PharmacoLearn

MPL102T Advanced Pharmacology I, M.Pharm Semester 1

Unit 1: General Pharmacology

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Advanced Pharmacology I, subject code MPL102T, is a core Semester 1 subject of M.Pharm Pharmacology. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. This subject rebuilds pharmacology from first principles at postgraduate depth. Unit 1 is the engine room: pharmacokinetics, the quantitative account of what the body does to a drug (absorption, distribution, biotransformation and elimination, compartment models and protein binding), and pharmacodynamics, what the drug does to the body (receptors, their structural and functional families, and the quantitation of drug receptor interaction). Unit 2 studies neurotransmission in detail, the autonomic transmitters acetylcholine and adrenaline, the central transmitters, NANC transmission and cotransmission, and then the autonomic drugs themselves. Unit 3 covers central nervous system pharmacology, from anesthetics and sedatives to the drugs of depression, psychosis, epilepsy, neurodegeneration and pain. Unit 4 covers cardiovascular pharmacology: diuretics, antihypertensives, anti-ischemic and antiarrhythmic drugs, heart failure and lipid drugs, and the drugs of blood coagulation. Unit 5 covers the autocoids: histamine, serotonin, kinins, prostaglandins and the endogenous opioids, with the antihistamines and 5-HT antagonists. Throughout, every drug class is studied the same way: the pathophysiology of the disease, the mechanism of action at cellular and molecular level, the pharmacology and toxicology, and the clinical uses, adverse effects and contraindications. A student who completes this subject should be able to work through the kinetics of a dosing problem, read a dose response curve quantitatively, and explain any major autonomic, CNS, cardiovascular or autocoid drug from its receptor to its adverse effects.

1.1 Pharmacokinetics: the dynamics of ADME

Pharmacokinetics is the quantitative study of the movement of a drug into, within and out of the body: what the body does to the drug. It rests on four processes, remembered as **ADME**:

- **Absorption:** the drug passes from its site of administration into the systemic circulation.
- **Distribution:** the drug spreads from the blood into tissues, reversibly, according to blood flow, tissue binding and barriers.
- **Biotransformation (metabolism):** the body chemically alters the drug, usually to more polar products.
- **Elimination (excretion):** the drug and its metabolites leave the body, mainly in urine and bile.

Four parameters convert these processes into numbers a prescriber can use:

Parameter	Meaning	Working relation
Bioavailability (F)	Fraction of the dose reaching the systemic circulation unchanged	Oral AUC compared with intravenous AUC
Volume of distribution (Vd)	Apparent volume the drug appears to occupy	Vd = amount in body / plasma concentration
Clearance (CL)	Volume of plasma cleared of drug per unit time	CL = rate of elimination / plasma concentration
Half life (t1/2)	Time for the plasma concentration to fall by half	t1/2 = 0.693 x Vd / CL

The half life relation is the most useful equation in this unit: half life rises when Vd rises (more drug hidden in tissues) and falls when clearance rises. A drug reaches a **steady state** concentration after about four to

five half lives of regular dosing, and falls away over the same span when dosing stops.

