoglycemia are higher in the elderly with hepatic or renal impairment. Chlorpropamide by virtue of its long half – life is more likely to produce hypoglycemia. In the second-generation sulfonylurea preparations, glibenclamide has a more chance for the development of hypoglycemia.

The other important adverse effects, sulfonylureas include weight gain which is undesirable in persons who are already obese. There is a possibility of drug interactions with sulfonamides, clofibrate, and salicylates which displace sulfonylureas from plasma binding sites and increase their plasma levels. Chlorpropamide is likely to develop alcohol – induced flush similar to that produced by disulfiram. Chlorpropamide has ADH – potentiating effects, the actions of which make it useful in mild forms of central diabetes mellitus.

Nonsulfonylurea derivatives

Repaglinide (structurally related to glybenclamide (glyburide) and Nateglinide act by binding to sulfonylurea receptor (SUR1) which is an integral part of ATP-sensitive potassium channel present on the β-cell membrane similar to sulfonylurea derivatives. They inhibit K+ outflux, depolarizing the β-cell membrane liberating insulin release through ca+ influx.

Both the drugs cause a brief rapid pulse of insulin when given before meal and reduce the postprandial rise in blood glucose levels. They can be used as monotherapy or in combination with biguanides (metformin) to reduce postprandial glucose levels and should be given just before meals.

ii) **GLP – 1 agonists:** Incretins are hormones that work to increase insulin secretion. There are two main incretins in the body, namely GLP – 1 (glucagon – like peptide – 1) and GIP (glucose – dependent insulotropic peptide, also known as gastric inhibitory peptide). Both of them are secreted by the endocrine cells (L – type cells) that are located in the epithelium of the small intestine. Incretins are carried through the circulation to the target tissue, the pancreatic β – cell. Incretin stimulation of β – cells cause them to secrete more insulin in response to the same amount of blood glucose.

Mechanism of action: GLP – 1 agonists (exenatide, liraglutide, dulaglutide, albiglutide, lixisenaside, semaglutide) act through GLP – 1 receptors expressed in pancreatic β- cells. Binding of agonists to GLP – 1 receptor activates cAMP – PKA pathway that results in increase of insulin secretion followed by exocytosis. GLP – 1 agonists also increase pancreatic β – cell function, cause decrease of glucagon, reduced glucose production in the liver by reducing hepatic gluconeogenesis and an increase of glucose uptake in the skeletal muscle and adipose tissue.

Adverse effects: GLP – 1 agonists may produce nausea, diarrhea, hypoglycemia and vomiting. Less common side effects include headache, constipation, dyspepsia, fatigue.

2. Classify the drugs for acid peptic disease and discuss the mechanism of action of any two major groups and their indications.

Ans: Drugs for acid – peptic disease can be classified as

a) Acid – neutralizing agents (antacids) – Aluminum hydroxide, magnesium hydroxide, magnesium tricylicate.
b) H_2 receptor antagonists – Ranitidine, famotidine, nizatidine.
c) Proton pump inhibitors – Omeprazole, rabiprazole, lansoprazole, pantoprazole, esomeprazole.
d) Anticholinergic drugs – Pirenzepine, glycopyrolate, mepenzolate.
e) Prostaglandin analogues – Misoprostal.
f) Mucosal protective agents – Sucralfate, colloidal bismuth compounds.
g) Drugs for H – pylori infection - Metronidazole, amoxacillin, clarithromycin.

1) **H_2 receptor antagonists:** They inhibit the acid production by reversibly competing with histamine for binding to H_2 receptor on the basolateral membrane of parietal cells. They also suppress basal acid secretion and suppress the acid secretion due to feeding, gastrin, hypoglycemia or vagal stimulation.

   These agents are particularly useful in suppressing nocturnal acid secretions which reflect mainly basal parietal cell activity. These agents promote ulcer healing because of their predominant effect on the nocturnal basal secretion. H_2 antagonists are available both for oral and parenteral use.

   Therapeutic uses: H_2 receptor antagonists are useful to treat all types of acid peptic disorders and they are as effective as proton pump inhibitors in providing ulcer healing when given in adequate doses and for adequate duration. Thus, they are indicated in healing of gastric and duodenal ulcers, to treat uncomplicated GERD and to prevent the occurrence of stress – induced ulcers, including prevention of bleeding from stress related gastritis, and for treating drug – induced ulcers. They are most effective for duodenal ulcers than for gastric ulcers.

2) **Proton pump inhibitors (PPIs)** (Omeprazole, lansoprazole, pantoprazole, rabeprazole, esomiprazole).

   Mechanism of Action: PPIs are inactive prodrugs which are activated in the acid medium in the parietal cell canaliculi. Oral preparations of these drugs are enteric coated to prevent premature activation. In the local acidic pH of the canaliculi, these become active and protonated to form the sulfonamide cations, which then react with a cysteine residue on the H^+/K^+/ATPase (Proton pump) to form a covalent disulfide bond. This binding inhibits the activity of the proton pump irreversibly, leading to prolonged and nearly complete suppression of acid secretion.

   Therapeutic uses

   (1) PPIs are used to treat active duodenal ulcers, H-Pylori associated ulcers in combination with antibiotics like amoxacillin, clarithromycin, and metronidazole; hemorrhagic ulcers and steroids induced ulcers. They provide more rapid relief of epigastric pain and heart burn and more rapid and effective gastric ulcer and esophageal ulcer healing than H_2 blockers.

   (2) They are the drugs of choice to treat Zolinger– Ellison syndrome

   (3) They are the first drugs of choice to treat gastroesophageal reflux disease (GERD). They ae useful to treat erosive and nonerosive reflux disease (erosive esophagitis, Barretts esophagitis, esophageal strictures and esophageal adenocarcinoma).

   (4) PPIs ae useful to reduce the risk for upper GI bleeding.

   (5) PPIs are extremely useful in treating pathological hypersecretory conditions like gastrinomas which are inoperable or metastatic in nature. By giving PPIs, the development of peptic ulceration, erosive esophagitis, and malabsorption can be prevented.

   (6) PPIs are useful in NSAID induced gastric and duodenal ulcers.

2. Short Essay Questions:

1. Explain the mechanism of action of high ceiling diuretics and their clinical indications.

Ans: High ceiling diuretics are also known as loop diuretics. They have high ceiling effect as far as natriuresis and diuresis are concerned in comparison to other groups of drugs in the category. High ceiling means the maximum capacity or the highest natriuresis when compared to the effect produced by other groups of diuretics.

High – ceiling diuretics have a predominant effect on thick ascending loop of Henle inhibiting reabsorption of Nacl. Frusemide, ethacrinic acide, bumetanide, torsemide are the available loop diuretics

for clinical use. At the thick ascending limb of Loop of Henle, they inhibit NKCC2 (Sodium potassium chloride cotranporter-2) in the apical (luminal) membrane of the loop epithelial cells and reduce the reabsorption of Nacl up to 25% of filtered load of Na+. They also cause a loss of Mg^+ and Ca^+ by inhibiting positive luminal potential.

Clinical uses

1) Loop diuretics are used to treat edematous states such as pulmonary edema, edema due to congestive heart failure, hepatic cirrhosis, nephrotic syndrome and hypertension.
2) They also cause a decrease of serum Ca^+ levels by increasing Ca^+ elimination and can be used in hypercalcemic states such as hyperthyroidism or parathyroid malignancy associated hypercalcemia.
3) They are also used to counteract hyperkalemia caused by potassium – retaining diuretic or ACE inhibitors.
4) They can be used to induce forced diuresis to facilitate rapid removal of toxic drugs when taken in excessive doses.

2. Explain the mechanism of action of oral anticoagulants and their clinical uses.

Ans: Oral anticoagulants can be broadly classified as Vitamin K antagonists and factor Xa and thrombin (FIIa) inhibitors. Vitamin K inhibitors like warfarin, acenocoumarol, dicoumarol and anisindione act as antagonists of vitamin K which is essential for the synthesis of coagulation factors II, VII, IX and X and the anticoagulant proteins C and S (coagulation regulatory factors).

Factor Xa (FXa) inhibitors like rivaroxaban, apixaban, edoxaban, betriaxaban prevent the formation of thrombin from prohrombin and thereby inhibit the conversion of fibrinogen to fibrin clot.

Factor IIa (FIIa) like dabigatran is a direct thrombin inhibitor.

Clinical uses of oral anticoagulants: Oral anticoagulants are used to treat conditions like venous thromboembolism, including deep venous thrombosis and pulmonary embolism. They are also used to prevent thrombus formation in conditions like atrial fibrillation, mechanical and prosthetic devices implants, in conditions like prosthetic cardiac valve replacement and thereby to prevent stroke, peripheral venous thromboembolism.

3. Mention the drugs used to treat Herpes viral infections and their clinical uses.

Ans: The drugs used to treat Herpes viral infections include idoxuridine, acyclovir, valacyclovir, famciclovir, docosanol, penciclovir.

Clinical uses of drugs for Herpes infections: Acyclovir and other drugs of this class are used to treat herpes simplex and varicella zoster infections. Herpes simplex virus – 1 causes herpes labialis (Cold sores) or herpes esophagitis; herpes simplex – 2 causes genital herpes, Varicella Zoster causes chicken pox and shingles. Acyclovir is also effective against Epsten – Barr viral infection which causes infectious mononucleosis, and cytomegalovirus infection which produces pneumonia, gastroenteritis, retinitis, encephalitis and mononucleosis in immuno compromised patients. Acyclovir is also used to treat herpes encephalitis and neonatal herpes simplex infections. Acyclovir is available for oral use as well as for topical use for genital herpes.

4. Mention the drugs used to treat acne vuglaris.

Ans: Acne vulgaris is a skin disorder seen in adolescents and is caused by Cubibacterium acnes and consists of lesions of comedones (small flesh – colored, white or dark bumps on the face, forehead, and chin) and inflammatory papules, pustules and nodules.

Drugs used to treat acne vulgaris

1) Topical antibiotics like clindamycin (1% gel); erythromycin (4% lotion); metronidazole (0.75%) cream; azelaic acid (20% cream and 15% gel); benzyl peroxide (2.5% gel)

2) Systemic antibiotics like erythromycin, tetracyclines, sarecycline (tetracycline derivative)
3) Topical retinoids like retinol, tretinoin, isotretinoin, acitretin, Tazarotene, bexarotene, adapalene.
4) Systemic retinoids like isotretinoin.

5. Mention the selective estrogen receptor modulators and their clinical uses.

Ans: Selective estrogen receptor modulators (SERMs) are the drugs that modulate the actions (differentiation of actions) of estrogen acting at different target sites. Thus, tamoxifene, the first SERM to be developed blocks the estrogen receptors (ER_{α}, ER_{β}) in the breast and causes regression of breast tumor growth in women with ER – Positive tumors. Tamoxifene produces estrogen effects (acts as agonist) on bone and plasma lipids and facilitate bone turnover and an increase of bone mineral density. However, tamoxifene demonstrates partial agonist activity in the uterus which explains the endometrial hyperplasia and the possible endometrial malignancy with its use.

Raloxifene is the second generation SERM has significant agonist activity of estrogen on bone mineral metabolism and hence useful to treat osteoporosis in post menopausal women and also for risk reduction of invasive breast cancer in post menopausal women. It has anti – estrogen action on the uterus and does not cause uterine hyperplacia. The third generation of SERMS includes ormeloxifene, toremifene, lasoxifene, arzoxifene and bazedoxifene and all of them are approved for the treatment of osteoporosis.

Clinical uses of SERMs

1) Breast cancer: Tomoxifene is used primarily in estrogen-positive breast tumor in women after the patients have completed their primary treatment with surgery and radiation and those with non-invasive breast tumor (ductal carcinoma in situ) and as prophylactic drug for invasive breast tumor. It is efficacious in younger women and is particularly recommended if there is a family history of invasive breast cancer.
2) Osteoporsis: Raloxifene and the third generation of SERMs are used to treat osteoporosis in post menopausal women. They reduce bone resorption and facilitate bone formation acting on osteoclastic and osteoblastic cells respectively.
3) Abnormal uterine bleeding (AUB) and contraception: Ormeloxifene is used for AUB and contraception.
4) Prevention of atherosclerosis – By virtue of their positive lipid lowering effects, they can be used for prevention of atherosclerosis and cardiovascular events.

6. Explain the antiarrhythmic action and clinical uses of lidocaine.

Ans: Lidocaine blocks both activated and inactivated Na^{+} channels and causes minimal phase-0 depression, decrease automaticity in Purkinje fibers, decrease the abnormal and triggered activity thus abolishing early and delayed after-depolarizations in Pukinje fibers. It also causes depression of slope of phase 4 depolarization and increase of excitability threshold in punkinje fibre. Refractory period is prolonged and reentry arrhythmias are abolished.

Uses: it is mainly used for rapid control of ventricular arrhythmias due to myocardial infarction, and those caused by inhalational general anesthetics.

3. Short Answer Questions:

1. **Levothyroxine:** It is used to treat hypothyroidism. It serves as replacement therapy if the natural production of thyroxine is inadequate or if there is total absence of the hormone after thyroid surgery. It is also used in pregnancy associated hypothyroidism wherein serum thyroxin – binding globulin levels are increased resulting in decrease of serum free thyroid hormone secretions (FT4). Hence requirements of the

hormone are increased during pregnancy. This is particularly important because total brain development of the fetus depends on maternal thyroid dose. Levothyroxine is also useful to treat myxedema coma.

2. **Methocobalamine:** It is used to treat megaloblastic anemia associated with Vitamin B12 deficiency or folate deficiency or both. B12 deficiency tends to cause neurogenic syndrome while folate deficiency is related to hematological changes. Methocobalamine is the active form of vitamin B12 and can be given both orally and parenterally. The oral dose is 500 – 1000mcg/ day and the parenteral dose is 500mcg IV/IM in 3 times a week. Improvement of neurological symptoms like paresthesias, burning sensations in the hand and feet, unsteadiness of gait, personality changes improve within a period of 3 months after initiation of therapy while the hematological changes may take a longer time for recovery.
3. **Enoxaparin:** It is a low – molecular weight heparin and exhibits more predictable anticoagulant activity than unfractionated heparin. Its bioavailability is more due to lesser plasma and endothelial binding. It has longer half – life and allows less frequent administration and has lesser antigenic reactions. Its action on osteoclasts is also less with lesser bone loss. It can be used safely during pregnancy.

   The chances of thrombocytopenia are also less and also lesser platelet aggregation when compared to unfractionated heparin. It is given in 30 – 40 mg once daily dose by subcutaneous route for prophylaxis of venous thromboembolism, deep vein thrombosis, pulmonary embolism, and acute coronary syndrome, percutaneous coronary intervention (PCI) for stent placement and in conditions of acute MI. It is given in patients who are bed ridden for longer periods due to any reason for prevention of any thromboembolic events.
4. **Indications of sodium Nitroprusside:** It is a vasodilator used in acute decompensated cardiac failure. It is given IV as infusion and has an onset of action of 30 seconds. It reduces both the preload and afterload thereby reduces cardiac workload and oxygen consumption and thus increases cardiac output. This is usually combined with loop diuretics like frusemide to off load the extracellular fluid volume to reduce the work load on the heart. It is also used to lower the blood pressure in hypertensive emergencies wherein it lowers the blood pressure rapidly.
5. **Clinical uses of methotrexate:** It is an antifolate. It inhibits the enzyme dihydrofolate reductase which catalizes the reduction of dihydrofolate to tetrahydrofolate and thus blocks the regeneration of tetrahydrofolate and prevents synthesis of purines and pyrimidines which in effect prevent the formation of DNA or RNA and key cellular proteins. Formation of methotrexate polyglutamate is essential for the antitumor activity.

   It is used mainly in childhood leukemias, choriocarcinoma, hydatiform mole, breast cancer and solid tumors such as osteogenic sarcoma in higher doses. It is also used in rheumatoid arthritis and psoriasis and psoriatic arthritis, squamous cell carcinoma of lungs, epidermoid cancers, and cutaneous T – Cell lymphoma.

   It produces anorexia, nausea, and vomiting affecting GI mucosa. It causes maximum damage to bone marrow and causes leucopenia, thrombocytopenia, and even agranulocytosis. **Leucovorin (**5- formyl derivative of folic acid**)** is given to reduce its toxicity and to counteract its adverse effects and to facilitate its elimination due to inadvertent over dosage.
6. **Indications of fluconazole:** Fluconzole is hydrophilic triazole and can be used both orally and intravenously for different fungal infections. Fluconzole is especially useful for cryptococcal and coccidiodial meningitis because of its high penetration into CSF. It is also useful to treat oropharyngeal candidiasis, esophagial candidiasis, for the prevention of systemic fungal infections in bone marrow transplant recipient and AIDS patients. It is also useful in vaginal candidiasis.
7. **Explain the rationale of combination of sulfamethoxazole and trimethoprim.**

Ans: Timethoprim/ pyrimethamine have antibacterial and antimalarial actions and it is because of their high affinity for dihydrofolate reductase. It binds the enzyme competitively and inhibits it in bacteria and

mammalian cells. Thus, trimethoprim inhibits the conversion of dihydrofolate to tetrahydrofolate (THF) and blocks the formation of thymidines, purines, methionine and glycine in bacteria leading to their rapid lysis. Sulfonamides (sulfamethoxazole and others) are structural analogs of PABA and competetively inhibit it, preventing the utilization of PABA by bacteria for folic acid synthesis.

When sulfamethoxazole and trimethoprim are given in a fixed dose ration of 5:1 equivalent to 800mg and 160mg respectively, they reach peak plasma levels (40mcg/ml and 2mcg/ml in that order). Thus, the combination of the two drugs causes sequential blockade of essential synthetic processes for the formation of folinic acid required for its vonversion to RNA and DNA in the bacteria. It provides a synergistic action and the combination is known as **cotrimoxazole.** Individually both the drugs are bacteriostatic but in combination produce bactericidal effect. The half-lives of trimethoprim and sylfamethoxazole are approximately 11 and 10 hours respectively. Cotrimaxazole is used in many bacterial infections like urinary tract infections, respiratory infections like chronic bronchitis, and upper respriratory tract infections, otitis media, acute maxillary sinusitis, Shigellosis, salmanosis, pneumocystis jiroveci infection (pneumonia in immunocompromised patients) and for gram negative infections in neutropenic patients.

8. Clinical uses of Artemether

Ans: Artemether is a derivative of dihydroartemicinin. It can be given orally, parenterally and rectally also. It is used in **multidrug – resistant P. falciparum malaria** infection. It is used in combination with lumifantrine and given for severe acute cases of drug – resistant P. falciparum malaria. When used alone it is given orally on a 7-day course with 4mg/kg/day for 3 days, followed by 1.6mg/kg/day for 4 days. But when nused in combination with lumifatrine it is given in a dose of 120 mg along with artemether dose of 20 mg.

9. Indications and adverse effects of INH: Isonicotinic acid hydrazine – **isoniazid (INH)** is the principal first line drug in the treatment of tuberculosis and given in combination with rifampicin, pyrazinamide and ethambutol during intensive 2 months therapy in a dose of 300 mg/day and in a dose of 600 – 900mg two times a week in the continuous 4 months treatment. Adverse effects of INH include hepatotoxicity, peripheral neuropathy, hypersensitivity reactions like rash, fever, jaundice. Hepatotoxicity usually occurs in patients with existing liver dysfucntion, and with the simultaneous use with other hepatotoxic toxic drugs like pyrazinamide or rifampicin and is chronic alcoholics. Peripheral neuropathy occurs in the absence of pyridoxine and also due to slow acetylation of the enzymatic (N – acetylation) metabolism of the drug.

