FMGE Pharmacology Sample Paper – 4

Duration: 60 Minutes **Maximum Marks: 40**

Instructions

- This paper contains **40 Multiple Choice Questions** modelled on the **Pharmacology** section of FMGE.
- Each correct answer carries **+1 mark**. There is **no negative marking** – attempt all questions.
- Questions follow the clinically integrated pattern of the FMGE examination.
- Click a question number in the answer key to navigate to its solution.

FMGE Pharmacology – Q1 to Q40

Q1. A clinical pharmacologist is teaching medical students about plasma protein binding of drugs. He explains that acidic drugs like warfarin, NSAIDs, and phenytoin predominantly bind to albumin, while certain basic drugs bind to a different plasma protein that behaves as an acute phase reactant and increases during inflammation and stress. Which plasma protein predominantly binds BASIC drugs such as propranolol, tricyclic antidepressants, lidocaine, and chlorpromazine?

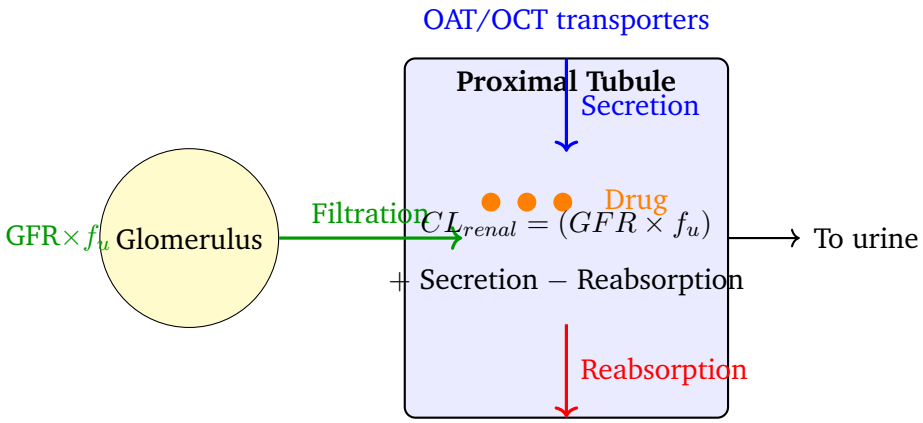
(A) Albumin – the most abundant plasma protein, binding both acidic and basic drugs equally

(B) Beta-globulin – transports lipid-soluble vitamins and binds basic drugs via hydrophobic interactions

(C) Transferrin – the principal carrier protein for basic lipophilic drugs in plasma

(D) Alpha-1-acid glycoprotein (orosomucoid) – an acute phase reactant that is the principal binding protein for basic drugs in plasma

Q2. A pharmacologist notes that a drug has a renal clearance of 650 mL/min in a patient with a GFR of 120 mL/min and negligible plasma protein binding. The diagram below shows the processes determining renal drug clearance:



Which process allows a drug's renal clearance to EXCEED the product of GFR and the free drug fraction (GFR × f_u)?

(A) Active tubular secretion by OAT/OCT transporters in the proximal tubule adds drug to the filtrate beyond what is filtered alone

(B) Passive glomerular filtration allows protein-bound drug to enter the tubule, increasing clearance

(C) Tubular reabsorption of the drug from filtrate back into blood is reduced at alkaline urinary pH

(D) The drug undergoes extensive hepatic extraction before reaching the kidney, reducing systemic levels

Q3. A pharmacology viva examiner asks a student to explain inverse agonism. The student correctly recalls that inverse agonists differ fundamentally from neutral competitive antagonists in their intrinsic efficacy. A ligand that binds a constitutively active receptor and reduces activity BELOW the basal level is termed an inverse agonist. Which statement CORRECTLY distinguishes an inverse agonist from a competitive antagonist?

(A) Both inverse agonists and competitive antagonists produce an effect opposite to the agonist when administered alone

(B) An inverse agonist produces an effect OPPOSITE to the agonist (negative intrinsic efficacy), whereas a competitive antagonist has zero intrinsic activity and produces no effect alone but blocks agonist binding

(C) A competitive antagonist permanently inactivates the receptor, while an inverse agonist is reversible

(D) An inverse agonist acts only at non-competitive allosteric sites, while competitive antagonists act at the orthosteric binding site

Q4. A 55-year-old patient with breast cancer develops multidrug resistance to several chemotherapeutic agents. The oncologist explains that P-glycoprotein (P-gp, encoded by the MDR1/ABCB1 gene) is an ATP-dependent efflux transporter expressed at the gut epithelium, blood-brain barrier, liver, kidney, and placenta that actively pumps drugs out of cells, reducing their intracellular concentrations. Which drug is a well-known INHIBITOR of P-glycoprotein that has been investigated to reverse multidrug resistance in cancer cells?

(A) Rifampicin – a potent inducer of P-gp that reduces oral drug bioavailability

(B) Carbamazepine – induces P-gp expression in the gut and liver

(C) Verapamil – inhibits P-gp, increasing intracellular drug accumulation and restoring drug sensitivity in MDR cells

(D) St. John's Wort – a herbal P-gp inducer that reduces drug absorption and plasma levels

Q5. Both pilocarpine and physostigmine are miotic agents used in the management of glaucoma. They both constrict the pupil and increase aqueous humour outflow through the trabecular meshwork, lowering intraocular pressure. However, their mechanisms of action differ fundamentally. Which of the following CORRECTLY distinguishes the mechanism of pilocarpine from physostigmine?

(A) Pilocarpine irreversibly inhibits acetylcholinesterase while physostigmine is a reversible inhibitor

(B) Pilocarpine blocks muscarinic M2 receptors in the ciliary body while physostigmine blocks nicotinic receptors

(C) Both drugs act by the same mechanism – indirect stimulation of muscarinic receptors via acetylcholinesterase inhibition

(D) Pilocarpine directly stimulates muscarinic receptors (direct agonist), while physostigmine inhibits acetylcholinesterase to indirectly increase acetylcholine at muscarinic receptors

Q6. A junior doctor is reviewing the cardiovascular effects of catecholamines for the FMGE. Norepinephrine (NE) acts predominantly on α_1, α_2, and β_1 receptors but has minimal β_2 activity. Epinephrine (Epi) acts on all four receptor subtypes (α_1, α_2, β_1, β_2). The diagram below shows their receptor selectivity:

Receptor	NE	Epi
α_1 (vasoconstriction)	+++	++
α_2 (presynaptic)	++	+
β_1 (cardiac)	++	+++
β_2 (bronchial/vascular)	±	+++

NE: pure vasoconstriction → reflex bradycardia

Epi: β_1 overrides baroreflex → tachycardia

Which cardiovascular effect of norepinephrine is NOT shared by epinephrine at equivalent doses?

(A) Reflex bradycardia – NE causes pure vasoconstriction elevating mean arterial pressure, triggering the baroreceptor reflex to slow the heart; epinephrine's β_1 stimulation causes tachycardia that overrides the baroreflex

(B) Increase in systolic blood pressure

(C) Increase in total peripheral resistance

(D) Stimulation of α_1 adrenergic receptors in vascular smooth muscle

Q7. A 32-year-old woman at 34 weeks of pregnancy presents with a blood pressure of 180/118 mmHg, severe headache, and epigastric pain. She

is diagnosed with severe pre-eclampsia. The obstetric team requires intravenous antihypertensive therapy. Labetalol is a combined α_1 and β (β_1 and β_2) receptor blocker with an α:β blockade ratio of approximately 1:7 when given intravenously. For which clinical scenario is labetalol SPECIFICALLY preferred over other antihypertensives?

(A) Acute aortic dissection requiring rapid heart rate reduction (target HR $<$ 60 bpm)

(B) Hypertensive emergency in pregnancy – labetalol is a first-line intravenous agent for severe hypertension in pregnancy due to its safety profile in mother and fetus

(C) Hypertensive emergency due to cocaine toxicity (pure α-agonism risk with non-selective β-blockade)

(D) Hypertensive urgency in a patient with severe bronchial asthma requiring hospitalisation

Q8. A 60-year-old patient on long-term antihypertensive therapy develops severe depression, bradycardia, and Parkinson-like symptoms. A review of his medication reveals he has been taking an old antihypertensive that depletes monoamine stores from sympathetic nerve terminals. The drug in question exerts its mechanism by:

(A) Blocking α_1 adrenergic receptors postsynaptically in vascular smooth muscle, reducing vasoconstriction

(B) Inhibiting tyrosine hydroxylase, reducing norepinephrine synthesis in adrenergic neurons

(C) Irreversible inhibition of vesicular monoamine transporter 2 (VMAT2), preventing storage of norepinephrine, dopamine, and serotonin in synaptic vesicles and depleting them from nerve terminals

(D) Competitive blockade of β_1 receptors in the heart and kidney, reducing cardiac output and renin release

Q9. A 38-year-old woman presents with fatigable ptosis and diplopia that worsens towards evening. Her neurologist suspects myasthenia gravis

and decides to confirm the diagnosis with a bedside pharmacological test using an ultra-short acting reversible anticholinesterase that acts by electrostatic binding to the anionic site of acetylcholinesterase without carbamylation, having a half-life of only 5–10 minutes. What is the PRIMARY clinical use of this drug?

(A) Long-term symptomatic management of myasthenia gravis in place of pyridostigmine

(B) Reversal of non-depolarising neuromuscular blockade at the end of surgery

(C) Treatment of Alzheimer's dementia by inhibiting central acetylcholinesterase

(D) Diagnosis of myasthenia gravis (Tensilon test) – brief improvement in ptosis and muscle strength within 30–60 seconds confirms the diagnosis

Q10. A 40-year-old man presents with episodic severe headaches, palpitations, and profuse sweating. His blood pressure during an attack reaches 230/130 mmHg. 24-hour urinary catecholamine levels are markedly elevated, suggesting pheochromocytoma. Prior to the availability of biochemical tests, a non-selective competitive α-blocker was used for pharmacological diagnosis. What is the CLASSIC diagnostic use of phentolamine?

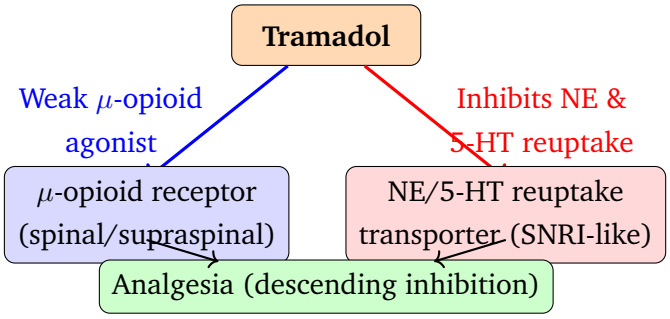
(A) Intravenous phentolamine test for pheochromocytoma – a fall in blood pressure of $>$35 mmHg systolic and $>$25 mmHg diastolic within 2 minutes of IV injection constitutes a positive test

(B) Phentolamine is used to diagnose primary hyperaldosteronism by measuring aldosterone suppression

(C) Phentolamine is used as the diagnostic agent in the clonidine suppression test for pheochromocytoma

(D) Phentolamine prevents the reflex tachycardia induced by vasodilators and is used to test baroreceptor integrity

Q11. A 45-year-old patient with moderate chronic low back pain is prescribed tramadol after failing simple analgesics. The pharmacologist explains that tramadol provides analgesia through two distinct and complementary mechanisms as shown in the diagram below:



Why is tramadol considered to have a DUAL mechanism of analgesia?

(A) It is a full μ-opioid agonist and also blocks NMDA receptors, preventing central sensitisation

(B) It is both a weak μ-opioid receptor agonist AND inhibits neuronal reuptake of norepinephrine and serotonin, enhancing descending pain inhibitory pathways

(C) It activates κ-opioid receptors for analgesia and δ-opioid receptors for mood elevation simultaneously

(D) It combines opioid receptor activation with COX-2 inhibition to reduce both central and peripheral pain

Q12. A 28-year-old patient undergoes a brief surgical procedure under general anaesthesia. A single intravenous bolus of thiopentone (5 mg/kg) is administered. The patient loses consciousness within 30 seconds and regains consciousness within 5–8 minutes, well before significant hepatic metabolism has occurred. Which of the following CORRECTLY explains why thiopentone has such an ultra-short duration of action after a single IV bolus?

