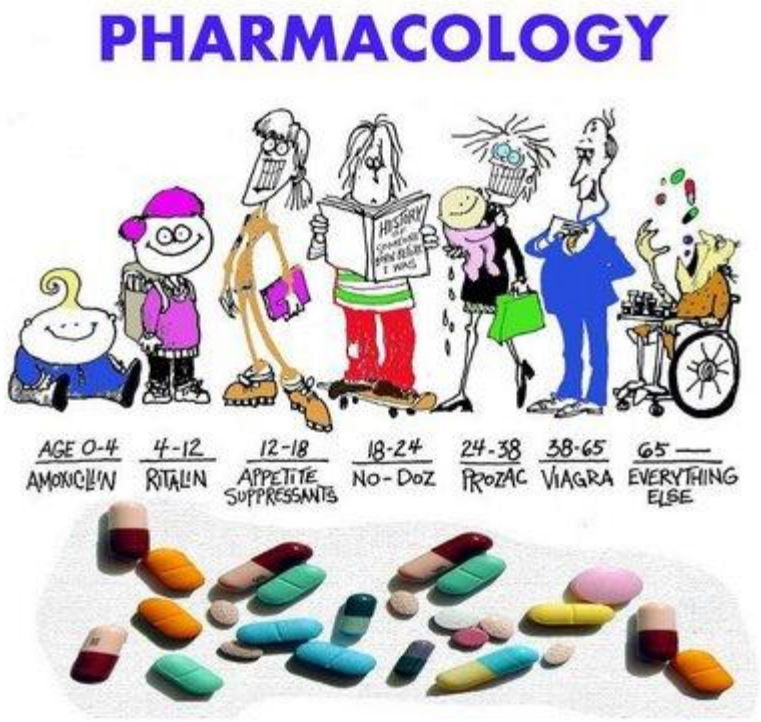
PHARMACOLOGY

2010-2011



DEVANGNA BHATIA

PRESCRIPTIONS

PRESCRIPTIONS

① Liquid powder against itching:

Rp.

Mentholi racemici 0.5
Zinci Oxidi
Talci aa 15.0
Bentoniti 3.0
Ethanoli 60%. 10.0
Glycerdi 85%
Aquae purificatae aa ad 100.0
M.f. susp.
D.S. Fluid powder against itching
Shake before use.

② Iodine sol. in alcohol for dressing of the wound environment:

Rp.

Iodi solutionis ethanolicae 20.0
D.S. For disinfection of the wound environment

③ LA for topical application on mucosal surface in ORL:

Rp.

Trimecaini hydrochloridi 0.4
Aquae pro iniectione ad 10.0
Epinephrini tartratis 1:1000 gtts. No. X (decem)
M.f. sol.
D.t.d. No. X (decem) ad ampullas
S. Cum formula. Ad usum medici

④ Solution of diluted hydrogen peroxide:

Rp:

Hydrogenii peroxidi 3% 100.0
Ad lagoenam fuscam
D.S. for disinfection of superficial wounds.

⑤ Dusting powder (without the active component):

Rp.

Zinci oxidi
Talci aa ad 100.0
M.f. pulv. adspers.
D.S. Dusting powder. Apply every 2 hours.

⑥ Disinfectant eye drops w/ adstringent effect: (for chlamydial infec)

Rp.

Argenti nitratis 0.05
Aquae pro iniectione ad 10.0
M.f. oculoguttae
Ad vitrum guttatum!
D.S. Eye drops. 3 times daily 2 drops into right/left eye.

⑦ Jarisch solution for the foments:

Rp:

Acidi borici 20.0
Glycerdi 85% 40.0
Aquae purificatae ad 1000.0
M.f. sol.
Sine antimicrobico!
D.S. For the warm foments.

⑧ LA for corneal anaesthesia:

Rp.

Tetracaini hydrochloridi 0.2
Aquae pro injectione ad 10.0
M.f. oculoguttae
Ad vitrum guttatum!
D.S. Suo nomine. Ad usum medici

⑨ I.V. infusion of 5% glucose solution - 1000ml:

Rp.