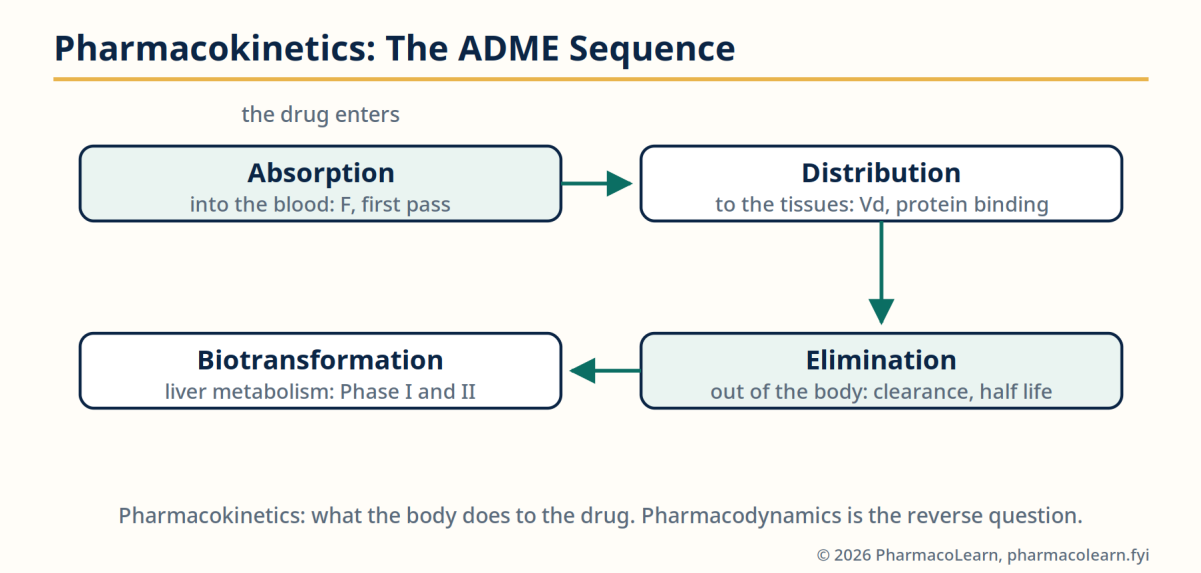


Figure: The ADME sequence. Absorption, distribution, biotransformation and elimination decide the concentration time course of every drug.

1.2 Absorption and bioavailability

Most small drug molecules cross membranes by **passive diffusion**, moving down a concentration gradient without energy. Only the unionised, lipid soluble fraction crosses easily, so absorption of a weak acid or base depends on the pH of the environment and the pKa of the drug: a weak acid such as aspirin is largely unionised in the acid stomach and absorbed there, while weak bases are ionised and trapped in acid (the basis of urinary acidification strategies and of poor absorption of bases from the stomach). Other routes across membranes include filtration through aqueous pores (small molecules only), facilitated diffusion, active transport by carriers such as P-glycoprotein (an efflux pump that limits absorption of many drugs and is a site of interactions), and endocytosis for very large molecules such as vitamin B12 complexes.

Factors deciding the rate and extent of absorption include the formulation (solutions absorb faster than tablets, which must disintegrate and dissolve), gastric emptying and gut motility, food (which delays most absorption but improves that of some lipophilic drugs), splanchnic blood flow, and disease of the gut wall.

Bioavailability is reduced by incomplete absorption and by the **first pass effect**: drug absorbed from the stomach and intestine travels in the portal vein to the liver and may be metabolised before it ever reaches the systemic circulation. Glyceryl trinitrate is so completely destroyed on first pass that it is given sublingually, a route that drains directly into the systemic veins; propranolol and morphine also lose a large fraction. Routes that partly or wholly bypass the liver include sublingual, rectal (partly), transdermal and parenteral routes.

1.3 Distribution and plasma protein binding

Once in the blood, a drug distributes according to cardiac output and regional blood flow (highly perfused organs first: liver, kidney, brain, then muscle, then fat), according to its ability to cross barriers (the blood brain barrier of tight endothelium and efflux pumps excludes most polar drugs), and according to binding. Many drugs bind extensively to plasma proteins, chiefly **albumin** for acidic drugs (warfarin, phenytoin, sulfonamides) and **alpha-1 acid glycoprotein** for basic drugs (lidocaine, imipramine).

The **significance of protein binding**, a named syllabus point, is fourfold:

- Only the **free (unbound) fraction** crosses membranes, reaches receptors and is filtered at the glomerulus. Total plasma concentration therefore misleads when binding changes.
- Binding is a **reservoir**: bound drug is released as free drug is cleared, prolonging action (one reason highly bound drugs often have long half lives).
- **Displacement interactions:** a second drug competing for the same sites raises the free fraction of the first. The classic pair is a sulfonamide displacing warfarin, or bilirubin in the newborn (sulfonamides displacing bilirubin from albumin caused kernicterus, a historical warning). Most displacement effects are clinically brief because the freed drug is also cleared faster, but they matter for narrow index drugs like phenytoin and warfarin.
- **Disease changes binding:** hypoalbuminaemia in liver disease, nephrotic syndrome and old age raises the free fraction of acidic drugs; acute inflammation and trauma raise alpha-1 acid glycoprotein and lower the free fraction of basic drugs. Phenytoin levels in a hypoalbuminaemic patient must be interpreted as free levels, or the patient is overdosed on paper readings alone.