(A) Thiopentone is rapidly eliminated by the kidneys, with a renal clearance that removes most of the dose within minutes

(B) Thiopentone is enzymatically hydrolysed in the plasma (by plasma esterases) within minutes of injection

(C) Redistribution of the highly lipophilic thiopentone from the brain (vessel-rich group) to peripheral tissues (muscle, then fat) rapidly reduces brain concentration, terminating CNS effect – NOT rapid metabolism

(D) Thiopentone is sequestered by plasma proteins immediately after injection, reducing free drug available to the brain

Q13. A 9-year-old child is brought to a paediatric neurologist for episodes of brief (5–10 second) staring spells with eye blinking, occurring up to 30 times daily, without post-ictal confusion. EEG shows a characteristic 3 Hz spike-and-wave pattern. The child is diagnosed with childhood absence epilepsy. Which drug is the MOST APPROPRIATE choice, and what is its mechanism?

(A) Carbamazepine – blocks voltage-gated sodium channels, reducing repetitive neuronal firing in the thalamus

(B) Valproate – inhibits GABA transaminase and blocks Na^+ channels, providing broad-spectrum anticonvulsant activity

(C) Phenytoin – inhibits voltage-gated Na^+ channels (use-dependent blockade) and reduces thalamic burst firing

(D) Ethosuximide – selectively blocks T-type voltage-gated calcium channels in thalamic neurons, interrupting the rhythmic 3 Hz spike-and-wave discharges that generate absence seizures

Q14. A 30-year-old male with treatment-resistant schizophrenia who has failed two adequate trials of conventional antipsychotics is started on clozapine. The psychiatrist counsels the patient and family about a severe, potentially fatal haematological adverse effect that mandates mandatory weekly white blood cell count monitoring for the duration of therapy. Which adverse effect SPECIFICALLY requires this mandatory monitoring?

(A) Agranulocytosis – occurring in approximately 1–2% of patients, it can be fatal if undetected; mandatory WBC monitoring (weekly for 6 months, then fortnightly) is required throughout clozapine therapy

(B) Tardive dyskinesia – irreversible involuntary movements requiring annual monitoring of the AIMS scale

(C) Neuroleptic malignant syndrome – requires monitoring of CK and core temperature weekly

(D) QTc prolongation – requires weekly ECG monitoring throughout clozapine therapy

Q15. A 52-year-old patient with refractory depression is prescribed phenelzine, an irreversible non-selective MAO inhibitor. The physician counsels the patient extensively about dietary restrictions. Three weeks later, the patient develops a severe throbbing occipital headache and blood pressure of 210/130 mmHg after eating aged cheddar cheese. Which food-drug interaction SPECIFICALLY caused this hypertensive crisis?

(A) Grapefruit juice inhibiting CYP3A4-mediated metabolism of phenelzine, raising plasma levels

(B) Tyramine in aged cheese – normally metabolised by intestinal and hepatic MAO; MAO inhibition allows tyramine to be absorbed intact, enter adrenergic nerve terminals, displace stored norepinephrine, and trigger a hypertensive crisis

(C) Calcium in dairy products chelating phenelzine and potentiating its antidepressant effect

(D) Phenylalanine in cheese competing with tyramine for renal excretion, increasing its half-life

Q16. A 35-year-old patient is scheduled for colonoscopy under procedural sedation. The anaesthetist selects propofol (2,6-diisopropylphenol) as the sole agent for induction and maintenance of sedation. Propofol potentiates GABA-A receptors, provides rapid loss of consciousness, and is remarkable for its pharmacokinetic profile. What property makes propofol MOST SUITABLE for day-case surgery and procedural sedation?

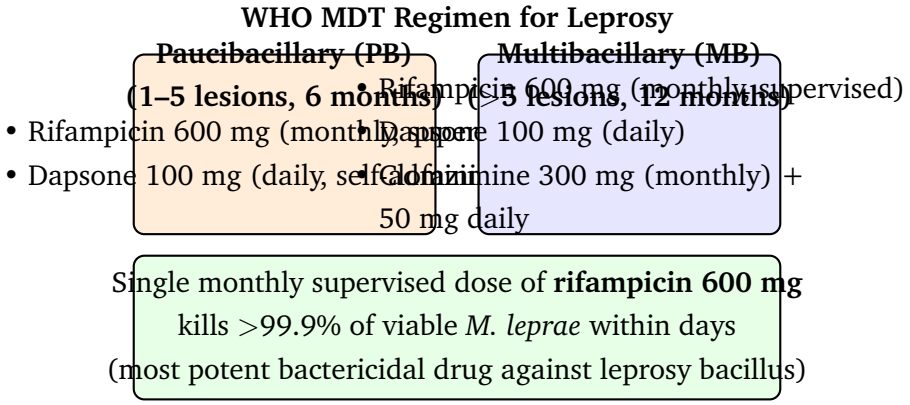
(A) Propofol is metabolised exclusively by plasma esterases, providing an ultra-short half-life independent of hepatic function

(B) Propofol causes amnesia and analgesia superior to benzodiazepines and opioids at standard doses

(C) Rapid and predictable recovery due to rapid redistribution and extensive hepatic metabolism (context-insensitive pharmacokinetics) even with prolonged infusion, enabling same-day discharge

(D) Propofol's anti-emetic properties make it uniquely suited to patients undergoing gastrointestinal procedures

Q17. Rifampicin is a cornerstone of multidrug therapy (MDT) for leprosy, as recommended by the WHO. The treatment regimen is illustrated below:



Which feature of rifampicin makes a SINGLE monthly supervised dose sufficient as the bactericidal component in MDT for leprosy?

(A) Its extremely long tissue half-life of 30–45 days, ensuring sustained drug levels throughout the month

(B) Its ability to penetrate the granuloma and kill dormant bacilli in their non-replicating phase

(C) Its combination with dapsone provides synergistic activity that allows monthly dosing

(D) Its extremely potent and rapid bactericidal action against *M. leprae* – a single 600 mg dose kills >99.9% of viable bacilli within days, eliminating the need for daily dosing

Q18. A 28-year-old patient newly diagnosed with paucibacillary leprosy is started on MDT with dapsone and monthly supervised rifampicin. The

pharmacologist explains that dapsone (diaminodiphenylsulfone) shares its antibacterial mechanism with the sulfonamide class of antibiotics. What mechanism does dapsone SHARE with sulfonamide antibiotics?

(A) Inhibition of dihydropteroate synthase (DHPS) – competitive antagonism of para-aminobenzoic acid (PABA) in the bacterial folate synthesis pathway, the same target as sulfonamides

(B) Inhibition of dihydrofolate reductase (DHFR) – the same target as trimethoprim

(C) Disruption of the mycobacterial cell wall by inhibiting mycolic acid synthesis

(D) Inhibition of RNA-dependent RNA polymerase in *M. leprae*, preventing transcription

Q19. A 35-year-old HIV-positive patient with a CD4 count of 80 cells/μL is started on cotrimoxazole (trimethoprim-sulfamethoxazole) for prophylaxis against *Pneumocystis jirovecii* pneumonia. The combination is more potent than either drug alone because it blocks two sequential steps in the bacterial folate synthesis pathway. Which combination of targets gives cotrimoxazole its SYNERGISTIC antibacterial activity?

(A) Sulfamethoxazole inhibits DHFR and trimethoprim inhibits DHPS – together blocking two steps of folate synthesis

(B) Sulfamethoxazole inhibits dihydropteroate synthase (DHPS) and trimethoprim inhibits dihydrofolate reductase (DHFR), preventing both steps of tetrahydrofolate synthesis sequentially

(C) Both trimethoprim and sulfamethoxazole inhibit DHFR at different binding sites, causing additive inhibition

(D) Sulfamethoxazole inhibits RNA polymerase and trimethoprim inhibits DNA gyrase, providing dual antibacterial mechanism

Q20. A 70-year-old patient with hospital-acquired Gram-negative pneumonia is started on gentamicin 5 mg/kg once daily (extended interval dosing). The treating team institutes a monitoring plan due to the drug's known

toxicities. Which monitoring parameter is MOST IMPORTANT during gentamicin therapy to detect early nephrotoxicity and adjust dosing?

(A) Weekly audiometry and vestibular function tests to detect early ototoxicity

(B) Liver function tests and serum bilirubin to detect hepatotoxicity

(C) Serum drug levels (peak and trough concentrations) AND serum creatinine – peak levels ensure efficacy (bactericidal concentration-dependent killing), trough levels detect accumulation predicting nephrotoxicity

(D) Complete blood count weekly to detect gentamicin-induced bone marrow suppression

Q21. A patient in the ICU has a polymicrobial wound infection with MRSA and ESBL-producing *E. coli*, both resistant to conventional tetracyclines. The infectious disease specialist prescribes tigecycline (a glycylcycline, third-generation tetracycline). Tigecycline retains activity against tetracycline-resistant strains. Which resistance mechanism does tigecycline OVERCOME compared to older tetracyclines?

(A) Tigecycline is stable against β-lactamase enzymes that inactivate conventional tetracyclines by hydrolysis

(B) Tigecycline penetrates the outer membrane of Gram-negative bacteria 100-fold more efficiently than doxycycline

(C) Tigecycline inhibits both the 30S and 50S ribosomal subunits, making it active against strains that have mutated the 30S binding site

(D) Tigecycline overcomes BOTH ribosomal protection proteins (Tet-M, Tet-O) AND tetracycline-specific efflux pumps (Tet-A to Tet-E) – the two major resistance mechanisms against earlier tetracyclines – due to its bulky glycylamido substituent

Q22. A 45-year-old patient with smear-positive pulmonary tuberculosis is started on RIPE therapy (rifampicin, isoniazid, pyrazinamide, ethambutol). After 4 weeks, routine blood tests show a serum uric acid of 9.8 mg/dL

(normal $<$ 6.8 mg/dL) and the patient complains of joint pain. He has no prior history of gout. Which drug in the RIPE regimen is MOST LIKELY responsible, and what is its mechanism?

(A) Pyrazinamide – its active metabolite, pyrazinoic acid, inhibits renal tubular secretion of uric acid (via URAT1 transporter), causing hyperuricaemia – the most common adverse effect of PZA

(B) Rifampicin – inhibits hepatic urate oxidase, preventing conversion of uric acid to allantoin

(C) Ethambutol – chelates zinc in the renal tubule, impairing uric acid secretion

(D) Isoniazid – competes with uric acid for renal tubular reabsorption transporters, elevating serum uric acid

Q23. A 55-year-old immunocompromised patient post bone marrow transplant develops invasive aspergillosis unresponsive to initial azole therapy. The haematologist switches to caspofungin, an echinocandin antifungal. What is the mechanism of action of echinocandins such as caspofungin?

(A) Binding to ergosterol in the fungal cell membrane, forming pores and disrupting membrane integrity (similar to amphotericin B)

(B) Inhibition of β-(1,3)-D-glucan synthase, disrupting fungal cell wall synthesis – a target absent in mammalian cells, accounting for its selective toxicity

(C) Inhibition of fungal lanosterol 14-α-demethylase (CYP51), reducing ergosterol synthesis in the cell membrane

(D) Inhibition of fungal dihydrofolate reductase (DHFR), blocking nucleotide synthesis in *Aspergillus* species

Q24. A 40-year-old patient with chronic Hepatitis C (genotype 1) is being treated in a resource-limited setting where direct-acting antiviral (DAA) agents are unavailable. Ribavirin, a broad-spectrum antiviral nucleoside

analogue (guanosine analogue), inhibits inosine monophosphate dehydrogenase (IMPDH), depleting guanosine nucleotides. It is highly teratogenic (Category X). Which combination represents the STANDARD treatment for Hepatitis C genotype 1 in resource-limited settings where DAAs are unavailable?

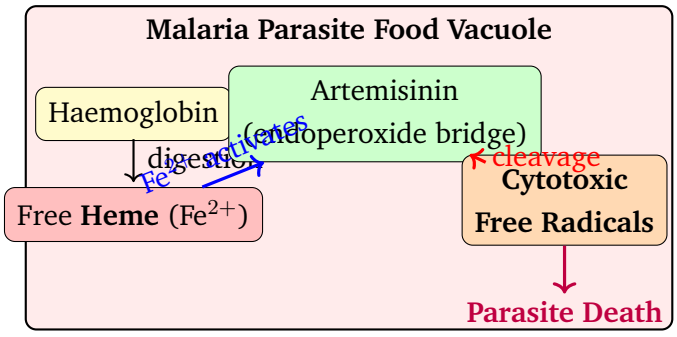
(A) Ribavirin monotherapy for 48 weeks – effective as a single agent for genotype 1 due to high barrier to resistance

(B) Interferon-α (non-pegylated) + ribavirin for 24 weeks – preferred due to lower cost and equivalent efficacy

(C) Pegylated interferon-α + ribavirin for 48 weeks (genotype 1) – the traditional regimen providing sustained virological response in 40–50% of patients

(D) Lamivudine + ribavirin – a nucleoside combination with synergistic activity against HCV genotype 1

Q25. Artemisinin (derived from *Artemisia annua*) is the fastest-acting antimalarial, forming the backbone of artemisinin-based combination therapy (ACT). The diagram below illustrates its mechanism of selective toxicity:



Uninfected RBCs: no free heme → artemisinin NOT activated → host cells SPARED

Which mechanism explains why artemisinin is SELECTIVELY toxic to malaria-infected red blood cells?