Glucosi 50.0
Aquae pro inject. ad. 1000.0
M.f. sol.
D.t.d. No. V (quinque)
Ad lag. pro infus.
Sterilisetur!
S. Suo nomine. Ad usum medici.

⑩ Codeine in drops (p.o.):

Rp.

Codeini phosphatis 0.40
Aquae purificatae ad 20.0
M.f. sol.
Da Ad. vitr. gutt.
D.S. 20 drops twice daily

(11) Expectorant w/ bronchodilator component:

Rp.

Kalii Iodidi 6.0
Ephedrini hydrochloridi 0.2
Sirupi plantaginis 30.0
Aquae purificatae ad 100.0
M.f.sol.
D.S. 1 teaspoon 3 times daily

(12) A cough suppressant (opioid derivative) in capsules:

Rp.

Codeini phosphatis 0.03
Lactosi ad 0.3
M.f. pulv.
D.t.d. No. X (decem)
Ad. caps. gelat.
D.S. 1 capsule twice a day

(13) Morphine for oral administration: BLUE BAND!

Rp.

Morphini hydrochloridi 0.045
Lactosi ad 0.3
M.f. pulv.
D.t.d. No. XX (viginti)
Ad caps. gelat.
D.S. Take 1 capsule every 5 hours

(14) Anti-tussive / expectorant mixture:

Rp

Codeini phosphatis hemihydrici 0.2
Kalii iodidi 3.0
Anisi spiritus compositi 10.0
Aquae purificatae ad 100.0
M.f.sol.
D.S. 1 spoonful 3 times a day

(15) Oral drops w/ atropine:

Rp.

Atropini sulfatis monohydrici 0.015
Aquae purificatae ad. 30.0
M.f. liq.
D. ad. vitr. gutt.
S. 20 drops 3 times a day

(16) Salicylic A. ointment (3%):

Rp.

Acidi Salicylici 3.0
Ethanoli 60%. ad 100.0
M.f.sol.
D.S. For rubbing. Apply every 4 hours.

GENERAL PHARMACOLOGICAL PRINCIPLES (SECTION A)

① Abnormal reaction to a drug (Q1+2 = same)

↳ Response depends on interindividual variability : age, body weight, gender, genetics

↳ Patho. changes occur → kidney/liver dysfunc.
- ↳ changes in drug biotransform.
- ↳ lack of plasma prot (eg albumin)
- ↳ ↓ B.F in liver
- ↳ altered haemostasis

↳ Repeated drug administration : → Cumulation → Sensitisation
- Tachyphylaxis (Q46)
- ↓ → Tolerance (down reg. of receptors)
- Resistance
  - ① prod of enzymes that inactivate drug
  - ② ↓ intracellular avail.
  - ③ ↓ affinity of drug binding

Types of drug responses:
① Normergic → degree of sensitivity typical of a norm. pop.
② Hyperergic → greater than norm sensitivity
③ Hypoergic → < norm. sensitivity
④ anergic → failure to react

Hypersensitive response :
↳ Drugs + Ag / metabolite ⇒ Allergic reaction → humoral (Atb's) / cellular (T-cells)

Incidence : Atb 5 - 10%
Acetylsalicylic A 0-2%
Phenylethylhyantoin = too high % (withdrawn fm market)

Criteria suggesting allergic reaction to drug:
↳ diff onset of effects & diff effects not "normal response"
↳ after small dose without any other pharmacodynamic effect
↳ after repeated admin

② Abnormal responses to drugs (Q1 + 2 = same)

- 4 types of hypersensitivity reactions:
  - Type 1 : Acute anaphylactic hyper...
    - ↳ e.g. penicillin, streptokinase, vaccines, hepain dextrans
  - Type 2 : Cytotoxic - Atb dependent
  - Type 3 : Immune-complex mediated
  - Type 4 : Delayed type (cell mediated) → skin reactions

Manifestations: Anaphylactic shock, haematological reactions (↓ aplastic anaemia, haemolytic '', thrombocytopenic), allergy

