Pharmacology

MBBS Recap: high-yield notes for revision

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Fast revision notes for MEC's MD/MS entrance, arranged by topic so that a wrong answer leads to the facts behind it.

Pharmacokinetics and drug handling

Kinetics of elimination

- **First-order**: a constant *fraction* is eliminated per unit time; half-life is constant. This is the usual pattern.
- **Zero-order (saturation)**: a constant *amount* per unit time; half-life lengthens as the dose rises. A small dose increase gives a disproportionate rise in level.
- Drugs that saturate within the therapeutic range: **phenytoin** (the classic), **alcohol**, **aspirin at high dose**, theophylline, warfarin (at high levels), and tolbutamide.
- Phenytoin shows **Michaelis–Menten kinetics**: first-order at low dose, zero-order near the therapeutic range.
- Lithium, gentamicin, amoxicillin and most drugs are first-order.

Key formulae

Quantity	Formula	Controls
Volume of distribution (Vd)	dose ÷ plasma concentration	**loading dose** = target concentration × Vd (÷ F if oral)
Clearance (CL)	rate of elimination ÷ concentration	**maintenance dose rate** = CL × target concentration (÷ F)
Half-life	0.693 × Vd ÷ CL	time to steady state, dosing interval
Bioavailability (F)	AUC oral ÷ AUC IV	100% by definition for IV

- Half-life depends on both Vd and CL; changing either changes it. Clearance and Vd are the independent variables.
- **Steady state** is reached in **4–5 half-lives**, whatever the dose (94% at 4, 97% at 5). Changing the dose changes the level at steady state, not the time taken. A loading dose shortens the wait.
- For a constant infusion, steady-state concentration = infusion rate ÷ clearance: doubling the rate doubles the level, reached in the same 4–5 half-lives. A loading dose brings the level up early but does not change the final value, which rests on the maintenance rate.
- Time to eliminate a drug after stopping is also 4–5 half-lives.
- Large Vd (more than about 40 L, body water 42 L): extensively tissue bound (amiodarone, digoxin, chloroquine). Small Vd (about 5 L): highly plasma-protein bound or too large or polar to leave plasma (heparin, warfarin).
- A drug with a very large Vd is not removed by dialysis or forced diuresis.

Absorption and first-pass metabolism

- **First-pass effect**: metabolism in gut wall and liver before the drug reaches the systemic circulation, lowering oral bioavailability. High first-pass drugs: **glyceryl trinitrate**, lidocaine, propranolol, morphine, verapamil, isosorbide dinitrate (less so), testosterone, salbutamol.
- Routes that avoid it: **sublingual, buccal, rectal (lower two-thirds partially), transdermal, inhalational, parenteral**. Sublingual venous drainage goes to the superior vena cava.
- GTN is active as given, not a prodrug; it is given sublingually for speed and to avoid first pass.
- Bioavailability depends on formulation, gut pH, transporters (P-glycoprotein efflux), and first pass.
- **Passive (lipid) diffusion**, the way most drugs cross membranes, depends on the concentration gradient, lipid solubility, degree of ionisation, molecular size and surface area; it needs no carrier or energy and is not saturable, so the number of transporters does not affect it (carrier-mediated transport is saturable and can be competed for).
- **Prodrugs** (need activation): clopidogrel, enalapril (and most ACE inhibitors except captopril and lisinopril), levodopa, dabigatran etexilate, cyclophosphamide, azathioprine (to 6-mercaptopurine), prasugrel, oseltamivir, valaciclovir, codeine (to morphine by CYP2D6), tamoxifen (to endoxifen), proguanil, losartan (partially).

Distribution and protein binding

- Acidic drugs bind **albumin**; basic drugs bind **α_1-acid glycoprotein**.
- Highly bound drug: **small Vd**, long action (a reservoir), little filtered or dialysed. Only free drug crosses to tissues and CSF and is active.
- Displacement interactions raise free drug transiently (warfarin with sulphonamides or phenylbutazone), but usually the effect is short-lived because clearance rises too; **clinically important enzyme-based interactions are far more common** than displacement.
- Barriers: blood–brain barrier restricts polar, ionised drugs; P-glycoprotein pumps substrates out.

Metabolism

- **Phase I** (oxidation, reduction, hydrolysis): mainly CYP450 in the liver; products may be active. **Phase II** (conjugation: glucuronidation, sulphation, acetylation, glutathione): makes polar, usually inactive products.
- **Enzyme inducers** (lower levels of co-drugs, shorter duration): **rifampicin, phenytoin, carbamazepine, phenobarbitone, griseofulvin, chronic alcohol, smoking** (CYP1A2), St John's wort. Mnemonic: "Rifampicin Phenytoin Carbamazepine Phenobarbitone Griseofulvin".
- **Enzyme inhibitors** (raise levels): **cimetidine, erythromycin and clarithromycin, ketoconazole and azoles, ritonavir, ciprofloxacin, grapefruit juice (gut CYP3A4), omeprazole (CYP2C19), sodium valproate, isoniazid, acute alcohol**,

amiodarone. With warfarin, an inhibitor (a macrolide such as clarithromycin, an azole, ciprofloxacin, amiodarone) raises the INR; an inducer (rifampicin, phenobarbitone, carbamazepine, St John's wort) lowers it.

- Rifampicin starting in a patient on warfarin: **INR falls** through CYP2C9/3A4 induction; the warfarin dose must be raised. Stopping an inducer later raises levels again.
- **Pharmacogenetics**: slow acetylators (isoniazid neuropathy, hydralazine and procainamide lupus); CYP2D6 ultrarapid metabolisers (codeine toxicity); CYP2C19 poor metabolisers (reduced clopidogrel activation); G6PD deficiency (primaquine, dapsone, rasburicase haemolysis); **HLA-B*5701** (abacavir hypersensitivity), **HLA-B*1502** (carbamazepine SJS/TEN, mainly in Han Chinese and South-East Asian ancestry, also reported in South Asians; screening advised before starting in those groups), **HLA-B*5801** (allopurinol hypersensitivity), TPMT (azathioprine), DPD deficiency (5-FU toxicity), pseudocholinesterase deficiency (suxamethonium apnoea).

Excretion and ion trapping

- Renal excretion = filtration + secretion − reabsorption. Weak acids are ionised in alkaline urine and so trapped; weak bases in acid urine.
- **Alkalinise urine (sodium bicarbonate)** for **salicylate, phenobarbitone, methotrexate** poisoning. High-dose methotrexate is given with hydration and urine alkalinised to pH above 7 so that the weak acid (and its 7-hydroxy metabolite) stays ionised and soluble, preventing crystal nephropathy; folinic acid (leucovorin) rescue follows. **Acidify** (rarely) for amphetamine, quinidine, pethidine.
- Only the unionised form diffuses back across the tubule; ionised drug is trapped in the lumen.
- Haemodialysis helps for small, poorly bound drugs with a small Vd: lithium, salicylates, methanol and ethylene glycol, metformin-associated lactic acidosis, theophylline, phenobarbitone, valproate in severe poisoning (mnemonic: I STUMBLED). Not for digoxin, tricyclics, organophosphates or paracetamol (large Vd or highly bound).
- Enterohepatic circulation prolongs the action of drugs excreted in bile; cholestyramine interrupts it.

Therapeutic drug monitoring and dose adjustment

- Monitor drugs with a narrow therapeutic index and variable kinetics: digoxin, lithium, phenytoin, aminoglycosides, vancomycin (trough or AUC-guided), theophylline, ciclosporin and tacrolimus.
- Renal impairment: reduce dose of renally excreted drugs (aminoglycosides, digoxin, lithium, metformin, dabigatran, enoxaparin).
- Therapeutic index = LD50 ÷ ED50 (animals); safety is better judged by the margin between effective and toxic concentrations in people.

Receptors and dose–response basics

- **G-protein-coupled receptors**: **Gs** (adenylyl cyclase ↑, cAMP ↑): β_1, β_2, β_3, D_1, H_2, V_2; **Gi** (cAMP ↓): α_2, M_2, D_2, opioid receptors; **Gq** (phospholipase C, IP_3 and DAG, Ca^{2+} ↑): α_1, M_1, M_3, H_1, V_1. Ligand-gated channels: nicotinic, GABA-A, 5-HT_3, NMDA; enzyme-linked: insulin, growth factors; intracellular (nuclear) receptors: steroids, thyroid hormone, vitamin D, retinoids.
- **Potency** (position on the dose axis, EC50) differs from **efficacy** (maximum effect). Efficacy matters more clinically: high-ceiling loop diuretics against low-ceiling thiazides.
- **Competitive antagonist**: parallel rightward shift, surmountable, maximum unchanged. **Non-competitive/irreversible**: lowers the maximum (phenoxybenzamine).
- **Partial agonist**: lower maximum than a full agonist; can act as an antagonist in the presence of a full agonist (pindolol, buprenorphine).
- Types of antagonism: **chemical** (protamine and heparin; chelators), **physiological** (adrenaline and histamine on bronchi), **pharmacokinetic** (inducers), **competitive** (naloxone and morphine), **non-competitive**.
- Tachyphylaxis (acute tolerance: ephedrine, nitrates) differs from tolerance and from drug resistance.

Drug development

- Phase I: healthy volunteers, safety and pharmacokinetics (patients in oncology). Phase II: small number of patients, dose and efficacy. Phase III: large controlled trials. Phase IV: post-marketing surveillance, which detects rare adverse effects.

Adverse drug reactions, dependence and rational prescribing (curriculum)

- **Type A (augmented)**: dose-related, predictable, the commonest (bleeding on warfarin, hypoglycaemia on insulin, bradycardia on a β-blocker); **type B (bizarre)**: unpredictable, not dose-related, **immunological (allergy) or idiosyncratic** (penicillin anaphylaxis, halothane hepatitis, Stevens-Johnson syndrome); type C chronic (adrenal suppression by steroids); type D delayed (teratogenesis, carcinogenesis); type E end-of-use (withdrawal rebound with clonidine or β-blockers).
- **Allergy** needs previous sensitisation and an immune mechanism (Gell and Coombs type I penicillin anaphylaxis; type II methyldopa haemolysis; type III serum sickness with antivenom, drug-induced lupus; type IV contact dermatitis); **idiosyncrasy** is a genetically determined abnormal response with no immune basis (primaquine haemolysis in G6PD deficiency, suxamethonium apnoea). **Overdose** or toxicity is an exaggerated dose effect; **iatrogenic disease** is disease caused by treatment (NSAID or steroid ulcers, Cushing syndrome from steroids, antipsychotic parkinsonism, aminoglycoside deafness).
- **Pharmacogenetic reactions named in the curriculum**:

Drug	Genetic basis	Reaction
Primaquine, furazolidone, dapsone, nitrofurantoin	**G6PD deficiency** (X-linked)	haemolysis (Heinz bodies, bite cells)
Suxamethonium	atypical or deficient plasma (pseudo)cholinesterase (low **dibucaine number**)	prolonged apnoea
Barbiturates, sulphonamides, oestrogens, griseofulvin, phenytoin	**acute intermittent porphyria** (induce ALA synthase)	acute attack
Nitrates, nitrites, sulphonamides, dapsone, local anaesthetic prilocaine	NADH methaemoglobin reductase deficiency (or G6PD)	methaemoglobinaemia
Corticosteroids (local or systemic)	steroid responders (first-degree relatives of open-angle glaucoma)	raised intraocular pressure

Drug	Genetic basis	Reaction
Diphenylhydantoin (phenytoin)	slow hydroxylation (CYP2C9 variants); HLA-B*1502	toxicity at usual doses; SJS
Isoniazid, hydralazine, procainamide	slow acetylators (NAT2)	neuropathy, drug-induced lupus
Volatile anaesthetics, suxamethonium	ryanodine receptor (RYR1) mutation	malignant hyperthermia
Oestrogens, combined pill	factor V Leiden, other thrombophilias	venous thrombosis

- **Dependence**: **tolerance** (needing more for the same effect), **physical dependence** (a withdrawal syndrome on stopping), **psychological dependence** (craving, compulsive use); **addiction** (now substance use disorder, DSM-5) is compulsive use despite harm. Factors: the drug's reinforcing effect (fast onset, short action), personality, peer pressure, availability, psychiatric illness, genes.
  - **Opioid withdrawal**: yawning, lacrimation, rhinorrhoea, mydriasis, piloerection ("cold turkey"), abdominal cramps, diarrhoea, aches; distressing but **not life-threatening**; starts 6-12 hours after the last heroin or morphine dose and peaks at 1-3 days (later and longer with methadone); treat with methadone or buprenorphine (substitution then taper), clonidine or lofexidine for autonomic symptoms; naltrexone for relapse prevention only after detoxification.
  - **Alcohol withdrawal**: tremor at 6-12 hours, hallucinosis 12-48, **seizures at 12-48**, **delirium tremens at 48-96 hours** (confusion, hallucinations, autonomic storm; mortality up to about 15% untreated, 1-5% with treatment); treatment: **benzodiazepines** (chlordiazepoxide or diazepam; lorazepam or oxazepam in liver disease), **thiamine before glucose** (Wernicke), fluids, correct magnesium; relapse prevention: **naltrexone, acamprosate, disulfiram**.
  - **Benzodiazepine and barbiturate withdrawal**: anxiety, insomnia, **seizures**; switch to long-acting diazepam and taper over weeks. **Nicotine**: irritability, craving; nicotine replacement, **varenicline** (partial α4β2 agonist, the most effective), bupropion. **Cocaine and amphetamine**: depression ("crash"), no specific drug.
- **Essential medicines (WHO)**: a list of drugs that meet the priority health needs of a population, chosen for **efficacy, safety, cost-effectiveness and quality**, available at all times in adequate amounts; the WHO Model List was first issued in 1977 and is revised every two years; countries adapt it as a national list.
- **Rational prescribing (WHO Guide to Good Prescribing), six steps**: (1) define the patient's problem; (2) specify the therapeutic objective; (3) **verify the suitability of the P-drug** (the "personal" drug chosen from experience for a common condition by **efficacy, safety, suitability and cost**); (4) start treatment (write the prescription: patient, drug by generic name, dose, form, duration, prescriber); (5) give **information, instructions and warnings**; (6) monitor and stop treatment.
- **Promotion by drug companies**: representatives, samples, gifts and sponsored events bias prescribing toward newer, costlier brands; WHO's ethical criteria require accurate, balanced, evidence-based claims; independent sources (WHO Model Formulary, BNF, Cochrane) should guide the choice.
- **Placental transfer and teratogenicity**: drugs cross by simple diffusion when **lipid-soluble, un-ionised, of low molecular weight (under about 600), and little protein-bound**; large polar molecules (heparin, insulin) do not cross. A **teratogen** causes a structural malformation (thalidomide); **dysmorphogen** is used for an agent producing abnormal form, from gross malformation to minor dysmorphic features (fetal hydantoin and fetal alcohol syndromes); the two terms overlap and are used loosely. The most sensitive period is **organogenesis (weeks 3-8)**; the all-or-none period before that rarely gives malformations; later exposure causes growth and functional effects (ACE inhibitors, tetracyclines on teeth). Milk transfer follows the same rules and **weak bases concentrate in milk** (slightly more acidic than plasma); avoid in breastfeeding cytotoxic drugs, radioactive iodine, lithium (caution), ergotamine, chloramphenicol, and drugs with a relative infant dose over about 10%.

Autonomic drugs

Adrenergic receptors

Receptor	Main effects	Agonist/antagonist examples
α_1	vasoconstriction, mydriasis, bladder neck and prostate contraction	phenylephrine; **prazosin, tamsulosin (α_1A), terazosin, doxazosin**
α_2	presynaptic inhibition of NA release, central fall in BP	clonidine, methyldopa, dexmedetomidine; yohimbine blocks
β_1	heart rate and contractility, renin release	dobutamine; atenolol, metoprolol, bisoprolol, nebivolol, esmolol
β_2	bronchodilatation, vasodilatation in muscle, uterine relaxation, hepatic glycogenolysis	salbutamol, terbutaline, salmeterol
β_3	lipolysis, bladder relaxation	mirabegron
D_1	renal and mesenteric vasodilatation	dopamine, fenoldopam

Adrenaline and other sympathomimetics

- **Adrenaline**: α and β agonist. **First-line, intramuscular (0.01 mg/kg of 1 mg/mL (1:1000), up to 0.5 mg in an adult, 0.3 mg at 6–12 years, 0.15 mg under 6 years (Resuscitation Council UK 2021), anterolateral mid-thigh, repeated after 5 minutes if needed) for anaphylaxis**; do not delay for steroids or antihistamines, which are adjuncts with a slow onset. IV adrenaline is for cardiac arrest (1 mg) and for refractory shock under monitoring.
- With local anaesthetics: prolongs action; avoid in end-arteries (fingers, penis, nose tip).
- **Dale's vasomotor reversal**: after an α-blocker, adrenaline *lowers* blood pressure, because unopposed β_2 vasodilatation is unmasked. Noradrenaline in the same setting merely loses its pressor effect.
- **Noradrenaline**: first-line vasopressor in septic shock. **Dopamine**: low dose D_1 (renal), moderate β_1, high α. **Dobutamine**: β_1 inotrope for acute heart failure and stress echo. **Phenylephrine**: α_1 pure; nasal decongestant, hypotension during anaesthesia, mydriatic. **Isoprenaline**: non-selective β; used in heart block while awaiting a pacemaker. **Ephedrine**: indirect and direct; shows tachyphylaxis.
- **β_2 agonists (salbutamol, terbutaline)**: tremor (the commonest), tachycardia and palpitations (partly β_1, partly reflex), and **hypokalaemia**: β_2 stimulation of Na^+–K^+-ATPase

moves K^+ into cells, which is why nebulised salbutamol is used for hyperkalaemia; repeated nebulisation in acute severe asthma, with steroids and diuretics, needs K^+ checks. Also hyperglycaemia and lactic acidosis at high doses.