Tissue binding matters too: thiopentone redistributes from brain to muscle and fat, which terminates its anesthetic effect within minutes even though elimination takes hours; tetracyclines deposit in growing teeth and bone; chloroquine accumulates in the retina and liver.

1.4 Biotransformation: Phase I and Phase II

Metabolism usually converts a lipophilic drug, which the kidney would reabsorb, into polar products it can excrete. It can also inactivate an active drug, activate a **prodrug** (levodopa to dopamine, codeine to morphine by CYP2D6, enalapril to enalaprilat), or create toxic products (paracetamol to the hepatotoxic NAPQI).

Phase	Reaction types	Enzymes and notes
Phase I	Oxidation, reduction, hydrolysis	Mostly microsomal cytochrome P450 (CYP) enzymes in the liver: CYP3A4, 2D6, 2C9, 2C19, 1A2 handle most drugs. Introduces or exposes a reactive group
Phase II	Conjugation: glucuronidation, sulfation, acetylation, methylation, glutathione and amino acid conjugation	Transferases attach a large polar group; products almost always inactive and readily excreted. Glucuronidation is the commonest route

Two clinical consequences dominate. **Enzyme induction** (rifampicin, carbamazepine, phenytoin, chronic alcohol, St John's wort) increases CYP synthesis, speeds the metabolism of other drugs and can cause therapeutic failure, for example of oral contraceptives or transplant immunosuppressants. **Enzyme inhibition** (cimetidine, ketoconazole, erythromycin, grapefruit juice on intestinal CYP3A4) slows metabolism and raises levels, a route to toxicity with drugs such as theophylline or simvastatin. Superimposed on this is **pharmacogenetics**: CYP2D6 ranges from absent (poor metabolisers, who get no analgesia from codeine) to duplicated (ultra-rapid metabolisers, who convert codeine dangerously fast); slow acetylators develop more isoniazid neuropathy and hydralazine or procainamide lupus. The neonatal liver is the mirror image: deficient glucuronidation made chloramphenicol accumulate to the fatal grey baby syndrome.

1.5 Elimination and clearance

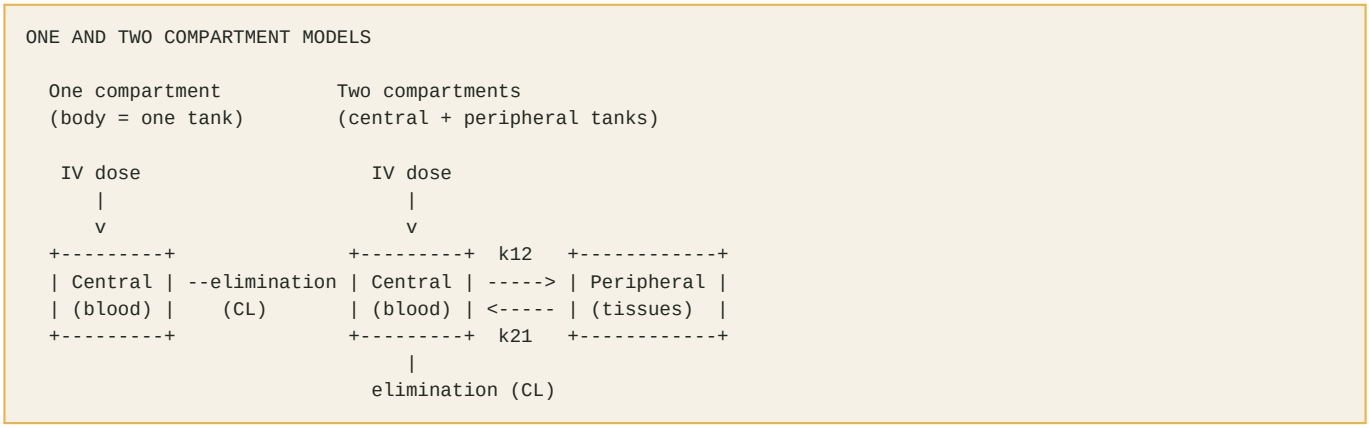
The kidney eliminates drugs by three processes acting together: **glomerular filtration** (free drug only, about 120 ml/min in health), **tubular secretion** (active carriers for acids and bases in the proximal tubule, the route penicillins use and probenecid blocks), and **tubular reabsorption** (passive, of the unionised fraction, which is why urinary alkalinisation speeds salicylate and phenobarbitone elimination in poisoning).