Idiosyncrasy : qualitatively abnormal + life-endangering reaction
- ↳ also after v. low doses ⇒ resembles allergic reaction
  several hrs after drug admin.
- ↳ damage in kidneys, liver, b. marrow; carcinogenic influence

↳ Necrosis can occur ⇒ hepatocytes
Chronic toxicity ⇒ apoptosis

Drugs causing allergy - penicillin
Ester LA
Hepain
SU
POAD
vaccines

Treatment for allergy / anaphylaxis ⇒ Anti-histamines (H_1)
Glucocort.
Adrenaline (0.3-0.5mg)
↓ epipen

Pharmakinetics ⇒ body does to the drug

③ Absorption + distribution of drugs pg105

Absorption: passage of a drug from its site of admin. → plasma inhalers
↳ imp. for all routes, except IV injec.; not always needed for action, e.g.
↳ routes of administration:
- Oral - Sublingual - Rectal - Inhalation
- App. to other epi. surfaces (skin, cornea, vagina + nasal mucosa)
- Injection: S.C, I.M, I.V, Intrathecal

Absorption: (ORAL)
↳ Mechanism ⇒ passive transfer; rate is determined by ionisation + lipid solubility of the drug; may also depend on carrier-mediated transport
↳ Factors: 4 main ones:
① Gastrointestinal motility: gastric stasis → ↓ absorp.
↳ xs rapid movement → ↓ absorp.
② Splanchnic blood flow: usually, drugs taken after meals have delayed absorp. (→ delayed progress to the s. intestine)
↳ some drugs, oppl ⇒ ↑ absorp. after a meal, because food ↑ B.F.
↳ ↓ splanchnic B.F. by hypovolaemia + H.F ⇒ ↓ drug absorp.
③ Particle size + formulation: smaller size = ↑ absorp.
↳ Formulation: produces desired absorption characteristics
↳ Capsules - remain intact for a few hrs after ingestion → delays absorption
↳ Tablets - resistant coating - same effect
④ Physiochemical factors: binding to metals, e.g. Tetracycline + Ca^{2+} ⇒ prevent absorp.
↳ pH dependent - lipid solubility

Bioavailability (F): the fraction of an orally administered dose that reaches the systemic circulation as intact drug, taking into account both absorption & local metabolic degradation. Neglets rate of absorption

Absolute bioavail: is the dose-corrected area under curve (AUC) non-IV / AUC IV

$$F = \frac{[AUC]_{po} \times \text{dose IV}}{[AUC]_{IV} \times \text{dose po}}$$

Distribution of drugs:

- major compartments are:
  - plasma (5% of body weight)
  - Interstitial fluid (16%)
  - Intracellular " (35%)
  - Transcellular " (2%)
  - Fat (20%)

$$V_d = \frac{Q}{C_p} \left(\frac{\text{total amnt of drug.}}{[\text{plasma}]} \right)$$

hypothetical vol of fluid into which a drug is dispersed

Volume of distribution (V_d): vol. of plasma that would contain the total body content of the drug at a conc. = to that in the plasma.

Lipid insoluble drugs - confined to plasma + interstitial fluids
- most don't enter the brain following acute dosing

Lipid soluble drugs - reach all compartments + accum. in the fat

For drugs that accum. outside the plasma, V_d may exceed total body vol.

Brain - no slit-junc. in cap. so only lipid sol. drugs can cross
Liver + spleen - discontinuous cap. mem.: prot can pass through

④ Adverse drug effects (AE)

↳ describes harm assoc. w/ the use of given medications at a normal dosage
↳ classified by cause + severity:

CAUSE:

↳ Type A: Augmented pharmacologic effects - dose dependent + predictable
  ↳ intolerance ↳ side effects
↳ Type B: Bizzare effects (idiosyncratic) - dose independent + unpredictable
↳ " C: chronic " , e.g. constant glucocor. admin ⇒ immunosupp.
↳ " D: Delayed "
↳ " E: End-of-treatment effects e.g. rebound effect, withdrawal sy.
↳ " F: Failure of therapy. DMARDS opioid, Anti-depres, CNS stim, Anti-psycho

SERIOUSNESS + SEVERITY:

↳ Death ↳ Life-threatening ↳ Hospitalisation (initial/prolonged)
↳ Disability (significant, persistent, permanent change ...)
↳ Congenital Anomaly
↳ Requires intervention to prevent permanent impairment or damage.