- **Orthostatic (neurogenic) hypotension**: after non-drug measures, **fludrocortisone** (mineralocorticoid, expands plasma volume) and **midodrine** (prodrug of an α_1 agonist; supine hypertension) are the classical drugs; droxidopa is a newer option.
- Indirect agents (tyramine, amphetamine) release stored noradrenaline; reserpine depletes it (so indirect agents fail).
- **Tyramine ("cheese") reaction** occurs with non-selective MAO inhibitors and is treated with an α-blocker (phentolamine). Levodopa with a non-selective MAO inhibitor gives a hypertensive crisis for the same reason (see Parkinson's disease under CNS drugs).

β-blockers

- Cardioselective (β_1): **atenolol, metoprolol, bisoprolol, esmolol, nebivolol, acebutolol**. Non-selective: **propranolol, nadolol, timolol, sotalol, pindolol, carvedilol, labetalol**.
- **Intrinsic sympathomimetic activity (ISA)**: **pindolol, acebutolol, (oxprenolol, celiprolol)**: less resting bradycardia and less lipid disturbance. Mnemonic: "PAC-man" for the ISA group.
- **Membrane-stabilising (quinidine-like)**: propranolol.
- **α plus β blockade**: **carvedilol, labetalol** (labetalol is mainly β; used in pregnancy hypertension and hypertensive emergencies).
- **Nebivolol** releases nitric oxide. **Esmolol**: ultra-short acting, IV, for perioperative tachycardia and SVT. **Sotalol** also blocks K^+ channels (class III) and may cause torsades.
- Adverse effects: **bronchospasm** (β_2 blockade: loss of bronchodilating tone, so avoid in asthma), bradycardia, AV block, fatigue, cold extremities, masked hypoglycaemia in diabetics (less with β_1-selective), dyslipidaemia, worsening of acute decompensated failure. Abrupt withdrawal gives rebound angina or hypertension.
- Evidence-based in heart failure: **bisoprolol, metoprolol succinate, carvedilol** (and nebivolol in the elderly).
- Uses: hypertension, angina, post-MI, arrhythmias, heart failure, thyrotoxicosis (propranolol also blocks T4 to T3 conversion), migraine prophylaxis, essential tremor, portal hypertension (propranolol, carvedilol), glaucoma (timolol topical).

α-blockers

- **Phenoxybenzamine**: non-selective, irreversible, long acting. **Phentolamine**: non-selective, reversible, IV.
- **Phaeochromocytoma**: start **α-blockade first (phenoxybenzamine, or doxazosin)** for 10–14 days; add a β-blocker only after α-blockade is established, because β-blockade alone leaves α vasoconstriction unopposed and may precipitate hypertensive crisis. Metyrosine (inhibits tyrosine hydroxylase) is an adjunct.
- **Prazosin, terazosin, doxazosin**: selective α_1; first-dose postural hypotension (start at bedtime). Used for hypertension and BPH.
- **Tamsulosin and silodosin**: **α_1A-selective** (prostate, bladder neck), so little postural hypotension; cause retrograde ejaculation and **intraoperative floppy iris syndrome** in cataract surgery.
- **Prazosin** also reduces the autonomic storm of **scorpion (Indian red scorpion, Mesobuthus tamulus) sting** (a cause of hypertension, sweating, priapism and pulmonary oedema in South Asia); prazosin lowers mortality. Scorpion antivenom is used for systemic envenoming in selected centres.
- Yohimbine: α_2 blocker. Clonidine and methyldopa: α_2 agonists; **methyldopa** is safe in pregnancy but can cause positive Coombs test and haemolysis; clonidine withdrawal causes rebound hypertension.

Cholinergic drugs

- **Direct muscarinic agonists**: **bethanechol** (not hydrolysed by cholinesterase, M_3; for **postoperative non-obstructive urinary retention** and neurogenic bladder, ileus), carbachol, **pilocarpine** (a tertiary-amine alkaloid: miosis, and contraction of the ciliary muscle pulls on the trabecular meshwork to raise aqueous outflow, so glaucoma, including with other drugs in acute angle closure; orally for xerostomia after head and neck radiotherapy or in Sjögren's syndrome), cevimeline, methacholine (bronchial challenge test).
- **Cholinesterase inhibitors**: reversible **neostigmine** (myasthenia gravis, reversal of non-depolarising block, paralytic ileus, urinary retention; does not cross the blood–brain barrier), **pyridostigmine** (myasthenia maintenance), **physostigmine** (crosses the BBB; anticholinergic poisoning), **edrophonium** (very short-acting, diagnostic), **donepezil, rivastigmine, galantamine** (Alzheimer's disease; rivastigmine also in Parkinson dementia). Organophosphates are irreversible; see the antidotes topic.
- **Cholinergic crisis vs myasthenic crisis**: edrophonium improves a myasthenic crisis and worsens a cholinergic one.
- Muscarinic antagonists: **atropine** (bradycardia, organophosphate poisoning, pre-anaesthetic drying), **hyoscine** (motion sickness, scopolamine patch; crosses BBB), **ipratropium and tiotropium** (COPD), **glycopyrronium** (drying, does not cross BBB), **oxybutynin, tolterodine, solifenacin** (overactive bladder; would worsen retention), **tropicamide, cyclopentolate** (mydriasis and cycloplegia), **benztropine, trihexyphenidyl** (parkinsonism), **dicyclomine** (spasm), **pirenzepine** (M_1).
- Atropine toxicity: "hot as a hare, dry as a bone, red as a beet, blind as a bat, mad as a hatter". Treat with physostigmine (central) plus supportive care.
- **Antimuscarinics are contraindicated in** angle-closure glaucoma, BPH with retention, paralytic ileus.
- Sweating is sympathetic anatomically but **cholinergic (muscarinic)**; so atropine causes dry skin, hyperthermia.

Neostigmine reversal, pyridostigmine and suxamethonium (details)

- **Reversal of a non-depolarising block**: neostigmine raises acetylcholine at the neuromuscular junction (nicotinic) **and** at muscarinic sites, so it also causes **bradycardia, bronchial secretions, salivation, bowel spasm and bronchospasm**; **atropine or glycopyrronium (glycopyrrolate)** is given **with** it to block the muscarinic effects only; it does not change the nicotinic action, and glycopyrronium, whose onset matches neostigmine's, is preferred. **Sugammadex** needs no antimuscarinic.
- **Myasthenia gravis**: **pyridostigmine** (about 60 mg orally three to four times daily) is the usual long-acting maintenance anticholinesterase; edrophonium is too brief for maintenance (diagnostic only). Add steroids, azathioprine, thymectomy;

crisis: IVIG or plasmapheresis. **Drugs that worsen myasthenia**: aminoglycosides, fluoroquinolones, macrolides, β-blockers, magnesium, penicillamine.

- **Suxamethonium (succinylcholine)**: a depolarising blocker broken down by **plasma cholinesterase** (pseudocholinesterase) in minutes. In **atypical or deficient enzyme** (genetic, dibucaine number low; also liver disease, pregnancy, organophosphate exposure) a normal dose gives **paralysis for hours**: ventilate and sedate until recovery (fresh frozen plasma or purified cholinesterase are rarely needed). **Phase I block** (depolarising: fasciculations, potentiated by anticholinesterases) can turn into a **phase II block** (non-depolarising-like, fade, reversed by neostigmine) with large or repeated doses. Adverse effects: **hyperkalaemia** (burns, denervation, crush injury, prolonged immobilisation), bradycardia, raised intraocular, intragastric and intracranial pressure, myalgia, **malignant hyperthermia**.
- **Skeletal muscle relaxants, classification**: neuromuscular blockers (non-depolarising: tubocurarine, pancuronium (vagolytic, tachycardia), vecuronium, rocuronium, atracurium and mivacurium (histamine release, hypotension, bronchospasm); depolarising: suxamethonium); **centrally acting** (**baclofen**, a GABA-B agonist for spasticity, with intrathecal use; **tizanidine**, α_2 agonist; diazepam; methocarbamol, chlorzoxazone, orphenadrine); **directly acting** (**dantrolene**); **botulinum toxin** (blocks presynaptic acetylcholine release). Neuromuscular blockers are **adjuncts to anaesthesia** (intubation, muscle relaxation, ventilation) and never replace anaesthesia or analgesia.
- **Nicotine**: a nicotinic agonist: at low doses it stimulates autonomic ganglia, the adrenal medulla and the CNS (tachycardia, rise in blood pressure, increased gut motility, alertness), at high doses it blocks ganglia (depolarising block) and causes convulsions and respiratory failure; tolerance and dependence are rapid. **Hazards of smoking**: lung cancer, COPD, ischaemic heart disease, stroke, peripheral vascular disease and Buerger disease, peptic ulcer, cancers of mouth, larynx, oesophagus, bladder and pancreas, low birth weight, passive-smoking harm to children; carbon monoxide shifts the haemoglobin curve and tars carry the carcinogens. Cessation aids: nicotine replacement (patch, gum, lozenge), bupropion, varenicline, cytisine.
- **Eye drugs**: **miotics** (pilocarpine, a muscarinic agonist; physostigmine, echothiophate): open-angle glaucoma and reversal of mydriasis. **Mydriatics**: antimuscarinics (**atropine: mydriasis and cycloplegia lasting 7-14 days**, homatropine 1-3 days, cyclopentolate about a day, **tropicamide 4-6 hours, the fundus-examination drug**) versus adrenergic (**phenylephrine**: mydriasis **without** cycloplegia, no loss of accommodation); both can precipitate **acute angle-closure glaucoma** in a narrow angle. **Glaucoma drugs**: prostaglandin analogues (latanoprost; first-line, raise uveoscleral outflow; eyelash growth, iris darkening), **timolol** (β-blocker, lowers aqueous production; not in asthma or bradycardia), brimonidine (α_2 agonist), dorzolamide and oral **acetazolamide** (carbonic anhydrase inhibitors), pilocarpine; **acute angle closure**: IV acetazolamide, topical agents, IV mannitol, then laser iridotomy. **Conjunctivitis**: chloramphenicol or quinolone drops for bacterial; viral is supportive; allergic uses antihistamine or mast-cell stabiliser drops; **trachoma**: single-dose oral **azithromycin** (the SAFE strategy's A) or topical tetracycline. Steroid drops can cause cataract and glaucoma and worsen herpetic keratitis.
- **Drugs for ENT problems**: **vertigo** (betahistine, cinnarizine, prochlorperazine, dimenhydrinate); allergic rhinitis (**intranasal corticosteroids** first, antihistamines; decongestants only for days); **streptococcal pharyngitis or tonsillitis** (penicillin V for 10 days, or one benzathine penicillin injection, to prevent rheumatic fever); acute otitis media (analgesia, then amoxicillin if needed); topical aminoglycoside ear drops are avoided with a perforated drum (ototoxic).

Neuromuscular blockers (brief)

- Depolarising: **suxamethonium** (fast, short; hyperkalaemia, malignant hyperthermia, prolonged apnoea in pseudocholinesterase deficiency). Non-depolarising: atracurium and cisatracurium (Hofmann elimination, best in renal and hepatic failure), vecuronium, rocuronium, **sugammadex** reverses rocuronium and vecuronium.
- **Dantrolene** treats malignant hyperthermia (blocks ryanodine receptor).

Cardiovascular and renal drugs

Diuretics

Class	Site and mechanism	Key points
Loop (**furosemide, bumetanide, torsemide**; **ethacrynic acid**)	thick ascending limb, Na^+–K^+–$2Cl^-$	high ceiling; **hypokalaemia, hypocalcaemia, hypomagnesaemia**; ototoxicity; hyperuricaemia; raises calciuria; ethacrynic acid, a phenoxyacetic acid, has **no sulphonamide group** (used in sulphonamide allergy, though cross-reactivity with the others is uncommon) and is the most ototoxic
Thiazide (**hydrochlorothiazide, chlortalidone, indapamide, metolazone**)	distal convoluted tubule, Na^+–Cl^-	**reduce urinary calcium** (calcium reabsorption rises); hypokalaemia, hyponatraemia, hyperglycaemia, hyperuricaemia, hypercalcaemia; used for calcium stones and nephrogenic diabetes insipidus
K^+-sparing (**spironolactone, eplerenone**: aldosterone antagonists; **amiloride, triamterene**: ENaC block)	collecting duct	**hyperkalaemia**; spironolactone gynaecomastia and antiandrogen effect; eplerenone does not
Carbonic anhydrase inhibitor (**acetazolamide**)	proximal tubule	bicarbonate loss, metabolic acidosis; glaucoma, altitude sickness, idiopathic intracranial hypertension
Osmotic (**mannitol**)	freely filtered	raised intracranial pressure; avoid in heart failure (expands volume)
Vasopressin antagonists (**tolvaptan**)	V_2 receptor	SIADH, ADPKD; correct sodium slowly

- Distal delivery of Na^+ increases K^+ loss in all except K^+-sparing agents; **the K^+-sparing diuretics, spironolactone above all, are the diuretics that cause hyperkalaemia**.
- Spironolactone and eplerenone reduce mortality in HFrEF and post-MI heart failure; **SGLT2 inhibitors** (dapagliflozin, empagliflozin) are now a fourth pillar of HFrEF therapy (with ACE inhibitor/ARB/ARNI, β-blocker, MRA) and also help HFpEF and CKD, independent of diabetes (ESC 2021/2023; AHA/ACC 2022).
- Hyperkalaemia with spironolactone is more likely when combined with ACE inhibitors, in CKD.
- **Nephrogenic diabetes insipidus** (lithium the commonest drug cause; no response to desmopressin): **thiazides**

paradoxically cut urine volume (up to about half): mild volume contraction raises proximal reabsorption so less water reaches the collecting duct; **amiloride** is preferred or added in lithium-induced disease because it blocks lithium entry through ENaC; NSAIDs and a low-salt, low-protein diet help too.

ACE inhibitors, ARBs, ARNI

- ACE inhibitors (**captopril** (not a prodrug, sulphydryl group, rash and taste loss), **enalapril, lisinopril, ramipril, perindopril**): lower angiotensin II, raise bradykinin. **Dilate the efferent arteriole**, lowering intraglomerular pressure, so they reduce proteinuria and slow **diabetic nephropathy** beyond blood pressure control.
- Adverse effects: **dry cough** (in about 5–20%; ACE is kininase II, so **bradykinin** and substance P accumulate in the airway; it settles within one to four weeks of stopping, occasionally longer, and an ARB is the substitute), angioedema, hyperkalaemia, first-dose hypotension, rise in creatinine (accept up to 30%), **bilateral renal artery stenosis: acute kidney injury**, **fetotoxic** (renal dysgenesis, oligohydramnios, skull hypoplasia). ARBs (**losartan, telmisartan, valsartan, candesartan**) lack cough and rarely cause angioedema, with the same pregnancy contraindication.
- **Sacubitril–valsartan (ARNI)** is superior to enalapril in HFrEF; never combine it with an ACE inhibitor (angioedema); a 36-hour gap is needed. **Aliskiren**: renin inhibitor, little added value.
- Dual ACE inhibitor + ARB: avoid (harm, no benefit).
- **Antihypertensives in pregnancy**: **labetalol, methyldopa, nifedipine** (long-acting). Avoid ACE inhibitors, ARBs, spironolactone, atenolol (growth restriction). For severe hypertension: IV labetalol, oral nifedipine, IV hydralazine; **magnesium sulphate** for eclampsia prevention.
- **Calcium channel blockers**: dihydropyridines (**amlodipine, nifedipine, felodipine**) vasodilate: ankle oedema, flushing, headache, gingival hyperplasia; short-acting nifedipine is not for chronic hypertension. **Verapamil, diltiazem** slow the AV node: constipation (verapamil), bradycardia; avoid with β-blockers. Because they depress the SA and AV nodes and vasodilate less, they cause the **least reflex tachycardia** (verapamil least); dihydropyridines, especially short-acting nifedipine, the most. Nimodipine for subarachnoid haemorrhage.
- Others: hydralazine (lupus-like, reflex tachycardia), minoxidil (hirsutism), sodium nitroprusside (cyanide toxicity), clonidine, methyldopa.
- First-line in uncomplicated hypertension: ACE inhibitor/ARB, CCB or thiazide-like diuretic (Black patients and older adults: CCB or thiazide-like first). Diabetes with proteinuria: ACE inhibitor/ARB.

Antianginals

- **Nitrates** (GTN, isosorbide mononitrate/dinitrate): release NO, raise cGMP. **Predominantly venodilators**, lowering preload and wall tension, reducing myocardial O_2 demand; they also dilate coronaries and relieve spasm. Headache, flushing, hypotension; tolerance avoided by a nitrate-free interval of 8–12 hours.
- **Sildenafil, tadalafil, vardenafil** (PDE-5 inhibitors) are contraindicated with nitrates (and riociguat): **profound hypotension**.
- β-blockers and rate-limiting CCBs reduce rate and contractility. In **vasospastic (Prinzmetal) angina**, CCBs and nitrates are used and non-selective β-blockers avoided.
- **Ivabradine** blocks the I_f current in the SA node, slowing heart rate without negative inotropy (sinus rhythm only); adverse effect: **luminous visual phenomena (phosphenes)**, bradycardia, atrial fibrillation. Used in angina and HFrEF with heart rate ≥ 70.
- **Ranolazine** inhibits late sodium current (QT prolongation). **Trimetazidine** metabolic modulator (can cause parkinsonism). **Nicorandil**: K^+ channel opener plus nitrate (oral and anal ulcers).