10. Domperidone: It is a prokinetic drug and has antiemetic action. It blocks predominantly D2 receptors without any major effect on other receptors. Unlike metoclopramide, it does not cross blood – brain barrier and consequently is less prone to produce central side effects. It is indicated in delayed gastric emptying of functional origin with GERD and/ or dyspepsia, control of nausea and vomiting of central and local origin, as an antiemetic in patients receiving cytotoxic drugs and radiation chemotherapy. It is also used to facilitate radiological examination of upper GI tract and in acute attacks of migrane. It is also indicated in diabetic patients with gastroperesis.

Answers to Question Paper given by Kaloji Narayana Rao University, Warangal – April/May 2022

1. Classify Antiepileptic drugs. Write the mechanism of action, therapeutic uses and adverse effects of sodium valproate.

Ans: Antiepileptic drugs can be classified as follows

1) **Hydantoin derivatives** – Phenytoin, phosphenytoin, mesantoin, ethotoin
2) **Barbiturates** – Phenobarbitone, mephobarbitone, thiopentone
3) **Succinimides** – Ethosuximide, methosuximide
4) **Benzodiazepines** – Diazepam, clonazepam, clobazam, clorazepate, lorazepam
5) **Iminostilbenes** – carbamazepine, oxcarbazepine
6) **Oxazolidinediones** - Trimethadiane, paramethadione
7) **Carboxylic acid derivatives (partial GABA agonists) –** valproic acid
8) **GABA agonists and GABA promoters** – Gabapentine, pregabalin, vigabatrine, tiagabine.
9) **Sulfonamide derivatives** – Zonisamide
10) **Miscellaneous** –Topiramate, lamotrigine, levetiracetam, retigabine, lacosamide, rufinamide.

Mechanism of action of sodium valproate (valproic acid)

- It abolishes both pentylenetetrazol, and maximum electroshock induced convulsions
- It blocks sustained, high – frequency, rapid, repetitive neuronal firing in the cortical areas. This action is brought about by blockade of Na+ channels similar to Phenytoin and carbamazepine.
- It blocks NMDA receptor – mediated excitatory responses.
- It blocks low threshold Ca2+ currents ('T' currents) similar to ethosuximide
- It also exhibits GABA like action by an increase of GABA levels by different mechanisms, such as increased synthesis, inhibition of GABA reuptake, or inhibition of GABA degradation.

Therapeutic uses of valproic acid

1) Valproic acid is very effective against **absence seizures** particularly when the patient also suffers from generalized tonic – clonic seizures simultaneously
2) Myoclonic seizures.
3) Primary generalized tonic – clonic seizures
4) Complex partial seizures as monotherapy or in combination therapy that occur either in isolation or in association with other types of seizures.
5) Prophylaxis for migraine, but not for an acute attack.
6) Manic episodes associated with bipolar disorder.

Adverse effects of valproic acid: Valproic acid causes GI effects like nausea, vomiting, anorexia; CNS effects like sedation, ataxia and tremors and is most likely to cause hepatotoxicity. It is also likely to cause insulin resistance, anovulatory cycles, and spinabifida. It is contraindicated in patients of hepatic disorders.

2. Classify Beta blockers. Write the mechanism of action, therapeutic uses and adverse effects of propranolol. What are the advantages of cardioselective beta blockers?

Ans: Beta blockers can be classified on the basis of their development.

1. First generation – Propranolol, Nadolol, Pindolol, Timolol, levobutanol, Penbutolol, sotalol, carteolol.

2. Second generation – **(β1 selective) –** Acebutolol, atenolol, metoprolol, bisoprolol, esmolol

3. Third generation -

a. With α – receptor blocking action – Carvedilol, labetalol, bucindolol, medroxalol

b. β1 selective – Betoxalol, celiprolol (with partial Beta-2 selectivity), nebivolol

Mechanism of action of propranolol

β – Blockers depending on their receptor selectivity completely block the receptor activity preventing the actions of catecholamines. Propranolol is a non – selective β blocker. It blocks both the β1 and β2 receptors present in different effector sites in the body

β1 receptor are present on cardiac myocytes, including the SA and AV nodes. When there is activation of these receptors, there is an increase in cyclic AMP, which leads to increased intracellular calcium which in turn leads to contractility of cardiac muscle fibres. When propranolol is given, this contractile force of heart is decreased followed by decreased cardiac workload which further causes a decrease of oxygen demand and myocardial remodelling. Similarly, propranolol decreases heart rate and cardiac output. Propranolol also blocks β**2** receptors present in the bronchial smooth muscles, the effect of which is not noticed in normal individuals. However, in patients of bronchial asthma and COPD, it results in severe bronchoconstriction.

Therapeutic uses of propranolol

Propranolol, similar with other β-blockers has wide variety of clinical uses that include hypertension, ischemic heart disease (IHD) (in early phase of acute myocardial infarction), prophylactic use for angina pectoris,(selective β1 receptor blockers are the drugs of choice in the IHD and prophylactic use for angina), cardiac arrhythmias, congestive heart failure (more preferentially carvedilol, bisoprolol, metoprolol), prophylaxis of migraine (propranolol is the drug of choice), alcohol withdrawal, thyrotoxicosis (for controlling the sympathomimetic effects associated with hyperthyroidism), situational anxiety states, for reduction of portal venous pressure, pheochromocytoma, and Marphan syndrome to effect a slow progression of aortic dilation.

Adverse effects of Propranolol

Common adverse effects of propranolol include bradycardia, cold extremities and aggravation of pre-existing peripheral artery disease, and withdrawal effects if the drug is stopped suddenly (rebound sympatomimetic activity). Propanolol can also cause bronchoconstriction and increase of airway resistance. Propranolol can cause hypoglycemia if the person is also taking antidiabetic drugs simultaneously.

Advantage of cardioselective β – blockers

Cardio selective β1 blockers like atenolol, metoprolol, bisoprolol, nebivolol have specific action on cardiac β1 receptors and thus have more selective and more effective action in the treatment of hypertension (antihypertensive activity), cardiac arrhythmias (antiarrhythmic action – supraventricular arrhythmias), ischemic heart disease, prophylaxis for angina pectoris, and congestive heart failure

(bisoprolol and metoprolol). However, they are likely to cause bradycardia, decreased exercise capacity, hypotension, and AV-nodal block. They do not cause any bronchoconstrictin and hence can be used safely in patients of bronchial asthma and COPD. However, they should be used with more causion to avoid potential risk. The advantage with their use is that they do not cause hypoglycemia when combined with antidaibetic drugs and also, they do not cause any peripheral vasoconstriction and hence do not cause Raynauod's disese or any other peripheral vascular disorder.

3. Write a short note on the following.

1) Define receptors, Explain ion channel receptors

Ans: Receptors are specific cell targets for the drug action. They are macromolecular components of the cell, which are regulatory proteins and for which the drug molecules (signalling molecule or ligand) show affinity and efficacy to varying degrees. The interaction between them results in the changes in the biological systems leading to the development of pharmacological actions. The receptors may be located on the cell surface or inside the cell (intracellular receptors). For each type of hormone (thyroid hormone, insulin, sex hormones, ovarian hormones), neurotransmitter (AD, NAD, DA, Ach, GABA, NMDA), growth factor or autacoids (Histamine, serotonin, prostaglandins), there is at least one specific receptor along with their subtypes commonly.

Ion receptors (Ligand gated ion channels)

They are also known as inotropic receptors and present on the surface of the cell. These ligand gated channels contain a ligand – binding site (receptor). The ligands that act through these channels include Ach, GABA, glutamate, glycine and 5 – HT (Serotonin) and the corresponding binding sites (receptor) are nicotinic acetylcholine – (nAch); 5 – HT1,5-HT2, and subtypes, glycine receptors, GABAA, GABAB, and glutamate receptors. In some channels the conductance of ligand is regulated by changes in the voltage across the plasma membrane. These channels are called Voltage gated ion channels that include Na^+, Cl^-, Ca^+,. These channels participate in neuronal transmission, cardiac conduction, and skeletal muscle contraction. G-protein coupled receptors are known as metabotropic receptors (adrenergic, histaminergic, serotonergic (5-HT), receptors for glucogon and other hormones.

2) Mention five prostaglandins with specific therapeutic uses.

Ans:

1. **PGE2 and PGF2α** – (**Dinoprostone, Carboprost**), Medical and therapeutic abortion **(Medical termination of pregnancy**).
2. **PGE1 (Alprostadil) – Erectile dysfunction.**
3. **PGE1** (**Misoprostol) – NSAID induced gastric ulcers, protection against NSAID – induced GI adverse effects.**
4. **PGF2α (Bimatoprost, Latanoprost**) – **glaucoma** by facilitating better drainage of aqeous humor and reducing intraocular pressure.
5. **PGI2 (Epoprostenol, iloprost) – Pulmonary hypertension effecting pulmonary vasodilation**.

3) Explain teratogenic agents with examples.

A teratogenic or mutagenic drug is one which causes characteristic fetal abnormalities or malformations if taken during the first trimester of pregnancy (period of organogenesis). Teratogenic effects produced by drugs may be the result of interference with the passage of oxygen or nutrients to the foetus through the placenta. Teratogenicity can also occur due to direct meternal and foetal toxicity of the drug.

Some drugs such as thalidomide, cytotoxic drugs (methotrexate), antithyroid drugs (Propylthiouracil), aromatic retinoids like isotretinoin (used for acne vulgaris, acne rosaseae) directly act on the fetus and produce several foetal abnormalities; other drugs that can cause fetal damage include alcohol (fetal alcohol syndrome), tetracyclines can cause yellow-gray-brown discoloration of teeth,hypoplasia of enamel and deposition in the bones in the infancy and later), Quinolones (abnormalities like arthralgia, and joint swelling in infants), ACE inhibitors (pregnancy fetopathy), Phenytoin(foetal hydantoin syndrome), and smoking during pregnancy can produce potential teratogenic effects, and alcohol consumption during pregnancy can cause fetal alcohol syndrome characterized by craniofacial abnormalities, central nervous system dysfunction, pre and postnatal stunting of growth, hearing defects and speech disorders.

Answers to Question Paper given by King George Medical University, Lucknow

1) Classify Antimalarial Drugs. Describe the mechanism of action, uses and adverse effects and contraindications of chloroquine.

Ans: Antimalarial drugs can be classified based on chemical structure

1) 4 – aminoquinolines – chloroquine, amodioquine

2) 8 – aminoquinolines – Primaquine

3) 4 – Quinoline methanol – Mefloquine

4) Cinchona alkaloids – Quinine, quinidine

5) Antimetabolites – proguanil, chlorproguanil, sulfadoxine, pyrimethamine (folate antagonists)

6) Sequiterpene lactone endoperoxides – Artemisinins

7) Antibiotics – Doxycycline, clindamycin, azithromycin

8) Hydroxynaphthoquinone - Atovaquone

Mechanism of action of chloroquine: Erythrocytic forms of the parasite thrive on the hemoglobin of the host erythrocytes in their food vacuoles and produce highly reactive byproducts like ferroprotoporphyrin, also known as **heme** and free radicals. Chloroquine is a weak base that in its neutral form freely diffuses into the food vacuole of the parasite and gets protonated (ionized) with a rise of internal PH. The protonated chloroquine binds to the toxic heme and prevents its polymirization to hemozoin (nontoxic product). Prevention of detoxification of heme (conversion toxic heme to non – toxic hemozoin) results in oxidative damage to the parasite due to the build-up of toxic heme, thereby causing lysis of the parasite.

Uses of chloroquine:

1) Chloroquine is used in the treatment of acute attack of malaria caused by P. Vivax and P. malaria. It is also effective against falciparum malaria, but resistance to its action on the parasite is common. Its action is on the erythrocyte forms of the parasites, and has no effect on the hypnozoites.
2) Chloroquine is also effective as suppressive chemoprophylactic agent of falciparum infection in endemic areas. In combination with proguanil it is used to eradicate P. Vivax and P. Ovale malaria
3) Other uses of chloroquine include its indication for amoebic abscess of the liver and chronic recurrent progressive rheumatoid arthritis, systemic lupus erythematosus and lepra reaction

Adverse effects of chloroquine: The adverse effects are usually dose related and reversible. They include nausea, vomiting, headache, anorexia, blurred vision, dizziness and fatigue. In prolonged usage permanent retinal damage (optic neuritis) can occur. The other adverse effects of chloroquine include bleaching of hair, widening of QRS interval and 'T' wave abnormalities.

Contraindications and precautions for use of chloroquine: Chloroquine is contraindicated in the presence of retinal or visual field changes. It is also contraindicated in patients with psoriasis and porphyria where it may aggravate the condition. Chloroquine should be used with caution in patients with liver disease or neurologic or hematologic disorder.

2) Enumerate low molecular weight heparins. Describe with clinical relevance their differences with ultra fractionated heparin

Ans: Enoxaparin, dalteparin, and tinzaparin, nadroparin are the low molecular weight heparins **(LMWH).** They act by inhibition of the final common pathway of coagulation cascade. The final common pathway is the conversion of fibrinogen into fibrin by the activity of thrombin. LMWH inhibit coagulation by activating antithrombin III. Antithrombin III binds to and inhibits factor Xa thereby preventing the conversion of prothrombin to thrombin. This leads to inhibition of conversion of fibrinogen into fibrin for the formation of the clot.

Clinical Relevance of differences of LMWHs and ultra fractionated heparin:

1) The inability of ultra fractionated heparin (Heparin) to inactivate surface – bound thrombin and factor Xa is of limited efficacy in unstable angina, high – risk coronary angioplasty, and coronary thrombolysis. This has led to the development of low molecular weight heparins (LMWHs) which have more activity of Antithrombin III and also have activity against factor Xa thereby increasing its efficacy.

2) Advantages of LMWHs include

- More predictable anticoagulant activity
- Improved safety profile over unfractionated heparin
- More bioavailability due to lesser plasma and endothelial binding
- Longer half-lives
- Less frequent administration and lesser antigenic reactions
- Less activation of osteoclasts and less bone loss (osteopenia) as a result of less binding to osteoclasts
- Safe for use during pregnancy because the incidence of thrombocytopenia is less than 2% with LMWHs, which do not cross the placental barrier.
- Not inactivated by factor IV unlike heparin (UFH)
- Increased platelet aggregation does not occur unlike that is seen with UFH use.

Clinical uses of LMWHs

- prophylaxis and treatment of deep vein thrombosis and pulmonary embolism in medium and high – risk groups (persons undergoing surgical, orthopedic, and medical procedures)
- Pulmonary embolism (PE) due to other causes
- Venous thromboembolism in pregnancy
- Peripheral artery embolism
- Treatment of embolization associated with atrial fibrillation or prosthetic valve replacement
- Prophylaxis of postoperative deep vein thrombosis (DVT)
- For prevention of possible DVT and PE in patients who are bedridden for longer periods
- Renal dialysis, blood transfusions
- Unstable angina or non – ST segment elevation or non – Q wave MI

3) What is menopausal hormone therapy (MHT) Mention the indications and describe the advantages and disadvantages of MHT.

Ans: Menopause by definition is the final menstrual period in a women's reproductive life. Menopause is diagnosed after 12 months of amenorrhea and is characterized by a myriad symptom. Hormonal changes and clinical symptoms occur over a period leading up to and immediately following menopause. This

period is frequently termed as **climacteric** or **perimenopause** and symptoms begin years before the menopause and usually in the form of delayed and irregular menstrual cycles and mild to moderate clinical features as that occur during the period of regular menopausal stage. The symptoms can be hastened because of oophorectomy, hysterectomy, autoimmune disorder, use of chemotherapy and radiation therapy.

The classical features of menopause include hot flushes, night sweats, insomnia, weight gain, floating mood changes, irregular menstruations, depression, anxiety states, headache, feelings of tiredness, vaginal dryness, reduced sex drive, dyspareunia, build – up of fat around waist, weight gain and charges skin colour.

Menopausal hormone therapy (MHT) is indicated in menopausal women when the expected benefits of treatment are anticipated to be greater than any possible adverse effects. MHT includes the use of conjugated equine estrogens, bazedoxifene (selective estrogen receptor modulator – SERM) and tibolone (an estrogen preparation having estrogenic, progestational and androgenic effect). MHT is the most effective treatment for vasomotor symptoms associated along with menopause related complaints such as joint and muscle pains, mood changes, sleep disturbances, CV risk, genitourinary complains, irregular menstrual cycles, and bone changes (osteoporosis). Vasomotor symptoms include hot flashes and nocturnal sweats.

Disadvantages of MHT: MHT can cause GI symptoms like anorexia, nausea, vomiting, increase of gall bladder stones, cholestatic jaundice. The cardiovascular effects include thrombophlebitis, thromboembolism producing deep vein thrombosis (DVT), increased risk of CV disease, uterine hyperplasia and uterine bleeding, and salt and water retention. MHT is contraindicated in women with underlying CV disease, history of earlier episodes of thromboembolism, hypercholesterolemia, stroke, and gall bladder disease and breast cancer.

4) Mention the limitation of benzylpenicillin (Penicillin – G). Describe with suitable examples how the other penicillins are useful to overcome these limitations.

Ans: Limitations of Benzyl Penicillin (Penicillin - G) include its short half – life of 20 – 30 minutes and frequent administrations, ingestion of food may delay oral absorption with an oral bioavailability of 30%, inactivation by β – lactamase enzyme, unstable in acid medium, hypersensitivity reactions and the need for administration by IM/IV routes for therapeutic effect. These short comings of Penicillin- G are overcome by the following mechanisms.

1) **Penicillin V** (potassium phenoxymethyl penicillin) – It is more stable in the acid medium and well absorbed from the gastrointestinal tract.
2) **Procaine Penicillin** – G – It is the suspension of penicillin - G in aqueous medium and is a long-acting penicillin and needs to be given by IM route only once daily. A dose of 3 lakh units produces plasma levels of 0.9 μg/ml within 1 – 3hr which falls to 0.1μg/ml at the end of 24hrs, further to 0.03 μg/ml at 48hrs.
3) **Benzathine Penicillin** – It is a suspension of Penicillin G - It is a suspension of Penicillin G in aqueous medium and made poorly soluble by the addition of ammonium (0.02%) and is long-acting penicillin that provides longer duration of action. Available in 6 lakh units given once in a month. A dose of 1.2 million units produces plasma levels of 0.09 μg/mL on the first, 0.02 μg/mL on the 14^{th} and 0.002 μg/mL on the 32^{nd} day after administration.
4) **Penicillinase resistant penicillins** – (**cloxacillin, dicloxacillin, methicillin, nafacillin, and oxacillin**) – These penicillins are resistant to the inactivation by β – lactamases produced by the sensitive organisms. They have a narrow spectrum of activity compared to natural penicillins (Penicillin G, Penicillin V). Their antimicrobial efficacy is aimed directly against penicillinase producing strains of Gram – Positive Cocci, particularly staphylococci.
5) **Combination penicillin G with Probenecid** – Higher and sustained plasma levels of Penicillin can be obtained when it is administered with Probenecid that blocks renal tubular secretion of Penicillin.

5) Enumerate five biological agents for rheumatoid arthritis (RA). Briefly describe mechanism of action and administration of each.

Ans: Biologic disease – modifying antirheumatic drugs (bDMARDs) include TNFα inhibitors, tocilizumab, and IL – 1 inhibitor like anakinra.