↳ Can be local or systemic

Abnormal pharmacokinetics: (can be the cause of these AE)

① Comorbid disease states: various diseases, esp. renal/hepatic insuff → alter drug metabolism
② Genetic factors: due to inherited factors of Phase I oxidation or Phase II conjugation
  ↳ Phase I: inheriting abnorm. alleles of CYP450
  ↳ HD will affect E.F.
  ↳ Phase II: " " pseudocholinesterase (butyrylcholinesterase)
  ↳ " " N-acetyltransferase
  ↳ " " thiopurine S-methyltransferase
③ Interactions w/ other drugs: risk of drug interaction ↑ w/ polypharmacy.
  ↳ Protein binding: transient + mild until a new steady state is found.
    ↳ mainly for drugs without much first-pass liver metabolism.
    ↳ Albumin, lipoproteins & α1 acid glycoprotein
  ↳ CYP450: abnorm. metabolism

⑤ Antagonism in drug effects

Drug antagonism: drug antagonists are drugs that compete for the available receptors. They can be:

- ↳ Competitive: capable of reversing/altering an effect already achieved
- ↳ Non-competitive: no pharmacological effect of their own
- ↳ Chemical ↳ Pharmacokinetic ↳ Physiological.
- ↳ Antagonism by receptor block (competitive)

① Chemical antagonism: uncommon situation where the 2 subs. combine in solution ∴ the effect of the active drug is lost.

e.g. chelating agents (e.g. dimercaprol) bind to heavy metals & ∴ ↓ their toxicity

② Pharmacokinetic antagonism: situation in which the "antagonist" effectively reduces the conc. of the active drug at its site of action.

- ↳ Rate of metabolic degradation of the active drug ↑
- ↳ ↓ " " absorption from the GIT
- ↳ ↑ " " renal excretion

③ Physiological antagonism: term used loosely to describe the interaction of 2 drugs whose opposing actions in the body tend to cancel each other out.

e.g. histamine works on receptors of parietal cells of the gastric mucosa → stimulate Acid secretion; omeprazole blocks this by inhib. the proton pump.

④ Antagonism by receptor block: 2 imp. mechanisms.

① Reversible, competitive antagonism
② Irreversible / non-equilibrium competitive antagonism

Flumazenil, Naloxone / Naltrexone, Ethanol, Protamine sulfate, B2D + carbamazepine

E.g. Tubocurarine (non-depol NMJ blocker) (low doses)

(5 contd.)

Reversible

Competitive antagonism:

↳ commonest + most imp. type of antagonism.

↳ drug binds selectively to a particular type of receptor without activating it, but also preventing the agonist frm binding

↳ sufficient antagonist will displace the agonist frm binding sites → ↓ freq. of receptor activation.

↳ ↑ [agonist] → restores the agonist occupancy + tissue response

↳ ∴ antagonism is known as SURMOUNTABLE

↳ presence of a competitive antagonist, will shift the dose-response curve to the RIGHT!

↳ shift ⇒ Dose ratio: the ratio by which the [agonist] has to be ↑ in the presence of the antagonist in order to restore a given level of response.

↳ Dose ratio ↑ linearly w/ [antagonist]; slope of this line is a measure of the affinity of the antagonist for the receptor

↳ basis for receptor classification

Displacement occurs, by the agonist occupying a proportion of the vacant receptors, ∴ it reduces the rate of association of the antagonist molecules; Consequently, the rate of dissociation exceeds that of association ∴ the overall antagonist occupancy falls.

Irreversible competitive antagonism:

↳ when the antagonist dissociates very slowly / not at all, frm the receptors ⇒ ∴ result = no change in the antagonist occupancy when the agonist is applied.