Other routes are biliary excretion with possible **enterohepatic recycling** (which prolongs the action of drugs such as oral contraceptives whose metabolites are deconjugated by gut bacteria), pulmonary excretion of volatile anesthetics, and minor losses in sweat, saliva and milk (milk matters for the nursing infant).

Clearance is the master elimination parameter. Total clearance is the sum of hepatic, renal and other clearances, and it decides the maintenance dose: at steady state the dosing rate equals CL multiplied by the target steady state concentration. Loading doses, in contrast, depend on Vd, not clearance: loading dose = Vd multiplied by the target concentration. Confusing the two is a classic examination and prescribing error.

1.6 Compartment models: linear kinetics

The body is too complex to model chamber by chamber, so pharmacokinetics uses **compartment models**: imaginary well mixed spaces between which drug moves at rates proportional to concentration.



In the **one compartment model**, drug distributes instantly and the plasma concentration after an intravenous bolus falls in a single exponential: a straight line on a log concentration against time plot. Most simple calculations (half life, Vd, clearance) assume this model. In the **two compartment model**, the log curve bends: an early steep **distribution phase**, as drug leaves blood for tissues, gives way to a shallower **elimination phase** once distribution equilibrates. Thiopentone and digoxin behave this way; sampling too early reads the distribution phase and underestimates the half life.

Linear (first order) kinetics means the rate of elimination is proportional to concentration: a constant *fraction* is removed per unit time, the half life is constant, and doubling the dose doubles the levels predictably. Most drugs behave linearly at therapeutic doses.

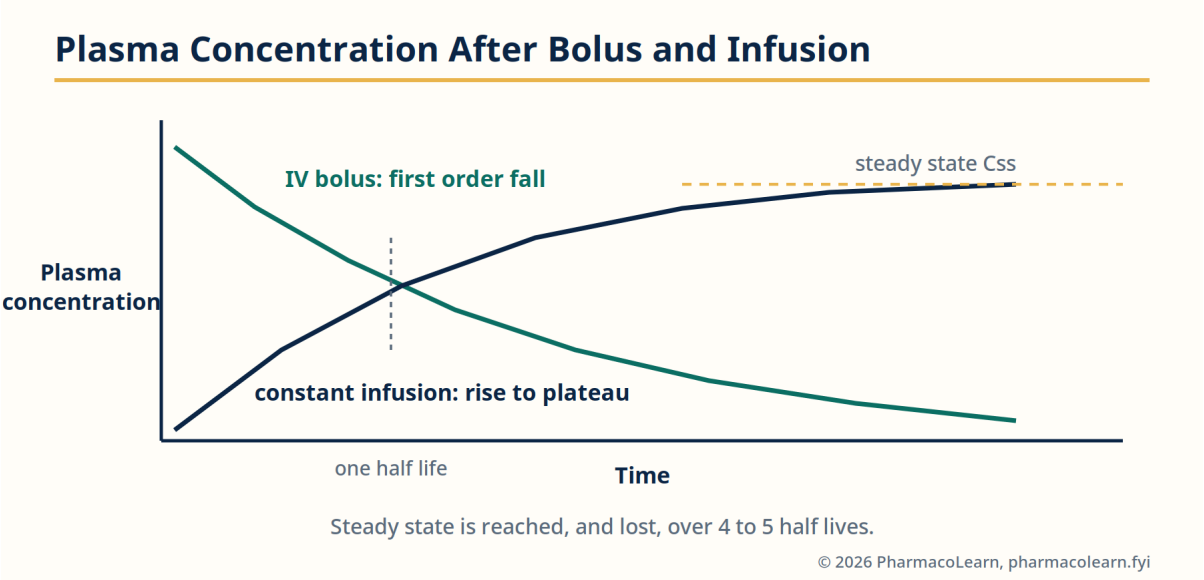


Figure: Plasma concentration after an IV bolus (first order fall) and during constant infusion (rise to the steady state plateau over 4 to 5 half lives).