Mechanisms of action of bDMARDs

1) **TNFαinhibitors** (**Adalimumab, Infliximab, etanercept**) Cytokines play an important role in immune response and rheumatoid arthritis (RA). Two important cytokines involved in RA are TNFα and IL1. The cellular function effects of TNFα are mediated through membrane bound receptors TNFR1 and TNFR2. Macrophages, mast cells, and activated TH cells secrete TNFα. TNFα increases phagocytic activity of macrophages. TNFα has also pyrogenic effect. It is implicated in the pathology of several autoimmune diseases like RA. TNFα inhibitors are shown to have beneficial effects in these conditions.
2) **IL6 inhibitors**: **Tocilizumab and sarilumab** are antagonists of IL6 receptor, IL-6 being a pivotal cytokine involved in the pathogenesis of RA. These agents have shown efficacy when combined with methotrexate or as monotherapy.
3) **IL1 inhibitors**: **Anakinra** is a recombinant human IL – 1 receptor antagonist and used as the second preferred drug to treat RA and less efficacious than other DMARDs.

Administration:

1. Adalimumab is administered in doses of 40mg subcutaneously on alternate weeks because of its long half – life of 10 – 20 days.
2. Infliximab – It is given as IV infusion in 5mg/kg single dose.
3. Etanercept – It is given in doses of 25mg twice weekly subcutaneously once in 3 – 4 days.
4. Tocilizumab – It is given IV in a dose of 4mg/kg as a 60-minute single drip infusion once every 4 weeks, which can be increased to 8 mg/kg given every 4 weeks as a 60- minute single drip.
5. Anakinra – It is given subcutaneously in a daily dose of 100mg

6) Classify antihypertensive drugs. Write mechanism of action, uses, adverse effects, and contraindications of calcium channel blockers.

Ans: Antihypertensive drugs can be classified as

1) Centrally acting – clonidine, α – methyldopa, guanfacine, moxonidine.
2) Adrenergic neuron blockers – guanethidine, guanadrel, bretylium
3) Ganglion blockers – Trimetaphan, mecamylamine, pempidine
4) Adrenergic receptor blockers – α – blockers – prazocin and its derivatives; β – blockers- Metoprolol, Nebivolol, bisoprolol
5) Calcium channel blockers - Nifedipine, verapamil, diltiazem, amlodipin, cilnidipine, lacidipine
6) ACE inhibitors – Enalapril, lisinopril, ramipril
7) AT1 receptor blockers –Losartan, Valsartan, telmisartan
8) Vasodilators – Arteriodilators – Hydralazine, minoxidil, dizoxide.
9) Arteriovenodilators- Sodium nitroprusside
10) Diuretics – Thiazide derivatives, Indapamide, hydrochlorothiazide, loop diuretics – frusemide; Potassium sparing diuretics – Eplerenone, Fenerenone
11) Renin antagonists – Aliskerin

Calcium channel blockers: Calcium channel blockers have predominant action on voltage gated Ca^{2+} channels and block the entry of Ca^{2+}, thereby causing relaxation of the vascular smooth muscle. Their action is most effective on depolarized cell membranes. They can act either on L type of Ca^{2+} channel or 'T' type Ca^{2+} channel. The calcium channel has two receptor binding sites, one for dihydropyridines such as nifedipine and its group and the other for verapamil and diltiazem.

Uses of calcium channel blockers: Calcium channel blockers are used in the treatment of hypertension, variant/Prinzmetal angina, exertional angina, cardiac arrhythmias, hypertrophic cardiomyopathy, peripheral vascular disorders, subarachnoid haemorrhage, renal failure, preterm labour, prophylaxis of migraine, and vestibular disturbances.

Adverse effects of Calcium channel blockers: Bradycardia, hypotension, cardiac depression, AV nodal block and heart failure can occur when they are used in excess doses. Dihydropyridines can cause reflex tachycardia and fluid retention. The other adverse effects include fatigue, flushing, constipation, gingivitis, gingival hyperplasia.

Contraindications of calcium channel blockers: Non – dihydropyridines (diltiazem, verapamil, bepridil) are contraindicated in those with heart failure with reduced ejection fraction, second or third – degree AV block, and sick sinus syndrome.

7) On the basis of mechanism of action, classify drugs effective in the treatment of cardiac failure. Describe the current status of digoxin and its interaction with drugs with potassium levels.

Ans: Classification of drugs for congestive heart failure based on the mechanism of action

a) Positive inotropic drugs

i. Cardiac glycosides – Digoxin, Ouabain

ii. Phosphodiesterase inhibitors – Amrinone, milrinone, vesnarinone, enoximone

iii. Sympathomimetics – Dopamine, dobutamine

b) Drugs affecting cardiac hemodynamic function

i. Angiotensin converting enzyme inhibitors (ACE inhibitors) – Ramipril, lisinopril

ii. AT1 receptor blockers – Telmisartan, losartan, valsartan

c) Drugs affecting cardiac – dynamics: β-blockers- Carvedilol, Metoprolol, Bisoprolol, Nebiolol

d) Drugs affecting renal function – Diuretics

e) Vasodilators – Sodium nitroprusside, nitro-glycerine (arteriovenodilators) and hydralazine, minoxidil, diazoxide (arteriodilatoras)

f) SGLT -2 inhibitors – Dapagliflozin, empagliflozin, sotaglifilozin

g) Aldosterone antagonists - Spiranolactone, eplerenone, finerenone

h) Newer agents – Neprilysin and angiotensin receptor antagonists-sacubitril/valsartan

i) Inodilators- Levosimendon, ivabradin

Didoxin is a positive inotropic drug used earlier for the treatment of congestive heart failure. But of late it is not the first line of treatment or drug of choice for this condition, the reason being its narrow margin of safety and narrow therapeutic index. However, digoxin can be considered as a reserve drug when symptoms of the disease are not adequately controlled with ACE inhibitors and diuretics. In chronic congestive failure associated with cardiomyopathy, combination therapy with ACE inhibitors, digoxin, and positive inotropic drugs can reduce the morbidity greatly and mortality to a lesser extent.

Interaction of digoxin with drugs with potassium levels

Digoxin toxicity is caused by an excess of calcium or a deficiency of potassium (hypokalemia). Excess calcium increases to cardiac excitability and also the hypokalemia can cause the blockade of Na^+-K^+ - ATP ase pump which results in delayed outflux of Na^+, followed by accumulation of intracellular Ca+ which results in delayed after depolarizations (DADs), ventricular arrhythmias manifested as prolonged PR intervals, shortening of QT interval, inverted 'T' wave and ST segment depression. Loop diuretics which reduce potassium levels potentially Increase digitalis toxicity. Close monitoring of renal function and potassium levels are very important in appropriate use of digoxin. Hyperkalemia diminishes digoxin's effectiveness.

8) Describe with examples the additional mechanism of second generation H1 blockers. Describe their disadvantages over first generation H1 blockers. Mention two H1 blockers used for topical application.

Ans: 2nd generation **H1** blockers include loratadine, desloratadine, levocabastine, fexofenadine, ebastine, rupatadine, azelastine, cetirizine, levocetirizine, olapatadadine, alcaftadine

Additional Mechanisms of action:

1) They are hydrophilic polar compounds, do not cross the blood: brain barrier and hence do not cause sedation and drowsiness.

2) They are selective peripheral H**1**receptor blockers.

3) They have long half lives and hence given once daily.

4) They do not cause adverse autonomic effects (anticholinergic effects) unlike first generation H_1 blockers.

5) They do not cause cardiac irregularities.

Disadvantages of 2nd generation H1 blockers: In general, second generation H1 blockers are supposed not to cause drowsiness and sedation. However, drowsiness and moderate sedation can be produced by the use of them. They can also cause fatigue and lessened alertness. Astemazole, fexofenadine, ebastine can cause ventricular tachycardia.

Second generation H1 blockers used for topical uses: Azalastine 0.05% and olopatadine 0.1% are used as eye drops to treat allergic conjunctivitis and other superficial allergic condition of the eye. Alcaftadine 0.25%, can also be used for allergic conjunctivitis.

Question Paper given by Kerala University of Health Sciences - February 2022
Paper I Pharmacology

1. **MR. X, a 65 year – old teacher has severe retrosternal chest pain radiating to shoulder and left arm. He was profusely sweating and his E.C.G revealed ST elevation and a diagnosis of Acute Myocardial infarction (AMI) was made**
   a. **Write the management of AMI with rationale for use of each drug.**
   b. **Enumerate the drugs to be prescribed at the time of discharge.**
   c. **Mention the lifestyle modifications to be advised to the patient.**

Ans: Acute myocardial infarction (AMI) is an emergency clinical condition which should be diagnosed at the earliest by the clinical presentation of the case with the aid of requisite diagnostic tests. On admission to the hospital the said patient should be continuously monitored by ECG and laboratory readings of serum cardiac markers (troponin T – cTnT and cTnI tropnin C) taken to confirm the diagnosis. The immediate supportive measures include cardiopulmonary resuscitation and maintaining balance between oxygen supply and demand to prevent further ischemia. The other measures that follow include monitoring oxygen saturation by pulse oximetry, continuous oxygen supplementation in patients who are breathless and hypoxic (oxygen saturation < 90%) and electric cardioversion if there are ventricular arrhythmias.

Drug therapy

1) Analgesics – They reduce the pain thereby decreasing sympathetic stress with a reduced preload. They ensure comfort to the patient, reduce pulmonary arterial pressure, and provide sedative and anxiolytic effect necessary for patients who experience chest discomfort due to MI. Diamorphine 2.5 - 5mg given IV and repeated as necessary is the drug of choice.
2) Drugs for immediate benefit include sublingual nitroglycerine three doses each of 4 mg at 5 minutes intervals. Buccal absorption of a tablet of aspirin containing 160 – 325 mg is helpful for rapid inhibition of COX_1 in platelets and inhibition of TXA_2 preventing further platelet aggregation.
3) Antithrombotic agents – These agents prevent the formation of thrombus associated with MI, pulmonary embolism, and stroke. The drugs that are used commonly for this purpose include unfractioned heparin, low molecular weight heparins (enoxaparin), fondaparinux, and bivaluridin.
4) Thrombolytic agents – These agents immediately lyse thrombus, prevent recurrent thrombus formation, and facilitate rapid restoration of coronary artery patency and arrest hemodynamic disturbances. They are effective if given within 3 – 6 hours of onset symptoms. The agents that are used for this purpose are alteplase, reteplase, tenecteplase, anistreplase and streptokinase.
5) Vasodilators: They oppose coronary artery spasm, augment coronary blood flow, and reduce cardiac work decreasing preload and afterload. Nitroglycerine is the drug choice given IV is doses of 5 – 10 mcg/min and the dose are titrated by reducing the same by 10% periodically till the systolic blood pressure does not fall below 90mm.
6) β – blockers: They inhibit chronotropic and ionotropic responses to β – adrenergic activation and reduce blood pressure and cardiac contractility which decreases myocardial oxygen demands within 8 hours of onset of symptoms. They reduce the risk of reinfarction apart from decreasing the associated

pain arising out of increased myocardial O_2 demand. The drug of choice is metoprolol given IV in a dose of 5mg and the same is repeated twice later.

7) Follow up medications:
   a. Antiplatelet drugs like low doses of aspirin 75 – 80mg and clopidogrel 75mg/ day given orally.
   b. Cardioselective β – blockers – metoprolol 25 – 50mg/day
   c. Cholesterol lowering drugs like atorvastatin 2
   d. 0 – 40mg/day, rosuvastatin 10mg/day; pitavastatin 2mg/day. Either of them given regularly prevents the formation of fresh/new thrombi in coronary arteries when given along with antiplatelet drugs.
   e. ACE inhibitors like ramipril 2.5mg – 5mg/day may be needed to prevent the possible post – MI CV events particularly cardiac remodelling
8) Lifestyle charges needed by the patient include lesser intake of cholesterol containing foods like diary products, regular physical activity, anxiety free state, cessation of smoking in case the patient is a smoker, containment of alcohol intake if the person is an alcoholic and maintaining a healthy body weight/Body mass index of 20kg/m^2.

2. Classify opioid analgesics. Write the pharmacological effects, therapeutic uses, adverse effects and contraindication of morphine

Ans: Opioid analgesics can be classified as

Phenanthrenes – Natural – morphine, codeine Semisynthetic – Diacetylmorphine, dihydrocodone, hydrocodone, hydromorphone, oxycodone, oxymorphone.

1) **Piperidine derivatives** - Phenylpiperidines – Meperidine, difenoxilate, loperamide
2) **Anilidopiperidines** - Fentanyl, alfentanyl, sufentanyl, remifentanyl
3) **Phenyl heptylamines** – methadone, propoxyphene, dextro - propoxyphene
4) **Benzomorphans** – Pentazocin, phenazocin
5) **Morphinans** – Levorphanol, butorphanol
6) **Opioid antagonists** – Nalmefene, naltrexone, naloxone.

Pharmacological effects of morphine

1) Analgesia – Morphine and other opioids produce analgesia, drowsiness, changes in mood and mental clouding. Pain threshold is increased and sharp piercing pain becomes less intense and more tolerable, while dull aching pain disappears. Apart from the analgesic effect, morphine also reduces the affective component of pain that is accompanied by a state of wellbeing. Morphine also reduces the anxiety states, particularly when given as preanesthetic medication.
2) Sedation – Morphine produces drowsiness and mental clouding without producing amnesia. Phenanthrenes produce a more sedative effect then other groups of opioids.
3) Euphoric effect – Morphine produces a sense of well being or euphoria and freedom from anxiety and distress, and there is a sense of contentment. This is an essential component of its analgesic effect because the agitation and anxiety associated with painful illness or injury are thereby relieved. This is also an essential component for its effects of dependence and addiction.
4) Respiration: Morphine and other opioids depress respiration by acting on the brainstem respiratory centers – medulla oblongatae. Respiratory rate, respiratory minute volume and tidal exchange are depressed in a dose – dependent manner.

5) Antitussive effect: Morphine and related opioids codeine, pholcodine, dextromethorphan suppresses cough reflex by acting on the medullary cough center and used in dry unproductive cough.
6) Nauseant and emetic effects: Morphine – like drugs stimulate CTZ and produce nausea and vomiting which occurs even in normal therapeutic doses.
7) Miosis: Morphine produces constriction of the pupils due to stimulation of oculomotor nucleus (parasympathomimetic effect). Tolerance to the miotic actions of morphine does not develop.
8) Truncal rigidity: Morphine – like drugs increase the tone of the trunkal muscles and produce rigidity. This action is more prominent in high lipid – soluble opioids like fentanyl, sufentanil and alfentanil.
9) Effects on gastrointestinal system: Opioids decrease the mobility and increase the tone of the smooth muscle of the GI tract. Amplitude of propulsive contractions is markedly decreased in the large intestine and delays the passage of fecal mass and allows increased absorption of water which leads to constipation.
10) Neuroendocrine effects: Morphine acts on the hypothalamus and inhibits the release of gonadotropic releasing hormone (GnRH), Corticotropin releasing hormone (CRH), FSH, LH, ACTH thus decreasing their circulating concentrations. Prolactin levels increase due to removal of inhibition of its release by dopamine.
11) Effects on biliary tract: Opioids constrict the biliary smooth muscle which may result in biliary colic. The sphincter Oddi also gets contracted that leads to reflux of biliary and pancreatic secretions.
12) Effects on cardiovascular spem: This is well maintained in normal therapeutic dose. But when CVS function is not adequate, the release of histamine and depression on central vasomotor center may cause peripheral vasodilation resulting in a fall of blood pressure. Pentazocine causes tachycardia due to antimuscarinic effects.
13) Histamine release: Opioids produce flushing of the face, warming of the skin, sweating, and itching and bronchoconstriction due to liberation of histamine.

Therapeutic uses:

1) Analgesic action: Opioids are mainly used to provide analgesia and relief of anxiety and sedation in acute myocardial infarction. Opioids are also used to relieve postoperative pain, pain due to trauma and pain due to malignancy. Morphine also acts as a good analgesic for relief of pain due to renal and biliary colic in combination with atropine.
2) Pre – anesthetic medication: Morphine is given preanesthetically to relieve anxiety and produce quieting and sedative effect.
3) Adjuvant to general anesthesia: Morphine can be given as adjuvant to general anesthesia to reduce the requirements of the general anesthetic agent and used during the perioperative period.
4) Epidural and intrathecal analgesia: Morphine can be given by epidural and intrathecal routes to relieve chronic pain due to malignancy.
5) Acute pulmonary edema: Morphine provides relief from dyspnea due to pulmonary edema associated with left ventricular failure.

Contraindications of morphine: Morphine is contraindicated in head injury, in patients with atrial flutter and supraventricular tachycardia, hypotensive states, acute abdominal state, convulsions, hypoxia or reduced respiratory reserve, elderly debilitated patients, patients with renal or hepatic dysfunction, Addison's disease, prostatic hypertrophy or urethral stricture, and use in children.

Answers to the Question Paper given in March 2022
Tamil Nadu MGR University of Health Sciences - Paper I

1. 60 years old is known HT and DM for the past 20 years has been admitted with c/o compressive swelling in the face and abdomen and legs for the past three months.

a) What is your diagnosis?

b) Classify diuretics

c) Describe the mechanism of action, uses and adverse effects of high ceiling diuretics

d) Justify the rationality in combining high ceiling diuretics with ACE inhibitors

Ans: a) It is a case of chronic congestive heart failure secondary to hypertension with associated comorbidity of diabetes mellitus as per the presentation of symptoms of the patient.

b) Diuretics are classified as

1. Osmotic diuretics	–	Mannitol
2. Carbonic anhydrase inhibitors	–	Acetazolamide, Methazolamide, Dichlorphenamide
3. Thiazide diuretics	–	Hydrochlorothiazide, bendroflumethiazide, Chlorthalidone, indapamide, polythiazide.
4. Loop diuretics	–	Ethacrynic acid, furosemide, bumetanide, torsemide
5. Potassium sparing diuretics	–	Spironolactone, amiloride, triamterene, eplerenone, fenerenone

c) High ceiling diuretics or loop diuretics like frusemide act at the thick ascending limb of loop of Henle inhibiting reabsorption of the Nacl.

They inhibit NKCC2 transporter in the apical (luminal) membrane of loop epithelial cells thereby reducing reabsorption of Nacl (upto 25% of the filtered sodium). Loop diuretics also cause an increase of Mg^{+} and Ca^{2+} excretion by inhibiting positive luminal potential.

Uses of highceiling diueretics

- Loop diuretics are indicated in edematous conditions like pulmonary edema, edema due to congestive heart failure, hepatic cirrhosis, nephritic syndrome, and in the treatment of hypertension.
- Hypercalcemic conditions as they facilitate excretion of calcium as in the conditions like hyperparathyroidism, or parathyroid malignancy associated hypercalcemia.
- Hyperkalemia caused by potassium retaining diuretics or use of ACE inhibitors or due to renalinsufficiency causing increased potassium levels.
- To induce forced diuresis to facilitate rapid removal of toxic drugs if taken in excess doses.

Adverse effects of loop diuretics

Loop diuretics are very potent in their action and can cause volume and electrolyte depletion, leading to hyponatremia, hypokalemia, and hypotension which can further lead to reduced GFR, circulatory collapse. Excessicve potassium loss can induce arrhythmias particularly in those persons receiving digoxin.

Intially fluid and electrolyte loss causes dryness of mouth, thirst, weakness, drowsiness, muscle spasms, muscle fatigue, and nausea.

Loopm diuretics can cause ototoxicity, hyperuricemia, and hyperglycemia, increased plasma LDL-C levels and decreased HDL-C levels

d) ACE inhibitors like lisinopril are combined with high ceiling diuretics so as to potentiate more Na^+ and water loss (diuretic effect) and better and effective control of congestive heart failure. This results in off loading of fluid from the circulation thereby reducing the cardiac workload, improve contractility and force of contraction and thus improve the symptoms associated with CHF. The combination is also useful in the eventual reduction and control of hypertension associated with CHF. Another important benefit of the combination is to control the serum potassium levels in the therapeutic range. This is the result of an increase of K^+ levels (retention of K^+) seen with ACE inhibitors countered by the loss of K+ associated with loop diuretics. This prevents development of arrhythmias also.