Antiarrhythmics (Vaughan Williams)

Class	Examples	Notes
Ia	quinidine, procainamide, disopyramide	QT prolongation; procainamide lupus
Ib	**lidocaine**, mexiletine, phenytoin	ventricular arrhythmias, post-MI
Ic	flecainide, propafenone	avoid after MI (CAST); AF pill-in-pocket
II	β-blockers	
III	**amiodarone**, sotalol, dofetilide, ibutilide	K^+ channel block; QT prolongation
IV	verapamil, diltiazem	

- **Adenosine**: drug of choice to terminate **PSVT** when vagal manoeuvres fail (6 mg rapid IV, then 12 mg); half-life seconds; transient flushing, chest tightness, bronchospasm (avoid in asthma); effect blocked by theophylline and caffeine, enhanced by dipyridamole.
- **Amiodarone**: very long half-life, large Vd. Adverse effects: **thyroid dysfunction (both hypo- and hyperthyroidism)**, **pulmonary fibrosis**, hepatotoxicity, corneal microdeposits, optic neuropathy, **blue-grey photosensitive skin pigmentation (slate-grey discolouration)**, bradycardia, QT prolongation; raises digoxin and warfarin levels (inhibits P-gp and CYP2C9). It is about 37% iodine by weight, which explains both thyroid effects (iodine-induced hypothyroidism, type 1 thyrotoxicosis; type 2 is a destructive thyroiditis).
- **Digoxin**: inhibits Na^+–K^+ ATPase. **Hypokalaemia, hypomagnesaemia, hypercalcaemia, hypothyroidism, renal impairment and old age increase toxicity** because K^+ competes with digoxin at the pump's K^+ site. Toxicity: nausea, visual disturbance (yellow vision), bradycardia, AV block, ventricular ectopy, **hyperkalaemia in acute overdose**. Treat with **digoxin-specific Fab fragments**; avoid calcium. Interactions: amiodarone, verapamil, quinidine and macrolides raise levels. Narrow therapeutic index; renal excretion.
- Torsades de pointes: IV magnesium sulphate.

Lipid-lowering drugs

Drug	Mechanism	Key points
Statins (atorvastatin, rosuvastatin)	inhibit HMG-CoA reductase	largest LDL fall; myopathy and rhabdomyolysis (with fibrates, macrolides), raised transaminases, small rise in diabetes risk; contraindicated in pregnancy (exam answer; the FDA removed the formal contraindication in 2021, but they are still stopped in most pregnancies)

Drug	Mechanism	Key points
Ezetimibe	blocks **NPC1L1** at the intestinal brush border	adds about 15–20% LDL lowering
Bile acid resins (cholestyramine, colesevelam)	bind bile acids	LDL falls; **triglycerides can rise**; bloating, bind other drugs
Fibrates (fenofibrate, gemfibrozil)	PPAR-α	lower triglycerides; myopathy, gallstones; gemfibrozil with statins is hazardous
Niacin	reduces VLDL secretion	flushing (prostaglandin, prevented by aspirin), hyperglycaemia, hyperuricaemia
PCSK9 inhibitors (evolocumab, alirocumab), inclisiran (siRNA)	raise LDL receptor recycling	50–60% LDL fall; for familial hypercholesterolaemia and very high risk
Bempedoic acid	inhibits ATP-citrate lyase	for statin intolerance; tendon rupture, raised uric acid
Orlistat (lipase inhibitor)		oily stools (steatorrhoea), fat-soluble vitamin malabsorption; an anti-obesity drug, not a lipid drug as such

Anticoagulants and antiplatelets

- **Heparin** (UFH): potentiates antithrombin; monitored by aPTT; **protamine sulphate** reverses it by **chemical antagonism** (a basic protein binding an acidic one). HIT. LMWH (enoxaparin): anti-Xa monitored when needed; renally cleared. **Fondaparinux**: indirect Xa inhibitor via antithrombin.
- **Warfarin**: blocks vitamin K epoxide reductase, impairing II, VII, IX, X, protein C and S; INR monitoring, **target 2.0–3.0** for DVT, PE and atrial fibrillation (2.5–3.5 for mechanical mitral and some other valves; below 2 protects too little, above about 4.5 bleeding risk rises sharply); teratogenic (warfarin embryopathy, avoided in pregnancy, use LMWH); starts with skin necrosis risk (protein C falls first). **Reversal: vitamin K (phytomenadione); for bleeding add prothrombin complex concentrate** (or fresh frozen plasma if unavailable). Interactions: rifampicin lowers INR; metronidazole, cotrimoxazole, amiodarone, azoles, macrolides raise it.
- **DOACs**: **dabigatran** (oral prodrug, direct thrombin inhibitor, **reversed by idarucizumab**); **rivaroxaban, apixaban, edoxaban** (factor Xa inhibitors, reversed by andexanet alfa or prothrombin complex concentrate). No routine INR monitoring. Preferred over warfarin in non-valvular AF; **not for mechanical valves or moderate-to-severe mitral stenosis**, and avoided in severe renal failure, pregnancy and **triple-positive antiphospholipid syndrome** (more arterial thrombosis than with warfarin).
- **Aspirin**: irreversible COX-1 inhibition (platelets cannot make new enzyme). **Clopidogrel**: prodrug activated by **CYP2C19**, irreversible $P2Y_{12}$ block; **omeprazole and esomeprazole inhibit CYP2C19 and weaken it**; pantoprazole interacts little. **Prasugrel, ticagrelor** (reversible, dyspnoea, bradyarrhythmia). **Abciximab, eptifibatide, tirofiban**: GP IIb/IIIa. **Dipyridamole**: adenosine reuptake and PDE inhibition. **Cilostazol**: PDE3 inhibition, for claudication.
- **Thrombolytics**: alteplase and tenecteplase (fibrin-specific); streptokinase (antigenic, can cause hypotension). Antidote for bleeding: tranexamic acid (antifibrinolytic); not a reversal agent for anticoagulants as such.

Hypertension and heart failure: curriculum points

- **Salt and water retention**: **direct vasodilators (hydralazine, minoxidil)** and, to a lesser extent, central and α-blockers and dihydropyridine CCBs, trigger reflex renin release and sodium retention, so a **diuretic** (and a β-blocker for the reflex tachycardia) is added; thiazides and loop diuretics themselves cause natriuresis; ACE inhibitors and ARBs do not retain salt.
- **Combination choices**: **ACE inhibitor or ARB with a calcium-channel blocker** (best outcomes, ACCOMPLISH) or with a thiazide-like diuretic; ACE inhibitors blunt the diuretic-induced rise in renin; avoid β-blocker with verapamil or diltiazem, and avoid ACE inhibitor plus ARB. β-blockers are not first-line for uncomplicated hypertension except after myocardial infarction, in heart failure, angina or arrhythmia; thiazide plus β-blocker worsens glucose and lipids.
- **Non-pharmacological measures**: salt under 5 g a day (WHO), DASH diet, weight loss, aerobic exercise, less alcohol, stopping smoking; each can lower systolic pressure by several mmHg.
- **Hypertensive emergency** (severe rise with acute organ damage): **IV labetalol, nicardipine, clevidipine, nitroprusside (monitored; cyanide), glyceryl trinitrate (in pulmonary oedema or ischaemia), esmolol (aortic dissection with a vasodilator), phentolamine (catecholamine crisis)**; lower the mean pressure by **no more than 25% in the first hour**, then to about 160/100 over hours, except in aortic dissection (systolic 120 mmHg or less within 20 minutes, β-blocker before any vasodilator: AHA/ACC 2017) and where cerebral perfusion is at risk; oral nifedipine capsules are not used. **Urgency without organ damage**: oral agents, no rapid fall.
- **Digoxin in heart failure**: inhibits the Na^+-K^+ ATPase, raising intracellular calcium (positive inotrope) and slowing the AV node through vagal action; symptomatic benefit and fewer admissions, no mortality benefit; given for AF with HF. Toxicity and interactions: see antiarrhythmics.
- **Other drugs in heart failure**: ACE inhibitor (or ARNI), β-blocker, MRA, SGLT2 inhibitor, loop diuretic for congestion, **ivabradine** (heart rate $\geq$ 70 in sinus rhythm), hydralazine with isosorbide dinitrate, **vericiguat** (soluble guanylate cyclase stimulator).

Nitroprusside, mannitol and K^+-sparing diuretics (details)

- **Nitroprusside** (infusions lasting days): breaks down to nitric oxide plus **cyanide**, which the liver converts to **thiocyanate**; accumulation (high dose, long use, renal impairment) gives **metabolic acidosis, confusion, seizures and thiocyanate toxicity**; monitor lactate; treat with sodium thiosulphate and hydroxocobalamin.
- **Mannitol**: a polyhydric alcohol that is **not absorbed from the gut** (oral dose causes osmotic diarrhoea); intravenously it is filtered and not reabsorbed, giving **osmotic diuresis** and lowering raised intracranial and intraocular pressure; it expands volume first (avoid in heart failure).
- **Aldosterone antagonists versus ENaC blockers**: **spironolactone** acts only when aldosterone is present (high-aldosterone states: cirrhosis, heart failure, primary aldosteronism); **triamterene and amiloride block the epithelial sodium channel directly** and work whatever the

aldosterone level (low or absent aldosterone). **Hydrochlorothiazide** increases excretion of **Na^+ and Cl^-** (the diuresis follows the sodium), with K^+ and some HCO_3^- loss; chronic thiazide or loop therapy with low intake causes **hypokalaemia** (arrhythmia, digoxin toxicity, alkalosis) corrected with potassium or a K^+-sparing drug.

Shock, myocardial infarction and anaemia (curriculum points)

- **Shock types and drugs**: **hypovolaemic** (volume: balanced crystalloid or blood; not vasopressors first), **cardiogenic** (**dobutamine**, a β_1 agonist that raises output with little rise in heart rate; **noradrenaline** if hypotensive; **dopamine** at 5-10 µg/kg/min is a β_1 inotrope but causes more arrhythmia than noradrenaline (SOAP II) and is not preferred), **septic** (30 mL/kg crystalloid, antibiotics within the first hour, **noradrenaline first-line to a mean pressure of 65 mmHg**, vasopressin added, hydrocortisone if refractory: Surviving Sepsis 2021), **neurogenic** (volume, a vasopressor such as noradrenaline or phenylephrine, atropine for bradycardia), **anaphylactic** (IM adrenaline). **Dopamine at low dose (renal-dose dopamine) does not protect the kidney**.
- **Myocardial infarction**: oxygen only if saturation is under 90% (ESC 2023), **aspirin 150-300 mg chewed (ESC 2023; 300 mg in the UK) plus a $P2Y_{12}$ inhibitor (prasugrel preferred to ticagrelor when going to PCI, ESC 2023; clopidogrel with fibrinolysis)**; **primary PCI** (the classic targets: **door-to-balloon within 90 minutes, door-to-needle within 30 minutes** for fibrinolysis); current practice (ESC 2023): primary PCI if it can be done **within 120 minutes of the ECG diagnosis**, otherwise **fibrinolysis within 10 minutes of diagnosis** for presentations within 12 hours (tenecteplase, alteplase; streptokinase is antigenic and not repeated once given, antibodies persisting for months to years), then transfer for angiography; **absolute contraindications to fibrinolysis**: **previous intracranial haemorrhage, ischaemic stroke within 3 months (AHA/ACC 2013; 6 months in ESC 2017), intracranial tumour, active bleeding, aortic dissection, significant head trauma**; add heparin or enoxaparin, an early β-blocker (not in shock or heart block), **ACE inhibitor**, **high-intensity statin**, an MRA if the ejection fraction is 40% or less with heart failure or diabetes (ESC 2017); analgesia with IV opioid and GTN for pain.
- **Iron deficiency anaemia**: oral ferrous (Fe^{2+}) sulphate 200 mg (65 mg elemental iron) once daily or **on alternate days (better absorption: BSG 2021)**, absorbed in the **duodenum**; absorption is **increased by vitamin C and gastric acid** and **reduced by tea, phytates, calcium, antacids, PPIs and tetracyclines**; adverse effects: nausea, constipation, black stools; haemoglobin rises 1-2 g/dL in 3-4 weeks and **treatment continues for about 3 months more to refill stores**. **Parenteral iron** (iron sucrose, **ferric carboxymaltose** (hypophosphataemia), ferric derisomaltose; iron dextran has more anaphylaxis) for intolerance, malabsorption, CKD, severe or late-pregnancy anaemia and ongoing loss. **Iron poisoning**: deferoxamine.
- **Vitamin B_{12} and folate**: B_{12} deficiency causes **megaloblastic anaemia with hypersegmented neutrophils and pancytopenia**, and **neurological damage (subacute combined degeneration of the cord, paraesthesia, optic neuritis, dementia)**; treat **pernicious anaemia with hydroxocobalamin 1 mg IM** on alternate days for 2 weeks (six doses) then **every 3 months for life** (oral 1-2 mg daily is an alternative); never give **folic acid alone** in B_{12} deficiency (it corrects the blood and lets the neurological damage progress); expect reticulocytosis in 3-7 days and early hypokalaemia. **Erythropoietin** (epoetin, darbepoetin) for anaemia of CKD (hypertension, pure red-cell aplasia, thrombosis).

Drugs for heart failure and shock (brief)

- **Inodilators** (inotropy with vasodilatation): **milrinone** (PDE-3 inhibitor: raised cAMP in myocardium and vascular smooth muscle, independent of β receptors, so it works in patients on β-blockers; arrhythmias, hypotension) and **dobutamine** (β_1 agonist with some β_2 vasodilatation); **levosimendan** sensitises troponin C to calcium and opens K-ATP channels. Noradrenaline and phenylephrine are vasopressors, not inodilators.
- Acute pulmonary oedema: IV furosemide, nitrates, oxygen as required. Digoxin: symptomatic benefit in AF with HF. Hydralazine plus isosorbide dinitrate: Black patients with HFrEF, or ACE/ARB intolerance. Vasopressors: noradrenaline first-line in septic shock; vasopressin add-on.

CNS drugs

Antiepileptics

Drug	Mechanism	Key points
Phenytoin	Na^+ channel (use-dependent)	zero-order kinetics; gingival hyperplasia, hirsutism, megaloblastic anaemia, osteomalacia, ataxia and nystagmus, purple glove with IV; fetal hydantoin syndrome; enzyme inducer; **can worsen absence seizures**
Carbamazepine	Na^+ channel	trigeminal neuralgia, focal seizures; hyponatraemia (SIADH), aplastic anaemia, SJS (HLA-B*1502), autoinduction; worsens absence and myoclonic seizures
Valproate	Na^+, GABA transaminase, T-type Ca^{2+}	broad spectrum; hepatotoxicity, pancreatitis, tremor, weight gain, thrombocytopenia, **highest teratogenic risk of the common antiepileptics (neural tube defects, lower IQ, autism risk)**; enzyme inhibitor
Ethosuximide	T-type Ca^{2+} channels (thalamus)	**drug of choice for pure absence seizures in children** (valproate if other seizure types coexist); GI upset, headache
Lamotrigine	Na^+ channel	broad spectrum, relatively safe in pregnancy; rash and SJS (slow titration; valproate raises its level); bipolar depression
Levetiracetam	SV2A	broad spectrum, low interaction; mood and irritability; safe in pregnancy
Topiramate	multiple	weight loss, kidney stones, paraesthesia, metabolic acidosis, glaucoma; migraine prophylaxis
Phenobarbitone	prolongs GABA-A channel opening	neonatal seizures; inducer; sedation
Vigabatrin	irreversible GABA transaminase inhibitor	infantile spasms in tuberous sclerosis; **visual field defects**
Tiagabine	blocks GABA reuptake	

Drug	Mechanism	Key points
Gabapentin, pregabalin	$\alpha_2\delta$ subunit of Ca^{2+} channels	neuropathic pain
Lacosamide, oxcarbazepine, zonisamide, perampanel	various	oxcarbazepine causes hyponatraemia

- **Status epilepticus**: **IV lorazepam** (0.1 mg/kg, up to 4 mg a dose, repeated once after 5–10 minutes; or IV diazepam, or **IM midazolam 10 mg** above 40 kg if no IV access) first; then IV phenytoin or fosphenytoin, valproate or levetiracetam; refractory: anaesthetic agents (propofol, thiopental, midazolam). Benzodiazepines are first-line because they act in seconds to minutes. Phenytoin needs ECG and BP monitoring (cardiac effects from the propylene glycol vehicle).
- First seizure choice: focal, carbamazepine or lamotrigine; generalised tonic–clonic, valproate (not in women of childbearing potential, where lamotrigine or levetiracetam are preferred).
- **In pregnancy**: lamotrigine and levetiracetam carry the lowest risk; give **folic acid** (higher doses 5 mg often advised, particularly with valproate or carbamazepine); vitamin K to the neonate when on enzyme inducers. Enzyme-inducing antiepileptics make the combined oral contraceptive ineffective.

Benzodiazepines and sedative-hypnotics

- Benzodiazepines **increase the frequency of GABA-A chloride channel opening** (need GABA); barbiturates **prolong the duration of opening** and at high dose open it directly, so overdose is more dangerous. **Zolpidem, zopiclone, zaleplon** act at the same receptor (ω_1), with little anticonvulsant or muscle-relaxant effect.
- **Flumazenil**: competitive benzodiazepine antagonist; can precipitate seizures in dependence and mixed overdose (with tricyclics).
- Long-acting: diazepam, chlordiazepoxide, clonazepam. Intermediate: lorazepam, oxazepam, temazepam (no active metabolites, preferred in liver disease and the elderly: **LOT**).
- Benzodiazepine withdrawal: seizures, anxiety; taper slowly.

Antipsychotics

- **Typical** (D_2 block): haloperidol, chlorpromazine, fluphenazine. Mesolimbic: therapeutic; nigrostriatal: **extrapyramidal effects** (acute dystonia, akathisia, parkinsonism, tardive dyskinesia); tuberoinfundibular: **hyperprolactinaemia**; chlorpromazine: sedation, hypotension, cholestatic jaundice, corneal and lens deposits.
- **Atypical** (5-HT_2A plus D_2): **clozapine** (treatment-resistant schizophrenia; **agranulocytosis: mandatory neutrophil monitoring**, myocarditis, seizures, hypersalivation, constipation, weight gain; the only antipsychotic that lowers suicide risk in schizophrenia), olanzapine (metabolic syndrome), risperidone (prolactin), quetiapine, aripiprazole (partial D_2 agonist), ziprasidone (QT).
- **Neuroleptic malignant syndrome (NMS)**: fever, lead-pipe rigidity, autonomic instability, altered consciousness, raised CPK. Stop the drug, cool, hydrate; **dantrolene** or **bromocriptine** in severe cases. Anticholinergics do not help and may worsen heat retention. Compare **serotonin syndrome** (clonus, hyperreflexia, diarrhoea; cyproheptadine) and **malignant hyperthermia** (anaesthetic agents and suxamethonium; dantrolene).
- Acute dystonia: IM/IV benztropine or promethazine.
- **Tardive dyskinesia**: late (months to years) involuntary orofacial movements (lip smacking, chewing, tongue protrusion) and choreoathetosis of limbs and trunk, from D_2 receptor supersensitivity after long blockade; commoner with typical agents, older age and women. The classical answer: stop or reduce the typical antipsychotic and switch to **clozapine** (least risk), or quetiapine. Current practice (APA 2020): a **VMAT2 inhibitor** (valbenazine, deutetrabenazine; tetrabenazine) for moderate or disabling cases. Anticholinergics do not help and may worsen it; raising the antipsychotic dose masks it only for a while.