↳ in drugs that possess reactive groups that form covalent bonds w the receptor e.g. Succinylcholine - depol NMJ blocker

Clopidogrel

e.g. NNRTI ⇒ Delaviridine
Phenoxybutamine
Foscarnet (DNA polymerase)

Non-competitive antagonism:

↳ the situation where the antagonist blocks the chain of events, at some point, that lead to the production of a response by the agonist.

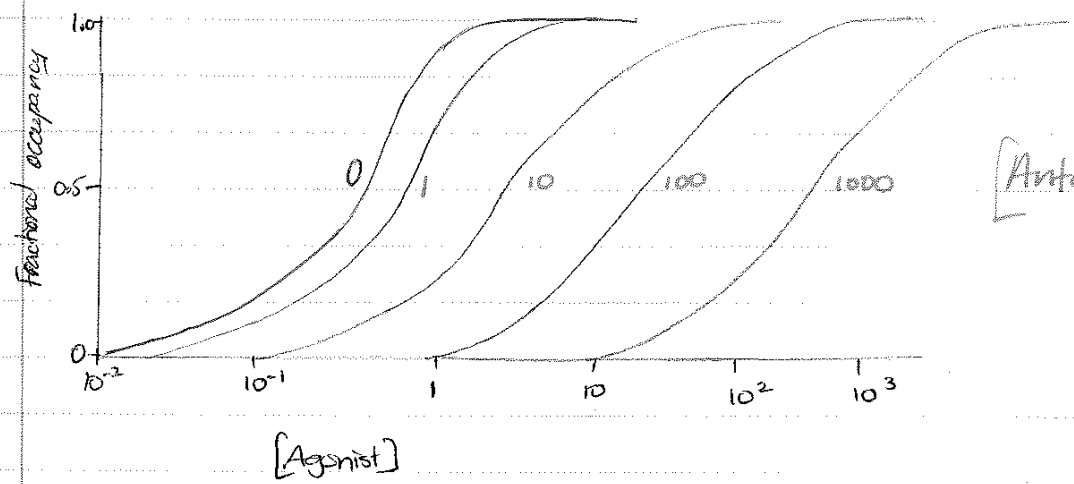
↳ bind to sites other than the agonist-binding site & exert their action.

↳ bound antagonists may prevent conformational changes in the receptor needed for receptor activation after the agonist binds.

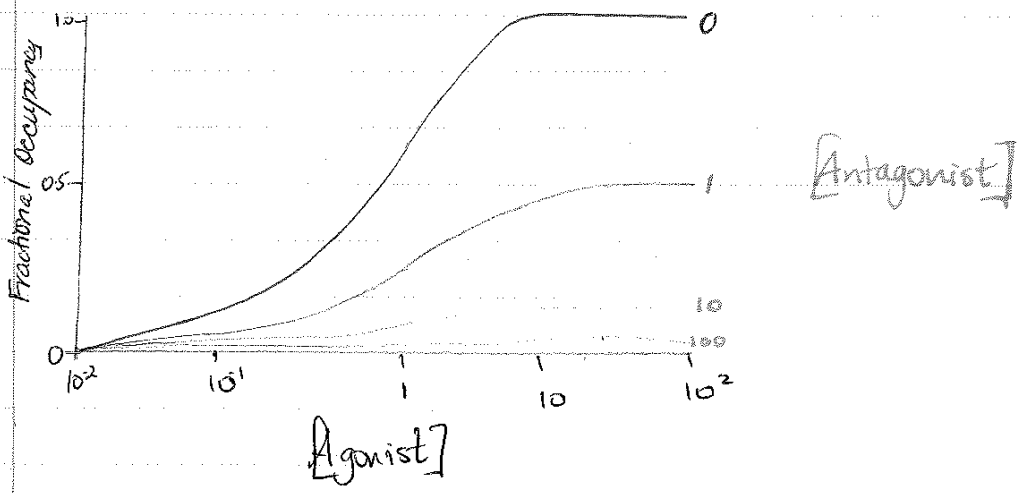
↳ no amount of agonist can completely overcome this inhibition.