2. A 65-year-old male on antipsychotic medications came with c/o of difficulty in walking, resting tremors and difficulty in swallowing.

a) What is the diagnosis?

b) How will you treat this patient?

c) Describe the mechanism of action, importance of combination therapy and adverse effects of Levodopa.

Ans: a) This is a case of Parkinsonism the symptoms of which also include muscular rigidity and postural instability apart from resting tremors and bradykinesia. As the patient is already on antipsychotic drugs therapy and the features described are more due to adverse effects caused by them, a probable diagnosis of drug induced Parkinsonism can be made out.

b) The drug induced Parkinsonism caused by the use of antipsychotic drugs like Phenothiazines, butyrophenones and metoclopramide and reserpine (all dopamine antagonists) can be treated with anticholinergic drugs like Benztropine, biperidin, procyclidine and trihexyphenidyl. Levodopa is not of use in the drug induced Parkinsonism and which may aggravate the mental disorders.

c) Levodopa is the initial drug to be prescribed for a case of classical Parkinsonism but not for drug induced Parkinsonism.

Dopamine by itself cannot cross the blood-brain barrier and hence its precursor levodopa needs to be given. However, when given orally 90% of levodopa is decarboxylated to dopamine peripherally and very little crosses the blood-brain barrier to enter the dopaminergic system. This peripheral conversion of levodopa to dopamine is responsible for many of its adverse effects. The peripheral conversion of levodopa to dopamine can be inhibited by dopa decarboxylase inhibitors carbidopa or benserazide, threby increasing the levels of levodopa, followed by its entry into the CNS.

The adverse effects that can be caused by levodopa include dyskinesia, behavioral effects, CVS responses like cardiac irregularities such as tachycardia and ventricular extrasystoles the incidence of which is very much limited when it is combined with carbidopa. Levodopa can also cause of GI side effects like anorexia, nausea and vomiting which are not seen when it is combined with carbidopa and also taken in divided doses. Most importantly, levodopa can cause fluctuations in the drug response

after the end of successful treatment for 3-5 years. The simplest form of fluctuation is end-of-dose or wearing off reaction that will occur with re-emergence of parkinsonian symptoms.

I. Write short notes on:

1. Mechanism of action and clinical uses of statins.

Ans: Statins like levostatin, atorvastatin, fluvastatin, rosuvastatin act by inhibiting an enzyme HMG-COA reductase. Statins exert their major effect of reduction of LDL cholesterol by competitively inhibiting HMG-COA reductase, thereby preventing the conversion of HMG-COA to mevalonic acid and its further conversion to cholesterol.

Statins are used to treat primary and secondary hyperlipidemia and cause a dose dependant lowering of LDL cholesterol levels. They prevent the onset of atherosclerotic coronary vascular disease by lowering LDL-C levels and thus prevent many cardiovascular events like ischemic heart disease, MI and anginal episode in patients who have recovered from MI.

2. Pharmacovigilance: It is a type of continued monitoring of untoward effects and other safety related aspects of drugs that are already marketed and currently being used in general populations. In general, Pharmacovigilance refers to voluntary or spontaneous reporting systems which allow health care professionals and regulatory authorities to take suitable action and decisions for withdrawal of the drugs from general use when the drug is not safe for consumption. It involves detection, assessment, understanding and prevention of both short and long-term adverse drug effects.

3. Therapeutic effects of atypical antipsychotics.

Ans: Atypical antipsychotic drugs are 2^{nd} generation antipsychotics drugs that include Clozapine, loxapine, olanzapine, risperidone, qetiapine, molindone, and ziprasidone act by blocking D_2 and 5-HT_2A receptors in the dopaminergic pathways of the brain-mesolimbic and mesocortical pathways. Atypical antipsychotics by virtue of their affinity for both D_2 and 5-HT_2A receptors alleviate both positive and negative symptoms of schizophrenia. They are safer and more efficacious. Apart from schizophrenia, they are also useful in acute mania, bipolar disorder, schizoaffective disorder, severe agitation, major depressive disorder along with antidepressants, Tourette syndrome, and obsessive-compulsive disorder and childhood autism (Clozapine is the drug of choice for the last two indications)

4. Brief phase II biotransformation reactions with suitable examples.

Ans: Phase II biotransformation reactions include **glucuronide, acetylation, glutathione, glycine, sulfate and methylation conjugation reactions**. The drugs which undergo phase I biotransformation initially also undergo phase II reactions subsequently by which the resultant drug product becomes highly ionized and rapidly eliminated.

i.	Glucuronide conjugation	–	Morphine, Acetaminophen, Diazepam, Chloramphenicol.
ii.	Acetylation	–	Sulphonamides, INH, dapsone, clonazepam
iii.	Glutathione	–	Ethacrynic acid
iv.	Glycine	–	Salicylic and Benzoic acids
v.	Sulfate	–	Estrone, methyldopa
vi.	Methylation	–	Dopamine, epinephrine

5. Therapeutic uses of adrenergic drugs.

Ans: Adrenergic drugs are used in a variety of clinical conditions that include mydriasis(phenylephrine), bronchial asthma(β_2 agonists), vasoconstrictor effect (adrenaline) to arrest local bleeding like epistaxis oral, facial,and nasopharyngeal bleeding; to prolong the duration of action of local anaesthetics (adrenaline, noradrenaline and phenylephrine); cardiogenic shock (adrenaline and isoprenaline),

anaphylactic shock (adrenaline); hypotensive states that include orthostatic hypotension(ephedrine, midodrine, mephenteramine); for the arrest of premature labor (ritodrine and isoetharine); stress incontinence (ephedrine), attention-deficit hyperactivity disorder (dextroamphetamine); glaucoma (apraclonidine, brimonidine) and also as CNS stimulants (narcolepsy, modafinil is the drug of choice),and as anorectic drugs to suppress appetite and used in obesity (dextramphetamine).

6. Drugs used in prophylaxis of migraine.

Ans: Triptans like sumatriptan, zolmitriptan, rizatriptan, almotriptan, and naratriptan are the main drugs used for prophylaxis of migraine. The other drugs that can be used for the similar purpose include topiramate, sodium valproate, Beta blockers (propranolol, timolol), methysergide, calcitonin gene-related peptide (CGRP) receptor antagonists like Erenumab; tricyclic antidepressants like amitryptiline; calcium channel blockers, selective serotonin reuptake inhibitors (fluoxetine, paroxetine) and NSAIDS.

7. Role of leukotriene antagonists used in bronchial asthma.

Ans: Leukotrienes (LT_{B4}, LT_{C4}, LT_{D4}) produce potent contraction of the bronchial smooth muscle causing bronchospasm and respiratory difficulty seen in patients of bronchial asthma. They are also responsible for airway hyperreactivity, mucous secretion, mucosal oedema, which are all seen in episodes of bronchial asthma.

(a) Leukotriene synthesis inhibitor like zileuton is a potent and selective inhibitor of 5-lipoxygenase activity and thereby inhibits formation of leukotrienes (LT_{B4}, LT_{A4}).

(b) Leukotriene receptor antagonists like montelukast, zafirlukast act by binding to LT_{C4}, LT_{D4} and LT_{E4} which are strong bronchoconstrictors and thereby relieve bronchospasm seen in bronchial asthma.

8. Brief the drugs used in hypertensive emergencies.

Ans: Hypertensive emergency is high rise in blood pressure levels which may cause life-threatening signs and symptoms that result in potential damage to organ systems that in turn result in stroke, MI, ocular damage (changes in vision), bleeding from nose and other areas. These are apart from the very common immediate signs and symptoms that include headache, dizziness, and altered mental status, shortness of breath, decreased urine output, vomiting and chest discomfort. The blood pressure readings may exceed 180/100 mm Hg.

Hypertensive emergency is usually due to sudden withdrawal of antiadrenergic drugs like clonidine, β-blockers, sudden state of rage, anxiety, grief and similar conditions of unexpected emotional states.

The treatment of hypertensive emergency consults of administering labetalol, clevidipine, nicardipine, nitroglycerine, sodium nitroprusside, diazoxide, fenoldopam, hydralazine (in eclampsia and pre-eclampsia). All of them act by different mechanisms with the end result being lowering the elevated blood pressure levels as early as possible. It is always mandatory to monitor the doses of the drug in use so as to see that they do not cause abrupt fall of BP which may cause irreparable damage to the organ systems.

9. Heparin versus warfarin.

Ans: Heparin and warfarin are both anticoagulants which act by different mechanisms, given by different routes and indicated for different clinical conditions.

Heparin acts by binding to plasma protease inhibitor antithrombin III, which is an endogenous anticoagulant that inactivates thrombin, in addition to inactivating thrombin, antithrombin also inactivates coagulation factors IXa, Xa, XIIa, and IIa which leads to inhibition of conversion of fibrinogen to fibrin with the ultimate result of inhibition of both intrinsic and extrinsic coagulation pathways thus preventing coagulation. Heparin is indicated in a number of clinical conditions that include deep vein thrombosis (DVT), pulmonary embolism (PE), atrial fibrillation (AF) and for

prevention of excess coagulation during surgery such as cardiac surgery, dialysis procedures, prevention of thrombosis due to chronic immobilization, as adjuvant in the treatment of unstable angina or non – ST segment elevation or non-Q wave MI.

Warfarin is an oral anticoagulant that acts as antagonist of vitamin K which is essential for the synthesis of coagulation factors II, VII, IX and X and the anticoagulant proteins C and S (coagulation regulatory factors). Warfarin is administered as continuation anticoagulation therapy after initiation with more rapid acting agents like heparin or synthetic heparin derivatives like fondaparinux. Warfarin is given for the prevention of thrombosis (DVT) and pulmonary embolism (further episodes). It is also indicated for prevention of thrombosis in stroke, during the process or during lifetime after cardiac valve replacement and atrial fibrillation.

10. Complication of spinal anesthesia.

Ans: The complications that could occur due to spinal anesthesia include neurotoxicity in the form back pain, pain in the buttocks, posterior thighs and in the groin. The cardiovascular adverse effects include hypotension. The effects on CNS include perioral and tongue numbness, visual and auditory disturbances, restlessness, sleepiness and light-headedness. Local anaesthetics can also produce allergic reactions, drug interaction with sulfonamides (procaine, benzocaine, tetracaine), and local sepsis if sterilization precautions not taken.

Answers to Question Paper given by March 2022 Tamil Nadu MGR University of Health Sciences

PAPER II

Long Essay Questions:

1. **a) Classify drugs used in peptic ulcer**

   b) Discuss the mechanism of action, uses and adverse effects of proton pump inhibitors

   c) Add a note on Anti-H-pylori drug regimens

Ans:

a) Classification of drugs used in peptic ulcer include the following:

1. Acid – Neutralizing agents (Antacids) – Aluminium hydroxide, Magnesium hydroxide, Magnesium trisilicate.

2. Gastric acid lowering agents:

i. H2 receptor antagonists – Ranitidine, famotidine, nizatidine

ii. Proton pump inhibitors – Omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole

iii. Anticholinergic agents – Pirenzepine, glycopyrrolate, mepenzolate

iv. Prostaglandin analogs (PGE_1 analog) – Misoprostol

3. Mucoprotective agents – Sucralfate, colloidal bismuth compounds

4. Drugs for eradication of H. Pylori – Metronidazole, amoxacillin, clarithromycin

b) Mechanism of action, uses and adverse effects of proton pump inhibitors.

Proton pump inhibitors are inactive prodrugs that require activation in the acid environment in the parietal cell canaliculi. Oral preparations of these drugs are enteric coated to prevent premature activation. They are concentrated in the secretory canaculus of the parietal cell where the local pH is less than 1.0. In this acid pH, the drugs become protonated to form the active sulfonamide cations, which then react with a cysteine residue on the H^+/K^+/ATP ase to form a covalent disulfide bond. Covalent binding of the drug inhibits the activity of the proton pump irreversibly leading to prolonged and nearly complete suppression of acid secretion.

Uses of PPIs: Proton pump inhibitors are used in peptic ulcer disease, gastroesophageal reflux disease (GERD), pathological hyper secretory conditions like gastrinomas which are inoperable, Zollinger – Ellison syndrome, H. Pylori infection in combination with antibiotics like amoxicillin, clarithromycin, NSAID – induced gastroduodenal ulcers, stress ulcers, reduction of risk for upper GI bleeding, add on therapy for patients on antiplatelet therapy with high risk of GI bleed, and prior to or following on endoscopy associated with an acute or high risk bleeding.

Adverse effects of PPIs: PPIs are usually well tolerated and the possible adverse effects include hypomagnesemia, possibility of intestinal infections with clostridium difficile, osteoporosis on long

term use, a minor reduction of B_{12} absorption, hypergastrinemia, and minor GI adverse effects like nausea, abdominal pain and diarrhea can occur occasionally.

c) Add a note on Anti – H. Pylori regimens

For the eradication of H. Pylori infection, preventing acute ulceration and promoting healing of the ulcer, triple therapy is usually instituted in a combination regimen. It consists of one proton pump inhibitor, and two antibiotics. The proton pump inhibitor is given twice daily (Omeprazole 20mg twice daily), Clarithromycin 500mg twice daily and metronidazole/amoxicillin 500mg twice daily. Alternatively giving four drugs is also of therapeutic benefit. It consists of bismuth subsalicylate (two tablets of 262mg), tetracycline (500mg 4 times/day), omeprazole 20mg twice daily and metronidazole 250 mg 4 times a day. Any regimen is given for a period of 7 to 14 days.

2. a) Classify antimalarial drugs

b) Describe the mechanism of action, uses and adverse effects of chloroquine

c) Write briefly on Artemisinin based combination therapy

Ans:

a) Antimalarial drugs can be classified as follows:(According to chemical groupings)

i. 4 – aminoquinolines – Chloroquine, amodiaquine
ii. 8 –aminoquinolines – Primaquine
iii. 4 – Quinoline methanol – Mefloquine
iv. Cinchona alkaloids – Quinine, Quinidine
v. Antimetabolites – Proguanil, chlorproguanil, sulfadoxine, pyrimethamine
vi. Sequiterpene lactone endoperoxides – Artemisinins
vii. Antibiotics – Doxycycline, clindamycin, azithromycin
viii. Phenanthrene methanol – Halofantrine
ix. Hydroxy naphthoquinone – Atovaquone

b) Mechanism of action, uses and adverse effects of chloroquine

Erythrocytic forms of the malarial parasites thrive on the hemoglobin of the host erythrocytes in their acidic food vacuoles and produce highly reactive by products like ferroprotoporphyrin, also known as heme and free radicals. Chloroquine is a weak base that in its neutral form freely diffuses into the food vacuoles of the parasite and gets protonated with a rise in pH. The accumulated protonated chloroquine binds with the toxic heme and prevents its polymerization to nontoxic hemozoin. Prevention of polymerization / detoxification of heme results in oxidative damage in the parasite due to the accumulation of toxic heme, thereby damaging the parasite.

Chloroquine is used in acute clinical attack of malaria caused by P. Vivax, P. Malarial, P. Ovale and susceptible strains of P. Falciparum. It is also used as a suppressive chemoprophylactic agent in endemic areas of falciparum malaria. The other uses of chloroquine include amebic abscess of the liver and chronic recurrent progressive rheumatoid arthritis. Its other uses include systemic lumps erythematosus and lepra reaction.

Adverse effects of chloroquine include headache, nausea, vomiting, anorexia, blurred vision, dizziness and fatigue. The use of chloroquine in high doses can cause serious and permanent retinal damage (optic neuritis). The other adverse effects of chloroquine include bleaching of hair, widening of QRS interval and T wave abnormalities.

Artemisinin based combination therapy

Artemisinins (Artemisinin, artemether, artesunate) have shorter half lives requiring followup treatment with mefloquine or combination therapy with lumefantrine. The combination therapy is useful for severe acute cases of drug – resistant P. falciparum malaria.

II. Write short notes on

1. Role of bisphosphonates in osteoporosis

Bisphosphonates bind to hydroxyapatite crystals in the bone and inhibit osteoclast mediated bone resorption. They increase the density of the bone and decrease the incidence of fractures. The commonly used bisphosphonates include alendronate, etidronate, pamidronate, risedronate, and ibandronate. For maximum gut absorption, all oral bisphosphonates should be taken on empty stomach or two hours after food with plenty of water in a sitting or upright posture to avoid esophageal regurgitation.

2. Therapeutic uses and adverse effects of cisplatin

Cisplatin is an alkylating agent that kills tumor cells in all stages of the cell cycle by binding to DNA and preventing its replication by forming intra as well as inter-strand cross links. It is used to treat non-small-cell and small-cell lung cancers, esophageal and gastric cancers, head and neck and genitourinary cancers, particularly testicular, ovarian and bladder cancers. It is used also as a second-line drug for the treatment of colorectal cancer following treatment with the combination of 5-flurouracil and leucovorin.

3. Mechanism of action and uses of ciprofloxacin

Ciprofloxacin is a fluoroquinolone derivative. It elicits bactericidal action by inhibiting DNA gyrase (topoisomerase II) and topoisomerase IV which are required for the bacterial DNA replication, transcription, repair and recombination. Quinolone inhibition of bacterial topoisomerase is very rapid, which explains the concept of rapid killing with ciprofloxacin along with other quinolones.

Uses of ciprofloxacin include genitourinary infections (Urinary tract infections including those complicated due to renal stones, secondary to catheter use, obstructive uropathies), Prostatitis, respiratory tract infections **(**bacterial sinusitis, acute bronchitis, community acquired pneumonia, atypical pneumonia and nosocomial pneumonia**)**; sexually transmitted infections **(**uncomplicated neisseria gonococcal urethritis, cervicitis, urethritis caused by H. Ducrei or chlamydia trachomatis; pelvic inflammatory disease in combination with cefoxitin, gastrointestinal infections **(**traveller's diarrhea**)**, typhoid fever, bone, joint, and soft tissue infections. It is the most potent fluoroquinolone agent against pseudomonal infections.

4. Discuss alkylating agents used as anti cancer drugs

Alkylating drugs (mechlorethamine, cyclophosphamide, busulfan, chlorambucil, carmustine, lomustine, cisplatin and others) are highly reactive molecules and transfer their alkyl groups to important cellular components of DNA or RNA at an electron rich site making them nonfunctional. In general, they react with sulfydryl, amino, hydroxyl, carboxyl groups. Mechlorethamine is used in the treatment of Hodgkin's disease, lymphomas, chronic myelogenic leukemia, chronic lymphoblastic leukemia. Cyclophosphamide is used in malignant lymphomas, Hodgkin's disease, lymphocytic leukemia, Burkitt's lymphoma, multiple myeloma, adenocarcinoma of ovaries, carcinoma breast, and retinoblastoma. Carmustine, lomustine are used for the treatment of brain tumors like glioblastoma and metastatic brain tumours and Hodgkin's lymphoma.

Cisplatin and oxaliplatin are used in various types of malignancies that include ovarian, testicular, breast, colorectal cancers apart from small-cell lung cancer and head and neck cancers.

5. Beta lactamase inhibitors

Clavulanic acid, sulbactam, tazobactam, avibactam are β-lactamase inhibitors that are able to inhibit the actions of many beta lactamases which are responsible for the inactivation of Beta lactam antibiotics. They are particularly useful against plasmid-encoded β-lactamases produced by staphylococci, H. influenzae, N. gonorrhoeae, Shigella, E. coli, Klebsiella pneumoniae.

Clavulanic acid is combined with amoxicillin to enhance its antimicrobial action in a fixed dose of 250mg, 500mg and 875mg of amoxicillin and 125mg of clavulanic acid.