Antidepressants, mood stabilisers

- **SSRIs** (fluoxetine, sertraline, escitalopram): first-line; sexual dysfunction, GI upset, hyponatraemia, bleeding; **serotonin syndrome** with MAO inhibitors, tramadol, linezolid, triptans, St John's wort. Paroxetine in pregnancy: cardiac malformations. Fluoxetine: long half-life, CYP2D6 inhibitor.
- **TCAs** (amitriptyline, imipramine): block NA and 5-HT reuptake; anticholinergic, **arrhythmias, QRS widening in overdose (treat with sodium bicarbonate)**. **MAO inhibitors**: tyramine crisis. **Mirtazapine**, **bupropion** (seizures; smoking cessation), **venlafaxine/duloxetine**.
- **Lithium**: narrow therapeutic index (maintenance 0.6–1.0 mmol/L, 12 hours after the dose; toxicity usually above 1.5); tremor, polyuria (nephrogenic diabetes insipidus), hypothyroidism, **Ebstein anomaly**; toxicity worsened by dehydration, thiazides, NSAIDs, ACE inhibitors; haemodialysis in severe toxicity.

Opioids

- **Morphine**: μ agonist; analgesia, euphoria, respiratory depression, miosis, constipation, urinary retention, biliary spasm, histamine release. **Tolerance develops to analgesia, euphoria, respiratory depression, sedation and nausea; little or none to miosis and constipation**, so a laxative is given with every regular opioid prescription.
- **Contraindicated or used with caution in head injury**: respiratory depression raises $PaCO_2$, causing cerebral vasodilatation and a rise in intracranial pressure; miosis and sedation mask neurological signs.
- **Pethidine**: serotonin syndrome with MAOIs, seizures (norpethidine); not for chronic pain. **Tramadol**: opioid plus SNRI action, seizures, serotonin syndrome. **Fentanyl** (potent, transdermal), **methadone** (maintenance in opioid dependence, QT), **buprenorphine** (partial agonist, ceiling effect), **codeine** (prodrug, CYP2D6), **loperamide** (gut), **diphenoxylate** (a pethidine congener for diarrhoea, combined with a sub-therapeutic dose of atropine that only makes an overdose unpleasant, to deter misuse). **Naloxone**: competitive antagonist, short acting (repeat doses or infusion for long-acting opioids), **naltrexone**: oral, relapse prevention.
- Opioid overdose triad: coma, pinpoint pupils, respiratory depression.
- **Opioid withdrawal** is the mirror image of intoxication (mydriasis, piloerection, yawning, lacrimation, rhinorrhoea, diarrhoea, not miosis or constipation): chronic opioids suppress the **locus coeruleus**, which rebounds on stopping; **clonidine or lofexidine** (α_2 agonists) reduce this noradrenergic overactivity and relieve the autonomic features,

not the craving (substitution with methadone or buprenorphine; see the dependence section).

- **Classes of opioids**: **natural opium alkaloids** morphine, codeine and thebaine (phenanthrenes) and papaverine (a benzylisoquinoline smooth-muscle relaxant without opioid action); **semisynthetic** heroin (diacetylmorphine), hydromorphone, oxycodone, buprenorphine; **synthetic** pethidine, methadone, fentanyl, tramadol.

Parkinson's disease and movement disorders

- **Levodopa + carbidopa**: carbidopa inhibits **peripheral dopa decarboxylase** and does not cross the BBB, so less levodopa is needed, with less nausea and hypotension. Long-term: wearing-off, dyskinesias, on–off phenomena; avoid high-protein meals; avoid vitamin B6 with levodopa alone.
- **COMT inhibitors** (entacapone, tolcapone: liver), **MAO-B inhibitors** (selegiline, rasagiline, safinamide; usable with levodopa at ordinary doses, whereas a **non-selective MAO inhibitor with levodopa causes a hypertensive crisis**: the dopamine and noradrenaline formed from levodopa are not broken down; stop the MAOI at least 2 weeks before), **dopamine agonists** (pramipexole, ropinirole: sleep attacks, impulse control; bromocriptine, cabergoline, rotigotine patch, apomorphine rescue), **amantadine** (dyskinesia), **anticholinergics** (benztropine, trihexyphenidyl: tremor).
- **Huntington chorea: tetrabenazine, deutetrabenazine** (VMAT2 inhibitors, depleting presynaptic monoamines; depression and suicidality). Benztropine does not help chorea.
- **Metoclopramide**: central D_2 blocker and 5-HT_4 agonist; antiemetic and prokinetic; **acute dystonia (oculogyric crisis, torticollis) especially in young people**, treated with anticholinergic. Domperidone does not cross the BBB (QT risk).
- Riluzole: motor neurone disease. Edaravone: ALS.

Anaesthetics (brief)

- Propofol (rapid recovery, antiemetic, pain on injection), thiopental, ketamine (NMDA antagonist; dissociative anaesthesia, raises BP and ICP), etomidate (adrenal suppression, haemodynamic stability), dexmedetomidine. Inhalational: sevoflurane (induction), isoflurane, desflurane (rapid), nitrous oxide (second gas effect, B12 inhibition), halothane (hepatitis). MAC inversely related to potency.
- Local anaesthetics: block voltage-gated Na^+ channels; amides (lidocaine, bupivacaine: cardiotoxic, treated with **lipid emulsion**) and esters (procaine). Lidocaine is also class Ib antiarrhythmic.

Alcohol, insomnia, anxiety, anaesthesia stages (curriculum points)

- **Alcohol**: depresses the CNS by enhancing GABA-A and blocking NMDA receptors; metabolised by **alcohol dehydrogenase to acetaldehyde, then aldehyde dehydrogenase to acetate**; the enzyme **saturates, so elimination is zero-order (about 7-10 g an hour, roughly one UK unit of 8 g)**. **Disulfiram** irreversibly inhibits aldehyde dehydrogenase, so alcohol causes **acetaldehyde accumulation: flushing, headache, nausea, vomiting, palpitations, hypotension, chest pain** within about 10-15 minutes (also with metronidazole). **Long-term toxicity**: fatty liver, alcoholic hepatitis, cirrhosis; gastritis, varices, pancreatitis; **Wernicke-Korsakoff**, cerebellar degeneration, neuropathy, dementia; cardiomyopathy, hypertension; macrocytosis; cancers of mouth, oesophagus, liver and breast; fetal alcohol syndrome. Detoxification and relapse drugs are in the dependence section above.
- **Sedative-hypnotics**: **benzodiazepines shorten sleep latency, increase stage 2 and reduce REM and slow-wave (stage 3-4) sleep**; barbiturates suppress REM more; on stopping there is **REM rebound with vivid dreams and insomnia**. Use for a few days to weeks; misuse and dependence are the problems. Alternatives: Z-drugs, melatonin (ramelteon), orexin antagonists (suvorexant, lemborexant), sedating antihistamines, trazodone; cognitive behavioural therapy is first-line.
- **Anxiety**: SSRIs or SNRIs first-line for generalised anxiety and panic (benzodiazepines only briefly), **buspirone** (5-HT_1A partial agonist; no sedation or dependence, effect after 1-2 weeks), propranolol for performance anxiety, hydroxyzine, pregabalin.
- **Antipsychotic classes by potency**: **chlorpromazine** (low potency: sedation, postural hypotension, anticholinergic, cholestatic jaundice), **thioridazine** (QT prolongation, retinopathy), **fluphenazine, trifluoperazine, haloperidol** (high potency: extrapyramidal effects). The dopamine (mesolimbic D_2) hypothesis explains the effect on positive symptoms; atypicals add 5-HT_2A blockade and treat negative symptoms somewhat better. Depot injections (fluphenazine, haloperidol decanoate, risperidone) for adherence.
- **Opioid comparisons with morphine**: **pethidine**: shorter action (2-3 hours), more tachycardia and mydriasis (atropine-like), less miosis; metabolite **norpethidine** is renally excreted and convulsant, so repeated doses in **renal failure** cause tremor, myoclonus and seizures (avoid; fentanyl is safer); serotonin syndrome with MAOIs. **Pentazocine**: κ agonist and weak μ antagonist: **dysphoria and psychotomimetic effects, raises blood pressure and pulmonary artery pressure (avoid in MI)**, ceiling effect, can precipitate withdrawal in dependent patients. **Buprenorphine**: partial μ agonist, long acting, sublingual; ceiling effect on respiratory depression; naloxone reverses poorly; precipitates withdrawal after full agonists; used for maintenance. **Dextropropoxyphene**: weak, withdrawn in the UK and EU for cardiotoxicity in overdose. All opioids: respiratory depression, constipation, urinary retention, biliary spasm; contraindicated or avoided in head injury, undiagnosed acute abdomen, asthma attacks, MAOI use.
- **Stages of general anaesthesia (Guedel)**: **I analgesia** (amnesia), **II excitement or delirium** (irregular breathing, laryngospasm, vomiting; passed quickly by fast induction), **III surgical anaesthesia** (planes 1-4; plane 4 has intercostal paralysis), **IV medullary paralysis** (respiratory and circulatory collapse). **Pre-anaesthetic medication**: anxiolytic (benzodiazepine), analgesic (opioid), antimuscarinic (glycopyrronium or atropine: reduces secretions and vagal reflexes), antiemetic, aspiration prophylaxis (H_2 blocker, PPI, sodium citrate); no longer routine for every patient.
- **Local anaesthetics**: **esters** (procaine, cocaine, tetracaine: hydrolysed by plasma cholinesterase, **allergy through para-aminobenzoic acid**) versus **amides** (lidocaine, bupivacaine, ropivacaine, prilocaine: hepatic metabolism, true allergy rare); **bupivacaine is the most cardiotoxic (lipid emulsion)**; **prilocaine can cause methaemoglobinaemia (methylene blue)**; maximum lidocaine about 3-4.5 mg/kg plain (200-300 mg in an adult), 7 mg/kg with adrenaline (500 mg); toxicity

starts with circumoral numbness, tinnitus and twitching, then seizures and collapse.

- **Analeptics (respiratory stimulants)**: doxapram, nikethamide, caffeine (apnoea of prematurity); limited because they cause seizures and arrhythmia, act briefly and do not replace ventilation; **flumazenil and naloxone** are specific antagonists.

Autacoids, NSAIDs and migraine

Arachidonic acid pathways

- Phospholipase A_2 (inhibited by corticosteroids via lipocortin) releases arachidonic acid → **COX** (prostaglandins, prostacyclin, thromboxane) or **5-lipoxygenase** (leukotrienes: LTB_4 chemotactic, **LTC_4, D_4, E_4 the cysteinyl leukotrienes causing bronchoconstriction**).
- COX-1: constitutive (gastric mucosa, platelet thromboxane A_2, renal blood flow). COX-2: inducible at inflammation sites, also in kidney and endothelium (prostacyclin).
- **Aspirin-exacerbated respiratory disease**: COX blockade diverts arachidonic acid to the lipoxygenase pathway, raising cysteinyl leukotrienes and causing bronchospasm and nasal polyps. Such patients may react to all COX-1 inhibitors; **selective COX-2 inhibitors are usually tolerated**.
- Leukotriene modifiers: **montelukast, zafirlukast** ($CysLT_1$ receptor antagonists; asthma, allergic rhinitis, exercise-induced bronchoconstriction, Churg–Strauss association); **zileuton** (5-lipoxygenase inhibitor); **roflumilast** (PDE4; COPD with exacerbations).
- Prostaglandin uses: **misoprostol** (PGE_1: NSAID ulcers, abortion, labour induction, postpartum haemorrhage; contraindicated in pregnancy except for these uses), **dinoprostone** (PGE_2, cervical ripening), carboprost ($PGF_2\alpha$: PPH, asthma is a contraindication), **alprostadil** (keeps the ductus arteriosus open), epoprostenol and iloprost (pulmonary hypertension), latanoprost (glaucoma), **indomethacin and ibuprofen** close a patent ductus.

NSAIDs

- **Aspirin**: irreversible COX inhibition; antiplatelet at low dose (75–150 mg), analgesic and antipyretic at 325–650 mg, anti-inflammatory at high dose. Adverse effects: gastric irritation and bleeding, **salicylism** (tinnitus, hyperventilation), Reye syndrome in children with viral illness, bronchospasm. Salicylate poisoning: mixed respiratory alkalosis and metabolic acidosis, treated with **urinary alkalinisation** and haemodialysis.
- **Paracetamol**: analgesic and antipyretic, minimal anti-inflammatory effect; hepatotoxicity through NAPQI in overdose (antidote: N-acetylcysteine).
- **Non-selective**: ibuprofen, naproxen, diclofenac, indomethacin (headache, PDA closure, gout), ketorolac (potent, short course), piroxicam, mefenamic acid. **Selective COX-2**: **celecoxib, etoricoxib**, parecoxib; fewer gastric ulcers but **cardiovascular risk (rofecoxib was withdrawn)**; avoid in ischaemic heart disease.
- Class effects: gastric ulceration, **renal impairment and sodium retention** (loss of prostaglandin-mediated afferent vasodilatation; "triple whammy" with ACE inhibitor/ARB plus diuretic), hypertension, platelet dysfunction, closure of fetal ductus (avoid in third trimester), analgesic nephropathy.
- **Nimesulide** and **metamizole**: hepatotoxicity and agranulocytosis respectively; restricted in many countries.
- Gout: acute attack with NSAID, colchicine (diarrhoea, bone marrow suppression) or steroid; prophylaxis with **allopurinol or febuxostat** (xanthine oxidase inhibitors; start after the attack settles, with cover), **probenecid, benzbromarone** (uricosurics), **pegloticase** and **rasburicase** (uric acid breakdown, tumour lysis).
- DMARDs: methotrexate first-line in rheumatoid arthritis (weekly dosing, folic acid cover), leflunomide, sulfasalazine, hydroxychloroquine (retinopathy), then TNF inhibitors (infliximab, adalimumab, etanercept: screen for TB), tocilizumab, JAK inhibitors (tofacitinib: VTE and zoster risk).

Histamine and antihistamines

- H_1 blockers: first-generation (chlorphenamine, promethazine, diphenhydramine: sedation, anticholinergic, motion sickness, antiemetic) and second-generation (**cetirizine, loratadine, fexofenadine**: non-sedating). Terfenadine and astemizole withdrawn for QT prolongation.
- **H_2 blockers** (ranitidine withdrawn for NDMA contamination; famotidine; cimetidine inhibits CYP enzymes and has antiandrogen effects). **PPIs** (omeprazole, pantoprazole): hypomagnesaemia, fractures, C. difficile; **omeprazole inhibits CYP2C19**.
- Serotonin: $5\text{-}HT_3$ antagonists (**ondansetron**, granisetron: chemotherapy emesis, QT prolongation), $5\text{-}HT_4$ agonists (prucalopride), buspirone ($5\text{-}HT_1A$).

Migraine

- **Acute attack**: simple analgesics and NSAIDs, then **triptans** (**sumatriptan**, rizatriptan: $5\text{-}HT_1B/_1D$ agonists; contraindicated in coronary disease, uncontrolled hypertension and with ergots), with an antiemetic (metoclopramide). **Ergotamine**: vasoconstriction and fibrosis, rarely used; **ergotism** (gangrene); contraindicated in pregnancy.
- **Gepants** (ubrogepant, rimegepant: CGRP receptor antagonists) and **lasmiditan** ($5\text{-}HT_1F$) are newer acute options without vasoconstriction.
- **Prophylaxis** (for frequent attacks, more than about 4 a month): **propranolol, amitriptyline, topiramate, sodium valproate**, flunarizine, candesartan; and **CGRP monoclonal antibodies** (erenumab, fremanezumab, galcanezumab) and botulinum toxin for chronic migraine. Propranolol, topiramate and amitriptyline are not for aborting an established attack.
- Cluster headache: high-flow oxygen and subcutaneous sumatriptan for attacks; verapamil for prevention.
- Trigeminal neuralgia: carbamazepine.

Respiratory drugs: asthma, cough and cold

- **Bronchial asthma**: objective is control of symptoms and prevention of exacerbations. **Relievers**: **short-acting β_2 agonists (salbutamol, terbutaline)**: tremor, tachycardia, **hypokalaemia**, hyperglycaemia; **ipratropium** in severe attacks. **Controllers**: **inhaled corticosteroids (budesonide, beclometasone, fluticasone) are the foundation** (oral candidiasis, dysphonia: rinse the mouth); **long-acting β_2 agonists (formoterol, salmeterol) never alone**, always with an inhaled steroid; **leukotriene antagonists (montelukast)**; **theophylline** (phosphodiesterase inhibition and adenosine blockade; narrow index, 10-20 mg/L, nausea, arrhythmia and seizures; level raised by ciprofloxacin, erythromycin, cimetidine; lowered by smoking and rifampicin; mainly second-line); **mast-cell stabiliser cromolyn**; biologics for

severe asthma (**omalizumab** anti-IgE, mepolizumab anti-IL-5, dupilumab). **GINA 2024 (unchanged in 2025), adults and adolescents**: the preferred track uses **low-dose ICS-formoterol (budesonide-formoterol) as the reliever**, as needed only at steps 1-2 and as maintenance-and-reliever therapy (MART) at steps 3-5; a short-acting β_2 agonist alone, without an inhaled steroid, is not recommended (SABA with a separate inhaled steroid is the alternative track).

