Pharmacology

Curated preclinical study track (not a medical degree, no licensure claim; illustrative values in labelled calculations only, INN names, no prescribing guidance). Original explanations and practice only, following the reviewed course handout.

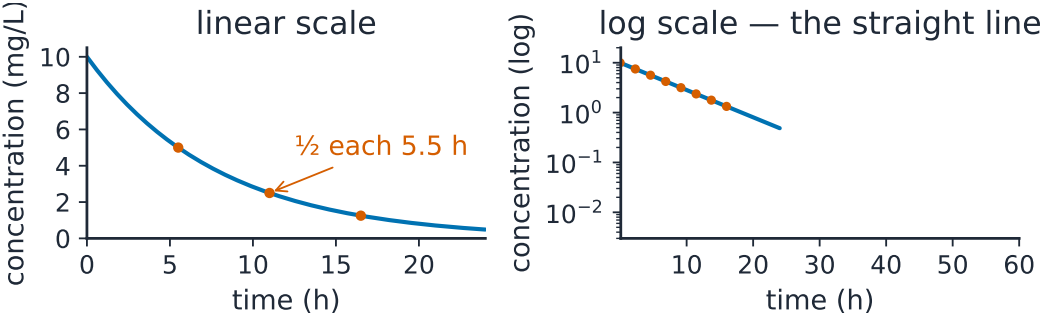
Exposure and effect

- 11.1-11.2 are the engine (kinetics, dynamics); 11.3-11.6 systems; 11.7 safety.
- Illustrative values only: every number lives in a labelled calculation.

Pharmacokinetics: three levers

1. **Levers** $t_{1/2} = 0.693 \times Vd/CL$ (illustrative Vd 40 L, CL 5 L/h $\rightarrow$ 5.5 h; CL halved $\rightarrow$ 11.1 h).
2. **Steady state** ~90 % at 3.3 half-lives, ~97 % at 5; loading = Ctarget $\times$ Vd/F (10 mg/L $\times$ 40 L = 400 mg illustrative).
3. **First pass** F = fraction past the liver: 100 mg oral at F 0.6 delivers 60 mg; liver bypass raises F.

Concentration–time curves



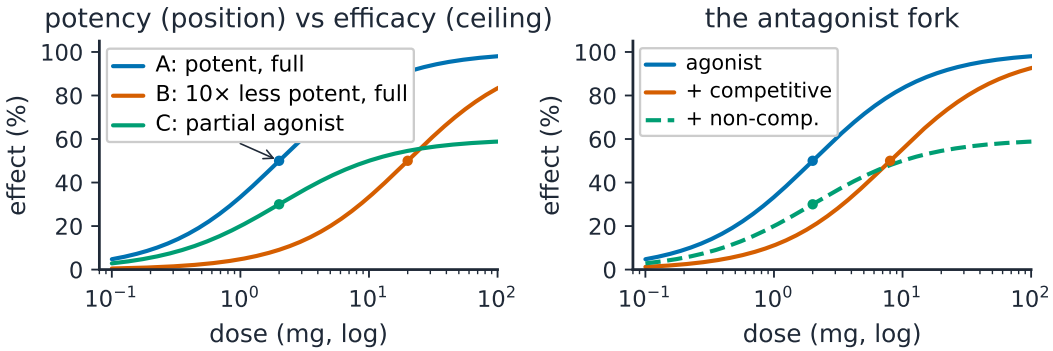
$t_{½} = 0.693 \cdot Vd/CL$ · steady state ≈ 90 % at 3.3 $t_{½}$, 97 % at 5 · loading = $C_{target} \cdot Vd/F$

Half-life is the log-linear slope; **steady state** after ~4-5 half-lives.

Pharmacodynamics: position and ceiling

1. **Curves** EC_{50} = **potency**; Emax = **efficacy**; partial agonist lowers the ceiling and displaces full agonists.
2. **Antagonists** Competitive: parallel right shift, surmountable. Non-competitive: ceiling falls - no dose wins.
3. **Margin** TI = TD_{50}/ED_{50} (illustrative $100/10 = 10$); narrow TI = monitor levels.

Dose–response curve families



TI = TD_{50} / ED_{50} · illustrative: 100/10 = 10 · surmountable vs unsurmountable

Potency is position, **efficacy** is ceiling; antagonists shift right or cut it.

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Autonomic pharmacology: one map

1. **Rows** $\alpha 1$ constricts/dilates pupil · $\beta 1$ heart · $\beta 2$ airway · M3 secretes, constricts pupil, speeds gut · M2 slows heart.
2. **Predictions** $\beta 1$ blocker $\downarrow$ rate; $\alpha 1$ blocker $\downarrow$ pressure (postural); $\beta 2$ agonist opens airways; M blocker dries.
3. **Toxidromes** Cholinergic = wet, slow, miosis · anticholinergic = dry, blind, fast · adrenergic = fast, tight, sweating.

Receptor-to-effect map

the map, read upside down, is the toxidrome — every finding is a receptor row

α1	vasoconstriction · mydriasis	agonist ↑ pressure; blocker ↓ (postural drop)
β1	heart rate and contractility	agonist ↑ output; blocker ↓ rate
β2	bronchodilation · vasodilation	agonist opens airways
M3	glands · gut motility · miosis	agonist = wet, cramps; blocker = dry
M2	slows the heart	agonist = slow; blocker = fast

CHOLINERGIC
wet and slow: salivation, miosis, bronchorrhoea, bradycardia, cramps

ANTICHOLINERGIC
dry, blind, fast: dry mouth, fixed dilated pupils, tachycardia, retention

ADRENERGIC
fast and tight: tachycardia, high pressure, mydriasis, sweating

One map, five receptor rows — every autonomic drug is an arrow into it.