Sulbactam is combined with ampicillin in equal proportions and given IM/IV. Tazobactam is combined with piperacillin in a fixed combination of 3g of piperacillin and 250mg of tazobactam and given parenterally every 6 hr in pseudomonal infections.

6. Drugs for psoriasis

Psoriasis is a complex, chronic, multifactorial inflammatory disease of the skin that involves hyperproliferation of keratinocytes in the epidermis, with an increase of epidermal cell turnover rate. It is characterized by thickened patches of inflamed red skin covered with thick, silvery scales. It can occur in elbows, knees, scalp, feet, palms and nape of the neck.

The drugs that can be used are topical corticosteroids (clobetasol, fludroxycortide, fludrocortolone, fluticasone), TNF-α inhibitors (infliximab, adalimumab given subcutaneously), immunosuppressive agents (alefacept, efalizumab, risankizumab given subcutaneously) and retinoids (acitretin, tazarotene given orally) and antiproliferative agents (methotrexate, cyclosporine, azathioprine given orally).

7. Mechanism of action and adverse effects of Amphotericin B

Amphotericin B is fungicidal and binds to ergosterol in the fungal cell membrane thereby placing the membrane in less a fluid, more crystalline state and forming pores. The formation of pores allows the leakage of intracellular ions K^+, Mg^+ and macromolecules eventually leading to cell death.

Adverse effects of amphotericin-B include hypersensitivity allergic reactions – fever, chills, headache, malaise, nausea and hypotension. It can also cause renal toxicity – decrease of GFR, renal tubular acidosis, potassium loss, hypomagnesemia and azotemia and normochromic, normocytic anemia.

8. Mechanism of action, uses and adverse effects of Cyclosporine

Cyclosporin A is an immunosuppressant that supresses T-cell mediated immune responses that are associated with transplant rejection and autoimmune diseases. It inhibits antigen-triggered signal transduction in T lymphocytes preventing the release and function of many lymphokines including IL-2, IL-3 and TNFα

Cyclosporine-A is used for prophylaxis against immune responses of organ transplantation of the kidneys, liver, heart and other allogenic transplants and used in combination with glucocorticoids.

The adverse effects of cyclosporin-A include hypertension, cardiac failure, nephrotoxicity, hepatic dysfunction, headache, tremors, confusion, dizziness, insomnia, vertigo, impaired concentration, neuropathy, alopecia, bullous eruptions, hypertrichosis, urticaria, cataract, gynecomastia and several GI adverse effects.

9. Selective estrogen receptor modulators

A selective estrogen receptor modulator interacts with estrogen receptors functioning as an agonist in some tissues and as antagonist in other tissues. Because of their high tissue selectivity, they produce the desired estrogenic effects (bone and plasma lipids) without possible stimulatory effects on the breast. There is variation in their selectivity. For example, Tamoxifene causes regression of breast tumor growth in women with estrogen receptor (ER) positive tumors, while at the same it shows partial agonist activity in the uterus which explains the endometrial hyperplasia and possible endometrial

malignancy with its use. It has an estrogen like effect on bone metabolism in postmenopausal women and is associated with preservation of bone mineral density in lumbar spine and femoral bones preventing pathological fractures. Raloxifene has estrogen agonist actions on the bone, lipids and breast without any effects on the uterus. It is used to treat osteoporosis, breast tumor in postmenopausal women. Lasoxifene, bazedoxifene, toremifene are the other SERMs which have both agonist and antagonist actions on estrogen receptors and thus used to treat breast cancer and osteoporosis.

10. Multidrug resistant TB

The mutated forms of TB microbes are extremely resistant to at-least two of the most powerful anti TB drugs – INH and rifampicin. People infected with TB that is resistant to first line drugs will transfer this resistant form of TB to the people they infect. Multidrug resistant TB (MDR-TB) is due to resistance to INH and rifampicin. Extremely drug resistant (XDR-TB) is the one in which patients become resistant to many drugs at-least three of the six classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thiamide, cycloserine and PAS). The treatment regimen of MDR-TB consists of 4 or 5 group of drugs which include streptomycin or kanamycin, fluroquinolone, ethambutol pyrazinamide and linezolid. The treatment is given for six months under direct observed therapy (DOT). Bedaquiline and delamanid are the other drugs used in combination with other anti TB drugs to treat MDR-TB.

Answers to the University Question Paper given by West Bengal University of Health Sciences – May 2022

1. **A 45-year-old male visits to a physician with complaint of insomnia due to stress in the office. He was prescribed one Benzodiazepine as hypnotic**
   a. **Enumerate two benzodiazepines used as hypnotic drugs**
   b. **Discuss mechanism of action and therapeutic uses of benzodiazepines as hypnotics**
   c. **Compare and contrast: Benzodiazepine and Barbiturates**

Ans:

a) Estazolam with a half – life of 10 – 24 hrs has very quick onset of action. Flunitazepam is another benzodiazepine drug that also has quick onset of action and the dose of each drug is 1mg/day. However, the most commonly prescribed drugs for insomnia include alprazolam, clonazepam, and lorazepam followed by diazepam.

b) Benzodiazepines bind to molecular components (α and γ sub units) of GABA receptor present in the neuronal membranes in the CNS and facilitate the opening of cl^- channel indirectly (GABA ergic action). GABA is the major inhibitory neurotransmitter in the CNS and benzodiazepines potentiate the GABA ergic inhibition at different levels of CNS.

Uses of benzodiazepines

- To treat anxiety disorders including generalized anxiety disorder and panic disorder and institutional anxiety disorder. They are used to treat phobias, various psychological disorders associated with organic medical conditions like MI, hypertension and all types of chronic illnesses.
- They are useful to treat sleep disorders (insomnia) associated with organic diseases, age-related factors, and surgical procedures.
- They are also used in convulsive and spastic disorders. Diazepam is one of the choices to treat status epilepticus. They are also useful to treat absence seizures (clonazepam and clobazam), myoclonic seizures, central spastic disorders (multiple sclerosis and paraplegia), restless leg syndrome, and chorea and intension myoclonus.
- Preanesthetic medication to reduce anxiety, provide sedation and produce amnesia. They reduce anesthetic requirements. They provide safe and effective sedation for mechanical ventilation following cardiac surgery. They are also useful to provide anxiolytic, sedative and amnestic effects in a wide range of stressful diagnostic procedures such as bronchoscopy, laryngoscopy, endoscopy and orthopaedic procedures.
- Midazolam is the most preferred drug for induction and maintenance of general anesthesia.
- Benzodiazepines are also useful to treat alcohol withdrawal symptoms.
- They are also useful to control hyperexcitability of CNS produced by drugs like phencyclidine and toxic doses of atropine and other CNS stimulants.
- In combination with NSAIDS, they can be used to treat pain disorders.

Compare and Contrast Benzodiazepines and barbiturate:

		Barbiturates	Benzodiazepine
1)	CNS effects	Sedative, hypnotic actions; anticonvulsant action, antianxiety action, no skeletal muscle relaxant action	Sedative, hypnotic actions, anticonvulsant actions, antianxiety action, skeletal muscle relaxant action
2)	Type of CNS action	Non – specific, narrow margin of safety	Specific target action, wide margin of safety
3)	Respiratory function	Dose dependent respiratory depression	No respiratory depressant effects
4)	Uses	Sedative, hypnotic, anticonvulsant, induction of anesthesia, preanesthetic medication, hyperbilirubinemia and kernicterus	Sedative, hypnotic, anticonvulsant, anxiety states, preanesthetic medication, induction and maintenance of anesthesia, alcohol withdrawal, hyperexcitability of CNS
5)	Antidote	No specific antidose	Flumazenil

2. **A 23-year-old male arrives at emergency with difficulty breathing, with a history of recurrent episodes of seasonal breathlessness, relieved on inhalational medication. Now, the patient is diagnosed as a case bronchial asthma**
   a. **Classify the drug used in bronchial asthma**
   b. **How will you manage a case of acute bronchial asthma?**
   c. **How do inhalational drugs act better in bronchial asthma?**

Ans:

a) Classification of drugs for asthma

1) Sympathomimetics (β_2 agonists) – Salbutamol, terbutaline, salmeterol, metaproterenol, formoterol, fenoterol, Bitolterol, pirbuterol.
2) Anticholinergic agents – Ipratropium, tiotropium, oxitropium.
3) Glucocorticoids – Hydrocortisone, budesonide, beclomethasone, fluticasone, mometasone, triamcinolone.
4) Leukotriene synthesis inhibitors – zileuton.
5) Leukotriene receptor antagonists – Zafirleukast, monteleukast.
6) Anti – IgE monoclonal antibodies – omalizumab.
7) Drugs acting on the mast cells (mast cell stabilizers) – Cromolyn sodium, nedocromil

b) Status asthmatics is an acute exacerbation of a chronic case of bronchial asthma. It is a medical emergency that needs immediate attention and need hospitalization.

Status asthmaticus can be managed by the following measures

a) Oxygen saturation below 92% that need O_2 administration
b) Albuterol/ salbutamol – 0.5ml of 0.5% solution (2.5mg) in 2.5ml of normal saline as nebulization given intermittently or four puffs (0.36 mg) of metered dose inhaler with spacer given every 20 minutes for 3 doses
c) Adrenaline – 0.3mL of 1:1000 solution given subcutaneously every 20 minutes for 3 doses. It has to be used with caution in patients older than 40 years and contraindicated in patients older than

40 years and also contraindicated in patients of CVS disorders like hypertension, arrhythmias and CHF.

d) Corticosteroids – Methylprednisolone – 60 – 125 mg **or** hydrocortisone 100mg gaven IV every 6 hrs.

e) Anticholinergics – Ipratropium 0.5 mg by nebulization hourly **or** 4 – 8 puffs (0.08 mg/puff) with spacer every 20 minutes 3 doses.

f) Aminophylline – 5mg/kg/IV over 20 minutes (slowly), being the last preferred drug.

c) Inhalational drugs directly reach to their sites of action and clinical response sets in within few minutes. This mode of administration decreases the dose required for the desired effect compared to oral route as it bypasses the first dose metabolism. The reduced systemic bioavailability also minimizes the side effects. Inhalational drugs used in asthma (β_2 agonists, corticosteroids, anticholinergics) are given through a nebulizer machine, metered – dose inhaler administered through spacer, and drug powder inhalers. Aerosol drug particles of the size 2.5 μ are best suited for local deposition, and particles of the size of 10 μ do not pass through the alvelar cell membrane and particles of the size 1-2 μ remain suspended and may be exhaled.

3)

a) Write a note on prophylactic treatment of malaria. Outline mechanism of action and four adverse effects of chloroquine

b) Classify oral contraceptives. Describe the clinical uses oral contraceptives

c) Clinical uses and adverse effects of aminoglycosides

a) Chemoprophylaxis (prophylactic treatment) of malaria is the strategy that uses medications before, during and after the exposure period to prevent or suppress symptoms caused by malarial parasites. Chemoprophylaxis is advised and to be given for a person who is likely to enter endemic areas of malaria where the incidence of malaria is highly prevalent. The aim of prophylaxis is to prevent or suppress symptoms caused by blood – stage of parasites (RBC sehizonts)

Drugs used for chemoprophylaxis of malaria include chloroquine, mefloquine, atovaquone, and proguanil/primaquin combination; doxycycline and primaquine combination for terminal prophylaxis of P. falciparum malaria. The prophylactic treatment is started one to two weeks before a person enters the endemic areas, continued during his stay there and 2 to 4 weeks after he leaves the endemic area.

b) Oral contraceptives can be classified as

1. Estrogen and progesterone combination pills
2. Progesterone only contraceptive pills
    1. Estrogen and progesterone combination pills consist of an estrogen preparation (ethynyl estradiol) and progestin (norethindrone, norgestrel, norgestimate, levonorgestrel)
    2. Progesterone only pills contain only progesterone (mini pills) norethindrone, norgestral
    3. Progestin – only emergency/ post coital pill consists of levonorgestrel.

Clinical uses of oral contraceptives

1) Contraception is the main clinical use of oral contraceptives
2) Oral contraceptives have also found to have benefitial effects like reduced incidence of ovarian and endometrial cancer risk, reduced risk of colorectal cancer, reduced abnormal uterine bleeding,

decreased perimenopausal vasomotor symptoms, favourable bone mineral density profile, decreased anemia, improvement in acne and hypergonadism, reduced incidence of ectopic pregnancy, decreased incidence of pre-menstrual symptoms.

c) Clinical uses of Aminoglycosides

1) Streptomycin is useful in bacterial endocarditis caused by enterococci, D streptococci, viridans streptococi in combination with penicillin or vancomycin. It is used to treat mycobacterium tuberculosis in combination with other anti TB drugs like pyrazinamide, INH, rifampicin, ethambutol). It is also effective to treat plague, tularemia brucellosis.
2) Gentamicin is the most preferred drug to treat serious, life – threatening Gram – negative infections such as septicemia, systemic bacteremia, infected burns, osteomyelitis, pneumonia and peritonitis caused by P aeruginosa, Enterobacter, Klebsiella, Serratia, Proteus and Acinobacter. It is usually combined with extended spectrum penicillin or a cephalosporin which provides a synergistic effect.

   The other uses of gentamiain include urinary tract infections, bacterial endocarditis, nosocomial pneumonia and sepsis. Topically it can be used for infected burns, wounds or skin infections and external ocular infections (as eye drops)
3) Tobramycin is used mainly for infections caused by P.aeruginosa
4) Amikacin has the same uses as gentamicin and tobramycin particularly if the bacterial strains are not sensitive and resistant to the infections of eye, skin and ear.

Adverse effects of aminoglycosides

All aminoglycosides produce potentially dangerous reversible and irreversible adverse effects such as ototoxicity, nephrotoxicity, and neuromuscular effects. Adverse effects are both time-and – concentration dependent and usually do not occur till a threshold concentration is reached and once reached it may result in critical situation. Usually, predictive level for toxicity is 2mcg/mL. Ototoxicity produced by aminoglycosides is irreversible and usually manifested as vestibular and auditory dysfunction as the drug gets accumulated in the perilymph and endolymph over a period and proportional to the plasma concentration of the drug. Nephrotoxicity is reversible and the intial manifestation of renal toxicity is an increase of excretion of brush border enzymes, followed by a decrese in renal concentration ability, protinuria, and appearance of casts in the urine, which then followed by reduced GFR and a reise of serum creatinine levels. Neuromuscular toxicity is manifested as decresed skeletal muscle contractions and respiratory difficulty, the effects being reversible.

3. Write short notes on the following

a. Pharmacotherapy of diabetic ketoacidosis
b. Rifampicin (Mechanism of action, therapeutic uses and ADR)

Ans:

a. Diabetic ketoacidosis is an acute clinical emergency associated with diabetis mellitus which is poorly controlled due to inadequate or improper use of antidiabetic drugs. Biochemically hyperglycemia, hyperketonemia, and metabolic acidosis are the manifestations. The severity of ketoacidosis can be assessed by clinical manifestations and by measuring plasma bicarbonate levels, with severe acidosis resulting if the bicarbonate levels are less than 12mmol/lit. The clinical features of diabetic ketoacidosis include polyurea, thirst, weight loss, weakness, nausea, vomiting, leg cramps, blurred vision, dehydration, hypotension, tachycardia, hypothermia, confusion, drowsiness, coma and a characteristic smell of actone in breath.

Diabetic ketosis can best be managed by the administration of fluid replacement and administration of short acting soluble insulin, potassium replacement, and administration of antibiotics to control any associatyed bacterial infection.

1) Short acting soluble insulins are given intravenously at regular intervals. Insulin (lispro, aspart) is given as bolus IV in a dose of 0.3 U/kg, followed by 0.1U/kg/hr as IV infusion till a blood glucose level reaches 200-250 mg/dL. The insulin infusion is reduced later to a dose of 0.05U/Kg given 4^{th} hourly till all the feeatues of DKA subside.
2) Fluid replacement – Intially, 1liter of 0.9% Nacl is given as infusion over a period of 30 minutes, followed by 0.5liter of the same solution after half an hour. This can be continued at hourly intervals before 5% glucose is given after 2½ hours.
3) Potassium replacement is done if the serum potassium levels are 3.5 – 5.5 mmols/L, 20mmols of KCL/L is infused for a period of nearly 2hrs after the patient is admitted with ketoacidosis.
4) 300ml of 1.26% sodium bicarbonate is given in patients who are severely acidotic (PH<7.0)

b. Rifampicin is an antituberculosis drug used in combination with pyrazinamide, INH and Ethambutol. Rifampicin is a bactrecidal drug that inhibits DNA dependent RNA polymerase of mycobacteria thereby inhibiting RNA synthesis. It is effective in both intracellular and extracellular microorganisms.

Therapeutic uses of rifampicin

The main indication of rifampicin is in the treatment of mycobacterium tuberculosis and given in combination with other drugs. The other important indications of rifampicin is its use for the treatment of leprosy. It is also useful or indicated for prophylaxis of meningococcal and H. Influenza meningitis in the carrier state. It also serves as a second – line drug for the treatment of skin and bone infections caused by staphylococci (osteomyelitis, cellulitis and wound infections)

Adverse reactions of rifampicin include hepatotoxicity which does not occur with normal hepatic function. However, in conditions of hepatic dysfunction, alcoholism, hepatotoxicity is considerably increased. Rifampicin can also have drug interactions with HIV protease inhibitors, digoxin, quinidine, disopyramide, oral contraceptives, ketoconazole, metoprolol and oral anticoagulants whose action is reduced due to enhanced metabolizing enzyme action.

4. Explain the following statements

a. Corticosteroid use over long term can be harmful

b. Tricyclic antidepressants are not preferred in elderly male subjects

c. Injection of thiopentone sodium is not used as maintenance agent in general anesthesia.

d. Ergometrine should not be used for induction of labor

e. Leucovorin rescue is mandatory in methotrexate therapy

Ans:

a. Long term use of glucocorticoids can cause the following conditions

1. Protein catabolism, gluconeogenesis that led to hyperglycemia and insulin resistance
2. Myopathy and muscle wasting
3. Retention of water and electrolytes (Na^+ retension) and loss of potassium leading to edema and hypokalemia, alkalosis, and hypertension.
4. Hypogonadism associated with decreased testosterone levels. In women anovulation, oligomenorrhea or dysfunctional uterine bleeding can occur.

5. Growth retardation in children
6. GI system may be affected causing gastric irritation and peptic ulcer
7. Subcapsular cataracts may occur
8. Osteoporosis, spontaneous fractures can occur
9. Several behavioural changes and neuropsychiatric disorders can also occur.

b. Anticholinergic antidepressants (tricyclic antidepressants) like amitryptiline, clomipramine, amoxapine, nortryptiline, desipramine, protryptiline, maprolitine can worsen the dementia, diabetis, and Parkinson's disease which are more common in elderly. Such drugs can cause postural hypotension and cardiac conduction abnormalities

c. Thiopentone is a short-acting barbiturate used mainly for induction of general anesthesia to be maintained by regular general anaesthetics like enflurane, sevoflurane, desflurane and isoflurane usually, and halothane occasionally. Thiopentone is having a very short duration of action and its action declines within 1-2 minutes after reaching peak blood levels. Hence it is not useful for the maintenance of general anesthesia which is required to last 1 to 1½ hours.

d. Ergometrine is used to control the postpartum hemorrhage as its action reaches to peak levels at the term of pregnancy. It causes rhythmic contractions of the uterus followed by relaxation in smaller doses and produces powerful and sustained contractions in higher doses. Its actions are most useful for the expulsion of the placenta after childbirth. It has an initial half-life of 10 minutes only and its action declines later. It cannot produce sustained contractions of the uterus which is required for initiation and maintenance of labor in conditions like delayed maturity, uterine inertia, premature rupture of membranes and preeclampsia.

e. Methotrexate is folate antagonist and can cause folate deficiency while it is being used in malignant conditions. Methtrexate toxicity due to overdosage is manifested as nausea, vomiting, diarrhea, stomatitis, mucositis, esophagitis, elevated hepatic enzymes, rash, renal failure, myelosupression, acute lung injury, hypotension, tachycardia, and neurologic dysfunction. The toxic features are due to accumulation of polyglutamated toxic product in the cells. It prevents the utilization of folic acid for the synthesis of purines, pyrimidines, and RNA and DNA synthesis. Hence folate deficiency occurs during methotrexate therapy. Leucovorin is 5-formyl derivative of folic acid and given as rescue therapy during methotrexate toxicity due to overdoasage. This is not needed for the conversion of dihydrofolate to tetrahydrofolate for utilization of DNA synthesis. It is a directly available folate preparation. It is started immediately before the toxic features appear (before the toxic polyglutamated product accumulates in the cells). It can be given orally, IM, and by IV routes. In methotrexate toxicity it is given IV in doses of $10mg/m^2$ every six hours for a total of 10 doses after which it can be given orally in doses of 10 mg 3 times a day.