1.7 Non-linear kinetics: when the rules change

Kinetics become **non-linear** when an eliminating pathway saturates. The enzymes or carriers reach their maximum rate (Vmax) and elimination becomes **zero order**: a constant *amount* per unit time, as with ethanol. The Michaelis-Menten equation governs the transition: at low concentrations the drug behaves first order, and as concentration approaches the Km of the metabolising enzyme it shifts to zero order.

Phenytoin is the clinical example every pharmacologist must command. Within the therapeutic range its hepatic enzymes saturate, so a small dose increase (say from 300 to 400 mg daily) can produce a disproportionate, sometimes toxic jump in plasma level; the apparent half life lengthens as the level rises, steady state takes weeks, and dose changes must be small and guided by plasma concentrations. Salicylates, alcohol and, at high doses, theophylline share the pattern. Non-linearity also arises from saturable protein binding, saturable tubular secretion and autoinduction (carbamazepine speeding its own metabolism over the first weeks of therapy).

1.8 Pharmacodynamics: how drugs produce their effects

Pharmacodynamics studies what the drug does to the body: the mechanism of action and the relationship between drug concentration and effect. Most drugs act on specific macromolecular targets, but the recognised mechanisms form a short list:

- **Receptors:** the majority of drugs bind receptors, the subject of sections 1.9 to 1.11.
- **Enzymes:** inhibited (ACE by enalapril, HMG-CoA reductase by statins) or, rarely, activated or used as false substrates (methyldopa).
- **Ion channels:** blocked (calcium channels by verapamil, sodium channels by local anesthetics) or opened (potassium channels by minoxidil).
- **Transporters:** blocked (serotonin transporter by SSRIs, Na-K-2Cl cotransporter by furosemide) or exploited for uptake.
- **Non receptor mechanisms:** antacids neutralise acid chemically, mannitol acts osmotically, chelators bind metal ions, and some drugs act by physical or anti metabolite routes (5-fluorouracil built into nucleic acids).

Even for receptor drugs, the effect is rarely the binding itself: binding triggers a chain, receptor activation, signal transduction, cellular response, organ response, and each link can amplify or saturate.

1.9 Receptors: structural and functional families

A **receptor** is a macromolecular component of the cell that a drug or endogenous messenger recognises, binds and thereby changes cellular function. The four superfamilies, by structure and signalling route, are:

Family	Structure	Mechanism	Speed	Examples
Ligand gated ion channels (ionotropic)	Multi subunit pore through the membrane	Binding opens the channel, ions flow, membrane potential changes	Milliseconds	Nicotinic acetylcholine, GABA-A, glutamate NMDA and AMPA, 5-HT3
G protein coupled receptors (metabotropic)	Seven transmembrane helices, one protein	Activate G proteins, which regulate enzymes and channels through second messengers	Seconds	Adrenoceptors, muscarinic, dopamine, opioid, angiotensin AT1
Kinase linked receptors	Single transmembrane helix with enzyme activity inside	Binding activates a kinase (often tyrosine kinase), phosphorylating proteins	Minutes to hours	Insulin, growth factors (EGF, VEGF), cytokine receptors (JAK linked)
Nuclear receptors	Intracellular, in cytosol or nucleus	The drug receptor complex binds DNA and changes gene transcription	Hours to days	Steroid hormones, thyroid hormone, vitamin D, PPARs

Functionally, receptors also divide by what the bound drug does: **agonists** activate, **antagonists** occupy without activating and block the agonist, **partial agonists** activate submaximally even at full occupancy, and **inverse agonists** reduce the receptor's baseline (constitutive) activity below resting level, a property of rimonabant at CB1 and several modern beta blockers at constitutively active receptors. Many receptors exist as **subtypes** (alpha1 and alpha2, beta1 and beta2, M1 to M5, D1 to D5), and subtype selectivity is the commonest engineering route to a cleaner drug: beta1 selective blockers for the heart, M3 emphasis in bladder drugs, D2 blockade for antipsychosis with 5-HT2A blockade moderating its cost.