(A) Artemisinin is actively transported into infected RBCs by a parasite-encoded transporter absent in normal erythrocytes

(B) Artemisinin inhibits haemozoin formation, accumulating toxic heme inside the parasite (same as chloroquine)

(C) Artemisinin blocks the parasite's mitochondrial ATP synthesis, selectively killing metabolically active infected RBCs

(D) The endoperoxide bridge of artemisinin is activated by abundant free heme iron (Fe^{2+}) in the parasite's food vacuole to generate cytotoxic free radicals; uninfected RBCs lack this free heme, so artemisinin remains inert in normal cells

Q26. A 35-year-old patient from a river-blindness endemic region of sub-Saharan Africa is treated with ivermectin for onchocerciasis caused by *Onchocerca volvulus*. Ivermectin is effective against many helminths and ectoparasites. It does not cross the human blood-brain barrier because it is a substrate for P-glycoprotein efflux at the BBB. What is the mechanism of action of ivermectin against parasites?

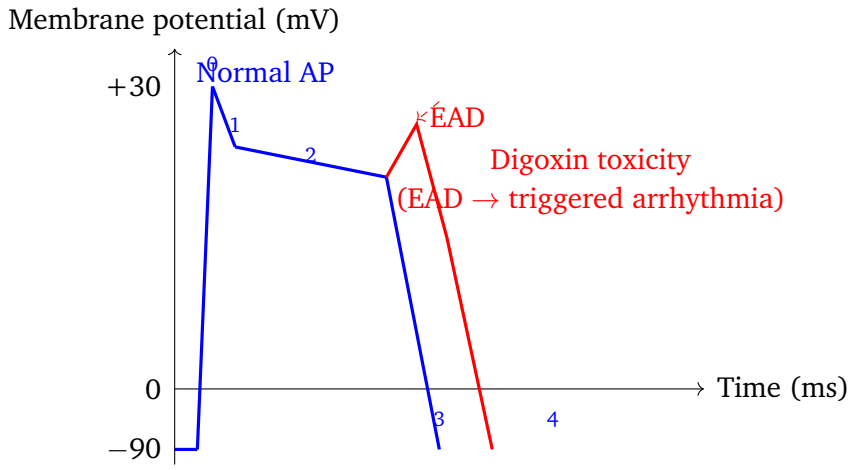
(A) Potentiation of glutamate-gated chloride channels (GluCl) and GABA-A receptors in helminths and arthropods, causing hyperpolarisation and flaccid paralysis of the parasite neuromuscular system

(B) Inhibition of microtubule polymerisation in helminths, preventing glucose uptake and causing larval death

(C) Inhibition of acetylcholinesterase in the helminth nervous system, causing spastic paralysis

(D) Chelation of divalent cations (Mg^{2+}, Ca^{2+}) in the parasite gut, disrupting neuromuscular transmission

Q27. A 78-year-old patient on digoxin 0.25 mg/day for atrial fibrillation develops nausea, visual disturbances (yellow-green halos), and the ECG below shows new bigeminy. The following diagram illustrates a typical early afterdepolarisation (EAD) seen in digoxin toxicity on the action potential:



His recent blood tests show: serum K^+ 2.8 mEq/L. Which electrolyte abnormality MOST POTENTIATES digoxin toxicity?

(A) Hypernatraemia – high serum sodium competes with digoxin at the Na^+/K^+-ATPase binding site

(B) Hypokalemia – potassium normally competes with digoxin at the Na^+/K^+-ATPase binding site; low serum K^+ reduces competition, enhancing digoxin binding and toxicity

(C) Hypermagnesaemia – excess magnesium inhibits the ATPase pump, synergising with digoxin

(D) Hypocalcaemia – calcium deficiency sensitises cardiac myocytes to digoxin-induced arrhythmias

Q28. A 24-year-old woman presents to the emergency department with sudden-onset palpitations and a heart rate of 210 bpm. ECG shows a narrow-complex regular tachycardia consistent with paroxysmal supraventricular tachycardia (PSVT). Vagal manoeuvres fail to terminate the episode. The emergency physician administers a rapid IV bolus of adenosine 6 mg, and sinus rhythm is restored within 15 seconds. How does adenosine terminate paroxysmal SVT?

(A) Adenosine blocks L-type calcium channels in the AV node, reducing calcium-dependent action potential conduction

(B) Adenosine activates β_2 receptors in the AV node, causing hyperpolarisation via adenylyl cyclase-cAMP signalling

(C) Adenosine activates A1 adenosine receptors (Gi-coupled) in the AV node, increasing K^+ conductance (IKAdo), hyperpolarising the cell, slowing AV nodal conduction, and interrupting the re-entry circuit responsible for PSVT

(D) Adenosine inhibits the Na^+/K^+-ATPase in the AV node, causing re-polarisation failure and conduction block

Q29. A 45-year-old man is brought to the emergency department following a road traffic accident with a depressed level of consciousness (GCS 9). CT head shows diffuse cerebral oedema with midline shift. The neurosurgical team requests immediate medical management to reduce intracranial pressure (ICP) while awaiting theatre. For which emergency condition is mannitol infusion SPECIFICALLY indicated?

(A) Acute pulmonary oedema – mannitol draws fluid from pulmonary interstitium into the vascular compartment

(B) Acute hypotension secondary to haemorrhagic shock – mannitol expands plasma volume rapidly

(C) Acute renal tubular necrosis – mannitol is filtered and maintains tubular flow, preventing cast formation in all settings

(D) Raised intracranial pressure due to cerebral oedema – mannitol, freely filtered but not reabsorbed, creates an osmotic gradient that draws fluid from brain parenchyma across the blood-brain barrier into the vascular compartment, reducing ICP

Q30. A 55-year-old man with type 2 diabetes presents with severe hypertriglyceridaemia (serum TG 1800 mg/dL) and low HDL (28 mg/dL). His physician starts him on fenofibrate. Fibric acid derivatives are the most effective drugs for reducing triglycerides. What is the PRIMARY mechanism by which fibrates lower triglycerides?

(A) Activation of peroxisome proliferator-activated receptor-α (PPAR-α) in hepatocytes and muscle, which upregulates lipoprotein lipase (LPL) gene expression, increasing clearance of VLDL and chylomicrons from the circulation

(B) Inhibition of HMG-CoA reductase in the liver, reducing cholesterol and triglyceride biosynthesis simultaneously

(C) Activation of PPAR-γ in adipose tissue, promoting fatty acid uptake and storage and reducing free fatty acid flux to the liver

(D) Inhibition of pancreatic lipase in the gut, reducing dietary triglyceride absorption

Q31. A 25-year-old patient with acute severe asthma is admitted and treated with intravenous methylprednisolone. Glucocorticoids provide potent broad-spectrum anti-inflammatory activity by modulating gene transcription after the glucocorticoid-receptor (GR) complex translocates to the nucleus. Which TRANSCRIPTION FACTOR is most importantly inhibited by glucocorticoids as the PRIMARY molecular mechanism of their anti-inflammatory action?

(A) AP-1 (activator protein-1) – glucocorticoids block AP-1 to prevent transcription of matrix metalloproteinases

(B) NF-κB (nuclear factor kappa B) – the GR complex directly inhibits NF-κB transactivation, reducing gene expression of pro-inflammatory cytokines (TNF-α, IL-1, IL-6), COX-2, and inducible nitric oxide synthase (iNOS)

(C) NFAT (nuclear factor of activated T cells) – glucocorticoids prevent NFAT dephosphorylation, blocking T cell cytokine production

(D) STAT3 (signal transducer and activator of transcription 3) – glucocorticoids bind the JAK-STAT pathway to reduce IL-6-driven inflammation

Q32. A 35-year-old woman with systemic lupus erythematosus (SLE) is started on hydroxychloroquine (HCQ) 400 mg/day as a disease-modifying agent. HCQ reduces disease flares, damage accrual, and mortality in SLE. It accumulates in melanin-containing tissues including the retinal pigment epithelium. Which is the MOST IMPORTANT monitoring requirement during long-term hydroxychloroquine therapy?

(A) Monthly complete blood counts (CBC) to detect hydroxychloroquine-induced bone marrow suppression

(B) Bi-annual liver function tests to detect early hepatotoxicity from HCQ accumulation in hepatocytes

(C) Annual ophthalmological examination with 10-2 visual field testing and spectral-domain OCT – to detect early hydroxychloroquine retinopathy (bull's-eye maculopathy), which can be irreversible if the drug is not stopped promptly

(D) Six-monthly pulmonary function tests to detect HCQ-induced interstitial pneumonitis

Q33. Probenecid is a uricosuric agent that inhibits URAT1 (uric acid transporter 1) in the proximal renal tubule, reducing uric acid reabsorption and increasing urinary uric acid excretion. It was historically used in a well-known drug interaction with penicillin antibiotics to prolong their plasma half-life before sufficient quantities could be manufactured. Which drug interaction of probenecid is CLINICALLY SIGNIFICANT in antibiotic therapy?

(A) Probenecid induces CYP3A4 enzymes, increasing the hepatic metabolism of penicillins and reducing their plasma levels

(B) Probenecid increases the renal glomerular filtration of penicillins, reducing their plasma levels more rapidly

(C) Probenecid chelates the β-lactam ring of penicillins in plasma, inactivating the antibiotic

(D) Probenecid inhibits tubular secretion of penicillins (and cephalosporins) by competing for the OAT transporter in the proximal tubule, prolonging their plasma half-life and increasing blood levels

Q34. A 60-year-old patient with type 2 diabetes is being counselled about the differences between glipizide (a sulfonylurea) and liraglutide (a GLP-1 receptor agonist) before choosing a regimen. The endocrinologist emphasises that one drug can cause hypoglycaemia even in a fasting state

while the other does not, because of a fundamental difference in how they stimulate insulin secretion. Which statement CORRECTLY contrasts the mechanism of sulfonylureas versus GLP-1 receptor agonists?

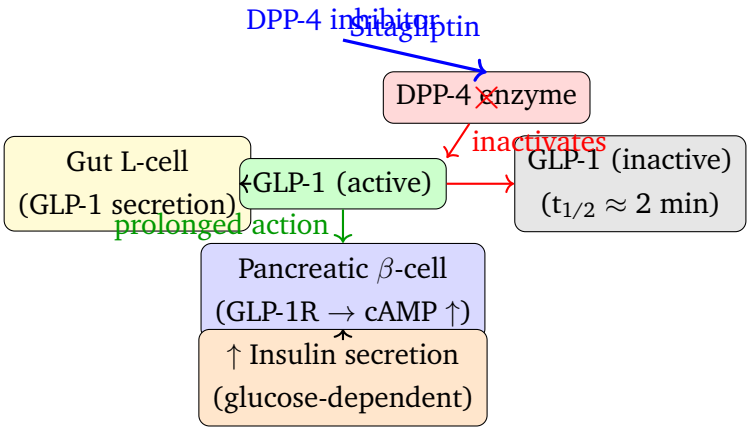
(A) Sulfonylureas close ATP-sensitive K^+ channels directly regardless of ambient glucose levels (risk of hypoglycaemia even when fasting), whereas GLP-1 receptor agonists amplify glucose-stimulated insulin secretion via Gs-cAMP pathway (minimal hypoglycaemia risk because insulin is only released when glucose is elevated)

(B) Sulfonylureas inhibit glucagon secretion from α-cells while GLP-1 receptor agonists directly stimulate insulin from β-cells

(C) Both drugs close K-ATP channels but sulfonylureas act faster, causing more severe hypoglycaemia

(D) GLP-1 receptor agonists close K-ATP channels more potently than sulfonylureas, producing greater hypoglycaemia risk

Q35. A 55-year-old patient with type 2 diabetes has poor glycaemic control on metformin alone (HbA1c 8.4%). Her physician adds sitagliptin to the regimen. The DPP-4 inhibitor class works by prolonging the action of endogenous incretins. The diagram below shows the incretin pathway targeted by sitagliptin:



What is the mechanism of action of sitagliptin?