- **Acute severe asthma**: oxygen, **nebulised salbutamol plus ipratropium, systemic corticosteroid (prednisolone 40-50 mg or IV hydrocortisone)**, IV magnesium sulphate, aminophylline rarely; no routine antibiotics or sedatives. **COPD**: LAMA and/or LABA, an inhaled steroid for frequent exacerbations with eosinophils $\geq$ 300 (GOLD 2024), roflumilast, azithromycin, **long-term oxygen over 15 hours a day if PaO_2 under 55 mmHg**; acute exacerbation: bronchodilators, prednisolone 5 days, antibiotics if sputum is purulent. Acute bronchitis usually needs no antibiotic; a lower respiratory tract infection or pneumonia in a child is treated with amoxicillin (WHO).
- **Antitussives** suppress the cough centre: **codeine, dextromethorphan (an NMDA antagonist with no analgesia or addiction; serotonin syndrome with MAOIs)**, noscapine, pholcodine (withdrawn in the UK and EU in 2023 after anaphylaxis to muscle relaxants), peripheral agents (levodropropizine, benzonatate); avoid codeine under 12 years. Use only for dry, distressing cough; never in productive cough or asthma.
- **Expectorants** (guaifenesin, ammonium chloride, potassium iodide) increase bronchial secretion volume; evidence is weak. **Mucolytics** change the **mucus** itself: **acetylcysteine** (breaks disulphide bonds), carbocisteine, bromhexine and ambroxol, **dornase alfa** (DNase, cystic fibrosis), hypertonic saline; acetylcysteine can cause bronchospasm; risk in asthmatics.
- **Nasal decongestants**: α_1 agonists (**xylometazoline, oxymetazoline** topically; **pseudoephedrine** orally) constrict mucosal vessels; **topical use beyond 5-7 days gives rebound congestion (rhinitis medicamentosa)**; oral agents raise blood pressure and cause insomnia, retention in BPH; oral phenylephrine is poorly effective (FDA advisory panel 2023). **Common cold remedies**: paracetamol or an NSAID, saline irrigation, first-generation antihistamines for rhinorrhoea; antibiotics are of no use; ipratropium nasal spray reduces rhinorrhoea.
- ***Pneumocystis jirovecii* pneumonia**: **co-trimoxazole** high dose (trimethoprim 15-20 mg/kg/day for 21 days) **with prednisolone if PaO_2 under 70 mmHg**; alternatives: IV pentamidine, primaquine plus clindamycin, atovaquone; prophylaxis for CD4 under 200 with low-dose co-trimoxazole.

Gastrointestinal drugs: acid, motility, diarrhoea, vomiting

- **Antacids**: neutralise acid; **aluminium hydroxide (constipating; hypophosphataemia) is combined with magnesium hydroxide or trisilicate (laxative)** so that bowel effects cancel; calcium carbonate (quick, rebound acid, hypercalcaemia and milk-alkali syndrome); **sodium bicarbonate** (gas, systemic alkalosis, sodium load: not for regular use); alginates for reflux; separate them from other drugs by 2 hours (chelation: tetracyclines, fluoroquinolones, iron, levothyroxine).
- **Acid suppression**: **PPIs** (irreversibly inhibit H^+-K^+ ATPase; most effective; take before the first meal; C. difficile, hypomagnesaemia, fractures, B_{12} deficiency) are first-line in peptic ulcer, GERD and with NSAIDs; **H_2 blockers** (famotidine) less potent, nocturnal acid; **sucralfate** (acid-activated mucosal coat, needs acid, constipation, aluminium); **bismuth** (coating, anti-H. pylori); **misoprostol** (PGE_1 analogue for NSAID ulcers; diarrhoea, abortifacient).
- ***H. pylori* eradication**: 14 days of PPI plus amoxicillin plus clarithromycin (**triple**) where clarithromycin resistance is under 15-20%; **bismuth quadruple therapy (PPI, bismuth, tetracycline, metronidazole)** is now preferred first-line where resistance is higher (Maastricht VI 2022, ACG 2024).
- **Antispasmodics**: **hyoscine butylbromide** (quaternary, no CNS effect), **dicyclomine**, mebeverine, peppermint oil, drotaverine; they reduce painful gut spasm in irritable bowel syndrome and colic; avoid in glaucoma, ileus, megacolon and prostatic obstruction.
- **Diarrhoea**: the first aim is **rehydration with oral rehydration solution** (WHO low-osmolarity ORS 245 mOsm/L: sodium 75, glucose 75 mmol/L; glucose drives sodium absorption through SGLT1) **plus zinc** for 10-14 days in children (20 mg a day; 10 mg under 6 months); IV fluids for severe dehydration (Ringer's lactate). **Antimicrobials only for** cholera (single-dose doxycycline or azithromycin), dysentery (ciprofloxacin or azithromycin), giardiasis, amoebiasis, *C. difficile* (oral vancomycin or fidaxomicin) and traveller's diarrhoea. **Antimotility drugs** (**loperamide**, μ agonist that does not cross the blood-brain barrier at usual doses; **diphenoxylate**, a pethidine congener sold with a sub-therapeutic dose of **atropine**, which adds nothing at normal doses but makes an overdose unpleasant and so deters misuse; codeine) are **harmful in dysentery, toxic megacolon and children under 2 years** (ileus, prolonged infection); racecadotril (enkephalinase inhibitor), bismuth, and adsorbents have little role.
- **Laxatives** produce a soft formed stool gently, **purgatives** a watery evacuation by stronger stimulation. Classes: **bulk-forming** (ispaghula, psyllium: need fluid), **osmotic** (**lactulose** (also for hepatic encephalopathy), macrogol, magnesium sulphate or hydroxide, sodium phosphate: nephropathy), **stimulant** (**bisacodyl, senna, sodium picosulfate**; chronic misuse gives the "cathartic colon"; castor oil), **faecal softeners and lubricants** (docusate; liquid paraffin: lipoid pneumonia, vitamin malabsorption), secretagogues (lubiprostone, linaclotide), prucalopride, and **methylnaltrexone or naloxegol for opioid constipation**. Contraindicated in intestinal obstruction. **Non-drug measures first**: fibre, fluid, exercise, a regular toilet habit.
- **Emetics** (ipecacuanha, apomorphine, hypertonic saline) are **no longer recommended** for poisoning (aspiration, no benefit over activated charcoal); contraindicated in corrosive, hydrocarbon or sedative ingestion and in drowsy patients. **Antiemetics by cause**: **5-HT_3 antagonists (ondansetron)**, acting at the chemoreceptor trigger zone (area postrema) and on gut vagal afferents, for chemotherapy and postoperative emesis (best against **cisplatin-induced vomiting**; headache, constipation, QT prolongation); **D_2 blockers (metoclopramide, domperidone, prochlorperazine, haloperidol)** (extrapyramidal effects; metoclopramide is also prokinetic); **H_1 antihistamines and anticholinergics (cyclizine, promethazine, cinnarizine, dimenhydrinate, hyoscine)** for motion sickness and vestibular causes (**hyoscine is the most effective for preventing motion**

sickness, oral 30-60 minutes before the journey or a transdermal patch lasting 3 days; much less effective once sickness has begun; ondansetron, domperidone and metoclopramide do not work, the vestibular pathway being muscarinic and histaminergic); **NK_1 antagonists (aprepitant)** with dexamethasone and a 5-HT_3 antagonist for highly emetogenic chemotherapy such as **cisplatin** (olanzapine added as a fourth drug: ASCO and MASCC/ESMO); doxylamine with pyridoxine for nausea of pregnancy; cannabinoids; olanzapine.

- **Amoebiasis**: **tissue amoebicides** (metronidazole 800 mg three times daily for 5-10 days, tinidazole) for invasive colitis and liver abscess, **then a luminal agent** (**diloxanide furoate**, paromomycin) to clear cysts, because metronidazole is absorbed high in the gut; **asymptomatic cyst passers** need only a luminal agent. **Giardiasis**: tinidazole (single 2 g dose), metronidazole for 5 days, nitazoxanide.
- **Intestinal helminths**: **albendazole** (single 400 mg dose for roundworm and hookworm, repeated after 2 weeks for threadworm; 3 days for whipworm; binds β-tubulin; teratogenic in the first trimester), mebendazole, **pyrantel pamoate** (nicotinic agonist causing spastic paralysis), **ivermectin** (glutamate-gated chloride channels: strongyloides, scabies, onchocerciasis), **praziquantel** (raises calcium permeability, tetanic paralysis: tapeworms, schistosomes, flukes except *Fasciola*, which needs triclabendazole), niclosamide, **diethylcarbamazine** (filariasis).

Endocrine drugs

Diabetes

Class	Mechanism	Key points
Metformin	**reduces hepatic gluconeogenesis** (AMPK), improves insulin sensitivity	first-line in type 2; no hypoglycaemia alone, no weight gain; GI upset, B12 deficiency, **lactic acidosis** (stop if eGFR below 30, in contrast studies, sepsis)
Sulfonylureas (glimepiride, gliclazide, glibenclamide)	close K_ATP channels, stimulate insulin release	hypoglycaemia, weight gain; glibenclamide worst in renal failure and the elderly
Meglitinides (repaglinide)	same, shorter	postprandial
Pioglitazone	PPAR-γ agonist	fluid retention and heart failure, fractures, bladder cancer concern; rosiglitazone restricted
α-glucosidase inhibitors (acarbose)		flatulence; treat hypoglycaemia with glucose
DPP-4 inhibitors (sitagliptin, linagliptin)	raise incretin	weight-neutral; pancreatitis reports
GLP-1 agonists (liraglutide, semaglutide, dulaglutide; tirzepatide is dual GIP/GLP-1)		weight loss, cardiovascular benefit, nausea, pancreatitis, **medullary thyroid carcinoma/MEN2 contraindication**; also used for obesity
SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin)	block proximal tubular glucose reabsorption	**genital mycotic infection**, urinary infection, volume depletion, **euglycaemic ketoacidosis** (stop 3 days before surgery, FDA 2020), Fournier gangrene; weight loss, heart-failure and CKD benefit
Insulin		hypoglycaemia, lipodystrophy; analogues: rapid (lispro, aspart, glulisine), long (glargine, detemir, degludec)

- ADA 2024 and ESC: in type 2 diabetes with cardiovascular, kidney or heart-failure disease, SGLT2 inhibitor or GLP-1 agonist is chosen irrespective of HbA1c.
- Insulin in DKA: IV soluble insulin with fluids and potassium replacement (potassium before insulin if below 3.3 mmol/L).
- **Anti-obesity drugs**: **GLP-1 agonists (semaglutide 2.4 mg weekly) and tirzepatide** give the largest weight loss (15–20%; semaglutide also cut cardiovascular events in non-diabetic obesity, SELECT 2023); orlistat (lipase inhibitor), phentermine–topiramate, naltrexone–bupropion. Sibutramine (cardiovascular events) and rimonabant (depression, suicide) were withdrawn.

Insulin preparations and diabetic emergencies

Type	Examples	Onset	Peak	Duration
Rapid-acting analogues	lispro, aspart, glulisine	10-20 min	1-2 h	3-5 h
Short-acting	**regular (soluble) insulin**	30-60 min	2-4 h	5-8 h
Intermediate	NPH (isophane)	1-2 h	4-12 h	12-18 h
Long-acting	glargine, detemir; **degludec** (over 42 h)	1-2 h	flat	about 24 h or more

- Adverse effects: **hypoglycaemia**, weight gain, **lipodystrophy or lipohypertrophy** (rotate sites), hypokalaemia, local allergy, oedema; the Somogyi effect (rebound after nocturnal hypoglycaemia) and the dawn phenomenon explain morning hyperglycaemia. **Insulin sensitisers**: metformin (first-line, with lifestyle), thiazolidinediones (pioglitazone).
- **Hypoglycaemia**: 15-20 g oral glucose if conscious; **IV 10% or 50% dextrose, or IM glucagon 1 mg**, if not. **Diabetic ketoacidosis**: IV fluids first (about 1-1.5 L in the first hour), then **a fixed-rate IV infusion of regular (soluble) insulin 0.1 unit/kg/hour once potassium is above 3.3 mmol/L** (only soluble insulin or a rapid analogue is given IV; NPH is a suspension, and glargine and degludec are made to act as subcutaneous depots), potassium replacement (20-30 mmol per litre), dextrose added when glucose falls below about 250 mg/dL, bicarbonate only for pH under 6.9; the **hyperosmolar state** needs more fluid and less insulin. **Ambulatory care**: diet and exercise, metformin, add agents by comorbidity (SGLT2 inhibitor or GLP-1 agonist for cardiovascular or kidney disease), sick-day rules, foot and eye checks.

Corticosteroid ranking and thyroid hormone preparations

Steroid	Anti-inflammatory (hydrocortisone = 1)	Sodium retention	Duration of action
Hydrocortisone, cortisone	1	1	short, 8-12 h
Prednisolone, prednisone	4	0.8	intermediate, 12-36 h
Methylprednisolone, triamcinolone	5	0.5 or none	intermediate
Dexamethasone, betamethasone	**25-30**	**none**	**long, 36-54 h**
Fludrocortisone	10	**125-250 (mainly mineralocorticoid)**	intermediate

- **Natural versus synthetic**: cortisol and cortisone bind corticosteroid-binding globulin and have mineralocorticoid effect; synthetic compounds are more potent (a 1,2 double bond and fluorination), longer acting and nearly free of sodium retention (except fludrocortisone). **Cortisone and prednisone are prodrugs** activated by hepatic 11β-hydroxysteroid dehydrogenase, so prednisolone or hydrocortisone is used in severe liver disease. Dexamethasone is the choice for cerebral oedema, antenatal lung maturation and as an antiemetic because it has no fluid retention.
- **Thyroid hormone preparations**: **levothyroxine (T_4)** is the drug of choice (half-life 7 days, once daily on an empty stomach, about 1.6 µg/kg a day; **monitor TSH 6-8 weeks after a change**; start low, 25 µg, in the elderly or with coronary disease); **liothyronine (T_3)** acts fast with a short half-life (the textbook answer for myxoedema coma; current practice gives IV levothyroxine, with or without liothyronine, plus hydrocortisone: ATA 2014; also used in preparation for radioiodine); desiccated thyroid is discouraged. **Antithyroid classification**: thionamides (carbimazole, methimazole, PTU), ionic inhibitors (perchlorate, thiocyanate), iodine and iodides, radioactive iodine, β-blockers, others (lithium).

Thyroid

- **Thionamides**: carbimazole (prodrug of methimazole), methimazole, **propylthiouracil (PTU)**: block thyroid peroxidase; PTU also inhibits peripheral T4 to T3 conversion. Adverse effects: **agranulocytosis (warn about sore throat and fever)**, rash, hepatotoxicity (PTU greater: boxed warning).
- **Pregnancy**: carbimazole/methimazole in the first trimester is associated with **congenital malformations** (aplasia cutis, choanal atresia, oesophageal atresia), so PTU is used in the first trimester and a switch back to carbimazole made afterwards (hepatotoxicity risk of PTU; ATA 2017).
- **Potassium iodide (Lugol's iodine)**: Wolff–Chaikoff effect; reduces gland vascularity and hormone release; given for **7–10 days before thyroidectomy** (and in thyroid storm, after a thionamide). Radioactive iodine (^{131}I) is contraindicated in pregnancy and breastfeeding.
- **Thyroid storm**: β-blocker (propranolol), PTU, iodide (an hour after the thionamide), hydrocortisone, cooling, fluids.
- Levothyroxine: take on an empty stomach; interactions with iron, calcium, PPIs, cholestyramine. Amiodarone and lithium cause hypothyroidism.

Corticosteroids

- Actions: anti-inflammatory and immunosuppressive; adverse effects: Cushingoid features, hyperglycaemia, osteoporosis, avascular necrosis, myopathy, peptic ulcer (with NSAIDs), cataract, glaucoma, psychosis, growth suppression, hypertension, infection.
- Potency: dexamethasone and betamethasone (about 25–30 × hydrocortisone, no mineralocorticoid effect); prednisolone 4 × (5 mg ≈ hydrocortisone 20 mg); **fludrocortisone** is mainly mineralocorticoid. Hydrocortisone: both effects.
- **HPA suppression** after more than about 3 weeks at prednisolone 5–7.5 mg or above. Abrupt withdrawal, or stress, may cause **adrenal crisis** (hypotension, vomiting, hyponatraemia, hyperkalaemia, hypoglycaemia): **IV hydrocortisone 100 mg and IV saline immediately**; ACTH is useless in a suppressed gland. Tapering is needed, and "sick-day rules" (double or triple dose in illness) apply.
- Antenatal steroids (dexamethasone or betamethasone) between 24 and 34 weeks reduce neonatal respiratory distress.
- Inhaled steroids: oral candidiasis, dysphonia; rinse the mouth.

Sex hormones, contraception, oxytocics and bone (curriculum points)

- **Oestrogens**: natural (estradiol, estrone, estriol, conjugated equine oestrogens), **synthetic steroidal (ethinylestradiol, mestranol)** and non-steroidal (diethylstilbestrol). The **17α-ethinyl derivatives are orally active, more potent and longer acting because they resist first-pass metabolism**. Uses: menopausal symptoms, hypogonadism, contraception, atrophic vaginitis. **Contraindications**: oestrogen-dependent cancer, **thromboembolism**, active liver disease, undiagnosed vaginal bleeding, pregnancy, migraine with aura. Adverse effects: nausea, breast tenderness, venous thrombosis, hypertension, gallstones, **endometrial hyperplasia and carcinoma if unopposed (so a progestogen is added when a uterus is present)**, breast cancer with combined therapy after about 5 years (WHI); diethylstilbestrol in pregnancy caused **clear-cell vaginal carcinoma in daughters**.
- **Menopausal hormone therapy**: oestrogen is the most effective treatment for hot flushes; a woman **with a uterus takes a progestogen with it** (cyclical or continuous, or the levonorgestrel IUS) to prevent endometrial hyperplasia and cancer, and **oestrogen alone is only for women after hysterectomy**; lowest effective dose, reviewed yearly; transdermal oestrogen carries less venous thrombosis risk than oral. Tamoxifen and raloxifene worsen flushes; androgens do not relieve them. Non-hormonal options: SSRIs or SNRIs, gabapentin, clonidine, and **fezolinetant** (neurokinin-3 receptor antagonist, FDA 2023).
- **Progestogens**: progesterone, medroxyprogesterone, norethisterone, **levonorgestrel**, desogestrel, drospirenone (anti-mineralocorticoid: hyperkalaemia), dydrogesterone. Uses: contraception, heavy bleeding, endometriosis, endometrial protection in HRT, luteal support, prevention of preterm birth (vaginal progesterone with a short cervix). Adverse effects: irregular bleeding, weight gain, acne (older, androgenic agents), mood change; contraindicated in undiagnosed bleeding, severe liver disease and some breast cancers.