Answers to the Questions given by Odisha University of Health Sciences

1. **A patient was taking drug 'A' (Plasma half-life 12 hours) 500mg twice daily for his disease**
   a) **What is steady state plasma concentration of a drug and at what time drug 'A' will achieve it? Justify your answer**
   b) **Differentiate between zero order and first order kinetics**
   c) **Define the different types of drug half-lives and mention the clinical significance of plasma half-life**

Ans: **a)** Steady state concentration is defined as the time during which the concentration of the drug remains stable or consistent when it is given repeatedly or continuously (IV infusion) at regular intervels. The steady- state concentration of a drug depends upon its elimination half-life ($t_{½}$) and is achieved when the rate of the drug (units of a drug given at fixed intervals) entering the systemic circulation equals the rate the elimination (units of the drug eliminated at fixed intervals). This is also referred to as the plateau concentration of the drug in the plasma.

In the case of drug, A, if its first half-life is12 hours, the following sequence explain the steady state concentration

Dose given (mg)	Amount of the drug present in the body (mg)	Amount of the drug eliminated (mg)	Number of half-lives required
500	500	250	1
500	750 (500+250)	375	2
500	875 (500+375)	437.5	3
500	937.5 (500+437.5)	468.5	4
500	968.5 (500+468.5)	484.5	5
500	984.7 (500+484.5)	492	6
500	992 (500+492)	496	7

Hence 7 half-lives are required to achieve the steady state level of the drug A and 3½ hours is required to reach the level

Ans: (b) First order kinetics:

All the four parameters of kinetics (absorption, distribution, metabolism and excretion) are directly proportional to the drug concentration in the body. The movement of drug across the cell membrane is proportional to its concentrations; it is more in higher concentrations and less in lower concentrations. In the first order kinetics, a known fraction or percentage of the drug is eliminated at regular intervals, which is known as elimination half-life of the drug (**$t_{½}$).** The rate of elimination and plasma concentrations are directly proportional. Majority of drugs follow first order kinetics.

Zero order kinetics: In the usual situations, the rate of elimination of a drug is directly proportional to its plasma concentrations. This process continues as long as the metabolizing enzymes are fully functional and non-saturated. But when enzyme system become saturated and reaches peak, further metabolism is not possible and it remains the same in spite of increase of dose. Here, certain amount of the drug is eliminated and the rate of elimination is not proportional to the plasma concentrations. Drugs which show zero order kinetics are alcohol and Phenytoin.

Ans: (c) There are three types of half-lives of a drug

1. Biological effective half life is the time in which the pharmacological effect of the drug and its active metabolites fall by one half or 50%
2. Elimination half life is the one in which the total amount of the drug in the body, after equilibrium of plasma with other compartments falls by one half or 50%
3. Plasma half life is the one where in the time taken for the plasma concentration to fall by 50% of its peak value.

Clinical significance of half life:

1. Half-life gives a gross idea about the pharmacokinetic and pharmacodynamic properties of a drug.
2. To predict the duration of a drug in the body
3. To formulate a dosage schedule- Amount of the drug to be given and to know the frequency of its administration. Drugs with long half-life can be given at lesser intervals and drugs with shorter half-life need to be given repeatedly.
4. To manage a case of overdosage of a drug.
5. To determine the time to achieve steady state concentration of the drug.

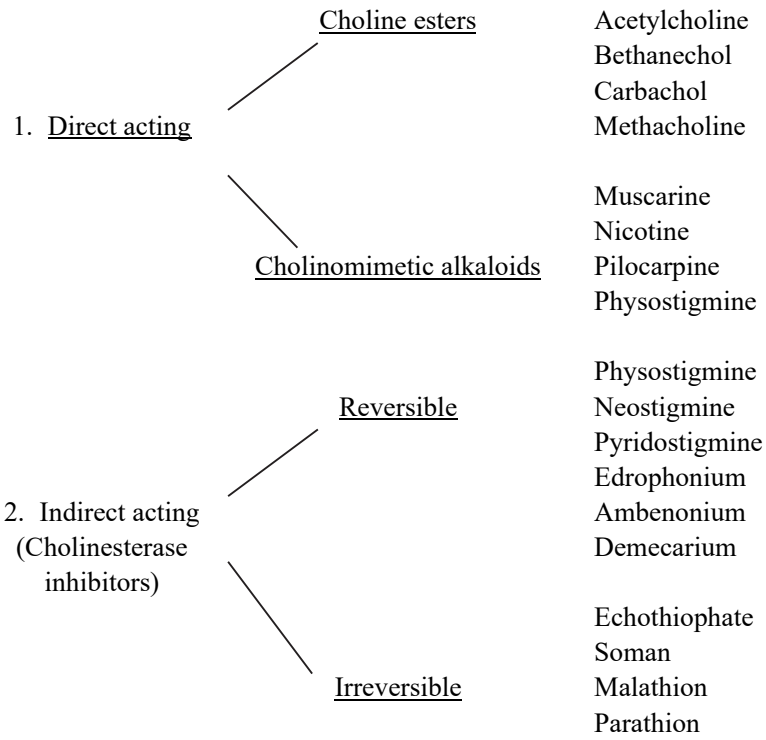
2. a) Classify parasympathomimetic drugs and discuss their clinical uses.

b) Discuss various types of drug antagonisms with examples

c) Give a note on the limitations of opioids as analgesics

d) What do you mean by microsomal enzyme induction? Give examples of such inducers. Discuss its clinical significance.

Ans: (a) Parasympathomimetic drugs can be classified as



Clinical uses of Parasympathomimetic drugs

1. Glaucoma (Carbachol, pilocarpine, echothiophate, physostigmine, demecarium)
2. Myasthenia gravis (Neostigmine, pyridostigmine, ambenonium, demecarium, edrophonium)
3. Alzheimer's disease – Tacrine, rivastigmine, galantamine, donepezil
4. Post operative Paralyticus ilues- Bethanichol, neostigmine
5. Post operative, post partum urinary retention, inadequate emptying of bladder in hypotonic, neurogenic and myogenic bladder conditions – Bethanechol, neostigmine
6. Atropine poisoning – Physostigmine

Ans: (b) Receptor antagonism: In this case the effects of an agonist are antagonized by the presence of an antagonist competing for the same receptor site, while the agonist shows both affinity and efficacy, the antagonist exhibits only affinity but no afficacy. The actions of antagonist can be overcome by increasing the concentration of the agonist and the feature is known as competitive antagonism.

Examples of receptor antagonism include

H1 receptor	-	Pheniramine
Opioids (μ) receptor		Naltrexone,
Neostigmine (nAch) receptor	-	Atracurium
Physostigmine (mAch) receptor	-	Atropine

c) Irreversible antagonism/ non-competetive antagonism

Here the agonist is unable to regain its full effect despite an increase in its concentration and not fully able to minimise the effects of the antagonist. In this case the antagonist binds irreversibly to the same site as the agonist and reduces the binding of the agonist

Example**:** Antagonism between adrenaline and phenoxybenzamine (for the α-receptor sites)

Physiological antagonism (Acting through different mechanisms)	–	Nitrates	–	Adrenaline

Ans: (c) Limitations of opioids as analgesics

Opioids are potent analgesics but there are certain limitations for their use. Respiratory depression is a dose related adverse effect of opioids. They also cause light-headedness, dizziness, sedation, nausea, vomiting and sweating. Opioids also cause euphoria, tolerance, drug abuse, physical and psychic dependence and addiction. Opioids can cause constipation and miosis. They are contraindicated in elderly and pediatric patients and use in head injury cases. They are not effective in nociceptive pain.

Ans: (d) Microsomal enzyme inducers with examples

Microsomal enzyme system may be induced by a variety of drugs, substances present in the environment, insecticides and hydrocarbon pollutants. Inducing agents are lipid soluble substances and have long half-lives. A majority of drug metabolising enzymes are located in the lipophilic membranes of the endoplasmic reticulum of the liver. There are two main microsomal systems in the body, namely NADPH CPY_{450} Oxidase and NADPH CPY_{450} reductase. Microsomal drug oxidation requires P_{450} oxidase, P_{450} reductase, NADPH and molecular oxygen. $CYP3A_4$ is said to be the most prominent CYP isoform involved in drug metabolism both in terms of quantity present in the liver as well as the variety of drugs that are metabolized by it. Few examples of enzyme inducing drugs and the drugs affected and whose pharmacological actions are decreased are shown below

1. Barbiturates Coumarin anticoagulants

2. Rifampicin	Phenytoin, oral contraceptives
3. Carbamazepine	Testosterone, oral contraceptives, doxorubicin

(Few examples of inhibiting agents and the affected agents with enhanced pharmacological action**)**

1. Allopurinol	Azathioprine, Mercaptopurine
2. Dicoumarol	Phenytoin
3. Phenylbutazone	Tolbutamide, Phenytoin

3. Answer the following questions:

a) Why long acting β-agonists should not be used alone in bronchial asthma

Ans: $\beta_2$agonists are the frontline drugs for acute treatment and prevention of bronchial asthma and COPD. According to their duration of action they are classified as short acting $\beta_2$agonists (salbutamol, terbutaline, pirbuterol) and long acting $\beta_2$agonists (salmeterol, and formoterol) and ultra long acting $\beta_2$agonists (Indacarterol, vilanterol). Long acting $\beta_2$agonists are likely to produce tolerance due to continued beta-receptor stimulation. A moderate or severe persistent asthma requires the use of corticosteroids followed by long acting $\beta_2$agonists. Usually, the single use of $\beta_2$agonists may not be effective to control the symptoms. They are combined with inhaled corticosteroids and anticholinergic drugs for the better control of the symptoms. But chronic use of long acting β_2 agonists alone in monotherapy can lead to continuous stimulation of β2 receptors that leads to tolerance for therapeutic effects with an overall increase in severe asthma incidence upto hospitalization, intubation or even mortality. But in combination therapy such incidences are far low.

b) Name the nasal decongestants. Give a note on their adverse effects

Ans: Xylometazoline, Oxymetazoline, Naphazoline and Tetrahydrozoline are the commonly used nasal decongestants. Burning, stinging, sneezing, dryness, local irritation and rebound congestion can occur with their use. In addition, Oxymetazoline can cause hypotension because of its $\alpha_2$agonist action (clonidine like action) preventing the release of NAD.

c) Give a note on $\beta_3$agonists

Ans: β_3 agonists are the drugs used to treat overactive bladder which act by relaxing detrusor muscle of the urinary bladder thereby decreasing the urinary urgency and incontinence. Vibegron and mirabegron are the β_3 agonists available for the treatment of overactive bladder. They are better alternatives to anticholinergics like oxybutynin, trospium as they do not produce anticholinergic related adverse effects, more so the cognitive decline. They also do not produce dementia unlike anticholinergics.

d) Explain why phenoxybenzamine is preferred to prazosin in pheochromocytoma

Ans: Pheochromocytoma is an adrenal medullary tumor that causes an increase of catecholamine release with the consequent pharmacological effects such as persistent elevated hypertension, tachycardia, sweating and other features of catecholamine excess. Surgical removal is the only option for the treatment. However, preoperative reduction of elevated blood pleasure and tachycardia are essential to reduce perioperative complication of a possible rise of blood pleasure for which α-blockers followed by beta blockers should be advocated. Phenoxybenzamine is a non selective α-blocker (α_1 and α_2) and prazosin is a selective α_1 blocker. The β- blockers that can be used include propranolol, carvedilol, and labetalol. During the perioperative period there is a possibility of rise of blood pressure in spite of preoperative treatment with α and β blockers. It can be controlled by phenoxybenzamine more effectively than with prazosin.

e) Enumerate the clinical uses of β blockers

Ans: β-blockers can be used in a variety of clinical conditions such as hypertension, cardiac arrhythmias, prophylaxis of angina, prophylaxis of migraine, anxiety disorders, pheochromocytoma, thyrotoxicosis, congestive heart failure, portal hypertension, glaucoma, alcohol withdrawal, dissecting aneurysm of aorta.

4. Fill in the blanks

a) The prostaglandin analog that is used in erectile dysfunction is _____ (sildenafil)

b) Niacin flush can be prevented by _____ (aspirin)

c) Hydroxychloroquine is preferred to chloroquine in rheumatoid arthritis because _____ (toxicity is less common with the former)

d) ----------(Indomethacin) is the most commonly used NSAID in gout

Answers to the Questions given by National Board of Examinations

Note: The questions given here might be for a higher level of examination. Since they are relevant to the subject at all levels and since most of them cover the clinical conditions, they are taken up in a broader perspective to upscale the knowledge of the students at graduate level also

1. **Discuss the therapeutic status and role of beta-blockers in the treatment of heart failure.**

Ans: Congestive heart failure (CHF) is a modified state of myocardial function in which the heart is not capable of delivering adequate blood into the body systems to meet the metabolic and functional requirements of the organs. Various conditions such as pressure (elevated blood pressure) and volume overload, loss of muscle mass, primarily muscle diseases (idiopathic cardiomyopathies), altered cardiac rhythm (cardiac arrhythmias), excessive peripheral demands such as present in anemias and nutritional deficiencies, ischemic heart disease, thyrotoxicosis, contribute to the reduced cardiac contractile function leading to cardiac failure.

However, several compensatory mechanisms come into play to cope up with the extra cardiac workload and to maintain the normal contractile function and that include primarily an enhanced sympathetic activity, activation of renin-angiotensin- aldosterone mechanism, which will result in increased preload, which in turn leads to myocardial hypertrophy. These compensatory mechanisms also lead to an increase in heart rate and cardiac contractility, expansion of extra cellular fluid volume with retention of salts and water. These compensatory mechanisms are continued for a limited period only before the heart is no longer able to maintain the status. This ultimately leads to decompensated heart failure which requires medical attention to reduce the morbidity, mortality and frequent hospitalizations.

There are many drug groups that could be used to partially or totally restore the cardiac function within the reasonable limits. The drug groups that can be effective to treat heart failure include 1)angiotensin converting enzyme inhibitors (ACE – inhibitors like lisinopril and others) 2)angiotensin receptor blockers (losartan, valsartan and others), 3)β- receptor blockers (carvedilol, metoprolol, and bisoprolol), 4)diuretics (loop diuretics), 5)cardiac glycosides (digoxin), 6)phosphodiesterase inhibitors (amrinone, milrinone, vesnarinone, enoximone), 7)vasodilators (sodium nitroprusside, glyceryl trinitrate), 8)aldosterone antagonists (eplerenone, fenerenone) and 9) sacubitril / valsartan combination and 10) SGLT-2 inhibitors(Empagliflozin, canagliflozin)

Therapeutic status and role of β-blockers in heart failure

β – blockers can be considered as second line drugs as far as their effectiveness is concerned in the treatment of heart failure. They are of much use in chronic congestive heart failure as combination drugs with more effective drugs like ACE-inhibitors and other groups of drugs.

The mechanism of action of β-blockers in congestive heart failure:

1. They attenuate the increased sympathetic activity leading to a decrease of heart rate, myocardial oxygen demand and improved exercise tolerance. Though the systolic function decreases initially, it improves over a time. There is an improved left ventricular ejection factor **(EF)** and left ventricular function.
2. They improve left ventricular structure and function with decrease in chamber size (**ventricular remodelling)** and an increase EF. This is because they decrease the chronic sympathetic activity

with a gradual reduction of cardiac β_1 receptor desensitization, cellular and molecular events, all of which are associated with cardiac remodelling.

3. They resensitize the cardiac β_1 receptor activity (decrease of down regulation of β_1 cell function as seen in CHF) thus improving myocardial contractility
4. The beneficiary effects of β-blockers are also due to their antiarrhythmic activity.
5. Carvedilol is of much use in this class as it blocks both α and β receptors and causes vasodilator effects and decrease in the afterload. In addition, it has antioxidant effect reducing the oxidative stress on the heart. The other β-blockers that are found effective intreating congestive heart failure include metoprolol, bisoprolol, and nebiolol.

2. How do you classify the insulin preparations according to their duration of action? Discuss the advantages of newer non-insulin antidiabetic drugs.

Ans: Insulin preparations can be classified as follows:

1. **Rapid acting insulins** – Lispro, aspart, glulisine

   When given subcutaneously these insulin preparations get converted to monomers, the active forms, getting converted from hexamers are absorbed very rapidly, reaching peak serum levels in less than 1hr in contrast to regular human insulin whose hexamers require more time to dissociate and become absorbed. These insulin preparations do not cause post pandreal hypoglycemia unlike regular insulin which requires longer time to reach peak levels and sustained action even after meals thus causing postpandreal hypoglycemia. Hence regular insulin is taken half an hour before meals.

2. **Short acting insulins** – Regular human insulin (crystalline insulin) is short acting insulin usually taken 30 minutes before meals, peak levels reaching at 2.5 – 5 hrs and the effects lasting more than 4 – 8 hours. The hexameric nature of regular insulin causes delayed onset of action when compared to rapid-acting insulins. This insulin is particularly useful to treat diabetic ketoacidosis.

3. **Intermediate acting insulins** – Lente insulin, NPH (Neutral Protamin Hegedorn) insulin.

   Lente insulin is a mixture of 30% of Semilente an amorphous precipitate of insulin with zinc ion to reduce solubility and pH adjusted to 7.4 and 70% Ultralente an insoluble crystal of zinc and insulin, PH adjusted to 5.5. Its onset of action is 1-2 hours and reaches peak levels 4-12 hrs later and has a longer duration of action of 18-24 hours.

   NPH is also known as isophane insulin and its onset of action is delayed by combining two parts of soluble crystalline insulin with one part of protamine zinc insulin. Conjugation of insulin molecule with either zinc or protamine or both will convert the normally rapidly absorbed parenterally administered insulin to a preparation with a longer duration of action. The onset of action, peak levels and duration of action are comparable to lente insulin. It is usually mixed with regular insulin and given at least twice daily for insulin replacement in type I diabetes.

4. **Long-acting insulins** – Humulin Ultralente, protamine zinc insulin (PZI), glargine, detemir, degludec

   Human ultra-Lente is crystalline insulin. It has an onset of action of 4-6 hrs, peak action of 16-18 hours and duration of action of more than 24 hours. Insulin glargine when injected in the neutral pH environment of subcutaneous tissue, forms micro precipitates that slowly release the insulin into circulation over a period of 24 hours, hence given once daily. It controls nocturnal (fasting) blood glucose levels better than NPH insulin.