(A) Direct binding to the GLP-1 receptor on pancreatic β-cells, mimicking the action of native GLP-1 with a longer half-life

(B) Inhibition of DPP-4 enzyme, preventing degradation of endogenous GLP-1 and GIP, thereby prolonging their incretin action and enhancing glucose-dependent insulin secretion with minimal risk of hypoglycaemia

(C) Stimulation of GLP-1 secretion from intestinal L-cells by activating bile acid receptors (TGR5)

(D) Reduction of gastric emptying by blocking GIP receptors in the stomach, reducing post-prandial glucose excursions

Q36. A 55-year-old man with metastatic prostate cancer is started on flutamide monotherapy as an antiandrogen. Flutamide is a non-steroidal competitive antagonist at the androgen receptor (AR). After 8 weeks, a paradoxical finding is noted on his hormone profile. Which finding on his hormone profile would be EXPECTED on flutamide MONOTHERAPY?

(A) Markedly reduced serum LH and FSH due to androgen receptor blockade at the pituitary level reducing gonadotropin release

(B) Undetectable serum testosterone due to negative feedback disruption causing complete hypothalamic-pituitary suppression

(C) ELEVATED serum testosterone – androgen receptor blockade prevents testosterone from exerting negative feedback on the hypothalamic-pituitary axis, leading to increased LH secretion and therefore increased testosterone production by the testes

(D) Normal serum testosterone and LH because flutamide acts exclusively at the peripheral androgen receptor without affecting the hypothalamic-pituitary axis

Q37. A 48-year-old woman is scheduled to receive her first cycle of cisplatin-based chemotherapy for ovarian cancer. Her oncologist prescribes antiemetic prophylaxis and explains the different phases of chemotherapy-induced nausea and vomiting (CINV). Ondansetron is a 5-HT3 receptor antagonist that acts at the chemoreceptor trigger zone (CTZ) and peripheral vagal afferents in the gastrointestinal tract. For which PHASE of CINV is ondansetron MOST EFFECTIVE?

(A) Anticipatory CINV (before chemotherapy administration – conditioned response to prior CINV)

(B) Breakthrough CINV (occurring despite adequate prophylaxis and requiring rescue antiemetics)

(C) Delayed CINV (24–120 hours after chemotherapy – primarily mediated by substance P/NK1 receptors; better managed by NK1 antagonist aprepitant + dexamethasone)

(D) Acute CINV (within the first 24 hours of chemotherapy – ondansetron's 5-HT3 blockade at the CTZ and GI vagal afferents provides highly effective prophylaxis during this serotonin-driven phase)

Q38. A 68-year-old patient with COPD is started on inhaled ipratropium bromide as a first-line bronchodilator. Unlike atropine (a tertiary amine), ipratropium is a quaternary ammonium compound. Despite blocking the same muscarinic M3 receptors in bronchial smooth muscle, ipratropium does NOT cause tachycardia (which atropine commonly produces by blocking cardiac M2 receptors). Why does ipratropium NOT cause tachycardia unlike atropine?

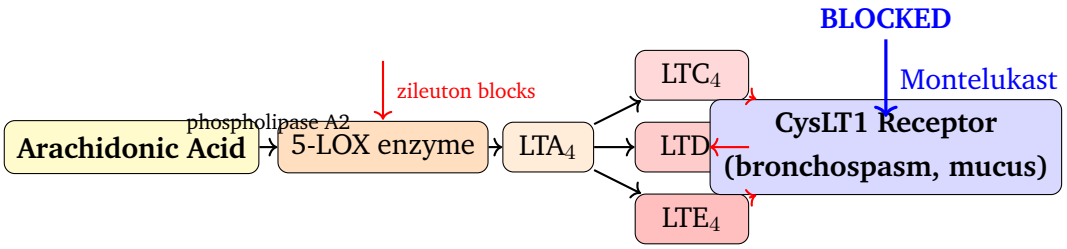
(A) Ipratropium is a quaternary ammonium compound – its permanent positive charge makes it poorly absorbed from the respiratory mucosa, preventing significant systemic concentrations from reaching the heart's muscarinic M2 receptors

(B) Ipratropium selectively blocks bronchial M3 receptors and has no affinity for cardiac M2 receptors

(C) Ipratropium is rapidly metabolised in the lung parenchyma by esterases before it can reach systemic circulation

(D) Ipratropium is a partial agonist at cardiac M2 receptors, causing neither full agonism nor antagonism at the heart

Q39. A 12-year-old child with mild persistent asthma and co-existing allergic rhinitis is prescribed montelukast as add-on therapy. Montelukast is a leukotriene receptor antagonist (LTRA). The diagram below shows the arachidonic acid pathway targeted by montelukast:



What is the mechanism of action of montelukast in asthma?

(A) Inhibition of 5-lipoxygenase (5-LOX), preventing conversion of arachidonic acid to LTA_4 and all downstream leukotrienes (this is zileuton's mechanism)

(B) Competitive antagonism at CysLT1 (cysteinyl leukotriene 1) receptors, blocking the bronchoconstrictor and pro-inflammatory effects of leukotrienes LTC_4, LTD_4, and LTE_4

(C) Mast cell membrane stabilisation, preventing degranulation and leukotriene release (this is cromolyn's mechanism)

(D) Inhibition of phospholipase A2, reducing arachidonic acid release and production of all eicosanoids

Q40. A 72-year-old patient with atrial fibrillation is stable on warfarin 5 mg/day with a therapeutic INR of 2.5. He is admitted with a new episode of rapid ventricular rate and is started on amiodarone for rhythm control. Two weeks later, his INR has risen to 5.8 and he develops haematuria. Warfarin is primarily metabolised by CYP2C9 (S-warfarin, the more potent enantiomer) and CYP3A4. Which drug, when added to a patient's stable warfarin regimen, would MOST PREDICTABLY INCREASE the risk of bleeding?

(A) Rifampicin – a potent inducer of CYP2C9 and CYP3A4 that accelerates warfarin metabolism, REDUCING INR

(B) Phenobarbitone – induces CYP enzymes and reduces warfarin plasma levels, requiring a higher warfarin dose

(C) Amiodarone – inhibits both CYP2C9 and CYP3A4, markedly reducing warfarin clearance and raising plasma warfarin levels and INR, significantly increasing bleeding risk

(D) Carbamazepine – a hepatic enzyme inducer that increases warfarin metabolism and lowers INR

Detailed Solutions

Q1.

Solution

Topic: Plasma Protein Binding of Basic Drugs

Basic drugs (propranolol, tricyclic antidepressants, lidocaine, chlorpromazine, verapamil, quinine) predominantly bind to **alpha-1-acid glycoprotein (AAG, also called orosomucoid)**, not albumin.

Key distinctions:

- **Albumin** – most abundant plasma protein (35–50 g/L); binds *acidic* drugs (warfarin, NSAIDs, sulfonamides, phenytoin, methotrexate) and a few basic drugs at separate sites
- **Alpha-1-acid glycoprotein (AAG)** – acute phase reactant (increases 2–3-fold in inflammation, surgery, trauma, myocardial infarction); principal binding protein for basic, cationic lipophilic drugs
- AAG levels vary with clinical state: *increases* in inflammation (reduces free drug fraction – may need dose increase), *decreases* in liver disease/nephrotic syndrome (increases free fraction – toxicity risk)
- Other proteins (transferrin, β-globulin, lipoproteins) bind some drugs but are not the principal carriers for basic drugs

Clinical pearl: In patients recovering from MI or post-surgery, elevated AAG can reduce the free fraction of lidocaine or propranolol, requiring higher doses for the same effect.

Answer: (D) Go Back to Q1

Q2.

Solution

Topic: Renal Drug Clearance and Active Tubular Secretion

The formula for renal drug clearance is:

$$CL_{renal} = (GFR \times f_u) + \text{Tubular Secretion} - \text{Tubular Reabsorption}$$

If a drug's $CL_{renal} > GFR \times f_u$, it **must be actively secreted** into the tubule.

Example in the question: $CL_{renal} = 650$ mL/min vs GFR $\times f_u = 120 \times 1.0 = 120$

mL/min. The clearance far exceeds filtration alone – only active secretion can account for this.

Active tubular secretion:

- Occurs in the **proximal tubule** via OAT (organic anion transporter) and OCT (organic cation transporter) transporters
- Energy-dependent (ATP), can be saturated, can be inhibited competitively (e.g., probenecid blocking penicillin secretion)
- Allows secretion even of protein-bound drug (albumin releases drug rapidly as free drug is removed)
- Examples of secreted drugs: PAH, penicillin, furosemide, uric acid, metformin

Maximum possible CL_{renal} by filtration alone: GFR $\times f_u$ (120 mL/min if fully unbound). Drugs with CL_{renal} approaching renal plasma flow (650 mL/min) are nearly completely cleared in one pass (e.g., PAH = gold standard for measuring renal plasma flow).

Answer: (A) Go Back to Q2

Q3.

Solution

Topic: Inverse Agonist vs Competitive Antagonist

Intrinsic efficacy (IA) spectrum:

- Full agonist: IA $= +1$ (maximal activation of receptor)
- Partial agonist: $0 <$ IA $< +1$
- Neutral/competitive antagonist: IA $= 0$ (no effect alone, blocks agonist)
- **Inverse agonist: IA =** -1 (produces effect *opposite* to agonist; reduces constitutive receptor activity *below* basal level)

Distinguishing features:

- An **inverse agonist** binds the same orthosteric site as the agonist, has **negative intrinsic efficacy**, and produces a pharmacological effect opposite to the agonist when given alone

- A **competitive antagonist** has **zero intrinsic activity** – it produces no effect alone but competitively blocks agonist binding (reversible by increasing agonist concentration)
- Both are displaced by excess agonist (both are competitive)

Clinical examples of inverse agonists:

- Some GABA-A ligands (beta-carbolines like DMCM) – anxiogenic, proconvulsant (opposite of diazepam)
- Histamine H1: mepyramine has been characterised as an inverse agonist
- β-blockers (e.g., carvedilol, metoprolol): inverse agonists at constitutively active β_1 receptors

Answer: (B) Go Back to Q3

Q4.

Solution

Topic: P-glycoprotein (P-gp/MDR1) and Drug Interactions

P-glycoprotein (P-gp):

- Encoded by the *MDR1/ABCB1* gene; an ATP-dependent efflux transporter
- Expressed at: gut epithelium (reduces absorption), blood-brain barrier (limits CNS entry), liver canalicular membrane (biliary excretion), renal tubule (urinary excretion), placenta
- Major mechanism of multidrug resistance (MDR) in cancer – pumps chemotherapeutic agents out of tumour cells

P-gp INHIBITORS (increase drug absorption/CNS penetration): **Verapamil** (first identified P-gp inhibitor), cyclosporin A, itraconazole, amiodarone, ritonavir, quinidine

P-gp INDUCERS (reduce drug levels): Rifampicin, carbamazepine, phenytoin, St. John's Wort, dexamethasone

Clinical significance:

- Rifampicin (inducer) + digoxin: reduces digoxin plasma levels by increasing P-gp-mediated intestinal efflux and biliary clearance

- Verapamil (inhibitor) + digoxin: increases digoxin levels (also inhibits renal P-gp) – monitor for toxicity
- Verapamil was investigated (as a chemosensitiser) to reverse MDR in cancer, allowing higher intracellular cytotoxic drug levels

Answer: (C) Go Back to Q4

Q5.

Solution

Topic: Pilocarpine vs Physostigmine in Glaucoma – Direct vs Indirect Mechanism

Feature	Pilocarpine	Physostigmine
Mechanism	Direct muscarinic agonist	Anticholinesterase (indirect)
Action	Directly stimulates M3	Inhibits AChE $\rightarrow \uparrow$ ACh $\rightarrow$ M3
Effect	Miosis, ciliary contraction	Miosis, ciliary contraction
IOP reduction	$\uparrow$ outflow via trabecular meshwork	Same
Duration	4–8 hours	12–36 hours
Clinical use	Open-angle glaucoma, angle-closure	Glaucoma (less used now)

Key distinction:

- **Pilocarpine** = *direct* muscarinic agonist – acts even in the absence of ACh, including denervated iris (useful in Adie's pupil testing at low concentrations)
- **Physostigmine** = *indirect* – requires intact cholinergic innervation; inhibits acetylcholinesterase (reversible carbamylation), increasing synaptic ACh to stimulate muscarinic receptors
- Reversibility: physostigmine – reversible (hours); organophosphates (e.g., DFP) – irreversible

Answer: (D) Go Back to Q5

Q6.