- **Combined oral contraceptive (30-35 µg ethinylestradiol): suppresses FSH and LH so ovulation is inhibited** (the main effect), thickens cervical mucus and thins the endometrium; non-contraceptive benefits: less dysmenorrhoea and menorrhagia, **less ovarian and endometrial cancer**, acne and PCOS improvement; risks: venous thrombosis (higher with drospirenone, desogestrel and gestodene than with levonorgestrel), hypertension, breast tenderness; contraindicated (WHO eligibility criteria): **migraine with aura, smoker over 35 (15 or more a day), blood pressure ≥ 160/100, past thromboembolism, breastfeeding under 6 weeks, active liver disease**; effectiveness falls with enzyme inducers and with vomiting or diarrhoea. **Progestogen-only pill** (levonorgestrel, norethisterone, desogestrel with a 12-hour window): works mainly on cervical mucus; suitable in breastfeeding. **Depot medroxyprogesterone acetate 150 mg IM every 3 months**: bone density loss, delayed return of fertility, amenorrhoea. **Implants** (etonogestrel 3 years, levonorgestrel 5 years) and the **levonorgestrel intrauterine system** are the most effective reversible methods; the **copper IUD** lasts up to 10 years.
- **Emergency contraception**: **levonorgestrel 1.5 mg once, within 72 hours** (effective up to 120 hours with falling efficacy), **ulipristal acetate 30 mg within 120 hours** (more effective than levonorgestrel; reduced by concurrent progestogens), and the **copper IUD within 5 days (most effective)**; they delay ovulation and do not end an established pregnancy.
- **Anabolic steroids** (nandrolone, stanozolol, oxandrolone, oxymetholone): a rational use only where protein anabolism or marrow stimulation is needed: **aplastic anaemia and marrow failure, anaemia of CKD, hereditary angioedema (danazol, stanozolol), wasting (HIV, burns), delayed puberty or Turner syndrome (oxandrolone)**. Adverse effects: **cholestatic jaundice, peliosis hepatis, hepatic adenoma and carcinoma (17α-alkylated oral agents)**, virilisation in women, **premature epiphyseal closure** in children, testicular atrophy and low sperm count in men, **low HDL**, fluid retention, polycythaemia, aggression; abuse in sport. **Testosterone** for hypogonadism: injectable esters or undecanoate (oral methyltestosterone is hepatotoxic); polycythaemia, prostate and sleep-apnoea cautions.
- **Calcium regulation and bone**: **PTH, 1,25-dihydroxyvitamin D (calcitriol) and calcitonin** regulate plasma calcium; **cinacalcet** (calcimimetic) for hyperparathyroidism; hypercalcaemia and tetany management is under the adverse-effects topic below (fluid and electrolyte emergencies).
- **Oxytocics**: **oxytocin** (IV infusion to induce or augment labour, 10 IU IM after delivery; half-life 3-5 minutes; adverse effects: **water intoxication** (ADH-like), hypotension with a fast IV bolus, hyperstimulation and uterine rupture); **ergometrine** (0.2 mg IM; sustained tetanic contraction, so **not for induction**; **contraindicated in hypertension, pre-eclampsia, heart disease and with a retained placenta**; vasoconstriction, nausea); **carboprost** ($PGF_2\alpha$, 250 µg IM every 15 minutes up to 8 doses; **contraindicated in asthma**; bronchospasm, diarrhoea); **misoprostol** (PGE_1; 800 µg sublingual to treat PPH when IV oxytocin is unavailable or fails, WHO 2025; 600 µg orally for prevention where oxytocin cannot be given); dinoprostone for cervical ripening; **carbetocin** (heat-stable oxytocin analogue). **Drugs of choice for postpartum haemorrhage**: **oxytocin first (WHO)**, then ergometrine, carboprost, misoprostol, tranexamic acid, with uterine massage. **Abortifacients**: **mifepristone then misoprostol** (under 12 weeks: mifepristone 200 mg, then misoprostol 800 µg 1-2 days later; from 12 weeks the same drugs with repeated 400 µg misoprostol doses; WHO 2022), misoprostol alone, methotrexate-misoprostol, extra-amniotic agents in later trimesters. **Tocolytics** (to delay preterm labour 24-34 weeks for 48 hours, for antenatal steroids and transfer): **nifedipine** (first-line in many centres), **atosiban** (oxytocin-receptor antagonist), **indomethacin** (under 32 weeks; ductus constriction, oligohydramnios), **β_2 agonists** (ritodrine, terbutaline: maternal pulmonary oedema, tachycardia, hypokalaemia, hyperglycaemia); magnesium sulphate is for eclampsia and fetal neuroprotection, not as a tocolytic. **Contraindications**: chorioamnionitis, placental abruption, severe pre-eclampsia, fetal death or distress, lethal anomaly.

Pituitary, sex hormones, bone

- **Dopamine agonists** for hyperprolactinaemia: **cabergoline** (preferred: better tolerated, once or twice weekly) and bromocriptine (nausea, postural hypotension; also acromegaly). Cabergoline valvulopathy at high doses (Parkinson's). Bromocriptine: occasionally used in lactation suppression (not recommended now).
- **Octreotide** (somatostatin analogue: acromegaly, carcinoid, VIPoma, and **acute variceal bleeding**, where an infusion causes splanchnic vasoconstriction and lowers portal pressure, given with endoscopic band ligation; **terlipressin** is the other vasoactive drug; a non-selective β-blocker such as propranolol or carvedilol is for preventing first and repeat bleeds, not the acute event; Baveno VII 2022). **Pegvisomant**: GH receptor antagonist. **Desmopressin**: V_2 agonist: central diabetes insipidus, nocturnal enuresis, haemophilia A and von Willebrand disease (releases factor VIII); hyponatraemia. **Clomiphene** (SERM, induces ovulation in anovulation: PCOS; letrozole now preferred first-line), **tamoxifen** (ER-positive breast cancer; endometrial cancer, VTE), **raloxifene**, **anastrozole, letrozole** (aromatase inhibitors in post-menopausal women: osteoporosis, arthralgia), **finasteride/dutasteride** (5α-reductase), **flutamide, bicalutamide** (anti-androgens), spironolactone.
- Combined oral contraceptive: avoid in migraine with aura, smokers over 35, thromboembolism, breast cancer; interactions with enzyme inducers.
- **Osteoporosis**: bisphosphonates (alendronate: oesophagitis, take upright; zoledronate; atypical femoral fracture, osteonecrosis of the jaw), denosumab (RANKL; rebound fractures after stopping), teriparatide and abaloparatide (anabolic), romosozumab (cardiovascular risk), calcium and vitamin D.
- Oxytocin and ergometrine in third-stage management; **carbetocin**; misoprostol where parenteral drugs are unavailable.

Chemotherapy of infections

General principles, sulphonamides, broad-spectrum and special groups

- **Principles**: treat only bacterial infection; take cultures before starting; choose by likely organism and local resistance, narrow spectrum where possible; correct dose, route and **duration**; combine drugs only for a reason (TB, synergy,

preventing resistance, mixed infections); drain pus; consider host factors (renal and liver function, pregnancy, allergy, immunity); prophylaxis only where proven. **Misuse**: antibiotics for viral illness or undiagnosed fever, too short or too long, wrong dose, unnecessary broad spectrum or combinations, over-the-counter sale, and agricultural use, all driving resistance.

- **Sulphonamides** (sulfamethoxazole, sulfadiazine, sulfacetamide, silver sulfadiazine, sulfasalazine) compete with para-aminobenzoic acid in folate synthesis. Today limited by resistance, but used in **co-trimoxazole**. Adverse effects: **crystalluria** (drink fluids, alkalinise urine), hypersensitivity and Stevens-Johnson syndrome, **haemolysis in G6PD deficiency**, marrow suppression, **kernicterus in the newborn and when given in late pregnancy** (they displace bilirubin). **Co-trimoxazole**: sulfamethoxazole with trimethoprim (5 : 1, giving 20 : 1 in plasma), **sequential blockade of folate synthesis, bactericidal and slower to select resistance**; uses: **Pneumocystis pneumonia and prophylaxis, toxoplasmosis, nocardiosis, UTI, shigellosis, MDR typhoid, Stenotrophomonas**; hyperkalaemia and creatinine rise.
- **Mainly against Gram-positive organisms**: **penicillin G and V** (streptococci, meningococcus, syphilis), **penicillinase-resistant penicillins** (cloxacillin, flucloxacillin), first-generation cephalosporins (cefazolin), macrolides, clindamycin, **vancomycin** (MRSA, *C. difficile* orally), linezolid, daptomycin. **Mainly against Gram-negative**: aminoglycosides, aztreonam, third-generation cephalosporins (ceftriaxone, ceftazidime), fluoroquinolones, carbapenems, colistin (nephrotoxic, neurotoxic) for XDR organisms, tigecycline.
- **Antipseudomonal drugs**: **piperacillin-tazobactam, ceftazidime, cefepime, ceftolozane-tazobactam, meropenem and imipenem (not ertapenem), gentamicin, tobramycin, amikacin, ciprofloxacin, aztreonam, colistin**; severe infections need two active drugs, at least until sensitivities return.
- **Broad-spectrum** antibiotics act on many Gram-positive **and** Gram-negative organisms (and atypicals): **tetracyclines, chloramphenicol, ampicillin and amoxicillin, third-generation cephalosporins, fluoroquinolones, carbapenems**; the price is disturbance of normal flora, **superinfection** (candidiasis, *C. difficile*) and faster resistance.
- **Intestinal protozoa other than amoeba and Giardia**: **Cryptosporidium**: **nitazoxanide** (inhibits pyruvate–ferredoxin oxidoreductase; paromomycin was the older answer), and in AIDS restoring immunity with ART matters most; **Cystoisospora (Isospora) and Cyclospora**: co-trimoxazole; **microsporidia**: albendazole (*Encephalitozoon*; *Enterocytozoon bieneusi* responds poorly, fumagillin). **Babesiosis**: atovaquone plus azithromycin, preferred in mild and severe disease (IDSA 2020); clindamycin plus quinine is the older alternative; exchange transfusion for high parasitaemia or organ failure.
- **Anaerobes**: **metronidazole** (drug of choice, with a disulfiram-like reaction), clindamycin, carbapenems, β-lactam with β-lactamase inhibitor, cefoxitin, chloramphenicol; **aminoglycosides are inactive**. **Tetanus**: human tetanus immunoglobulin, wound debridement, **metronidazole** (preferred to penicillin, which is a GABA-A antagonist), spasm control with benzodiazepines and magnesium, and a vaccine course, since the disease gives no immunity.
- **Antiviral development is hard** because viruses replicate inside host cells (poor selectivity), establish latency, mutate quickly, and treatment must start early.
- **Leprosy multidrug therapy**: rifampicin 600 mg monthly (supervised), dapsone 100 mg daily, clofazimine 300 mg monthly plus 50 mg daily; multibacillary 12 months, paucibacillary 6 months (older teaching: two drugs for paucibacillary). **Lepra reactions**: type 1 (reversal): prednisolone; **type 2 (erythema nodosum leprosum)**: prednisolone, clofazimine, **thalidomide (never in women who may become pregnant)**; treatment of the reaction does not stop the MDT.
- **Visceral leishmaniasis (kala-azar)**: **liposomal amphotericin B, a single IV infusion of 10 mg/kg, is the first-line regimen in South Asia** (WHO 2010; adopted by Nepal, India and Bangladesh) with cure over 95%; alternatives: **paromomycin plus miltefosine**, miltefosine alone (oral; **teratogenic: not in pregnancy**), amphotericin B deoxycholate (infusion reactions, nephrotoxicity), sodium stibogluconate (resistance in Bihar and Nepal's border areas, cardiotoxicity, pancreatitis); post-kala-azar dermal leishmaniasis: miltefosine for 12 weeks (the older South Asian regimen; WHO 2026 favours shorter liposomal amphotericin B regimens, alone or with miltefosine); a confirmed relapse after the single dose is not treated with the same single dose again (WHO 2026); HIV co-infection needs repeated liposomal doses and secondary prophylaxis.
- **Lymphatic filariasis**: **diethylcarbamazine (DEC)** kills microfilariae rapidly and adult worms partly, usually with albendazole in annual mass treatment (and **ivermectin as a third drug in the triple-drug regimen (IDA)** WHO 2017, where onchocerciasis and loiasis are absent); **DEC is avoided in onchocerciasis (Mazzotti reaction) and loiasis (encephalopathy)**; doxycycline for 6 weeks kills adult worms through *Wolbachia*.
- **Neurocysticercosis** (*Taenia solium* larvae): **albendazole 15 mg/kg a day for 10-14 days, given with a corticosteroid (prednisolone or dexamethasone) started first** to blunt inflammation from dying cysts, **plus an antiepileptic** for seizures; praziquantel is added for multiple cysts; calcified (dead) lesions need no antiparasitic drug; intraventricular cysts and hydrocephalus need surgery.
- **Sexually transmitted infections**:

Infection	Treatment
Syphilis	**Benzathine penicillin G 2.4 million units IM once** (early); weekly for 3 weeks in late latent disease; IV aqueous penicillin G for 10-14 days for neurosyphilis; doxycycline 100 mg twice daily for 14 days if allergic (28 days in late latent); in pregnancy desensitise and give penicillin; azithromycin not used (resistance); **Jarisch-Herxheimer reaction** within 24 hours
Gonorrhoea	**Ceftriaxone 500 mg IM once** (CDC 2021; 1 g at 150 kg or more), **1 g IM once in WHO 2024 and BASHH 2025**, because of fluoroquinolone and cefixime resistance; treat chlamydia as well unless excluded
Chlamydia	**Doxycycline 100 mg twice daily for 7 days** (CDC 2021) or azithromycin 1 g once (pregnancy)
Chancroid (*H. ducreyi*)	Azithromycin 1 g once or ceftriaxone 250 mg IM once
Lymphogranuloma venereum	Doxycycline for 21 days

Infection	Treatment
Donovanosis (granuloma inguinale)	Azithromycin for at least 3 weeks, until healed
Trichomoniasis	**Women: metronidazole 500 mg twice daily for 7 days; men: metronidazole 2 g once** (CDC 2021); tinidazole 2 g once as the alternative; treat partners
HIV	Dolutegravir-based antiretroviral therapy, as above

- **Common skin infections and infestations**: **scabies**: **permethrin 5% cream** from neck to toes for 8-14 hours, repeated in a week (or benzyl benzoate 25%, oral ivermectin 200 µg/kg twice a week apart, sulphur ointment in infants and pregnancy); treat the whole household; **pediculosis**: permethrin 1% lotion, malathion, dimeticone, combing, repeat in 7-10 days. **Psoriasis**: topical steroids, vitamin D analogues (calcipotriol), coal tar, dithranol; methotrexate, ciclosporin, acitretin, biologics (anti-TNF, IL-17, IL-23) for severe disease. **Acne**: benzoyl peroxide, topical retinoids, topical or oral antibiotics (doxycycline), hormonal treatment, **isotretinoin** (teratogenic; dry skin, raised triglycerides and liver enzymes; pregnancy prevention). **Vitiligo**: topical steroids or tacrolimus, narrow-band UVB or PUVA, ruxolitinib cream. **Local anti-infectives**: povidone-iodine, chlorhexidine, **silver sulfadiazine (burns)**, mupirocin (MRSA decolonisation), fusidic acid, gentian violet, potassium permanganate. **Antifungals**: topical azoles, terbinafine, nystatin for *Candida*, **griseofulvin** for tinea capitis (6-8 weeks, with fatty food; inducer, teratogenic), oral terbinafine for nail infection (12 weeks).
- **Urinary tract infection drugs**: **nitrofurantoin, trimethoprim, fosfomycin (single 3 g dose), pivmecillinam, cefalexin** for uncomplicated cystitis; fluoroquinolones kept in reserve; gentamicin or a cephalosporin for pyelonephritis; methenamine for prophylaxis; **in pregnancy avoid fluoroquinolones, tetracyclines, co-trimoxazole in the first and third trimesters, aminoglycosides, and nitrofurantoin near term**; treat asymptomatic bacteriuria. Phenazopyridine only relieves pain.
- **Tuberculosis, additional points**: **DOTS** has five elements: political commitment, case detection by sputum microscopy, standardised short-course chemotherapy **under direct observation**, regular drug supply, and recording and reporting (replaced by the Stop TB and End TB strategies). **Corticosteroids** are added in **TB meningitis (dexamethasone improves survival)**, pericarditis, severe respiratory failure from miliary disease, IRIS, adrenal disease and severe hypersensitivity reactions; not in routine pulmonary TB. **Primary (first-line) drugs**: isoniazid, rifampicin, pyrazinamide, ethambutol (streptomycin now rare); **second-line**: fluoroquinolones, bedaquiline, linezolid, clofazimine, cycloserine, ethionamide, delamanid.