   Insulin detemir is also a long-acting insulin preparation and because of modification of amino acid sequence of the basal insulin, it facilitates longer blood sugar control by an increase of self-aggregation in the subcutaneous tissue and reversible binding to albumin molecules. Unlike NPH

and glargine, detemir insulin remains as a liquid depot after subcutaneous injection, providing a longer surface area of absorption. It has an onset of action of 1-2hr, peak action of 6-7hrs and duration of action of 20hrs. It is administered twice daily. Insulin degludec is ultra long acting insulin analog and self associates into multiple hexamers after subcutaneous injection and forms a depot from which it dissociates into monomers gradually and gets absorbed continuously into the circulation. It has a half life of nearly 42hrs. Insulin icodec a once-weekly based insulin has a long half-life of week and has a pharmacokinetic and pharmacodynamic profile suitable for once weekly injection. It is given subcutaneously is a weekly dose of 70 U and titrated or weekly basis depending upon the glycemic control.

Newer generation of Non-insulin antidiabetic drugs

In the recent past, quite a good number of newer generation of antidiabetic drugs have come in handy to treat diabetes more effectively and more safely with wider clinical applications other than treating diabetes. These groups of drugs have become favourable to treat diabetic patients with associated comorbidities like atherosclerotic vascular disease, congestive heart failure, chronic kidney disease and obesity (for weight reduction). They include the following classes of drugs:

1. GLP-I analogs like exenatide (ER, SR), dulaglutide, liraglutide, albiglutide, lixisenaside, semaglutide.
2. Dipeptidyl peptidase – 4 inhibitors (DPP-4 inhibitors) like sitagliptin, saxagliptin, linagliptin, alogliptin.
3. Sodium glucose co-transporter-2 (SGLT-2) inhibitors like dapagliflozin, canagliflozin, remogliflozin, empagliflozin.

1) GLP-I analogs/agonists(Glucagon-like peptide 1 analouges)

   GLP-I agonists have anti-diabetic action by an increase of or augmentation of glucose dependant insulin secretion, increase of β-cell function, β-cell mass, reduced β-cell apoptosis, decrease of glucagon secretion, decreased glucose production in the liver by reducing hepatic gluconeogenesis and increased uptake of glucose by skeletal muscle and adipose tissue. GLP-I agonists are considered as incretins which are released in the small intestine and carried to the pancreatic β-cells the stimulation of which causes the release of insulin.

2) Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)

   Dipeptidyl peptidase-4 enzyme is responsible for degradation of various biologically active peptides including endogenous GLP-I and GIP. By binding DPP-4, these drugs increase the levels of endogenous GLP-I and they in turn cause increased insulin secretion by an action on the pancreatic β-cells.

3) SGLT-2 inhibitors – (sodium-glucose co-transporter 2 inhibitors)

   They act by inhibiting a carrier protein, sodium-glucose co-transporter 2 (SGLT-2) responsible for glucose reuptake in the proximal renal tubule thus facilitating its elimination in the urine which is followed by a decrease of blood glucose levels. They have an additional action of increased insulin sensitivity, uptake of glucose in muscle cells, decreased gluconeogenesis and improved first-phase insulin release from β-cells.

3. Outline the importance of therapeutic drug monitoring (TDM). Explain target level strategy in drug monitoring. Give examples of clinical conditions and drugs requiring monitoring.

Ans: When a drug is being administered for a clinical condition there would be not only the desired pharmacological and clinical effects but also some undesirable adverse effects which are dependent on plasma levels of the drug. Monitoring of plasma levels is not necessary with the drugs with a high therapeutic index. But in the case of drugs with narrow margin of safety and narrow therapeutic index,

drug monitoring (monitoring of drug plasma levels) is essential. This is in order to know whether the desired optimal therapeutic range has been reached and maintained over the treatment period and also for individualizing the dose and thus adjust the dose to avoid any adverse effects that the drug may produce. TDM is particularly indicated when the dosage regimens of the drug are continued over extended periods and which require lifelong use. TDM is also indicated when there is a possibility of fluctuations in the blood concentrations due to drug-drug interactions when multiple drugs are given simultaneously. TDM is necessary to correlate the dose given and the desired response it produces, and to adjust the dose in the presence of any organ insufficiency or disease and in conditions like renal failure, hepatic failure and cardiac insufficiency and further to avoid drug use that is likely to cause direct organ toxicity. TDM also helps to know about patient compliance with the dosage regimen and whether the therapeutic response is adequate or the dosage adjustments needed to avoid undesirable adverse effects.

Examples of clinical conditions and drugs requiring monitoring

1) Psychotic disorders – Desipramine, imipramine, amitriptyline, nortriptyline, lithium
2) Cardiac disorders – Digoxin, disopyramide, quinidine, flecainide, amiodarone
3) Microbial disorders – Gentamicin, tobramycin, kanamycin, vancomycin
4) Convulsive disorders – Phenytoin, carbamazepine, ethosuximide, sodium valproate
5) Graft rejections – Immunosuppressants – cyclosporine, sirolimus, tacrolimus
6) Malignancies – Methotrexate, bleomycin, 5-FU
7) Asthma, COPD – Bronchodilators – Theophylline
8) Pain management – Salicylates
   And inflammatory conditions

4. Discuss the pharmacological approaches for treatment of tobacco dependence and withdrawal

Ans: Nicotine addiction is the second leading cause of death worldwide and also the preventable cause of death. Nicotine addiction (of any tobacco products) can cause accelerated heart rate, increased blood pressure, and weight loss. In addition to its physical effects, nicotine exerts a strong behavioural influence. It may increase alertness and also can stimulate a frantic, almost manic picture. Speech may also be accelerated in line with the behaviour. Cessation on continued use can contribute to irritability, which is smoothened by a fresh dose of nicotine use.

Nicotine addiction can best be explained by any two of the features like longer periods of tobacco consumption, persistent desire or unsuccessful efforts to cut down the use of tobacco, a craving or strong desire or urge to use tobacco, continued tobacco use despite having persistent or recurrent social or interpersonal problems (arguments with others about tobacco use), giving up of important social, occupational, or recreational activities, continued use of tobacco (cigarette smoking) despite knowing that it can cause several morbid and fatal clinical conditions like bronchitis, persistent cough, bronchial asthma, COPD, lung cancer, peripheral artery disease, cardiovascular diseases and several mental and psychological disorders. Cigarette smoking during pregnancy can lead to miscarriage, still birth, preterm labor, fetal growth retardation, and congenital anomalies. Nicotine is not carsinogenic by itself but in concert with other ingredients present in the tobacco which number about 5000 carsinogenic compounds out of which 73 potential carsinogenic(genotoxic) have been identified to have carcionogenic effect. Tobacco smoke containing these chemicals which include heavy metals like nickel, tin, and lead cause oxidative stress on the repitory pathways and damage the lungs and other respiratory components.

Nicotine withdrawal and the treatment choices

Nicotine is the ingredient primarily responsible for tobacco addiction. Nicotine acts on reward pathway and causes both physical and psychological dependence. Withdrawal from nicotine may cause

unpleasant adverse effects, including anxiety, irritability, difficulty concentrating, anger, fatigue, drowsiness, depression and sleep disruption. The aim of treating nicotine dependence is to reduce cravings and reduce withdrawal symptoms.

Nicotine replacement therapies after smoking cessation reduce withdrawal symptoms. Several nicotine replacement therapies are available.

1. **Nicotine polacrilex** is a chewing gum which is available in 2mg and 4mg proportions. Usually, 2mg pieces are to be used by individuals who smoke less than a pack per day and 4mg pieces are to be used for individuals who smoke one pack or more per day. These chewing gums are to be used at 1 hourly interval for 2 weeks and later can be reduced gradually over the next 3 months.
2. **Transdermal nicotine patches** are available for replacement therapy which is well tolerated.
3. **Nicotine nasal spray** and inhaler preparations are also available.
4. **Buproprion an antidepressant drug** is also effective for smoking cessation and is used in persons who have not responded adequately to nicotine gums and nicotine patches. The oral dose of bupropion is 150mg once a day for 3 days increased to twice a day, followed by 150mg once a day.
5. The other drug used in smoking cessation is **varenicline** which is a partial agonist selective for α-4, β-2 nicotinic Ach receptors. Its action is thought to result from activity at nicotine receptor subtype, where its binding produces agonist activity while simultaneously preventing nicotine binding (dose dependent agonist and antagonist action on nicotine receptor types)
6. E-cigarettes (Vapes) are the electronic nicotine delivery systems containing nicotine which are battery operated devices. They heat a liquid to create aerosols that are inhaled by the users. They also contain additives, flavours, and chemicals which are harmful to health. Nicotine content varies from zero to vey high levels. They are meant to wean away from smoking cigarettes that containe nicotine which is highly addictive.

5. Discuss clinically applicable classification of glucocorticoids with appropriate examples. Enumerate the side effects and drug interactions of chronic use of glucocorticoids.

Ans: The classification of corticosteroids based on clinical applications is not practical in view of their uses in different conditions which are all based on their antiinflammatory actions. However, the following classification may be adopted to meet the criteria.

1	Rheumatic fever, rheumatic arthritis, rheumatoid arthritis, osteoarthritis, Polymyalgia rheumatica including local intra-articular and intralesional therapy	Prednisolone, triamcinolone, methyl prednisolone, dexamethasone, betamethasone, hydrocortisone
2	Bronchial asthma (Oral, inhalational, IV preparations)	Budesonide, beclomethasone, hydrocortisone, prednisolone, fluticasone, flucinolide, triamcinolone, mometasone
3	Dermatological conditions (Topical application)	Alcometasone, Betamethasone, Dexamethasone, fluticasone, clobetasol, halcinolide, fludrocortisone
4	Malignancies (Acute lymphatic leukemia in children, Hodgkin's disease)	Prednisolone, Dexamethasone
5	Inflammatory bowel disease (ulcerative colitis, crohn's disease – particularly in acute exacerbations	Hydrocortisone (rectal anemata), prednisolone

Table *Contd…*

6	Connective tissue disease (Lupus erythematosus, vasculitis, polymyositis)	Prednisolone, betamethasone, Triamcinolone, Dexamethasone
7	Nephrotic syndrome	Prednisolone
8	Immunosuppression (for organ transplantation)	Prednisone and methylprednisolone
9	Allergic disorders including anaphylactic shock, angioneurotic edema, hay fever, serum sickness, urticaria, contact dermatitis and other types of acute and chronic allergic disorders	Methyl prednisolone, dexamethasone, betamethasone, triamcinolone, Fluoromethalone, difluprednate
10	Occular diseases (uveitis, allergic conjunctivitis, keratoconjunctivitis)	Dexamethasone, fluocinolone – Topical drops, ointments
11	Acute adrenal insufficiency	Hydrocortisone
12	Cerebral edema	Dexamethasone

Adverse effects of corticosteroids – Hyperglycemia and insulin resistance, myopathy and muscle wasting, development of diabetes on chronic therapy, immune suppression and eventual bacterial and viral infections, GI system adverse effects like nausea, vomiting, gastric irritation, and peptic ulcer, ocular complications like subcapsular cataracts, osteoporosis and spontaneous fractures; water, electrolyte retention, and metabolic effects that can cause edema, hypokalemia; growth retardation in children, neuropsychiatric disorders, and inhibition of gonadotropin synthesis.

Drug interactions of glucocorticoids: The blood levels of several drugs are decreased with the simultaneous use of glucocorticoids and effected drugs include aspirin, coumarin anticoagulants, insulin, INH, oral hypoglycemic agents, and lithium. The blood levels are increased with the drugs like cyclophosphamide, and cyclosporine when used with corticosteroids.

6. Discuss the pharmacology of reverse transcriptive inhibitors

Ans: HIV reverse transcriptase inhibitors are a class of drugs that block replication of viral genome by competitively inhibiting incorporation of native nucleotides (thymidine triphosphate, guanine triphosphate and adenine triphosphate) into DNA by inhibiting reverse transcriptase thereby preventing the conversion of viral RNA to DNA. These drugs block replication of new entrants and also have effect on the already infected cells. These group of drugs not only inhibit viral cellular and mitochondrial DNA polymerases and cellular kinases but also that of host cell (CD_4 cell) resulting in toxicity. There are three types of reverse transcriptors

1) Nucleoside reverse transcriptase inhibitors (NRTIs) – Zidovudine, stavudine, lamivudine, emtricitabine, zalcitabine, didanosine, abacavir
2) Nucleotide reverse transcriptase inhibitors – Tenofovir
3) Non – nucleoside reverse transcriptase inhibitors (NNRTIs) – Nevirapine, efavirenz, rilpivirine, delavirdine, etravirine
4) Protease inhibitors- Amprenavir, indinavir, lopinavir, ritonavir, saquinavir

Treatment guidelines to HIV infection

1) To effectively supress the virus, that is to reduce the viral load as quickly and as substantially as possible to undetectable levels and to keep it there as long as possible.
2) Restoration of CD_4 counts.
3) To improve patient survival rates
4) Drugs should be easy for administration and to follow the schedule, and have minimal adverse effects

5) Combination therapy – A single drug is not effective in supressing HIV on its own. It has to be taken in combination with other retroviral drugs to combat the disease. This is done usually by a combination of three drugs belonging to three different classes of different mechanisms of action. This combination prevents drug resistance, duration treatment and also the possible adverse effects apart from the synergistic effect.

The combination usually consists of two NRTIS (Abacavir, lamivudine, zidovudine, delavirdine, etravirine, nevirapine) and protease inhibitors (indinavir, saquinavir, amprenavir).

7. What ae the selective COX – 2 inhibitors? Discuss briefly their advantages over non – selective COX inhibitors. What are the evidences for the cardiovascular risk of selective COX – 2 inhibitors? What was the basis of banning COX – 2 inhibitors

Ans: Selective COX – 2 inhibitors (celecoxib, rofecoxib, etoricoxib, valdecoxib) selectively inhibit COX – 2 which is predominantly inducible immediately after injury, and upregulated by a variety of inflammatory stimuli – cytokines like interleukins – 1, 2, TNFα, bacterial lipopolysaccharides, mitogens and reactive O_2 intermediates. COX – 2 is predominantly present in macrophages, monocytes, fibroblasts, chondrocytes, all of which are involved in inflammatory reactions. It is absent in platelets, stomach, kidney and endothelium. Non – selective and relatively COX – 1 selective cyclooxygenase inhibitors (Salicylates, ibuprofen, ketorolac, piroxicam, diclofenac, aceclofenax, naproxen, indomethacin inhibits both COX – 1 and COX – 2 and they produce adverse gastrointestinal adverse effects like nausea, gastric irritation, heart burn, gastritis, gastric ulcer and renal disorders which limits their use for inflammatory conditions. However, drugs like aspirin have antiplatelet action which in lacking with selective COX – 2 inhibitors. The GI adverse effects of non – selective COX (COX-1 and COX-2) inhibitors are due to the inhibition of cytoprotective PGs (PGI_2, PGE1 and PGE_2) which protect GI mucosa against erosion and the development of GI symptoms. However, selective COX-2 inhibitors do not affect the synthesis of cytoprotective prostaglandins and hence do not produce GI adverse effects in contrast to non-selective COX inhibitors.

However, selective COX – 2 inhibitors are likely to cause adverse cardiovascular evens like hypertension, arrhythmias, peripheral edema, MI, stroke and death. The CV risk is more in patients of MI, CHF and renal disease. They are definitely contraindicated in patients with high CV risk. Rofecoxib is a banned drug. At present valdecoxib, etoricoxib, parecoxib are the only COX – 2 inhibitors in clinical use.

8. Mention antiemetic drugs acting on vomiting center and chemoreceptor trigger zone Enumerate drugs used for chemotherapy induced vomiting, motion sickness, and hyperemesis gravidarum

Ans: Antiemetic drugs acting on CTZ and vomiting center include the following

1) Dopamine receptor antagonists – Prochlorperazine, chlorpromazine, droperidol, metoclopramide, domperidone.
2) H_2 receptor antagonists – Dimenhydrinate, cyclizine, meclizine, diphenhydramine
3) 5 – HT_2 receptor antagonists – Ondansetron, granisetron, tropisetron, dolasetron.
4) Anticholinergic agents – Hyoscine (Scopolamine)
5) NK1 receptor antagonists – Apripilant, Fosaprepilant
6) Miscellaneous agents acting by different mechanisms – Cannabinoids (Nabilone), dexamethasone, dronabinol.

Chemotherapy induced vomiting can be managed with 5 – HT_3 receptor antagonists like ondansetron, granisetron, palonosetron, dolasetron, tropisetron and Ramosetron. 5 – HT_3 receptor are distributed centrally in the area prostrema, nucleus tractus solitarius, cerebral cortex and hippocampus, and peripherally in the gut mucosa, vagal nerve endings, and spinal afferent nerve endings. Antagonism of 5 – HT_3 receptor can prevent the emesis that follows the increased 5 – HT_3 concentration which usually occurs after chemotherapy or radiation therapy.

The other drugs that could be given for the condition include cannabinoids like Dronabinol, Nabilone and neurokinin (NK_1) receptor antagonist like Apripitant, Fosapripitant used either alone or in combination with corticosteroids like dexamethasone

Drugs used for travel or motion sickness include scopolamine which can be given orally or as trandermal patch (0.25-0.5 mg); and dimenhydrate(50mg), hydroxyzine(25mg), meclizine(25mg), and promethazine (12.5-25 mg) which are H1 antagonists given orally useful to treat travel sicknes.

Drugs used to treat hyperemesis gravidarum include pyridoxine (10mg) given in combination with doxylamine (10 mg) three times a day. The other drugs used in the condition include diphenhydramine (25-50 mg given three times a day)), prochlorperazine (25 mg given twice daily), promethazine (12.5-25 mg given 3 times a day), and metoclopramide (10 mg given three times aday).

9. Enumerate clinically used haemopoietic growth factors. Discuss their pharmacology and adverse effects?

Ans: Erythropoietin, darbepoietin, methoxy polyethyleneglycol epoetin beta are the growth factors that stimulate erythroid proliferation and differentiation by interacting with specific erythropoietin receptors on red cell progenetors and cause an increase of RBC. They are used in the treatment of anemia associated with chronic renal failure, cancer related anemia, anemia in AIDS patients, preoperative anemia to reduce the requirement of blood transfusion, anemia of prematurity, HIV infection, primary bone marrow disorders, myelodysplasia and secondary anemias like aplastic anemia and anemia of multiple myeloma.

Discussion of the role of erythropoietin in anemia associated with chronic renal failure

Erythropoietin produced in the kidneys stimulates erythroid proliferation in the bone marrow and increases the levels of RBC in the circulation. In chronic renal disease the production and activation of erythropoietin is decreased causing anemia. Endogenous erythropoietin production is controlled by a sensor mechanism present at the molecular level. Hypoxia – inducible factor (inducible factor liberated in response to hypoxia -**HIF - 1α**) causes activation of erythropoietin expression and increased erythropoiesis. The state of hypoxia is vital for the activation of erythropoiesis through erythropoietin. HIF propyl hydroxylase is an enzyme that is responsible for the breakdown of HIF - 1α. **Vadadustat** is an oral HIF propyl hydroxylase inhibitor that inhibits the breakdown of HVFIα and thereby causing an increase of erythropoietin and is used in anemia associated with CKD.

The other hemopoietic growth factors include myeloid growth factors (rHuG – CSF **filgrastim, pegylated filgrastim**) – granulocyte macrophase colony stimulating factor (rHuGM – CSF **sargramostim**). These colony stimulating factor are used in cancer chemotherapy – induced neutropenia, acute myeloid leukemia, congenital, cyclic or idiopathic neutropenia, and myelodysplasia. These colony stimulating factors are also used for patients undergoing high – dose chemotherapy and requiring autologous stem cell transplantation in tumor treatment.

