

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.

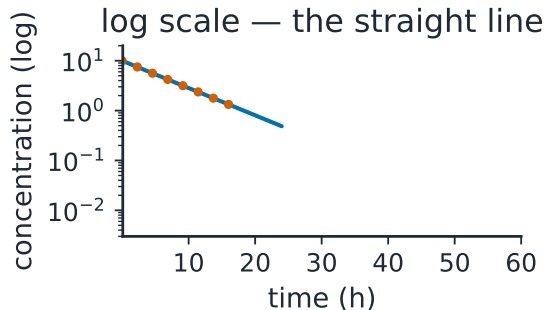
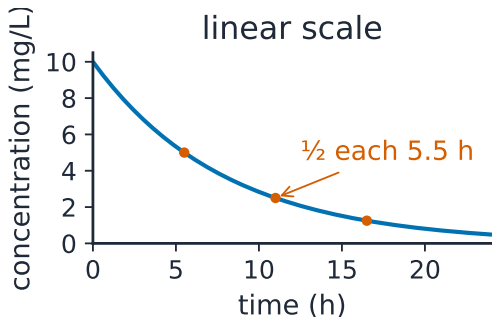
Exposure and effect

- 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** $\sim 90\%$ at 3.3 half-lives, $\sim 97\%$ at 5; loading = $C_{target} \times Vd/F$ (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



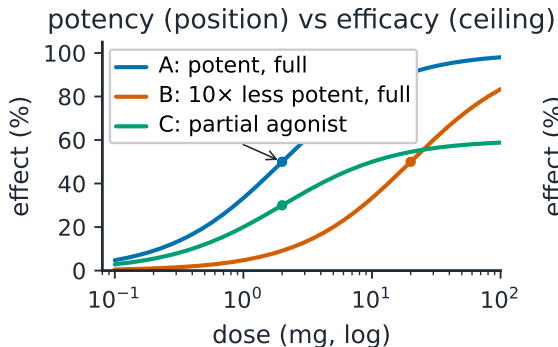
$t_{1/2} = 0.693 \cdot V_d / CL$ · steady state $\approx 90\%$ at $3.3 t_{1/2}$, 97% at $5 t_{1/2}$ · loading = $C_{\text{target}} \cdot V_d / F$

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

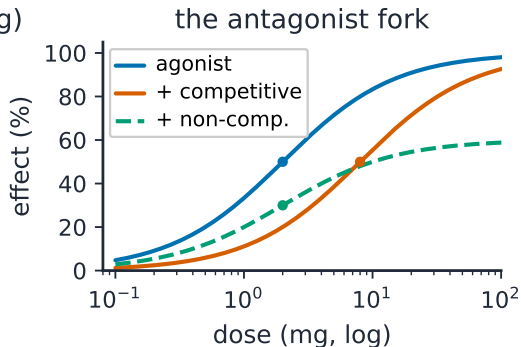
Pharmacodynamics: position and ceiling

- 1 **Curves** EC_{50} = **potency**; E_{max} = **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.

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

$\alpha 1$	vasoconstriction · mydriasis	agonist $\uparrow$ pressure; blocker $\downarrow$ (postural drop)
$\beta 1$	heart rate and contractility	agonist $\uparrow$ output; blocker $\downarrow$ rate
$\beta 2$	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

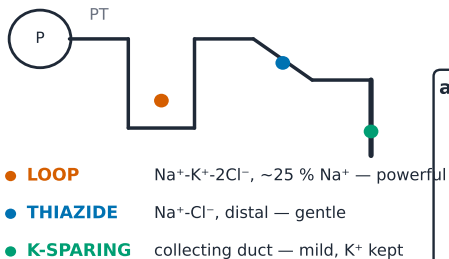
One map, five receptor rows — every autonomic drug is an arrow into it.

Cardiovascular and renal drugs: named steps

- 1 **Pressure** Diuretics (volume) · **ACE inhibitors** (bradykinin cough) · ARBs · CCBs · β_1 blockers.
- 2 **Nephron** Loop $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ (~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.

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 (MED08)

wall	β -lactams → PBPs
ribosome	30S/50S, ours untouched
DNA enzymes	gyrase · RNA pol
folate	made here, imported by us

anticancer — by TIMING (cell cycle)

S-phase	antimetabolites: methotrexate, fluorouracil
M-phase	vinca alkaloids (spindle), taxanes
any phase	alkylators — DNA damage, cycle-independent

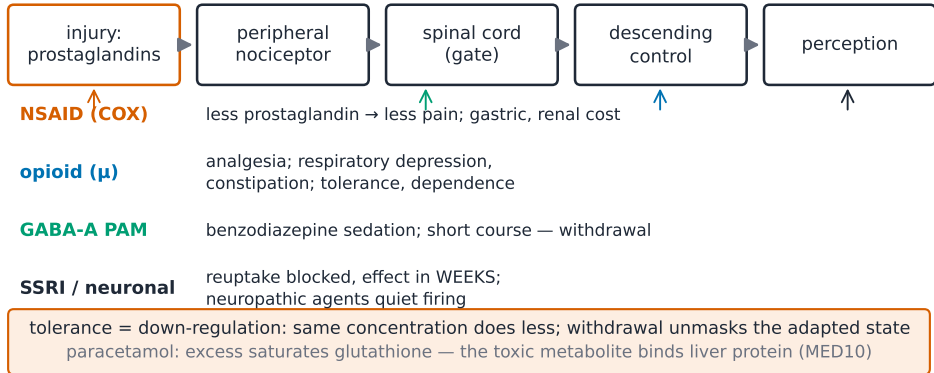
selectivity by ABSENCE (bacteria lack our targets) is wide; by TIMING (cycling cells) is narrow — marrow, gut and hair cycle too. Schedule follows the cycle: fractionation meets more cells in phase.

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



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

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

- V_d 40 L, CL 5 L/h $\rightarrow t_{1/2}$...? (5.5 h.)
- Competitive antagonist does what to the curve...? (Right shift, surmountable.)
- Anticholinergic toxidrome looks like...? (Dry, blind, fast, blocked.)
- **Warfarin** + rifampicin $\rightarrow$ INR...? (Falls - induction.)