Solution

Topic: Norepinephrine vs Epinephrine – Cardiovascular Effects

Key receptor profile:

- **Norepinephrine (NE):** α_1 (+++), α_2 (++), β_1 (++), β_2 ($\pm$)
- **Epinephrine (Epi):** α_1 (++), α_2 (+), β_1 (+++), β_2 (+++)

Why NE causes reflex bradycardia but Epi causes tachycardia:

(a) NE: predominant α_1 stimulation $\rightarrow$ marked vasoconstriction $\rightarrow \uparrow$ mean arterial pressure $\rightarrow$ baroreceptor activation $\rightarrow$ increased vagal tone $\rightarrow$ **reflex bradycardia** (HR may fall despite $\uparrow$ BP)

(b) Epi: strong β_1 stimulation $\rightarrow$ direct tachycardia + positive inotropy; this chronotropic effect **overrides** the baroreflex $\rightarrow$ net tachycardia; β_2 vasodilation lowers diastolic BP

Clinically:

- NE IV infusion: $\uparrow$ systolic, $\uparrow$ diastolic, $\uparrow$ MAP, HR may fall or unchanged
- Epi IV infusion: $\uparrow$ systolic, $\downarrow$ or $\uparrow$ diastolic, $\uparrow$ HR, $\uparrow$ pulse pressure
- **Reflex bradycardia is the cardiovascular effect of NE NOT shared by epinephrine**

Answer: (A) Go Back to Q6

Q7.

Solution

Topic: Labetalol in Hypertensive Emergency in Pregnancy

Labetalol pharmacology:

- Combined α_1-blocker + non-selective β-blocker (β_1 and β_2)
- α:β blockade ratio = 1:7 (IV) or 1:3 (oral)
- Reduces BP without reflex tachycardia (unlike pure α-blockers)
- Maintains uteroplacental blood flow – safe in pregnancy (does not cause uterine vasoconstriction)

Preferred in hypertensive emergency in PREGNANCY because:

(a) Established safety record in pregnancy (crosses placenta minimally)

(b) Effective BP reduction without major fetal adverse effects

(c) IV labetalol: 20 mg bolus initially, repeated every 10 min up to 300 mg total; or infusion

(d) Alternative: hydralazine IV; oral nifedipine

Contraindications/caution in other scenarios:

- Asthma: β_2 blockade causes bronchospasm – **contraindicated**
- Cocaine toxicity: pure β-blockade (if used alone) allows unopposed α-stimulation worsening hypertension – labetalol has α component but cocaine toxicity management is complex
- Aortic dissection: esmolol (ultra-short β_1 selective) preferred for precise rate control

Answer: (B) Go Back to Q7

Q8.

Solution

Topic: Reserpine – VMAT2 Inhibition and Monoamine Depletion

Reserpine mechanism:

- Irreversibly inhibits **VMAT2 (vesicular monoamine transporter 2)** in adrenergic nerve terminals
- VMAT2 normally pumps norepinephrine, dopamine, and serotonin INTO storage vesicles
- Inhibition $\rightarrow$ monoamines cannot be stored $\rightarrow$ degraded by intraneuronal MAO $\rightarrow$ progressive depletion from nerve terminals
- Effect is *irreversible* – recovery requires synthesis of new VMAT2 (days to weeks)

Pharmacological consequences:

- Antihypertensive: depletes NE $\rightarrow$ reduced sympathetic vasoconstriction

- Depression (contraindicated in depressed patients): depletes serotonin and dopamine centrally
- Sedation, nasal congestion (parasympathetic predominance)
- Parkinson-like symptoms: depletes central dopamine
- GI hypermotility, diarrhoea

Historical note: First effective antihypertensive; largely abandoned due to severe depression, GI symptoms, and Parkinson-like effects. Still used in low doses for Huntington's chorea (Tetrabenazine, a related VMAT2 inhibitor, is used for hyperkinetic disorders).

Answer: (C) Go Back to Q8

Q9.

Solution

Topic: Edrophonium – Diagnosis of Myasthenia Gravis (Tensilon Test)

Edrophonium (Tensilon):

- Ultra-short acting reversible anticholinesterase
- Mechanism: binds the **anionic site** of AChE by electrostatic interaction (no carbamylation) $\rightarrow$ very rapid and reversible
- Half-life: 5–10 minutes only
- Route: intravenous (2 mg test dose, then 8 mg if no reaction)

Tensilon test for myasthenia gravis:

- Positive: brief (1–5 min) objective improvement in ptosis, extraocular muscle weakness, or limb weakness confirms MG
- Negative: no improvement (suggests non-myasthenic cause of weakness)
- Differentiating myasthenic crisis from cholinergic crisis: in cholinergic crisis (excess ACh), edrophonium worsens weakness – patient has fasciculations, increased secretions
- Atropine (0.5–1 mg IV) should be available as antidote before Tensilon test

Why NOT used for long-term management: Half-life too short (minutes) – pyridostigmine (oral, 3–4 hours duration) is used for chronic management of MG.

Answer: (D) Go Back to Q9

Q10.

Solution

Topic: Phentolamine IV Test for Pheochromocytoma Diagnosis

Phentolamine:

- Non-selective competitive α-blocker (α_1 and α_2)
- Blocks NE/catecholamine-induced vasoconstriction

Phentolamine test (historical diagnostic test for pheochromocytoma):

- Procedure: IV phentolamine 5 mg (adults) administered rapidly
- **Positive test:** BP falls >35 mmHg systolic and >25 mmHg diastolic within 2 minutes of injection
- Interpretation: if marked BP fall occurs, it suggests BP was catecholamine-mediated $\rightarrow$ pheochromocytoma
- Largely superseded by biochemical tests (24-hour urinary catecholamines, metanephrines, plasma metanephrines) which are more sensitive and specific

Current use of phentolamine:

- Management of pheochromocytoma-induced hypertensive crisis (pre-operatively or intra-operatively)
- Prevention of tissue necrosis from extravasated norepinephrine/dopamine – local injection of phentolamine into the infiltrated area
- Reversal of local anaesthetic vasoconstrictor (dental procedures)

Drug of choice for pheochromocytoma pre-op preparation: Phenoxybenzamine (irreversible non-selective α-blocker) – started 10–14 days before surgery.

Answer: (A) Go Back to Q10

Q11.

Solution

Topic: Tramadol – Dual Mechanism of Analgesia

Tramadol pharmacology – two distinct analgesic mechanisms:

Mechanism 1: Weak μ-opioid receptor agonist

- About 10-fold weaker than morphine at μ-receptors
- Active metabolite O-desmethyltramadol (M1) has higher μ-opioid affinity and accounts for much of opioid effect
- Blocked by naloxone (about 30% of analgesia reversed)

Mechanism 2: Inhibits reuptake of norepinephrine (NE) and serotonin (5-HT)

- Enhances descending pain inhibitory pathways from the brainstem (locus coeruleus, raphe nuclei)
- This SNRI-like component is NOT reversed by naloxone
- Explains why tramadol cannot be fully antagonised by naloxone

Clinical properties:

- Lower abuse/dependence potential than morphine (dual mechanism provides analgesia at lower μ-receptor occupancy)
- **Lowers seizure threshold** – avoid in epilepsy or concurrent MAOI/SSRI use
- Risk of **serotonin syndrome** with concurrent SSRIs, SNRIs, MAOIs (due to NE/5-HT reuptake inhibition)
- Avoid with MAOIs (hypertensive crisis risk)

Answer: (B) Go Back to Q11

Q12.

Solution

Topic: Thiopentone – Redistribution Terminates Action After Single IV Dose

Thiopentone pharmacokinetics – the redistribution phenomenon:

(a) IV bolus → high initial plasma concentration → rapid equilibration with **vessel-rich group (VRG)** = brain, heart, liver, kidney

(b) Brain: thiopentone's high lipophilicity ensures rapid CNS penetration → **unconsciousness within 30 seconds**

(c) After 5–8 minutes: thiopentone redistributes from brain to **muscle** (large mass, lower blood flow) → brain concentration falls below threshold → **wakefulness**

(d) Subsequently redistributes to **fat** (very large depot, slow uptake) → very prolonged terminal elimination

Key concept: The short duration of action of a SINGLE dose is due to **redistribution**, NOT metabolism. Hepatic metabolism of thiopentone is actually slow ($t_{1/2}$ = 6–12 hours).

Clinical consequence (context-sensitive half-life):

- With repeated/continuous dosing, the muscle and fat depots saturate
- The drug can no longer redistribute efficiently → prolonged duration, "hangover" effect
- **Contrast with propofol:** propofol has rapid *metabolism* in addition to redistribution – truly context-insensitive

Answer: (C) Go Back to Q12

Q13.

Solution

Topic: Ethosuximide – T-type Calcium Channel Blockade in Absence Seizures

Ethosuximide mechanism:

- Selectively blocks **T-type (transient, low-threshold) voltage-gated Ca^{2+} channels** in thalamic neurons
- These channels generate the rhythmic low-threshold calcium spikes (LTCS) that underlie thalamo-cortical oscillations
- Blockade interrupts the **3 Hz spike-and-wave** discharges characteristic of absence seizures
- Does NOT have significant activity on Na^+ channels or GABA systems

Indications:

- **Drug of choice for childhood absence epilepsy (petit mal)** – especially when absence seizures occur in isolation
- Does NOT worsen primary generalised tonic-clonic seizures (unlike carbamazepine and phenytoin which can worsen absences)

Adverse effects: GI upset (most common: nausea, vomiting, anorexia), drowsiness, headache. Rarely: blood dyscrasias (leucopenia, aplastic anaemia), SLE-like syndrome. Monitoring: CBC periodically.

Note: Valproate is used when absence seizures coexist with generalised tonic-clonic seizures (broader spectrum), but ethosuximide is preferred for pure absence epilepsy in children (better safety profile).

Answer: (D) Go Back to Q13

Q14.

Solution

Topic: Clozapine – Agranulocytosis Requiring Mandatory WBC Monitoring

Clozapine – pharmacology:

- Atypical antipsychotic; blocks D4 $>$ D2, 5-HT2A, H1, α_1, muscarinic receptors
- **Drug of choice for treatment-resistant schizophrenia** (fails $\geq$2 antipsychotics)
- Only antipsychotic proven to **reduce suicide risk** in schizophrenia

Agranulocytosis (the critical adverse effect):

- Incidence: 1–2% (absolute neutrophil count $<$ 500 cells/μL)
- Potentially **fatal** if undetected – overwhelming bacterial sepsis
- Mechanism: immune-mediated (drug-reactive metabolite + neutrophil surface proteins)
- Onset: typically within first 18 weeks of treatment (peak risk at 6–18 weeks)
- **Mandatory WBC monitoring:** Weekly for first 6 months, then every 2 weeks for 6 months, then monthly thereafter

- Clozapine MUST be stopped immediately if ANC falls $< 1000/\mu L$

Other important adverse effects of clozapine:

- Metabolic syndrome (weight gain, dyslipidaemia, type 2 diabetes) – very common
- Dose-dependent seizures (EEG monitoring for doses > 600 mg/day)
- Excessive sedation, hypersalivation (sialorrhoea), constipation
- Minimal EPS (no tardive dyskinesia – advantage of atypical profile)

Answer: (A) Go Back to Q14

Q15.

Solution

Topic: MAO Inhibitors and Tyramine "Cheese Effect" – Hypertensive Crisis

Normal tyramine metabolism:

- Tyramine (found in aged cheese, red wine, Chianti, yeast extract, salami, smoked fish, fermented foods) is normally metabolised by **MAO-A** in the gut wall and liver during first-pass metabolism
- Normally only trace amounts reach systemic circulation

With irreversible MAO inhibitors (phenelzine, tranylcypromine):

(a) Gut and liver MAO is inhibited $\rightarrow$ tyramine is **NOT** degraded during first pass

(b) Tyramine absorbed intact into systemic circulation $\rightarrow$ enters adrenergic nerve terminals (indirect-acting sympathomimetic)

(c) Tyramine **displaces stored NE** from vesicles into synapse $\rightarrow$ massive NE release $\rightarrow$ severe vasoconstriction

(d) Result: **Hypertensive crisis** ("cheese reaction") – throbbing occipital headache, BP $> 200/120$ mmHg, risk of intracranial haemorrhage

Foods to AVOID on MAOIs: aged cheese, red wine/Chianti, Marmite/Bovril, pickled herrings, salami, sauerkraut, broad bean pods, over-ripe avocados.