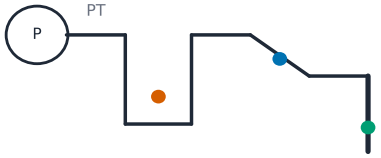
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Cardiovascular and renal drugs: named steps

1. **Pressure** Diuretics (volume) · **ACE inhibitors** (bradykinin cough) · ARBs · CCBs · β1 blockers.
2. **Nephron** Loop Na^+-K^+-2Cl^- (~25 % Na^+) · thiazide distal · K-sparing collecting duct - electrolytes follow the site.
3. **Clotting** Heparin immediate (aPTT); **warfarin** blocks NEW factor carboxylation (INR, days); DOACs one factor, unmonitored.

Diuretic action sites on the nephron

three diuretic sites down the nephron — the fraction of Na^+ falls as you go



anticoagulants — mechanism sets the monitor

heparin: immediate, IV — aPTT

warfarin: blocks vitamin-K factor CARBOXYLATION — stored factors must decay first; INR, days to onset

direct oral anticoagulants: one factor (Xa or thrombin), predictable kinetics, mostly unmonitored

ACE inhibitor cough = bradykinin not degraded

Three **diuretic** sites down the nephron; the monitor follows the mechanism.

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Antimicrobial and anticancer drugs: two selectivities

1. **Absence** Antibacterial targets human cells lack: wall, 30S/50S, gyrase, folate (MED08).
2. **Timing** S-phase antimetabolites (methotrexate, fluorouracil); M-phase vinca, taxanes; alkylators any phase.
3. **Margin** Narrow margin = marrow, gut, hair cycle too; fractionation meets more cells in phase.

Drug-class target map

antibacterial: by ABSENCE

wall	β-lactams → PBPs
ribosome	30S/50S; ours spared
DNA, RNA	gyrase · RNA polymerase
folate	made by them, not us

anticancer: by TIMING

S-phase	antimetabolites (methotrexate, 5-FU)
M-phase	spindle poisons (vincas, taxanes)
any phase	alkylators: DNA damage, any phase

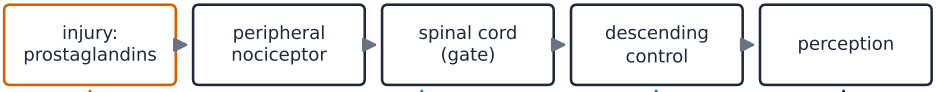
ABSENCE (bacteria lack our targets) is wide; TIMING is narrow — marrow, gut and hair cycle too; repeated doses catch more cells in phase.

Bacterial targets by absence, anticancer targets by cell-cycle timing.

CNS drugs and analgesia: sites along the pain pathway

1. **Sites** NSAID at peripheral COX (gastric, renal cost); opioid at μ (respiratory, constipation); GABA-A PAM; SSRI reuptake.
2. **Adaptation** Chronic activation down-regulates - **tolerance**; withdrawal unmasks - **dependence** (WHO ladder 1986/1996).
3. **Paracetamol** Excess uses up glutathione; the toxic metabolite (NAPQI) binds liver protein; acetylcysteine restores it - MED10 applies.

Drug action sites along the pain pathway



NSAID (COX)	less prostaglandin → less pain; gastric, renal cost
opioid (μ)	analgesia; respiratory depression, constipation; tolerance, dependence
GABA-A PAM	benzodiazepine sedation; short course — withdrawal
SSRI / neuronal	reuptake blocked, effect in WEEKS; neuropathic agents quiet firing

tolerance = down-regulation: same concentration does less; withdrawal unmasks the adapted state

paracetamol: excess saturates glutathione — the toxic metabolite binds liver protein (MED10)

Peripheral COX, spinal gate, descending opioid control - the pathway with its drug sites.

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Adverse reactions, interactions and safe-medication principles

1. **Types** Type A dose-related, predictable (β-blocker bradycardia); type B idiosyncratic - population reporting (Yellow Card UK, MedWatch US).
2. **Kinetics** Induction (rifampicin): levels fall, days on/off; inhibition (clarithromycin, grapefruit CYP3A4): rises from first dose.
3. **Backstop** Five rights - patient, drug, dose, route, time; **warfarin** INR is where interactions surface.

Interaction mechanisms on the level axis

two kinds of harm

Type A — dose-related
predictable from pharmacology
(β-blocker bradycardia)

Type B — idiosyncratic
not dose-related: allergy, rare toxicity
— found by population reporting

kinetic interactions

INDUCTION ↓
rifampicin, phenytoin:
new enzyme — days on,
days off; outlasts course

INHIBITION ↑
clarithromycin,
grapefruit (CYP3A4):
rises from first dose

warfarin + inhibitor → INR ↑ · + inducer → INR ↓
the INR is where the interaction surfaces

the five rights — patient, drug, dose, route, time — are the behavioural backstop
reporting systems: UK MHRA Yellow Card · US FDA MedWatch (population detects type B)

Induction lowers exposure, inhibition raises it; ADR types split by dose-relatedness.

Check yourself

- Vd 40 L, CL 5 L/h → t½…? (5.5 h.)
- Competitive antagonist does what to the curve…? (Right shift, surmountable.)
- Anticholinergic toxidrome looks like…? (Dry, blind, fast, blocked.)
- **Warfarin** + rifampicin → INR…? (Falls - induction.)