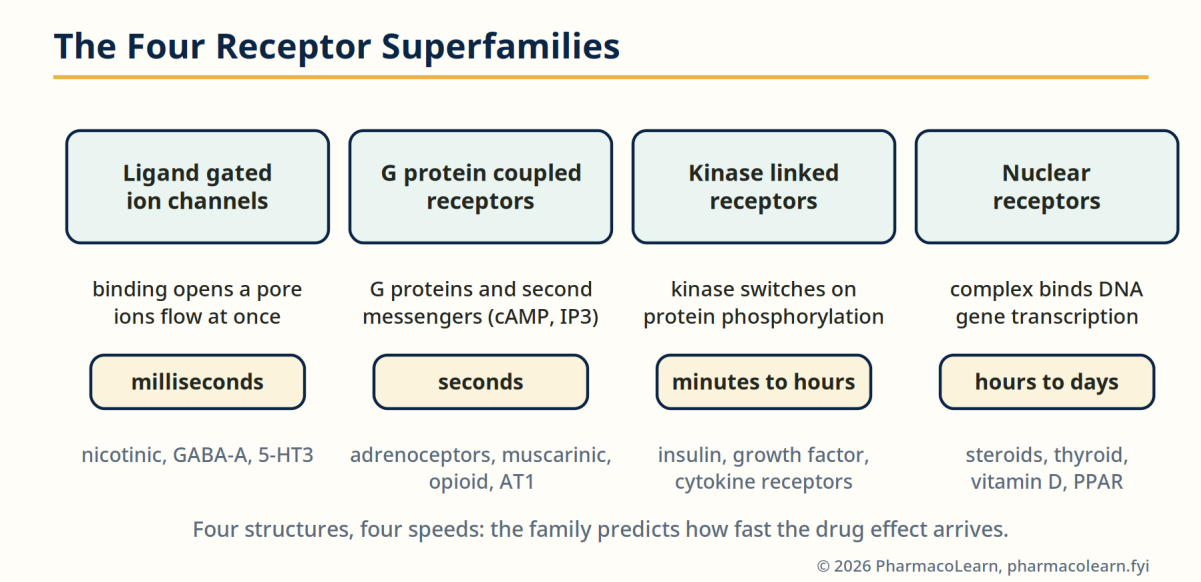


Figure: The four receptor superfamilies and their characteristic speeds of response, from milliseconds for ion channels to days for nuclear receptors.

1.10 Signal transduction: second messengers

Between receptor and response sit the **second messenger** systems, which amplify a single binding event into a large cellular answer:

- **cAMP system:** Gs stimulates adenylyl cyclase (beta adrenoceptors), Gi inhibits it (alpha2, opioid, M2). cAMP activates protein kinase A. Phosphodiesterase inhibitors such as milrinone and sildenafil prolong the signal by blocking its breakdown.
- **Phosphoinositol system:** Gq activates phospholipase C, splitting PIP2 into **IP3** (releases calcium from stores) and **DAG** (activates protein kinase C). Used by alpha1, AT1, H1 and M3 receptors.
- **cGMP system:** nitric oxide activates soluble guanylyl cyclase; the pathway of nitrates and of sildenafil's target enzyme PDE5.
- **Ion channel coupling:** Gi/o proteins open potassium channels and close calcium channels directly, the route by which opioids and M2 receptors slow the heart and quieten neurons.
- **Enzyme cascades:** kinase linked receptors drive phosphorylation cascades (Ras, Raf, MAP kinase), the pathways growth factor drugs and many anticancer agents target.

Amplification explains **spare receptors**: a maximal tissue response may need only a small fraction of receptors occupied, because each activated receptor generates many second messenger molecules. Insulin and histamine responses show large receptor reserves; irreversible antagonists such as phenoxybenzamine first eat into the reserve (shifting the curve right) before they depress the maximum.

1.11 Quantitation of drug receptor interaction and effects

The graded **dose response curve** (response against log dose) is sigmoid and yields two independent numbers. **Potency**, read from the position of the curve (EC50, the concentration giving half the maximal response), says how much drug is needed. **Efficacy** (Emax, the height of the curve) says how much effect the drug can produce at best. Furosemide is more efficacious than thiazides (a higher ceiling), while bumetanide is more potent than furosemide (works at lower milligram doses) with the same ceiling: potency decides the size of the tablet, efficacy decides whether the drug can do the job at all.