Management: IV phentolamine (α-blocker) or oral nifedipine for acute hypertensive crisis.

Reversible MAO inhibitors (moclobemide – RIMA, selective MAO-A): dietary tyramine interaction much less significant (displacement is competitive; tyramine can displace moclobemide).

Answer: (B) Go Back to Q15

Q16.

Solution

Topic: Propofol – Context-Insensitive Pharmacokinetics for Day-Case Surgery

Propofol (2,6-diisopropylphenol):

- Mechanism: positive allosteric modulator of GABA-A receptor (like barbiturates – prolongs duration of Cl^- channel opening)
- Highly lipophilic, rapid onset (1 arm-brain circulation time)

Why propofol recovery is rapid even after prolonged infusion:

- **Very high metabolic clearance:** hepatic metabolism (glucuronidation, hydroxylation) exceeds hepatic blood flow – suggesting extrahepatic metabolism (lung, kidney, intestine contribute)
- Total body clearance: 1.5–2.2 L/min (greater than hepatic blood flow of 1.4 L/min)
- **Context-insensitive half-time:** does not accumulate significantly with prolonged infusion (unlike thiopentone which accumulates in fat)
- Rapid redistribution PLUS rapid metabolism $\rightarrow$ quick, clear-headed recovery
- Patients can be discharged within 1–2 hours of day-case procedures

Additional benefits: anti-emetic properties, antipruritic, amnestic but NOT analgesic (analgesia must be supplemented).

Propofol infusion syndrome (PRIS): rare but potentially fatal with high-dose ($>$ 5 mg/kg/hr) prolonged ($>$ 48 hours) infusion in ICU – metabolic acidosis, rhabdomyolysis, renal failure, cardiac failure. Avoid in prolonged ICU sedation, especially in children.

Answer: (C) Go Back to Q16

Q17.

Solution

Topic: Rifampicin in Leprosy MDT – Potent Bactericidal Action Against *M. leprae*

Rifampicin's activity against *M. leprae*:

- Most **potent bactericidal drug** against *Mycobacterium leprae* currently available
- A single dose of rifampicin 600 mg kills >99.9% of viable *M. leprae* within a few days
- This extreme bactericidal potency means that monthly supervised dosing provides complete coverage for the entire monthly period

Why once-monthly supervised dosing works:

- The 99.9% kill from one dose essentially eliminates the viable (replicating) bacillary load
- Remaining organisms are non-viable or metabolically inactive (paucibacillary leprosy) or handled by dapsone/clofazimine (multibacillary)
- Supervised monthly dosing ensures adherence to the most bactericidal component
- This is fundamentally different from TB (where daily rifampicin is needed because *M. tuberculosis* replicates faster and requires sustained levels)

WHO MDT for leprosy:

- PB leprosy (1–5 skin lesions): Rifampicin 600 mg monthly + Dapsone 100 mg daily × 6 months
- MB leprosy (>5 lesions): Rifampicin 600 mg monthly + Dapsone 100 mg daily + Clofazimine 300 mg monthly + 50 mg daily × 12 months

Answer: (D) Go Back to Q17

Q18.

Solution

Topic: Dapsone – DHPS Inhibition Shared with Sulfonamides

Dapsone (diaminodiphenylsulfone, DDS) mechanism:

- Inhibits **dihydropteroate synthase (DHPS)** – the same enzyme inhibited by sulfonamides
- Mechanism: competitive antagonism of **para-aminobenzoic acid (PABA)**, preventing its incorporation into dihydropteroic acid (first step in folate synthesis)
- Blocks folate synthesis selectively in bacteria and *M. leprae* (mammalian cells cannot synthesise folate and use dietary preformed folate – same basis for sulfonamide selectivity)

Dapsone adverse effects (must know for FMGE):

- **Methaemoglobinaemia** – most important adverse effect; dapsone oxidises Hb $\rightarrow$ metHb; treat with methylene blue
- **Haemolytic anaemia** – especially severe in G6PD-deficient patients (test before starting)
- Agranulocytosis, peripheral neuropathy, hepatitis (rare)
- "Dapsone syndrome" – fever, rash, lymphadenopathy in first 6 weeks

Other uses of dapsone: PCP prophylaxis in HIV (when allergic to cotrimoxazole), dermatitis herpetiformis (skin disease associated with coeliac disease), Brown recluse spider bite (experimental).

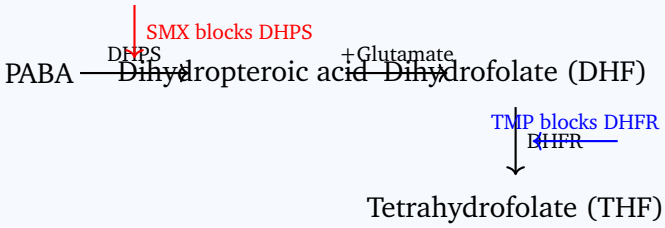
Answer: (A) Go Back to Q18

Q19.

Solution

Topic: Cotrimoxazole – Sequential Double Blockade of Folate Pathway

The two-step folate synthesis pathway and cotrimoxazole:



- **Sulfamethoxazole (SMX):** competitive PABA antagonist, inhibits DHPS (Step 1)
- **Trimethoprim (TMP):** inhibits DHFR (Step 2) – very selectively for bacterial DHFR (50,000× more potent against bacterial vs human DHFR)
- **Sequential blockade** → synergistic inhibition (combination more potent than either alone; COMBINATION provides bactericidal activity where either alone is bacteriostatic)
- Ratio TMP:SMX = 1:5 (optimal synergistic ratio)

Clinical uses of cotrimoxazole:

- **PCP prophylaxis and treatment** (first-line in HIV patients)
- UTI (uncomplicated), urinary tract prophylaxis
- *Toxoplasma gondii* prophylaxis and treatment
- Nocardiosis, Stenotrophomonas maltophilia, Listeria (alternative)

Answer: (B) Go Back to Q19

Q20.

Solution

Topic: Gentamicin Monitoring – Serum Drug Levels + Creatinine for Nephrotoxicity

Gentamicin toxicity profile:

- **Nephrotoxicity (10–20%):** proximal tubular cell damage; accumulates in tubular cells; rises in serum creatinine, BUN; usually reversible if detected early; risk factors: prolonged therapy, high trough levels, elderly, pre-existing renal impairment, concurrent nephrotoxins (NSAIDs, vancomycin, cyclosporin, contrast dye)

- **Ototoxicity (cochlear/vestibular):** accumulates in endolymph; cochlear toxicity (high-frequency hearing loss) often irreversible; vestibular toxicity (ataxia, vertigo); detected early by audiometry

Extended-interval (once-daily) dosing – rationale:

- Aminoglycosides are **concentration-dependent** bactericidal agents + have **post-antibiotic effect (PAE)**
- High peak (Cmax/MIC $\geq$ 8–10) ensures maximal kill; drug-free interval reduces tubular accumulation $\rightarrow$ less nephrotoxicity
- Trough $<$ 1 μg/mL (once-daily) predicts less nephrotoxicity

Monitoring parameters:

- **Serum drug levels:** Peak (30 min post-infusion) for efficacy; Trough (pre-dose) for toxicity
- **Serum creatinine:** baseline and every 48–72 hours; rise of $\geq$ 0.5 mg/dL warrants dose adjustment or switch
- Audiometry: for prolonged courses ($>$ 10 days) or high-risk patients

Answer: (C) Go Back to Q20

Q21.

Solution

Topic: Tigecycline – Overcoming Tetracycline Resistance Mechanisms

Two main tetracycline resistance mechanisms:

(a) **Efflux pumps (Tet-A to Tet-E):** actively pump tetracycline out of the cell before it can bind the ribosome

(b) **Ribosomal protection proteins (Tet-M, Tet-O):** GTPase enzymes that bind the ribosome and displace tetracycline from the binding site

How tigecycline overcomes both:

- Tigecycline has a **9-t-butylglycylamido substituent** at position 9 of the D ring (a "glycylcycline")
- This bulky substituent creates **steric hindrance** that prevents efflux pumps from recognising and expelling tigecycline

- The same modification provides high affinity binding to the ribosome that overcomes ribosomal protection protein-mediated displacement (5-fold higher affinity than minocycline)

Spectrum: MRSA, VRE, ESBL-producers, Acinetobacter, anaerobes, atypicals; **NOT** active against *Pseudomonas* (intrinsic MexXY efflux pump) or *Proteus* (intrinsic efflux + reduced permeability).

Route: IV only (poor oral bioavailability). **Side effects:** nausea/vomiting (most common), hepatotoxicity, increased mortality in HAP/VAP (use with caution).

Answer: (D) Go Back to Q21

Q22.

Solution

Topic: Pyrazinamide – Hyperuricaemia as Most Common Adverse Effect

Pyrazinamide (PZA) pharmacology:

- Prodrug: converted to **pyrazinoic acid** by *M. tuberculosis* pyrazinamidase (pncA gene product)
- Active mechanism: pyrazinoic acid acidifies the intracellular environment + disrupts membrane transport/energetics; active against slowly replicating/dormant bacilli in the **acidic environment of macrophage phagolysosomes**
- **Sterilising activity:** essential for shortening TB treatment to 6 months (kills "persister" organisms)

Hyperuricaemia mechanism:

- Pyrazinoic acid **inhibits URAT1** (uric acid reabsorption transporter 1) in the proximal renal tubule – *paradoxically this reduces uric acid secretion* (competes with the secretory pathway), net effect is hyperuricaemia
- Actually inhibits the tubular secretion of urate, causing uric acid to accumulate
- Incidence: nearly universal (>80%) in patients on standard doses
- Clinically significant gout in 5–10%; asymptomatic hyperuricaemia in majority
- Management: allopurinol or NSAIDs for acute gout if needed; do NOT stop PZA unless severe

Other PZA adverse effects: Hepatotoxicity (most serious – monitor LFTs), arthralgia (joint pain without gout), fever, rash, photosensitivity.

Answer: (A) Go Back to Q22

Q23.

Solution

Topic: Caspofungin – Echinocandin Mechanism (β-1,3-D-glucan Synthase Inhibition)

Echinocandin mechanism:

- Inhibit **β-(1,3)-D-glucan synthase** – the enzyme responsible for synthesising β-glucan, the main structural polymer of the fungal cell wall
- β-glucan is **absent in mammalian cells** – accounts for excellent selective toxicity and low systemic toxicity
- Disruption of β-glucan synthesis $\rightarrow$ weakened cell wall $\rightarrow$ osmotic lysis of the fungal cell

Spectrum of caspofungin:

- **Candida species** (including fluconazole-resistant *C. krusei*, *C. glabrata*) – fungicidal
- **Aspergillus species** – fungistatic
- **NOT active** against *Cryptococcus neoformans* (has little β-glucan in its cell wall, which is mostly glucuronoxylomannan)
- NOT active against Fusarium, Zygomycetes (*Mucor*)

Echinocandins: Caspofungin, Micafungin, Anidulafungin – all IV only, well tolerated.

Comparison of antifungal targets:

- Amphotericin B: binds ergosterol (cell membrane)
- Azoles: inhibit lanosterol 14-α-demethylase (ergosterol synthesis)
- **Echinocandins: inhibit β-glucan synthase (cell wall)**
- Flucytosine: inhibits DNA/RNA synthesis

Answer: (B) Go Back to Q23

Q24.

Solution

Topic: Ribavirin + Pegylated Interferon for Hepatitis C in Resource-Limited Settings

Ribavirin pharmacology:

- Guanosine nucleoside analogue; **mechanism:** inhibits inosine 5′-monophosphate dehydrogenase (IMPDH) $\rightarrow$ depletes guanosine nucleotides; also acts as RNA mutagen (lethal mutagenesis of viral RNA)
- **Highly teratogenic (Category X):** contraception required during therapy AND for 6 months after (both male and female patients)
- Causes haemolytic anaemia – reduces ribavirin dose if Hb falls

HCV treatment evolution:

- Old standard: **Pegylated IFN-α + ribavirin** – genotype 1: 48 weeks (SVR 40–50%); genotype 2/3: 24 weeks (SVR 70–80%)
- Now largely replaced by **DAAs** (direct-acting antivirals: sofosbuvir, ledipasvir, daclatasvir, glecaprevir/pibrentasvir) – pan-genotypic, 8–12 weeks, SVR $>$ 95%, minimal side effects
- **Resource-limited settings:** Peg-IFN + ribavirin remains relevant where DAAs are unavailable or unaffordable

Ribavirin monotherapy is NOT effective for HCV (no meaningful antiviral activity as monotherapy for HCV).