Thrombopoietin administration leads to an increase of platelets and used clinically wherever an increase of platelets is required. **Interleukin – II (oprelvekin**) is indicated for the prevention of severe thrombocytopenia and for a reduction of the need for platelet transfusions following myelosuppressive chemotherapy in patients with nonmyeloid malignancies.

All the hemopoietic growth factors are potentially toxic, for example with erythropoietin use there would be rapid increase of hematocrit and hemoglobin levels, hypertension and thromboembolic complications, a functional or absolute iron deficiency and allergic, hypersensitivity reactions. IL – II can causes CVS effects such as tachycardia, palpitation, vasodilation and syncope.

10. Discuss briefly the basic etiopathologies of Alzheimer's disease (AD), what is the role of oxidative stress? Mention the current approach for management of Alzheimer's disease.

Ans: Alzheimer's is a neurodegenerative disease of the CNS which is presented by a decline of behavioural and cognitive abilities enough to interfere with activities of daily living and also the most common type of

dementia. It is a disease of aging and the other risk factors or predisposing factors of Alzheimer's disease include traumatic head injury, depression, cardiovascular and cerebrovascular disease, family history of dementia, smoking and increased homocysteine levels,

Pathophysiology: Alzheimer's disease is characterised by an accumulation of extracerebellar amyloid plaques and intracellular neurofibrillatory tangles which are associated with neuronal destruction particularly in cholinergic neurons. **Plaques** develop in the hippocampus, the area that helps in memory function and in other areas of cerebral cortex that are involved in thinking and making decisions. Amyloid deposition occurs around meningeal and cerebral vessels and grey matter. Gray matter deposits are multifocal and coalesce to form miliary structures called plaques. **Neurofibillatory tangles** are fibrillatory intracytoplasmic structures in neurons formed by a protein called **tau.** The primary function of tau protein is to stabilize axonal microtubules. Microtubules run along neuronal axons and are essential for intracellular transport. Microtubule assembly is held together by tau protein. In Alzheimer's disease due to **aggregation of β – amyloid**, there is hyperphosphorylation of tau which then causes the formation of aggregates. Tau aggregates form twisted paired helical filaments known as neurofibrillary tangles which occur in the hippocampus and then in the cortex.

There are mainly two types of AD - familial and sporadic forms. The familial form is the result of mutations of one of the genes (amyloid precursor protein, presenilin 1 or presenilin 2). The sporadic form which is more common occurs usually after 65 years of age. The development of β – amyloid plaques and neurofibrillary tangles are thought to be intricately related to the cause and development of the disease. Synaptic degeneration, hippocampal neuronal loss, and aneuploidy (Presence of abnormal number of chromosomes in the neuronal cells) are the predominant pathological changes causing AD. It is possible that inflammation around plaques destroys neighbouring neurons.

Management of Alzheimer's disease: There is no cure for Alzheimer's disease. Only symptomatic treatment is available.

1) Cholinesterase inhibitors (Donepezil, Rivastigmine, galantamine act by increasing the level of Acetylcholine which plays an important role in memory, learning, and cognitive functions. Donepezil and galantamine are rapid, reversible inhibitors of acetylcholinesterase. Rivastigmine is a slow, reversible inhibitor of both acetylcholinesterase and butyrylcholinesterase. Donepezil is usually preferred of all because of once daily – dosing (5mg – 10mg). Galantamine is available as twice daily (4mg x 2, increased up to 12 mg twice a day) tablets. It cannot be used in end – stage renal disease or severe hepatic dysfunction. Rivastigmine is available as oral and transdermal patch forms and given in daily dose of 4.6mg Side effects of cholinesterase inhibitors include bradycardia, cardiac conduction defects and syncope all due to increased vagal activity.
2) Partial (N – methyl D – aspartate (NMDA) antagonist (Memantine): Memantine blocks NMDA receptors and slows intracellular calcium accumulation and given in daily doses of 5mg increased to 10mg/day.
3) Melatonin – Current studies suggest that melatonin is a prospective drug for the prevention and cure of AD. It is a tryptophan derivative synthesized mainly by the pineal gland. In patients with AD, decreased melatonin levels in serum and CSF and loss of diurnal rhythms are observed. Melatonin has been shown effective in preventing damage caused by exposure to amyloid beta protein
4) Selegiline is a MAO_B inhibitor and has shown improvements in cognition, behaviour, and mood and is a second line drug to treat AD because of drug interactions with sedatives, antipsychotics and antidepressants.

Answers to the Questions given by Rajiv Gandhi University of Health Sciences 2020 (February)

1. Classify anti – hypertensive drugs. Discuss in detail about the management of hypertensive emergency and urgency. Which anti – hypertensives are to be avoided in pregnancy and why?

Ans: Antihypertensive drugs may be classified according to their sites of action and the following categories are included

1. Centrally acting – clonidine, moxanidine, α – methyldopa, guanabenz, guanfacine, imidazole receptor agonists (rilmenidine, moxanidine).
2. Adrenergic neuron blockers – Guanethidine, guanadrel, bretylium, reserpine
3. Ganglion blockers – Trimetaphan, mecamylamine, pempidine
4. Adrenergic receptor blockers – α – blockers – prazocin and its derivatives
   B – blockers such as propranolol, metoprolol, and others
5. Calcium channel blockers – Nifedipine, verapamil, amlodipine, diltiazem
6. ACE inhibitors – Enalapril, lisinopril, Ramipril
7. Angiotensin receptor blockers – Losartan, Valsartan, Telmisartan.
8. Vasodilators –Arteriodilators – hydralazine, minoxidil, dizoxide, fenoldopam
9. Arteriovenodilators- Nitrates, Sodium nitroprusside
10. Diuretics – Frusemide, hydrochlorthiazide, aldosterone antagonists – Eplerenone, finerenone, spironolactone, amiloride.
11. Renin antagonists – Aliskiren

Hypertensive emergency and urgency

Hypertensive emergency is a condition of acute and sudden elevation of blood pressure which is the result of sudden and rapid withdrawal of antiadrenergic drugs like clonidine or β – adrenergic blockers. The condition may also arise due to an imbalance in the functioning of autonomic nervous system, sudden states of rage, anxiety, grief, and similar conditions of unexpected emotional states.

Hypertensive urgency is one type of hypertensive emergency in which blood pressure increases gradually and hypertension – mediated organ damage is present or evident in organs such as heart, kidney, brain, vascular system, and lungs. This needs immediate attention for rapid control of blood pressure. Hypertensive emergencies include hypertension associated with vascular damage termed as chronic hypertension, and hypertension associated with altered hemodynamic states such as heart failure, stroke, or dissecting aneurysm. Pheochromocytoma induced hypertensive crisis also forms part of hypertensive emergency. In hypertensive crisis/emergency nausea, vomiting, headache, chest pain, abnormal cardiac rhythms, nosebleeds, dyspnea, fainting can occur. The most common presentations of hypertensive emergencies are central ischemia, pulmonary edema, hypertensive encephalopathy and heart failure.

Management of hypertensive emergencies: Blood pressure should be lowered slowly over a period of minutes to hours with an antihypertensive agent. Hypertensive emergencies differ from hypertensive

urgency in that they are treated parenterally, while in urgency it is recommended to use oral antihypertensives to reduce the risk of ischemia. Labetalol, esmolol, calcium channel blockers like nicardipine, clevidipine; vadodilators like nitropruside, nitroglycerine, hydralazine, dizoxide, fenoldopam and α_2 agonists like clonidine are the preferred drugs to treat hypertensive emergencies on controlled administration of the drugs concerned with monitoring of blood pressure periodically and adjusting the dose as per requirements.

ACE inhibitors and AT**1** receptor blockers are to be avoided in all trimesters of pregnancy, as they are likely to cause fetopathy, neonatal renal failure, and fetal death: β–blockers are also avoided as they cross placental barrier and are associated with several adverse effects, such as delayed intrauterine growth, respiratory depression, neonatal bradycardia, and hypoglycemia, particularly when the treatment is started early on in the pregnancy (12 – 24 weeks). The other drugs to be avoided during pregnancy include diuretics alone except in combination with other safe drugs as they are likely to cause fetal electrolyte disturbances and a reduction in maternal blood volume. Similarly, calcium channel blockers (Amlodipine) are also avoided as their use is likely to cause maternal hypotension and fetal hypoxia. Methydopa is the most preferred drug for treating gestational and chronic hypertension in combination with diuretics. Labetalol is the other alternative. Intervention is usually needed when diastolic blood pressure is around 100 mmHg and the drugs are given in lower doses particularly in patients with associated diabetes, renal disease or target organ damage. It is to be noted that no antihypertensive drug is safe during 1st trimester of pregnancy (the period of fetal organogenesis).

2. Write short notes on

1) Discuss in detail about Phase II biotransformation reactions with suitable examples

Phase II biotransformation reactions also know as **conjugation reactions** that involve endogenous substrate such as glucuronic acid, sulfuric acid, acetic acid or amino acid that combines with the newly incorporated functional group of phase I reaction and the resultant product becomes highly ionized and rapidly eliminated

Important Phase II reactions include

Glucuronide – morphine, acetaminophen, diazepam

Acetylation – Sulfonamides, INH, clonazepam, dapsone

Glutathione – Ethacrinic acid

Glycine – Acetyl salicylic acid, benzoic acid, nicotinic acid

Sulfate – Estrone, acetaminophen, methyldopa

Methylation – Dopamine, adrenaline, pyridine, thiouracil

2) Enumerate 2nd generation H_1 antagonists and their uses. Discuss the differences between 1st and 2nd generation antihistamines.

Ans: The second generation H_1 antagonists include fexofenadine, loratadine, desloratadine, levocarbastine, rupatadine, azelastine, cetirizine, levocetirizine.

Uses of second generation H_1 antagonists are the same as those used for by the 1st generation H1 antagonists. They are quite useful is managing seasonal rhinitis, conjunctivitis, and common cold to relieve sneezing, rhinorrhea, and itching of the eyes, nose and throat. They are also used for utricaria, contact dermatitis, napkin rash, atopic dermatitis, eczema, drug – induced skin rashes, and allergic cough. However, either 1st generation or 2nd generation H1 antagonists are not effective to counter the effects of anaphylactic reaction for which glucocorticoids are the preferred drugs

The difference of 1st and 2nd generation H_1 antagonists

1st generation		2nd generation	
1.	They are lipophilic compounds, easily cross the blood: brain barrier, enter CNS and cause sedation	1.	They are hydrophilic polar compounds, do not cross blood: brain barrier and do not cause sedation or drowsiness
2.	They block both central and peripheral H_1receptors	2.	They selectively block the peripheral H_1receptors
3.	They have short – half liver and need to be given 3 times /day	3.	They have long half- life and need to be given once daily
4.	They produce anticholinergic effects such as dryness of mouth, tachycardia	4	They do not cause adverse anticholinergic effects

3) Discuss the mechanism of action, uses and techniques of local anesthetics

Ans: Local anesthetics are a class of drugs which reversibly block impulse conduction along the axons and other excitable membrane areas that facilitate Na^+conduction for the propagation of action potential. They block the voltage – gated Na^+ channel which contains the receptor site for the agents, thought to be located at its cytoplasmic (inner portion) thereby preventing the permeability or flux of Na^+ into the excitable membrane.

1. **Surface anesthesia**: Local anesthetics are used to anaesthetize local areas for the relief of pain caused by minor burns; pruritis due to dermatoses or hemorrhoids. **Pramaxine/pramocaine** is used to facilitate sigmoidoscopic examinations. Local anesthetics can be applied to the skin, ear, eye, nose, mouth as well as other mucous membranes to anesthetize local areas for different clinical purposes.
2. **Local infiltration**: This involves extravascular placement of local anesthetics in the area to be anesthetized. Minor surgical produces can be undertaken by this technique. Lidocaine, prilocaine and mepivacaine are mainly used for this purpose.
3. **Nerve block anesthesia (Conduction anesthesia)**– Local anesthetics like lignocaine can be injected into tissues surrounding individual peripheral nerves (ulnar, radial or intercostal nerves) to block nerve conduction and to facilitate surgical procedures pertaining to those areas.
4. **Epidural or Extradural anesthesia**: Here the local anesthetics are placed in the epidural place between the dura matter and the periosteum lining the vertebral column. This is used in obstetric practice for undertaking caesarian section or control of labor pains.
5. **Spinal anesthesia**: Here the local anesthetics are injected into lumbar subarachnoid space and this is useful to undertake surgical procedures below the lumbar spine such as involving lower abdomen, pelvic region, and lower limbs.
6. **Intravenous anesthesia:** This is useful in providing analgesia for minor surgical procedures. It is also known as IV regional anesthesia or **Bier's block**. It is an anesthetic technique on the body extremities where a local anesthetic is injected IV (as closely as possible to the area of surgical procedure) and the area isolated from circulation to provide a bloodless field by applying a proximal double-cuffed pneumatic tourniquet. It is safe and does not require the use of any general anesthetic

4) Compare and contrast conventional and atypical antipsychotic drug

Ans: Conventional antipsychotics (antidepressants) have different mechanisms of action acting primarily on 5 – HT receptor subtypes. The examples include

1) **Tricyclic compounds**
   a. Tertiary amines – Amitryptiline, Imipramine, doxepin, clomipramine
   b. Secondary amines – Amoxapine, desipramine, maprolitine, nortryptiline, protryptiline
2) **Selective 5 – HT uptake inhibitors** – Citalopram, fluoxetine, fluvoxamine, paroxamine, Sertaline, paraoxetine
3) **MAO inhibitors** – Selegiline, rasagiline

Atypical antidepressants – Clozapine, loxapine, olanzapine, quetiapine, molindone, risperidone, ziprasidone, aripiprazole

Miscellaneous atypical antipsychotics: Bupropion, duloxetin, mirtazapine, trazadone, nefazodone, velnafaxine

Conventional antidepressants produce sedation, antimuscarinic action, and 5 – HT receptor blockade as well NAD blockade.

Atypical antipsychotics have affinity for both D_2 and 5-HT_{2A} receptors and block them and alleviate both positive and negative symptoms of schizophrenia while typical antipsychotic drugs block only D_2 receptors. They do not have antimuscarinic action, and produce minimal or moderate 5-HT and NAD blockade.

5) Discuss the role of vasodilators in acute heart failure

Ans: Vasodilators like sodium nitroprusside, nitroglycerine reduce both preload and afterload thereby reduce the cardiac workload and oxygen consumption and thus increasing the cardiac output. Sodium nitroprusside is given IV as infusion and has an onset of action of 30 seconds and the dose given is usually 0.25 – 1.5 mcg/kg/min.

Nitroglycerine (glyceryl trinitrate) is the most preferred vasodilator drug for treating acute congestive heart failure because it has anti – ischemic effect and less likely to produce coronary steal than nitroprusside. It is given in doses of 10 – 20 mcg/min and increased by 10mcg/min every 2 -3 min as per the progress in relief of symptoms of congestive heart failure.

6) Discuss the mechanism of action, uses and adverse effects of spironolactone.

Ans: Spironolactone is an aldosterone antagonist and acts by binding to the mineralocorticoid receptors in the renal tubules (distal collecting tubules) and acts as competitive inhibitor of aldosterone. It decreases Na^+ reabsorption and decreases K^+elimination, both the actions leading to natriuresis and K^+retention. It has very limited diuretic action when used alone because the distal Na^+/K^+exchange, the site where it acts accounts for reabsorption of only 2% of filtered $Na^{+.}$

It is used in hypertension, Congestive heart failure in combination with diuretics.

The adverse effects produced by spironolactone include hyperkalemia, progestational and antiandrogenic effects like gynecomastia.

III. Write short notes on

1. Define bioavailability, why is it less when the drug is given orally?

Ans: Bioavailability of a drug is defined as its net fraction or amount that reaches the circulation in an unchanged form given by any route. It can also be defined as the extent to which and the rate at which the active moiety of a drug enters the systemic circulation thereby gaining access to the site of action and resulting in the desired pharmacological response. Whereas the bioavailability is 100% when the drug is given intravenously, and it varies considerably when given orally or by any other routes as it requires the drug to be first absorbed into the system to varying extents which may reduce bioavailability.

Bioavailability also depends upon the rate of absorption and first – pass metabolism when given orally. It is also likely to get reduced by local conditions (acidic pH, alkalinity, gastric mucosal patency)

2. Why is pralidoxime not used as antidote for carbamate anticholinesterases poisoning?

Ans: Oximes such as pralidoxime and diacetyl monoxime containing oxime group(=NoH)have high affinity for the phosphorous atom and these drugs are able to hydrolyze the phosphorylated enzyme complex when it is not aged. Organophosphorus compounds are irreversible cholinesterase inhibitors, bind to the active site of the enzyme (cholinesterase) and prevent the accessibility of Ach to AchE. The covalent phosphorous enzyme bond is extremely stable and hydrolyzes in water at a very slow rate of hundreds of hours, thereby increasing the accessibility of Ach in higher levels to the tissues causing muscular paralysis. While oximes act on the phosphorylated enzyme complex, they do not have action on carbamolated enzyme complex formed by the action of carbamates such as physostigmine and neostigmine.

3. Mention the adverse effects of theophylline

Ans: The common adverse effects of theophylline include heartburn, abdominal pain, nausea and vomiting due to gastric irritation consequent to and increase in gastric acidity. The CNS manifestations include headache, anxiety, tremor, and insomnia. If higher levels of theophylline are reached in the blood, seizures and cardiac arrhythmias can result.

4. List four differences between buspirone and benzodiazepines

Ans:

Benzodiazepines	Buspirone
Benzodiazepines have GABA-ergic/GABA mimitic activity and facilitate opening of cl^- channel indirectly. Benzodiazepines have hypnotic, sedative, antianxiety, muscle relaxant, anticonvulsant properties. They are likely to impair motor or driving skills and potentiate the actions of CNS depressants like alcohol, sedative hypnotic drugs, and likely to ptoduce tolerance and dependence.	It acts through central 5-HT, A and D_2 receptors as agonist and has no abuse liability, unlike diazepam and other benzodiazepines. It does not impair motor or driving skills and does not potentiate the depressant actions of alcohol, sedative hypnotic drugs. It is a non – benzodiazepine anxiolytic drug and has no hypnotic or euphoritic effects. It also does not have anticonvulsant or muscle relaxant effects.

5. Mention four common drug interactions in an alcohol individual

Ans:

1) CNS depressants such as opioids, hypnotics, tranquilizers can potentiate the CNS depressant effects
2) Antihistamines, reserpine, methyldopa, and clonidine can cause severe depression in the presence of alcohol.
3) Vasodilators (hydralazine and nitroglycerine) can cause additive orthostatic hypotension.
4) Alcohol potentiates the adverse effects of aspirin (GI bleeding) sulfonylureas (hypoglycemia) and oral anticoagulants (bleeding).
5) INH and acetaminophen can cause hepatic toxicity in chronic alcoholics because of their increased conversion to toxic metabolites.
6) Ketoconazole, chlorpropamide, metronidazole, tolbutamide can cause a disulfiram like effect in chronic alcoholics.

6. Adenosine

Ans: It is given IV as bolus to terminate reentrant supraventricular arrhythmias and their conversion to sinus rhythm. It has very short half – life (10 seconds) and hence given as bolus. It's mechanism of action involves activation of inward rectifier K^+ current and inhibition of calcium current. This results in hyperpolarization and suppression of Ca^+ dependent action potentials. It causes shortening of AP duration.

When given IV, it inhibits SA nodal conduction and increases AV nodal refractory period due to blockade of Ca^+current. Intracellular cyclic AMP accumulation is decreased with reduced sym- pathetic activity.