Antibiotic classes and mechanisms

Class	Mechanism	Key adverse effects and points
β-lactams (penicillins, cephalosporins, carbapenems, monobactams)	inhibit transpeptidase (PBP)	hypersensitivity; carbapenems seizures (imipenem); aztreonam safe in penicillin allergy
Glycopeptides (**vancomycin**)	bind D-Ala-D-Ala	red man syndrome (infusion rate), nephrotoxicity; VRE alters target to D-Ala-D-Lac
Aminoglycosides (gentamicin, amikacin)	30S, bactericidal	nephrotoxicity, ototoxicity; **ineffective against anaerobes (uptake needs oxygen-dependent transport)**; concentration-dependent killing, once-daily dosing
Macrolides (azithromycin, clarithromycin, erythromycin)	50S (23S rRNA), block translocation	QT prolongation; erythromycin prokinetic; CYP3A4 inhibition (clarithromycin, erythromycin)
Tetracyclines (doxycycline)	30S	teeth and bone staining, avoid in pregnancy and under 8 years (exam answer; doxycycline courses of up to 21 days are now accepted at any age, AAP 2021); photosensitivity; doxycycline is the drug of choice for scrub typhus, common in Nepal
Chloramphenicol	50S	aplastic anaemia, grey baby syndrome
Clindamycin	50S	**pseudomembranous colitis (C. difficile)**
Linezolid	50S initiation	MRSA, VRE, VRSA; reversible myelosuppression, chiefly **thrombocytopenia after about 10-14 days** (weekly blood counts in courses over 2 weeks), optic and peripheral neuropathy, lactic acidosis, serotonin syndrome with SSRIs (weak MAO inhibitor)
Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)	DNA gyrase and topoisomerase IV	tendon rupture, QT prolongation, seizures, dysglycaemia; **avoided in pregnancy and children (cartilage damage concern)**
Co-trimoxazole	sequential folate block	marrow suppression, hyperkalaemia, SJS; interacts with methotrexate and warfarin
Metronidazole	DNA damage in anaerobes, protozoa	**disulfiram-like reaction with alcohol**, metallic taste, peripheral neuropathy
Nitrofurantoin		lower UTI; avoid near term (neonatal haemolysis) and when eGFR is below 45 (BNF; a short course may be used at 30–44)

Resistance mechanisms

- **MRSA**: **mecA gene encoding PBP2a**, a low-affinity penicillin-binding protein; resistant to nearly all β-lactams (not ceftaroline); β-lactamase is a separate mechanism (inhibited by clavulanate). Treatment: vancomycin, linezolid, daptomycin (not for pneumonia).
- **Macrolide resistance**: erm gene methylates 23S rRNA (also MLS_B resistance, including inducible clindamycin resistance); efflux pump mef.
- Gram-negatives: ESBLs (carbapenems), carbapenemases (NDM-1, KPC, OXA-48), porin loss, efflux.
- Beta-lactamase inhibitors: clavulanate, sulbactam, tazobactam, avibactam.
- Antimicrobial resistance is a major problem in Nepal and South Asia; use the WHO AWaRe classification (Access, Watch, Reserve) to guide choice.

Tuberculosis

- **WHO standard regimen for drug-susceptible pulmonary TB: 2 months of isoniazid, rifampicin, pyrazinamide,**

ethambutol (2HRZE), then 4 months of isoniazid and rifampicin (4HR), given daily as weight-banded fixed-dose combinations. Nepal's National Tuberculosis Programme uses 2HRZE/4HR for new cases and a longer continuation phase for TB meningitis, bone and joint and miliary TB (WHO: 2HRZE/10HR, 12 months in all); the old streptomycin-containing retreatment regimen (Category II) has been dropped (WHO 2017), and previously treated patients are tested for rifampicin resistance (Xpert MTB/RIF) before a regimen is chosen. Isoniazid-resistant, rifampicin-susceptible TB: 6 months of HRZE plus levofloxacin (WHO 2018). Doses (adult, daily): isoniazid 5 mg/kg (max 300 mg), rifampicin 10 mg/kg (max 600 mg), pyrazinamide 25 mg/kg, ethambutol 15 mg/kg.

- **4-month regimens (WHO 2022, kept in the consolidated Module 4, 2025)**: **2HPMZ/2HPM** (isoniazid, rifapentine, moxifloxacin, pyrazinamide) for drug-susceptible pulmonary TB at **12 years and over** (and at least 40 kg; conditional recommendation, costly because of rifapentine); and **2HRZ(E)/2HR** for **children and adolescents aged 3 months to 16 years with non-severe TB** (the SHINE trial). Exam answer: 2HRZE/4HR; the 4-month options are current practice where adopted.
- Adverse effects: **isoniazid**: hepatitis, peripheral neuropathy (give **pyridoxine**), lupus, seizures; **rifampicin**: hepatitis, orange body fluids, enzyme induction, flu-like syndrome (**rifabutin**, a weaker inducer, replaces it with boosted HIV protease inhibitors; with dolutegravir, rifampicin is kept and dolutegravir given twice daily); **pyrazinamide**: hepatotoxicity, **hyperuricaemia and gout**; **ethambutol**: **optic neuritis (dose-related, loss of red–green colour vision and acuity, reversible if stopped early)**: check vision at baseline; **streptomycin**: ototoxicity.
- **MDR-TB**: resistance to at least isoniazid and rifampicin (RR-TB: rifampicin resistance, treated the same way). Injectable agents (kanamycin, amikacin, capreomycin) are no longer used. WHO prefers all-oral regimens: **6-month BPaLM (bedaquiline, pretomanid, linezolid 600 mg, moxifloxacin)** for MDR/RR-TB at **14 years and over** (WHO 2022; moxifloxacin left out, BPaL, in pre-XDR-TB); **6-month BDLLfxC (bedaquiline, delamanid, linezolid, levofloxacin, clofazimine)**, added in 2025, usable also in children and in pregnancy, where BPaLM is not; and 9-month all-oral bedaquiline-containing regimens when fluoroquinolone resistance is excluded; longer individualised regimens otherwise. Bedaquiline: QT prolongation; linezolid: myelosuppression and peripheral and optic neuropathy.
- Definitions (WHO 2021): **pre-XDR-TB** = MDR/RR-TB plus resistance to a fluoroquinolone; **XDR-TB** = pre-XDR plus resistance to bedaquiline or linezolid (or both). The old definition (MDR plus a fluoroquinolone and a second-line injectable) is obsolete.
- TB preventive treatment (WHO 2024): 6 or 9 months of isoniazid, **3HP (weekly rifapentine plus isoniazid for 12 weeks; now WHO's preferred option for adults and adolescents with HIV, 2025)**, 1HP (daily for 1 month), 3HR (daily for 3 months) or 4R (rifampicin for 4 months).
- Leprosy: WHO multidrug therapy: **rifampicin, dapsone, clofazimine** (multibacillary 12 months, paucibacillary 6 months). Exam answer from older texts: paucibacillary rifampicin plus dapsone only; WHO 2018 gives all three drugs to both types. Single-dose rifampicin is post-exposure prophylaxis for contacts (WHO 2018); dapsone causes haemolysis in G6PD deficiency and methaemoglobinaemia; clofazimine skin pigmentation.

Malaria

- **Uncomplicated P. falciparum: artemisinin-based combination therapy (ACT)**, for example artemether–lumefantrine (WHO guidelines for malaria, 2022 onwards), for 3 days; a single low dose of primaquine (0.25 mg/kg) is added in low-transmission settings to block transmission (no G6PD test needed for this dose). Severe malaria: **IV artesunate (2.4 mg/kg at 0, 12 and 24 hours, then daily; 3 mg/kg in children under 20 kg)**, then a full ACT course; quinine only where artesunate is unavailable. Chloroquine resistance is widespread in falciparum and increasingly in vivax in parts of the region.
- **Vivax and ovale**: chloroquine (25 mg base/kg over 3 days) or an ACT for blood stages, plus **primaquine 0.25–0.5 mg/kg daily for 14 days (or tafenoquine, single dose) to kill liver hypnozoites and prevent relapse**; **test G6PD first**: primaquine in deficiency causes haemolysis (in mild deficiency, 0.75 mg/kg weekly for 8 weeks); primaquine is avoided in pregnancy and under 6 months.
- **Nepal** (National Malaria Treatment Protocol, EDCD 2019): vivax, chloroquine for 3 days plus primaquine for 14 days; uncomplicated falciparum, artemether–lumefantrine for 3 days plus single-dose primaquine; severe malaria, artesunate. Malaria is **mostly P. vivax** (70–95% of cases historically), but the **falciparum share has risen** (about 14% in 2021 to about 25% in 2023), and **most cases are now imported**, chiefly from India (in 2024 about 1,000 of some 1,040 cases; under 40 indigenous). Indigenous transmission is in the Terai and inner Terai districts of the west (Sudurpashchim, Lumbini, Karnali); the elimination target was moved from 2026 to 2030.
- Prophylaxis for travellers to chloroquine-resistant falciparum areas: **doxycycline 100 mg daily** (from 1-2 days before to 4 weeks after; photosensitivity, not in pregnancy or young children), **atovaquone–proguanil** (from 1-2 days before to 7 days after), or **mefloquine** weekly (neuropsychiatric effects); chloroquine fails where there is resistance, and sulfadoxine–pyrimethamine is not used for travellers.
- **Quinine**: cinchonism (tinnitus, deafness, headache, nausea), **hypoglycaemia** (it stimulates insulin release, added to the hypoglycaemia of severe malaria and pregnancy, so glucose is checked during infusion), QT prolongation (halofantrine prolongs it most), haemolysis.
- Amoebiasis and giardiasis: metronidazole or tinidazole, then a luminal agent (diloxanide, paromomycin); **asymptomatic cyst passers need only the luminal agent (diloxanide furoate)**, since metronidazole is absorbed before reaching the colon.

Antifungal, antiviral, anthelmintic

- **Amphotericin B** (polyenes, bind ergosterol): nephrotoxicity, infusion reactions, hypokalaemia; liposomal version safer. **Azoles** (fluconazole, itraconazole, voriconazole): block ergosterol synthesis, CYP inhibition, hepatotoxicity; voriconazole is first-line for invasive aspergillosis. **Echinocandins** (caspofungin) for candidaemia. **Terbinafine** (squalene epoxidase), **griseofulvin** (inducer).
- **HIV**: WHO's preferred first-line for adults and adolescents is **tenofovir + lamivudine (or emtricitabine) + dolutegravir (TLD)**; dolutegravir is an integrase inhibitor with a high barrier to resistance (WHO 2019 and 2021; kept in WHO's updated

recommendations on HIV clinical management, 2025, released January 2026, which make darunavir/ritonavir the preferred protease inhibitor after dolutegravir failure and allow long-acting injectables and oral two-drug regimens in selected stable patients). Children: dolutegravir-based too (paediatric dispersible tablets), with abacavir + lamivudine. Exam answer in older texts: efavirenz-based (TDF + 3TC/FTC + EFV); now an alternative only. NNRTIs: efavirenz, nevirapine (hepatotoxicity, rash), etravirine, rilpivirine, doravirine. Dolutegravir: weight gain, insomnia; neural tube defect concern has been downgraded and it can be used in pregnancy. Efavirenz: CNS effects; abacavir: HLA-B*5701 hypersensitivity; zidovudine: anaemia; tenofovir: renal toxicity, bone loss (TAF safer); protease inhibitors are boosted (ritonavir, a CYP3A4 inhibitor). PEP: three-drug regimen (TLD preferred, WHO 2024) started as soon as possible and within 72 hours, for 28 days. Cabotegravir long-acting is a newer option.

- **Hepatitis**: sofosbuvir-based DAAs cure HCV; entecavir or tenofovir for HBV.
- Aciclovir (herpes), ganciclovir (CMV, marrow suppression), oseltamivir (neuraminidase). **COVID-19**: **remdesivir**, an IV-only prodrug of an adenosine nucleotide analogue whose triphosphate is built into viral RNA by the RNA-dependent RNA polymerase and stops chain elongation; **nirmatrelvir–ritonavir** (oral 3CL protease inhibitor, boosted; many CYP3A4 interactions); molnupiravir (mutagenic nucleoside).
- Anthelmintics: albendazole (single dose for roundworm, hookworm; 3 days or mebendazole for whipworm; teratogenic in the first trimester), ivermectin (strongyloides, scabies), **levamisole and pyrantel** (nicotinic agonists, spastic paralysis of the worm; piperazine is a GABA agonist causing flaccid paralysis; levamisole also restores T-cell function, an immunomodulator once used in frequently relapsing nephrotic syndrome), **triclabendazole** (drug of choice for **fascioliasis**, *Fasciola hepatica* and *F. gigantica*, the flukes that resist praziquantel: WHO), praziquantel (schistosomes, other flukes, tapeworms; **albendazole, not praziquantel, is the drug of choice for hydatid disease and neurocysticercosis**, praziquantel an adjunct), diethylcarbamazine (filariasis).

Antibiotics in pregnancy

- Safe: penicillins, cephalosporins, **cefalexin, amoxicillin**, erythromycin, azithromycin, clindamycin, **nitrofurantoin (except near term)**, metronidazole.
- **Avoid: fluoroquinolones, tetracyclines, aminoglycosides (ototoxicity of the fetus), chloramphenicol (grey baby), co-trimoxazole in the first (folate) and third (kernicterus) trimesters, and fluconazole at high dose**.
- Asymptomatic bacteriuria must be treated in pregnancy.

Anticancer drugs

Cell-cycle specificity

- **S phase**: antimetabolites (**methotrexate, 5-fluorouracil, 6-mercaptopurine, cytarabine, gemcitabine, hydroxyurea**), topoisomerase I inhibitors (topotecan, irinotecan). **G2**: bleomycin, and etoposide (topoisomerase II). **M phase**: **vinca alkaloids** (prevent microtubule polymerisation) and **taxanes** (stabilise microtubules). Alkylating agents, anthracyclines, cisplatin and most others are cell-cycle non-specific. (Ergot alkaloids are not anticancer drugs.)
- Log-kill hypothesis: a given dose kills a fixed fraction of cells; combination chemotherapy uses non-overlapping toxicities.

Drug-by-drug

Drug	Mechanism	Characteristic toxicity
Doxorubicin, daunorubicin	intercalate DNA, topoisomerase II, free radicals	**dose-related cumulative cardiomyopathy** (above about 450–550 mg/m^2), alopecia; dexrazoxane protects; liposomal form safer for the heart
Bleomycin	DNA strand breaks	**pulmonary fibrosis**, skin changes; little myelosuppression
Cisplatin	DNA cross-links	**nephrotoxicity** (with magnesium wasting), **ototoxicity** (high-frequency hearing loss), the most emetogenic drug, neuropathy; hydration, amifostine; carboplatin: myelosuppression
Cyclophosphamide, ifosfamide	alkylating prodrugs	**haemorrhagic cystitis from acrolein: prevented by mesna** and hydration; ifosfamide neurotoxicity
Methotrexate	inhibits dihydrofolate reductase	myelosuppression, mucositis, hepatic fibrosis, pneumonitis; **rescue with folinic acid (leucovorin)**: a reduced folate that bypasses the DHFR block; also used in ectopic pregnancy, rheumatoid arthritis, psoriasis
5-Fluorouracil, capecitabine	thymidylate synthase inhibition	mucositis, hand–foot syndrome, DPD deficiency; leucovorin potentiates
Vincristine	M phase	**peripheral neuropathy**, ileus; little marrow suppression. **Vinblastine**: marrow suppression
Paclitaxel, docetaxel	**stabilise microtubules, block mitosis in M phase**	neuropathy, hypersensitivity (premedicate), neutropenia
Etoposide	topoisomerase II	myelosuppression, secondary leukaemia
Busulfan	alkylating	pulmonary fibrosis, skin pigmentation
Carmustine, lomustine (nitrosoureas)	alkylating	lipid-soluble, **cross the blood–brain barrier** (gliomas); delayed myelosuppression, pulmonary fibrosis
Cladribine, pentostatin, fludarabine	purine analogues (pentostatin inhibits adenosine deaminase)	**hairy cell leukaemia** (cladribine or pentostatin: long remissions after one course); fludarabine in CLL; marrow and lymphocyte (CD4) suppression
Dactinomycin	intercalates DNA	Wilms tumour, rhabdomyosarcoma, gestational trophoblastic disease
Mitomycin C	alkylating (bioreductive)	anal and bladder cancer; haemolytic uraemic syndrome, delayed myelosuppression
6-Mercaptopurine, azathioprine	purine analogue	marrow suppression; allopurinol raises levels (reduce dose); TPMT
L-asparaginase		pancreatitis, thrombosis
Arsenic trioxide, ATRA		acute promyelocytic leukaemia, differentiation syndrome

Targeted therapy and immunotherapy (modern practice)

Agent	Target	Use
Imatinib (dasatinib, nilotinib)	BCR-ABL tyrosine kinase; also c-KIT	CML, GIST

Agent	Target	Use
Trastuzumab	HER2	HER2-positive breast and gastric cancer; cardiotoxicity (check ejection fraction)
Rituximab	CD20	B-cell lymphoma, CLL; hepatitis B reactivation
Bevacizumab	VEGF	colorectal, lung cancers; bleeding, perforation
Cetuximab, panitumumab	EGFR	RAS wild-type colorectal cancer; acneiform rash
Erlotinib, gefitinib, osimertinib	EGFR mutation	non-small-cell lung cancer
Vemurafenib, dabrafenib	BRAF V600E	melanoma
Olaparib	PARP	BRCA-mutated breast, ovarian, prostate cancer
Pembrolizumab, nivolumab	PD-1	checkpoint blockade in melanoma, lung and many cancers; immune-related colitis, pneumonitis, thyroiditis, hepatitis
Ipilimumab	CTLA-4	melanoma
CDK4/6 inhibitors (palbociclib)		hormone-receptor-positive breast cancer
CAR-T cells		refractory B-cell leukaemia and lymphoma

- **Regimens that have changed**: **CLL**: fludarabine–cyclophosphamide–rituximab (FCR) is the older answer; first-line now a BTK inhibitor (ibrutinib, acalabrutinib, zanubrutinib) or venetoclax with obinutuzumab (ESMO 2021; NCCN 2025). **Multiple myeloma**: bortezomib (proteasome inhibitor), lenalidomide and dexamethasone (VRd), now usually with daratumumab (anti-CD38) as a quadruplet, then autologous transplant if fit (PERSEUS trial 2024). **Granulomatosis with polyangiitis**: glucocorticoid with cyclophosphamide (the classical answer) or **rituximab**, now preferred for induction (ACR/Vasculitis Foundation 2021).