Answer: (C) Go Back to Q24

Q25.

Solution

Topic: Artemisinin – Heme-Activated Endoperoxide Mechanism and Selective Toxicity

Artemisinin mechanism of selective toxicity:

(a) Malaria parasites digest haemoglobin in the food vacuole, releasing large amounts of **free heme (Fe^{2+})**

(b) The **endoperoxide bridge (-O-O-)** of artemisinin reacts with free heme iron

in a Fenton-type reaction

(c) This generates highly reactive **carbon-centred free radicals** and reactive oxygen species (ROS)

(d) Free radicals alkylate and damage parasite proteins (TCTP – translationally controlled tumour protein, PfATP6, etc.) and membranes → **parasite death**

(e) Uninfected RBCs contain haemoglobin bound to globin with haem iron in Fe^{3+} state (methaemoglobin) and minimal free Fe^{2+} → artemisinin is NOT activated → host cells spared

Clinical features of artemisinin:

- Fastest-acting antimalarial – rapid fever clearance (24–48 hours)
- Active against all stages of asexual parasite (including ring stage) and reduces gametocyte carriage
- Always used in combination (ACT) to prevent resistance: artemether-lumefantrine (Coartem), artesunate-amodiaquine, DHA-piperaquine
- Artesunate IV = first-line for severe malaria (replaces quinine)
- Well tolerated; QTc prolongation with piperaquine partner drug

Answer: (D) Go Back to Q25

Q26.

Solution

Topic: Ivermectin – GluCl Channel and GABA-A Potentiation Causing Flaccid Paralysis

Ivermectin mechanism:

- Potentiates **glutamate-gated chloride ion channels (GluCl)** – receptors found exclusively in invertebrates (helminths, arthropods); absent in mammals
- Also potentiates **GABA-A receptors** in nematodes – increases Cl^- conductance → hyperpolarisation
- Both actions cause **irreversible flaccid paralysis and death of the parasite**

Why ivermectin is safe in humans:

- GluCl channels do not exist in mammals (mammalian GABA-A receptors are less sensitive to ivermectin)
- Ivermectin does **not cross the human BBB** (substrate of P-gp at BBB – efluxed out)
- Exception: Loa loa (loiasis) – microfilaraemia $>$ 30,000/mL – risk of fatal encephalopathy (ivermectin kills microfilariae rapidly in CNS)

Clinical uses of ivermectin:

- *Onchocerca volvulus* (river blindness) – annual mass treatment
- Lymphatic filariasis – combination with albendazole
- Strongyloidiasis (drug of choice)
- Scabies (first-line for crusted/Norwegian scabies; alternative for ordinary scabies)
- Pediculosis (head lice)

Answer: (A) Go Back to Q26

Q27.

Solution

Topic: Digoxin Toxicity – Hypokalemia Most Potentiates Toxicity

Why hypokalemia worsens digoxin toxicity:

- Digoxin inhibits Na^+/K^+-ATPase by binding to the **K^+ binding site** on the extracellular domain of the α-subunit
- Potassium and digoxin **compete** for the same binding site – K^+ normally displaces digoxin
- **Low serum K^+** (hypokalemia) $\rightarrow$ *less competition* from K^+ $\rightarrow$ digoxin binds more avidly to the pump $\rightarrow$ greater ATPase inhibition at the *same plasma digoxin level* $\rightarrow$ **toxicity at therapeutic or even subtherapeutic concentrations**

Early afterdepolarisations (EADs) in digoxin toxicity:

- Intracellular Ca^{2+} overload (from Na^+/K^+-ATPase inhibition) $\rightarrow$ oscillatory afterpotentials during phase 2–3 of action potential

- EADs can trigger **torsade de pointes**, ventricular tachycardia, ventricular fibrillation

Electrolytes in digoxin toxicity management:

- **Correct hypokalemia** (K^+ supplementation reduces digoxin binding)
- **Correct hypomagnesaemia** (Mg^{2+} deficiency facilitates K^+ loss and worsens toxicity)
- Hypercalcaemia worsens toxicity (increased intracellular Ca^{2+})
- Definitive treatment for severe toxicity: **Digoxin-specific Fab antibody fragments (Digibind/DigiFab)**

Causes of hypokalemia that worsen digoxin toxicity: Thiazides, loop diuretics (very common co-prescribing), vomiting, diarrhoea, hyperaldosteronism.

Answer: (B) Go Back to Q27

Q28.

Solution

Topic: Adenosine – A1 Receptor Mechanism Terminates PSVT

Adenosine pharmacology:

- Endogenous purine nucleoside; acts on **A1 adenosine receptors** (Gi-coupled) in the AV node
- A1 receptor activation $\rightarrow$ Gi $\rightarrow$ $\downarrow$cAMP; also directly activates IKAdo (adenosine-sensitive K^+ current, IK,Ach) $\rightarrow$ **increased K^+ conductance** $\rightarrow$ hyperpolarisation of AV nodal cells $\rightarrow$ **slowing/blockade of AV nodal conduction**
- Half-life: $<$**10 seconds** – inactivated by cellular uptake (equilibrative nucleoside transporters) and adenosine deaminase in RBCs and endothelium
- Given as rapid IV bolus (6 mg then 12 mg) followed immediately by rapid saline flush (central vein preferable)

Mechanism of PSVT termination:

- Most PSVTs involve a re-entry circuit incorporating the AV node
- Adenosine-induced transient AV block $\rightarrow$ breaks the re-entry circuit $\rightarrow$ sinus rhythm restored

- Also useful diagnostically (reveals underlying flutter waves, dissociation in VT)

Contraindications: Asthma (bronchospasm via A2B receptors), second/third-degree AV block, sick sinus syndrome without pacemaker, Wolff-Parkinson-White syndrome with pre-excitation (use procainamide/cardioversion instead).

Side effects: Transient flushing, chest tightness, dyspnoea, headache – all very brief (<30 seconds) due to ultra-short half-life.

Answer: (C) Go Back to Q28

Q29.

Solution

Topic: Mannitol – Osmotic Diuretic for Raised Intracranial Pressure

Mannitol mechanism:

- **Osmotic diuretic:** freely filtered at the glomerulus, **NOT reabsorbed** by the tubule → retains water in the tubular lumen by osmosis → osmotic diuresis
- **Effect on brain (ICP reduction):** creates osmotic gradient between plasma and brain parenchyma; draws water from brain tissue across the intact BBB into the vascular compartment → reduces cerebral oedema and ICP
- Effect begins within 15–30 minutes; duration 2–6 hours
- Dose: 0.25–1 g/kg IV over 15–20 minutes as 20% solution

Indications for mannitol:

- **Raised ICP** (cerebral oedema, traumatic brain injury, stroke, hepatic encephalopathy with cerebral oedema)
- Acute angle-closure glaucoma (reduces IOP by drawing water from vitreous)
- Acute oliguric renal failure (maintains tubular flow, prevents cast formation)
- Forced diuresis in poisoning (increases urine flow)

Contraindications: Anuria (no effect if not filtered), pulmonary oedema (initial volume expansion can worsen), intracranial bleeding (controversially).

Important: Mannitol requires an *intact* BBB to create the osmotic gradient between plasma and brain. If the BBB is severely disrupted (e.g., contusion), mannitol may leak into brain tissue and **worsen** oedema ("rebound effect"). Hypertonic saline (3%) is an alternative, especially in patients with renal impairment.

Answer: (D) Go Back to Q29

Q30.

Solution

Topic: Fenofibrate (Fibrate) – PPAR-α Activation Lowers Triglycerides

Mechanism of fibrates:

- Fibrates (fenofibrate, gemfibrozil, bezafibrate) are **PPAR-α agonists**
- PPAR-α (peroxisome proliferator-activated receptor alpha) activation in hepatocytes and skeletal muscle:
  (a) **Upregulates lipoprotein lipase (LPL) gene** $\rightarrow$ increased LPL activity $\rightarrow$ enhanced hydrolysis of VLDL and chylomicron triglycerides $\rightarrow$ rapid clearance of plasma TG
  (b) **Reduces apoC-III** (inhibitor of LPL) $\rightarrow$ further increases LPL activity
  (c) **Increases apoA-I and apoA-II** synthesis $\rightarrow$ raises HDL
  (d) **Reduces VLDL synthesis** by reducing fatty acid delivery to liver

Net lipid effects of fibrates:

- TG: $\downarrow$ 30–50% (most potent class for TG reduction)
- HDL: $\uparrow$ 10–20%
- LDL: variable (may increase in severe hypertriglyceridaemia as VLDL converts to LDL)

Adverse effects:

- **Myopathy/rhabdomyolysis** – especially with statin combination (gemfibrozil inhibits statin glucuronidation via UGT1A3 $\rightarrow$ higher statin levels; fenofibrate safer with statins)
- **Cholelithiasis** (gallstones) – increases biliary cholesterol secretion
- GI symptoms, hepatotoxicity (rare)

Answer: (A) Go Back to Q30

Q31.

Solution

Topic: Glucocorticoids – NF-κB Inhibition as Primary Anti-inflammatory Mechanism

Glucocorticoid molecular mechanism:

(a) Glucocorticoid enters cell $\rightarrow$ binds cytoplasmic glucocorticoid receptor (GR)

(b) GR-glucocorticoid complex translocates to nucleus

(c) In nucleus: two main mechanisms of action:

- **Transactivation:** binds GRE (glucocorticoid response elements) $\rightarrow$ induces gene expression of anti-inflammatory proteins (annexin-1/lipocortin, IkBα, IL-10, GILZ)
- **Transrepression:** GR complex directly interacts with and inhibits **NF-κB** and AP-1 transcription factors $\rightarrow$ reduces pro-inflammatory gene transcription

NF-κB inhibition – the primary mechanism:

- NF-κB controls transcription of: TNF-α, IL-1, IL-2, IL-6, IL-8, COX-2, iNOS, ICAM-1, VCAM-1
- GR physically interacts with NF-κB subunit p65 $\rightarrow$ blocks its transactivation domain
- Also: GR induces IκBα (the inhibitor of NF-κB), trapping NF-κB in cytoplasm

Note on annexin-1 (lipocortin):

- Induced by glucocorticoids $\rightarrow$ inhibits phospholipase A2 $\rightarrow$ reduces arachidonic acid release $\rightarrow$ reduces ALL eicosanoids (prostaglandins AND leukotrienes)
- This is the mechanism for the clinical observation that corticosteroids inhibit both COX and LOX pathways
- However, **NF-κB inhibition** is considered the primary and most important anti-inflammatory transcriptional mechanism

Answer: (B) Go Back to Q31

Q32.

Solution

Topic: Hydroxychloroquine – Annual Ophthalmological Monitoring for Retinopathy

Hydroxychloroquine (HCQ) pharmacology:

- Mechanism: increases lysosomal pH $\rightarrow$ impairs antigen presentation (prevents loading of peptides onto MHC class II) $\rightarrow$ reduces T cell activation $\rightarrow$ reduces TNF-α, IL-1, IL-6 production
- Accumulates in **melanin-containing tissues**: retinal pigment epithelium, skin, liver
- Uses: SLE (reduces flares, prevents organ damage, reduces mortality), RA (DMARD), malaria prophylaxis/treatment, antiphospholipid syndrome

HCQ retinopathy (critical adverse effect):

- **Bull's-eye maculopathy** – ring of parafoveal RPE damage surrounding fovea on OCT/visual field testing
- Incidence: $<$1% in first 5 years; rises to $\geq$20% after 20 years at $>$5 mg/kg/day
- **Irreversible** – drug must be stopped at earliest sign of damage; retinopathy may continue to progress even after stopping
- Detected early by: 10-2 visual field testing (Humphrey), spectral-domain OCT (SDOCT), multifocal electroretinography
- **Risk factors:** daily dose $>$ 5 mg/kg/day actual body weight, cumulative dose $>$ 1000 g, therapy $>$ 5 years, pre-existing maculopathy, renal impairment, tamoxifen co-use

Monitoring: Baseline ophthalmological exam, then **annual** review after 5 years (or earlier if risk factors). ACR recommends $\leq$ 5 mg/kg/day to minimise retinopathy risk.

Answer: (C) Go Back to Q32

Q33.