Antagonism is read off curve shifts. A **competitive antagonist** (surmountable, binding the same site reversibly) shifts the agonist curve to the right in parallel, Emax unchanged; the dose ratio quantifies it, and the Schild analysis converts dose ratios into the antagonist affinity constant pA2. A **non competitive or irreversible antagonist** depresses Emax once the receptor reserve is consumed. A **partial agonist** has its own lower Emax and, in the presence of a full agonist, behaves as an antagonist, the dual behaviour of pindolol at beta receptors and aripiprazole at D2 receptors. Repeated exposure changes sensitivity: **desensitisation and tachyphylaxis** (fading response, as with ephedrine's depleted stores), receptor **down regulation** with chronic agonist use, and **up regulation and supersensitivity** with chronic antagonist use, which is why beta blockers are withdrawn gradually, never stopped abruptly in angina.

Safety is quantitated by the **quantal dose response** curves of a population: the median effective dose ED50, median toxic dose TD50 and median lethal dose LD50. The **therapeutic index**, TD50/ED50, and the more conservative margin of safety, (TD1 minus ED99)/ED99, express how far treatment sits from harm. Warfarin, digoxin, lithium and phenytoin have narrow indices and demand monitoring; penicillins have a very wide index and forgive dosing error. Finally, variability is itself pharmacology: idiosyncratic reactions (unpredictable, often genetic, such as primaquine haemolysis in G6PD deficiency) differ from dose related toxicity, and both differ from hypersensitivity, which is immune mediated and unrelated to dose.

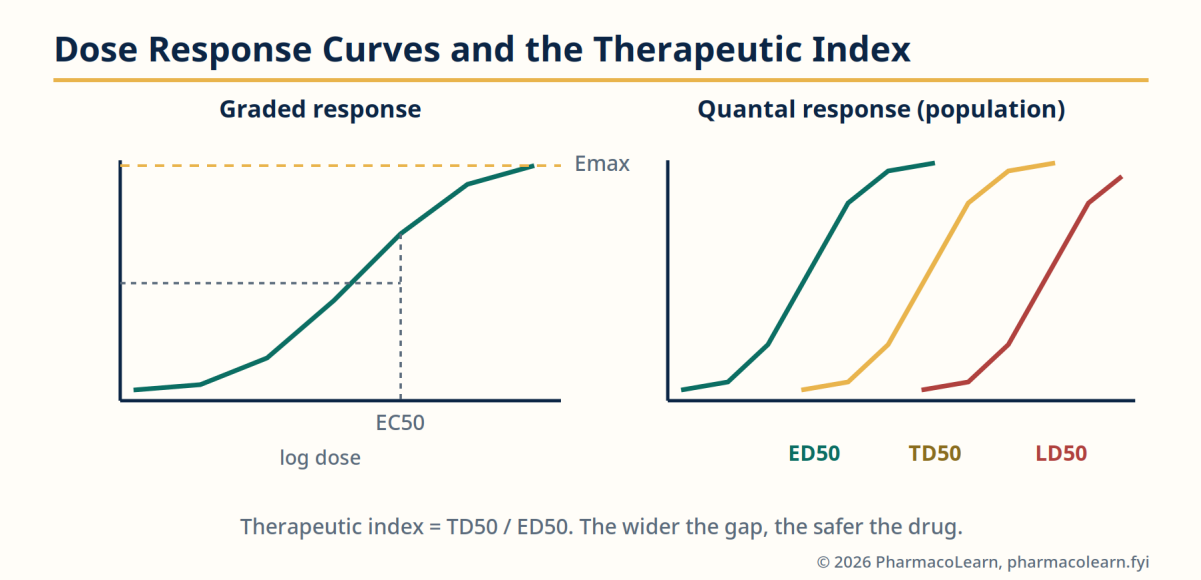


Figure: Graded and quantal dose response curves. The therapeutic index, TD50 divided by ED50, measures the margin between effect and toxicity in a population.

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