Supportive care

- Antiemetics: **5-HT$_3$ antagonists, dexamethasone, NK$_1$ antagonists (aprepitant)**, olanzapine. Mesna for oxazaphosphorines; leucovorin for methotrexate; dexrazoxane for anthracyclines; amifostine for cisplatin; **allopurinol and rasburicase** for tumour lysis syndrome; G-CSF (filgrastim; sargramostim is GM-CSF) for febrile neutropenia risk. **Thrombopoietin receptor agonists** (romiplostim, eltrombopag, avatrombopag) raise platelets in chronic ITP; oprelvekin (IL-11) is obsolete.
- Hormonal agents: **tamoxifen** (a SERM: antagonist in breast, partial agonist in endometrium and bone; prodrug to endoxifen by CYP2D6), so **endometrial hyperplasia, polyps and carcinoma** (postmenopausal bleeding needs ultrasound and biopsy), venous thromboembolism, hot flushes, cataract; it preserves bone after the menopause and does not raise ovarian or cervical cancer; **fulvestrant** is a pure anti-oestrogen that degrades the receptor (SERD); aromatase inhibitors, GnRH analogues (leuprolide: flare, so give with an anti-androgen at the start), abiraterone, enzalutamide.
- Carcinogenic or teratogenic: alkylating agents (secondary leukaemia), methotrexate (teratogenic, abortifacient).

Adverse effects, interactions and antidotes

Antidotes

Poison or drug	Antidote
Paracetamol	**N-acetylcysteine** (replenishes glutathione, which neutralises NAPQI); best within 8 hours, the Rumack–Matthew nomogram is used; UK practice treats all staggered overdoses
Organophosphates (cholinesterase inhibitors)	**atropine** (muscarinic), **pralidoxime** (reactivates phosphorylated acetylcholinesterase before ageing; mainly restores nicotinic and muscle function); benzodiazepines for seizures
Opioids	naloxone
Benzodiazepines	flumazenil
Heparin	**protamine sulphate** (chemical antagonism)
Warfarin	**vitamin K$_1$ (phytomenadione)**, plus prothrombin complex concentrate for major bleeding
Dabigatran	idarucizumab
Factor Xa inhibitors	andexanet alfa, prothrombin complex concentrate
Digoxin	digoxin-specific Fab
Methanol, ethylene glycol	**fomepizole** (alcohol dehydrogenase inhibitor), ethanol if not available; dialysis
Iron	deferoxamine
Lead, arsenic, mercury	dimercaprol (BAL), succimer, calcium disodium EDTA (lead)
Copper, Wilson disease	penicillamine, trientine
Cyanide	hydroxocobalamin; sodium nitrite plus sodium thiosulphate
Methaemoglobinaemia	methylene blue (not in G6PD deficiency)
Carbon monoxide	100% oxygen, hyperbaric oxygen in severe cases
Beta-blocker overdose	glucagon
Calcium channel blockers	calcium, high-dose insulin euglycaemia
Tricyclics	sodium bicarbonate
Anticholinergics	physostigmine
Snake bite (neurotoxic and haemotoxic)	polyvalent anti-snake venom (ASV); neostigmine with atropine as an adjunct for neuroparalytic bites (works in cobra bites, not reliably in krait bites)
Methotrexate	leucovorin
Cyclophosphamide cystitis	mesna
Isoniazid	pyridoxine
Thrombolytics	tranexamic acid
Malignant hyperthermia	dantrolene
Local anaesthetic toxicity	lipid emulsion
Serotonin syndrome	**cyproheptadine** (5-HT$_2$A antagonist) after stopping the drugs, cooling and benzodiazepines

Poison or drug	Antidote
Neuroleptic malignant syndrome	dantrolene or bromocriptine (not anticholinergics)
Acute dystonia from antipsychotics or metoclopramide	benztropine or promethazine

- **Organophosphate poisoning** is a major cause of poisoning in Nepal; the intermediate syndrome appears at 1–4 days and delayed neuropathy at 2–3 weeks. Atropine (adult: 1.8–3 mg IV, the dose doubled every 5 minutes until atropinised, then about 10–20% of the loading dose an hour as infusion) is titrated to drying of chest secretions, a systolic pressure above 80 mmHg and heart rate above 80, not to pupil size. Pralidoxime's benefit in clinical trials is doubtful (WHO lists it; many centres in South Asia use atropine alone).
- **Snakebite in Nepal**: the antivenom used is the **Indian equine polyvalent ASV**, raised against the "big four" (spectacled cobra, common krait, Russell's viper, saw-scaled viper); Nepal has no locally made or monovalent antivenom. It is given for **signs of envenoming** (neurotoxicity: ptosis, ophthalmoplegia, bulbar or respiratory weakness; or haemotoxicity: incoagulable blood on the **20-minute whole blood clotting test**, spontaneous bleeding), never for the bite alone. Cobra (including the monocled cobra) and krait bites of the Terai are mainly neurotoxic; krait bites at night often cause no local swelling. **Green pit viper bites (common in the hills) are not covered by the Indian ASV** and are managed conservatively. Its cover of Nepal's other species is unproven, and early anaphylactoid reactions are common: keep IM adrenaline ready (pretreatment is not routine; WHO SEARO 2016). Ventilation is lifesaving in neuroparalysis. Neostigmine (with atropine) helps in cobra bites (postsynaptic toxin), not in krait bites (presynaptic toxin).
- Paracetamol: hepatic necrosis peaks at 72–96 hours (transaminases rise from 24 hours); **an ingestion of 150 mg/kg or more (about 7.5–10 g in an adult) is potentially toxic**; above about 250 mg/kg severe toxicity is likely. The Rumack–Matthew treatment line starts at 150 mg/L at 4 hours (US); the UK uses a line from 100 mg/L at 4 hours (MHRA 2012). Mechanism: at therapeutic doses paracetamol is mostly glucuronidated and sulphated, and a small part goes by **CYP2E1** to **NAPQI**, which glutathione neutralises; in overdose the conjugation pathways saturate and glutathione runs out. **Chronic heavy drinking** induces CYP2E1 and depletes glutathione (with malnutrition), so liver injury can follow lower doses; fasting, malnutrition and enzyme inducers raise the risk too (acute alcohol, by competing for CYP2E1, may even protect). Renal tubular necrosis comes from the same metabolite, made in the kidney.

Suxamethonium apnoea, renal failure, calcium and fluid emergencies

- **Prolonged apnoea after suxamethonium**: a normal dose that leaves the patient apnoeic for hours points to **atypical or deficient plasma cholinesterase** (inherited, low dibucaine number; or acquired in liver disease, pregnancy, organophosphate exposure); repeated doses can add a phase II block; ventilate and sedate until recovery. It is not explained by renal failure, hyperkalaemia or malignant hyperthermia (which causes rigidity, rising end-tidal CO_2 and fever).
- **Renal failure**: **pethidine's metabolite norpethidine (renally cleared) accumulates and causes tremor, myoclonus and seizures** (avoid; use fentanyl or hydromorphone). Also avoid or reduce NSAIDs, aminoglycosides, metformin (eGFR under 30), lithium, digoxin, enoxaparin, nitrofurantoin, tetracyclines other than doxycycline, contrast and gadolinium.
- **Hypercalcaemia and tetany**: hypercalcaemia: IV saline (3-4 L a day), **zoledronate or pamidronate**, calcitonin (fast, tachyphylaxis in 48 hours), steroids in sarcoidosis, myeloma or vitamin D excess, denosumab, dialysis; **tetany: IV calcium gluconate 10% 10-20 mL slowly with ECG monitoring**, then oral calcium and vitamin D; correct magnesium. **Vitamin D preparations**: cholecalciferol (D_3), ergocalciferol (D_2), calcifediol, **calcitriol and alfacalcidol (1-hydroxylated; used in renal failure)**; toxicity: hypercalcaemia, hypercalciuria, nephrocalcinosis, stones, polyuria.
- **Fluid and electrolyte emergencies**: **hyperkalaemia** with ECG change: **IV calcium gluconate** (stabilises the membrane), **insulin with glucose**, **salbutamol nebulised**, sodium bicarbonate in acidosis, loop diuretic, potassium binders (sodium zirconium cyclosilicate, patiromer), dialysis; **hyponatraemia**: correct no faster than 8-10 mmol/L in 24 hours (osmotic demyelination), 3% saline 100-150 mL boluses only for severe symptoms; severe metabolic acidosis (pH under 7.1): bicarbonate selectively; hypovolaemia: isotonic saline or Ringer's lactate.
- **Glomerulonephritis, nephrotic syndrome, renal failure**: nephrotic syndrome in a child: prednisolone; adults: ACE inhibitor or ARB, diuretics, statin, anticoagulation if albumin is very low, specific therapy by histology; acute nephritic syndrome: fluids and salt restriction, loop diuretic, antihypertensive, penicillin for a streptococcal focus; **crescentic disease**: steroids, cyclophosphamide, plasma exchange.

Serotonin syndrome versus neuroleptic malignant syndrome

Feature	Serotonin syndrome	NMS
Cause	SSRIs, MAOIs, tramadol, linezolid, triptans, pethidine	dopamine antagonists, withdrawal of levodopa
Onset	hours	days
Tone	clonus, hyperreflexia	lead-pipe rigidity, hyporeflexia
Features	diarrhoea, agitation, mydriasis	bradykinesia, stupor
Treatment	benzodiazepines, **cyproheptadine**	dantrolene, bromocriptine

Important interactions

- **Warfarin**: raised INR with metronidazole, cotrimoxazole, azoles, macrolides, amiodarone, allopurinol, alcohol (acute), cimetidine; lowered with rifampicin, carbamazepine, phenytoin, barbiturates, St John's wort.
- **Methotrexate + co-trimoxazole (trimethoprim)** or NSAIDs: additive folate antagonism and reduced clearance, giving **pancytopenia and mucositis**: avoid. Trimethoprim inhibits human DHFR at high dose.
- **Sildenafil and nitrates**: profound hypotension (cGMP accumulation).
- **Clopidogrel + omeprazole**: CYP2C19 inhibition.
- **Digoxin**: amiodarone, verapamil, quinidine, macrolides and diuretic-induced hypokalaemia raise toxicity.
- **Lithium**: thiazides, NSAIDs, ACE inhibitors raise levels.
- **Theophylline**: ciprofloxacin, erythromycin, cimetidine raise levels; smoking lowers.

- **Statins**: macrolides, azoles, gemfibrozil, ciclosporin raise the risk of myopathy.
- **Serotonergic combinations**: SSRIs with MAOIs, tramadol, linezolid.
- **Tyramine and MAOIs**; **MAOI with pethidine**: excitatory crisis.
- Oral contraceptives: enzyme inducers (rifampicin, antiepileptics) reduce effectiveness.
- **Disulfiram-like reaction** (acetaldehyde accumulation from aldehyde dehydrogenase inhibition) with alcohol: **metronidazole, tinidazole, disulfiram, cefoperazone, cefotetan, griseofulvin, chlorpropamide**, procarbazine; amoxicillin, doxycycline and azithromycin do not. Features: flushing, headache, palpitations, vomiting.
- Aminoglycosides with loop diuretics or cisplatin: additive ototoxicity and nephrotoxicity.
- Grapefruit juice inhibits gut CYP3A4: raises felodipine, simvastatin, ciclosporin.
- Disulfiram is used in alcohol dependence; acamprosate and naltrexone reduce craving.

Immunosuppressants for transplantation

- **Calcineurin inhibitors**: **ciclosporin** binds **cyclophilin**, **tacrolimus** binds **FKBP-12**; each complex inhibits **calcineurin**, so NFAT is not dephosphorylated and **IL-2 transcription** and T-cell activation fail. Both: **nephrotoxicity**, hypertension, hyperkalaemia, hypomagnesaemia, neurotoxicity (tremor, posterior reversible encephalopathy), many CYP3A4 and P-gp interactions (levels monitored). Ciclosporin: **hirsutism, gum hyperplasia**, hyperlipidaemia; tacrolimus: more potent and **more diabetogenic** (post-transplant diabetes), the usual first choice now (KDIGO).
- **Antiproliferatives**: **mycophenolate** (inhibits inosine monophosphate dehydrogenase; diarrhoea, marrow suppression, teratogenic), azathioprine (purine analogue; TPMT, allopurinol interaction). **mTOR inhibitors**: **sirolimus, everolimus** bind FKBP-12 but block mTOR, not calcineurin (less nephrotoxic; poor wound healing, hyperlipidaemia, mouth ulcers, pneumonitis). **Induction antibodies**: **basiliximab** (anti-CD25, the IL-2 receptor α chain), antithymocyte globulin; **belatacept** (CTLA-4–Ig, blocks CD28 co-stimulation).

Teratogenic drugs

- **Thalidomide** (phocomelia), **warfarin** (nasal hypoplasia, stippled epiphyses), **ACE inhibitors and ARBs** (renal dysgenesis, oligohydramnios), **valproate** (neural tube defects), phenytoin, carbamazepine, **isotretinoin** and acitretin (craniofacial and cardiac defects), **lithium** (Ebstein anomaly), **tetracyclines** (teeth), methotrexate, misoprostol (Moebius), carbimazole, statins, diethylstilbestrol (clear-cell vaginal carcinoma), androgens, fluconazole (high dose), mycophenolate, leflunomide.

Common serious adverse reactions

- **Drug-induced lupus**: hydralazine, procainamide, isoniazid (anti-histone antibodies). **Gynaecomastia**: spironolactone, cimetidine, digoxin, ketoconazole. **SJS/TEN**: allopurinol, carbamazepine, lamotrigine, phenytoin, sulphonamides, nevirapine. **Cough**: ACE inhibitors. **Hepatotoxicity**: paracetamol, isoniazid, rifampicin, valproate, halothane, amiodarone, methotrexate. **Pulmonary fibrosis**: amiodarone, bleomycin, busulfan, nitrofurantoin, methotrexate. **Ototoxicity**: aminoglycosides, loop diuretics, cisplatin, vancomycin, quinine. **QT prolongation**: macrolides, fluoroquinolones, haloperidol, ondansetron, amiodarone, sotalol, methadone. **Haemolysis in G6PD deficiency**: primaquine, dapsone, nitrofurantoin, rasburicase, sulphonamides. **Hypoglycaemia**: sulfonylureas, insulin, quinine, β-blockers (masking). **Hypokalaemia with hypomagnesaemia**: **amphotericin B** (pores in the distal tubule cells waste K^+ and Mg^{2+} and cause distal renal tubular acidosis; check and replace both, saline loading and the lipid forms lessen nephrotoxicity), cisplatin, loop and thiazide diuretics; β_2 agonists, insulin and steroids lower potassium. **A rise in creatinine without a fall in GFR**: **trimethoprim**, cimetidine, dolutegravir, cobicistat and bictegravir block tubular creatinine secretion (OCT2, MATE), so creatinine rises by 10-30% with normal cystatin C and urine; trimethoprim also causes hyperkalaemia by blocking ENaC like amiloride. **Hyperkalaemia**: spironolactone, ACE inhibitors, suxamethonium, trimethoprim, heparin. **Red man syndrome**: vancomycin. **Grey baby**: chloramphenicol. **Fanconi syndrome**: out-of-date tetracycline, tenofovir. **Agranulocytosis**: clozapine, carbimazole, dapsone, carbamazepine, chloramphenicol. **Peripheral neuropathy**: isoniazid, vincristine, metronidazole, nitrofurantoin, cisplatin, dapsone.

Sources

Katzung, Basic and Clinical Pharmacology; KD Tripathi, Essentials of Medical Pharmacology; Goodman and Gilman, The Pharmacological Basis of Therapeutics; Harrison's Principles of Internal Medicine; Rang and Dale's Pharmacology; British National Formulary; WHO consolidated guidelines on tuberculosis, Module 4: treatment and care (2025, consolidating the 2022 4-month and BPaLM recommendations); WHO TB definitions update (2021); WHO TB preventive treatment, Module 1 (2024); WHO guidelines for malaria (2022 onwards); Nepal EDCD National Malaria Treatment Protocol (2019); WHO consolidated HIV guidelines (2021) and updated recommendations on HIV clinical management (2025, released January 2026); WHO PEP guidelines (2024); WHO SEARO guidelines for the management of snakebites (2nd ed., 2016); WHO leprosy guidelines (2018); Resuscitation Council UK emergency treatment of anaphylaxis (2021); ESC heart failure guidelines 2021 and 2023 update; AHA/ACC/HFSA heart failure guideline 2022; ESC/EAS dyslipidaemia guideline 2019; ADA Standards of Care 2024; American Thyroid Association hyperthyroidism guideline 2016 and pregnancy guideline 2017; WHO AWaRe classification 2023; National Tuberculosis Programme Nepal guidelines; WHO Guide to Good Prescribing (1994); ESC STEMI guideline 2017; AHA/ACC STEMI guideline 2013; WHO abortion care guideline 2022; WHO postpartum haemorrhage guideline 2025 and WHO Model List of Essential Medicines (23rd list 2023, 24th 2025); GINA 2024 and 2025 update; GOLD 2024; Maastricht VI consensus (2022) and ACG H. pylori guideline (2024); ESC acute coronary syndromes guideline 2023; AHA/ACC hypertension guideline 2017; ATA hypothyroidism guideline 2014; IDSA/ASTMH neurocysticercosis guideline 2017; WHO guideline on leishmaniasis treatment (2026); BASHH gonorrhoea guideline 2025; Surviving Sepsis Campaign 2021; BSG iron deficiency guideline 2021; WHO 2010 Expert Committee on leishmaniasis control (TRS 949); CDC STI treatment guidelines 2021 and WHO STI guidelines 2024; WHO eligibility criteria for contraceptive use; Guedel's stages as in Miller's Anesthesia; APA practice guideline for schizophrenia (2020, tardive dyskinesia); Baveno VII portal hypertension consensus (2022); ACR/Vasculitis

Foundation ANCA-associated vasculitis guideline (2021); PERSEUS trial (NEJM 2024); ASCO antiemetic guideline (2020); KDIGO kidney transplant recipient guideline (2009); WHO foodborne trematodiases fact sheet (triclabendazole for fascioliasis); FDA approval of fezolinetant (2023); IDSA/SHEA babesiosis guideline (2020); ESMO CLL guideline (2021).