Solution

Topic: Probenecid – Blocks Tubular Secretion of Penicillins (OAT Inhibition)

Probenecid pharmacology:

- **Primary mechanism for hyperuricaemia:** inhibits URAT1 in the S1 segment of proximal tubule → reduces uric acid reabsorption → increases urinary uric acid excretion (uricosuric)
- **Drug interaction with penicillins:** probenecid also inhibits **OAT (organic anion transporter) 1 and OAT3** in the proximal tubule – the same transporters responsible for secretion of penicillins, cephalosporins, NSAIDs, methotrexate into the tubular lumen

Clinical significance of penicillin interaction:

- Probenecid blocks tubular secretion of penicillin → prolongs plasma $t_{1/2}$ of penicillin → higher sustained blood levels
- Historically used (1950s) when penicillin was scarce and expensive – probenecid extended its duration of action
- Still used today: probenecid + benzylpenicillin for single-dose gonorrhoea treatment; probenecid + cidofovir to reduce nephrotoxicity (also blocks tubular accumulation of cidofovir)
- Also used to reduce methotrexate renal excretion (though this increases methotrexate toxicity – caution)

Important adverse effects of probenecid itself:

- Uric acid nephrolithiasis (increases urinary uric acid) – maintain hydration, alkalinize urine
- Do NOT start during acute gout attack (mobilises urate crystals, worsening acute attack)
- GI intolerance, hypersensitivity rash

Answer: (D) Go Back to Q33

Q34.

Solution

Topic: Sulfonylurea vs GLP-1 Receptor Agonist – Mechanism Contrast and Hypoglycaemia Risk

Sulfonylurea (glipizide, glibenclamide, glimepiride) mechanism:

- Bind to the **SUR1 subunit** of the K-ATP channel complex in pancreatic β-cells
- Close K-ATP channels **DIRECTLY and INDEPENDENTLY of glucose concentration**
- Cell depolarises $\rightarrow$ voltage-gated Ca^{2+} channels open $\rightarrow$ Ca^{2+} influx $\rightarrow$ insulin exocytosis
- **Result:** Insulin is released even when blood glucose is low $\rightarrow$ **risk of hypoglycaemia**, especially with fasting, missed meals, or alcohol

GLP-1 receptor agonist (liraglutide, exenatide, semaglutide) mechanism:

- Bind GLP-1R on β-cells $\rightarrow$ Gs $\rightarrow$ adenylyl cyclase $\rightarrow$ $\uparrow$cAMP $\rightarrow$ PKA activation
- PKA phosphorylates K-ATP channel and other targets $\rightarrow$ enhanced insulin secretion
- **But:** this effect is **glucose-dependent** – only amplifies insulin secretion when glucose is elevated; when glucose normalises, GLP-1R stimulation no longer causes significant K-ATP closure $\rightarrow$ **minimal hypoglycaemia risk**
- Additional benefits: reduce glucagon, slow gastric emptying, promote satiety and weight loss

Key distinction for FMGE: "Glucose-dependent" insulin secretion (GLP-1 RAs, DPP-4 inhibitors) vs "glucose-independent" closure of K-ATP (sulfonylureas $\rightarrow$ hypoglycaemia risk).

Answer: (A) Go Back to Q34

Q35.

Solution

Topic: Sitagliptin – DPP-4 Inhibition Prolongs Incretin Action

Incretin system:

- Incretins (GLP-1 and GIP) are gut hormones secreted after meals by L-cells

(GLP-1) and K-cells (GIP)

- GLP-1 $t_{1/2}$ only $\sim$**2 minutes** – rapidly inactivated by **DPP-4 (dipeptidyl peptidase-4)** cleaving 2 N-terminal amino acids

Sitagliptin mechanism:

- Selectively inhibits **DPP-4 enzyme**
- Prevents cleavage/inactivation of GLP-1 and GIP
- Endogenous GLP-1 and GIP concentrations are maintained (2–3 fold increase after meals)
- Prolonged incretin action $\rightarrow$ **glucose-dependent** insulin secretion $\uparrow$ and glucagon secretion $\downarrow$

Clinical profile of DPP-4 inhibitors (gliptins):

- Sitagliptin, saxagliptin, vildagliptin, alogliptin, linagliptin
- HbA1c reduction: 0.5–1.0% (modest)
- **Weight neutral** (unlike sulfonylureas which cause weight gain)
- **Very low hypoglycaemia risk** (glucose-dependent)
- Well tolerated; sitagliptin can be used in CKD (dose adjust); linagliptin – no dose adjustment in renal impairment
- Adverse effects: nasopharyngitis, pancreatitis (rare), joint pain (arthralgia); saxagliptin/alogliptin – possible heart failure risk (observe in HF patients)

Answer: (B) Go Back to Q35

Q36.

Solution

Topic: Flutamide Monotherapy – Paradoxical Elevation of Serum Testosterone

Flutamide pharmacology:

- Non-steroidal, competitive antagonist at the **androgen receptor (AR)**
- Blocks testosterone and DHT from binding and activating AR in prostate cells

and other tissues

- Does NOT reduce testosterone production (no direct effect on the HPG axis when given alone)

Paradoxical testosterone elevation (the key concept):

(a) Normal feedback: Testosterone binds AR in hypothalamus and pituitary → negative feedback → reduces GnRH, LH, FSH

(b) With flutamide: AR is BLOCKED → testosterone *cannot* signal negative feedback at hypothalamic-pituitary level → **GnRH and LH increase** → testes stimulated to produce **MORE testosterone**

(c) Serum testosterone rises ABOVE normal levels – paradoxically elevated despite antiandrogen therapy

(d) However: even though testosterone is elevated, it cannot act at the prostate AR (which is blocked) → antiandrogen effect maintained

Combined androgen blockade: Flutamide is usually combined with an LHRH agonist (leuprolide/goserelin) to prevent the testosterone surge:

- LHRH agonist (paradoxical effect after 2–3 weeks): downregulates GnRH receptors → reduces LH → reduces testosterone to castrate levels
- Flutamide blocks any residual androgen activity + prevents the initial testosterone flare

Adverse effects of flutamide: Gynaecomastia, hepatotoxicity (LFT monitoring), diarrhoea, hot flushes.

Answer: (C) Go Back to Q36

Q37.

Solution

Topic: Ondansetron – Most Effective for Acute Phase CINV (Within 24 Hours)

Phases of chemotherapy-induced nausea and vomiting (CINV):

Phase	Timing	Mediators & Best Drugs
Acute	0–24 h post-chemo	5-HT3: ondansetron, granisetron
Delayed	24–120 h post-chemo	Substance P/NK1: aprepitant + DEX
Anticipatory	Before chemo	Conditioned reflex: benzodiazepines
Breakthrough	During prophylaxis	Rescue: prochlorperazine, droperidol

Why ondansetron is most effective for ACUTE CINV:

- Chemotherapy (especially cisplatin) damages intestinal enterochromaffin cells → massive release of **serotonin (5-HT)** into the gut
- 5-HT stimulates **vagal afferent 5-HT3 receptors** → signals to CTZ and NTS → nausea/vomiting
- **Also activates 5-HT3 receptors in the CTZ** directly
- Ondansetron blocks BOTH peripheral (vagal) AND central (CTZ) 5-HT3 receptors → highly effective for acute phase

Delayed CINV: 5-HT returns to baseline; substance P/NK1 pathway predominates. Ondansetron alone is **less effective** for delayed CINV. Standard triple therapy for highly emetogenic chemo: **NK1 antagonist (aprepitant) + 5-HT3 antagonist (ondansetron) + dexamethasone**.

Ondansetron adverse effects: Headache, constipation, QTc prolongation (dose-dependent – avoid IV $>$ 32 mg single dose), liver enzyme elevation.

Answer: (D) Go Back to Q37

Q38.

Solution

Topic: Ipratropium – Quaternary Structure Prevents Systemic Absorption and Tachycardia

Structural basis for ipratropium's safety:

- Atropine: **tertiary amine** → uncharged at physiological pH → crosses biological membranes → reaches heart, CNS, bladder, eye
- Ipratropium: **quaternary ammonium compound** → permanently positively charged → **poorly absorbed** from mucous membranes of the airways ($<$1% systemic bioavailability after inhalation)
- Low systemic concentrations → negligible blockade of cardiac M2 receptors

→ **no tachycardia**

Pharmacological profile of ipratropium:

- Blocks **muscarinic M3 receptors** in bronchial smooth muscle → bronchodilation (by preventing ACh-mediated bronchoconstriction)
- Also blocks M3 in mucous glands → reduced secretions (useful in COPD)
- Does NOT cross BBB (quaternary structure) → no CNS effects, no dry mouth/urinary retention at standard inhaled doses

Clinical use:

- **COPD:** first-line bronchodilator (LAMA tiotropium preferred for maintenance); ipratropium for acute exacerbations
- **Asthma:** not first-line (salbutamol preferred) but used in acute severe asthma in combination with β_2-agonists
- Rhinorrhoea: ipratropium nasal spray for non-allergic rhinitis

Answer: (A) Go Back to Q38

Q39.

Solution

Topic: Montelukast – CysLT1 Receptor Antagonism in Asthma

Leukotriene synthesis and action:

- Arachidonic acid (from phospholipid via PLA2) $\xrightarrow{\text{5-LOX + 5-LOXAP}}$ LTA4
- LTA4 $\xrightarrow{\text{LTC4 synthase}}$ LTC4 → LTD4 → LTE4 (cysteinyl leukotrienes)
- LTC4, LTD4, LTE4 act on **CysLT1 receptors** (Gq-coupled) on bronchial smooth muscle and mucosa
- Effects: bronchoconstriction (1000× more potent than histamine), mucus hypersecretion, mucosal oedema, eosinophil recruitment

Montelukast mechanism:

- Competitive antagonist at **CysLT1 receptors** – blocks LTC4, LTD4, LTE4
- Reduces bronchoconstriction, mucus secretion, airway oedema, and eosinophilic inflammation

Clinical uses:

- Mild persistent asthma (add-on to ICS, or ICS-sparing)
- **Exercise-induced bronchospasm** (dose 2 hours before exercise)
- **Aspirin-exacerbated respiratory disease** (NSAID-induced asthma) – leukotrienes are key mediators; montelukast is particularly effective
- **Allergic rhinitis** – improves nasal symptoms (approved for this indication)
- Co-existing asthma + allergic rhinitis (one drug, two conditions)

Adverse effects: Generally well tolerated; neuropsychiatric effects (depression, suicidal ideation – FDA black box warning 2020; inform patients); headache.

Zileuton: Inhibits 5-LOX (step upstream) – less used (hepatotoxic, requires LFT monitoring, many drug interactions).

Answer: (B) Go Back to Q39

Q40.

Solution

Topic: Warfarin Drug Interactions – Amiodarone Increases Bleeding Risk via CYP Inhibition

Warfarin pharmacology:

- Vitamin K antagonist – inhibits VKORC1 (vitamin K epoxide reductase) $\rightarrow$ reduces γ-carboxylation of factors II, VII, IX, X and protein C/S
- **S-warfarin** (more potent enantiomer) metabolised by **CYP2C9**; R-warfarin by CYP3A4 and CYP1A2
- Narrow therapeutic index – small changes in CYP activity cause large INR changes

Amiodarone (CYP inhibitor) + warfarin interaction:

- Amiodarone and its active metabolite (desethylamiodarone) are potent **inhibitors of CYP2C9 and CYP3A4**
- Inhibition of CYP2C9 $\rightarrow$ reduced S-warfarin metabolism $\rightarrow$ **markedly elevated warfarin plasma levels** $\rightarrow$ $\uparrow$INR $\rightarrow$ bleeding risk
- Effect is pronounced and prolonged (amiodarone's $t_{1/2}$ = 40–55 days; tissue accumulation persists for months)

- When amiodarone is started in a warfarin patient: **reduce warfarin dose by 30–50%** and monitor INR closely for 4–8 weeks

CYP INDUCERS that REDUCE warfarin effect (increase warfarin dose needed):

- Rifampicin (most potent), phenobarbitone, carbamazepine, phenytoin, St. John's Wort

CYP INHIBITORS that INCREASE warfarin effect (↑INR, ↑bleeding risk):

- **Amiodarone** (CYP2C9 + CYP3A4), fluconazole (CYP2C9), metronidazole (CYP2C9), omeprazole (CYP2C19/2C9), erythromycin/clarithromycin (CYP3A4), isoniazid

Answer: (C) Go Back to Q40

Answer Key – FMGE Pharmacology Sample Paper 4

1	D	2	A	3	B	4	C	5	D
6	A	7	B	8	C	9	D	10	A
11	B	12	C	13	D	14	A	15	B
16	C	17	D	18	A	19	B	20	C
21	D	22	A	23	B	24	C	25	D
26	A	27	B	28	C	29	D	30	A
31	B	32	C	33	D	34	A	35	B
36	C	37	D	38	A	39	B	40	C