↳ ↓ slope + max. of the agonist log conc & some degree of shift to the RIGHT!

Reversible!



IRREVERSIBLE!



(6) Basic pharmacokinetic processes

pg 746, Liki

"what body does to the drug"

Pharmacokinetics (PK): branch of pharmacology, dedicated to the determination of the fate of subs. admin. externally to a living organism
↳ divided into several areas, incl:

A: Absorption (subs → circulation)
D: Distribution (dispersion of subs. throughout the fluids/tissues of the body)
M: Metabolism (irreversible transformation of parent compounds → daughter metab)
E: Excretion (elim. of the subs fm the body)
"L": Liberation => process of release of drug fm the formulation.

Distribution depends on: tissue permeability between tissues
B.F.
perfusion rate of the tissue
ability of the drug to bind plasma prot⁻ + tissue.
pH partition
(tendency fr acids to accum. in basic fluid compartments; bases → Acidic compartments)
↳ Vd. (vol of distribution) - end of Q3

⑦ Biopharmaceutical drug interactions pg 745

Drug interactions: occur when the effect of a particular drug is altered, when it is taken w/ another drug or food.

Admin. of one drug (A) can alter the action of another (B) by 2 mech:
① modification of the pharmacological effect of B without altering its conc. in tissue fluid ⇒ PHARMACODYNAMIC INTERACTION
② alteration of the conc. of B that reaches its site of action ⇒ PHARMACOKINETIC INTERACTION
↳ ADME!

End of Q4 - "Interactions w/ other drugs"

Biopharmaceutical - prod by means other than direct extraction fm biological/human/engineered source
e.g. human insulin

Homoreceptors
Heteroreceptors
Autoreceptors, e.g. α_2 agonists - Clonidine, Methyldopa

⑧ Classification of receptors

pg 27. ↳ -ve feedback)

Drug receptor: any part of a cell (usually a large prot molecule) on the cell surface / in the cytoplasm w/ which a drug molecule interacts to trigger a response or effect

↳ elicit many diff types of cellular effects & take diff. amounts of time

↳ 4 receptor types:

① Ligand-gated ion channels: (ionotropic receptors)

↳ found in membranes

↳ pentameric structure ($\alpha_2, \beta, \gamma, \delta$ subunits) + central pore

↳ 2 ACh binding sites; both have to be occupied to be active

↳ effector ⇒ ion channel

↳ direct coupling (since it is really fast ⇒ AP generated + decayed in few milliseconds)

↳ fast neurot usually act here ⇒ nicotinic Ach receptor (nAChR)

↓

↑ mem. permeability to ions

$GABA_A$ Receptor; $5\text{-}HT_3$ receptors

Glutamate receptors of NMDA, AMPA types

↳ NO intermediate biochem. steps are involved in the transduction process

② G-prot-coupled receptors: (metabotropic receptors)

↳ found in membranes

↳ effector ⇒ channel or enzyme

↳ single polypeptide chain of upto 1100 residues; 7 transmembrane α-helices

↳ largest family + inc. receptors for many hormones & slow transmitters, e.g. muscarinic ACh receptor (mAChR); adrenergic receptors + chemokine receptors

↳ 3 distinct families; similarity within a fam. but none between fams.:

↳ ① A: largest; monoamine, neuropeptide + chemokine receptors

↳ ② B: some other peptides - calcitonin + glucagon

③ C: smallest; metabotropic glutamate + GABA receptors + the Ca^{2+}-sensing receptors

↳ consist of 3 subunits (α, β, γ) — GTPase activity

↳ guanine (GTP) nucleotides bind to the α subunit (enzymatic activity) GDP

↳ $\beta\gamma$ complex

↳ $G_i\alpha$ subunits: 4 types

Cholera toxin → activation (prevents) / Pertussis toxin → prevents dissociation of $\alpha\beta\gamma$ complex

① $G_{\alpha s}$ - stimulatory - stimulates adenylyl cyclase → ↑ cAMP form. → ↑ PKA

② $G_{\alpha i}$ - inhibitory - inhibits adenylyl cyclase → ↓ cAMP form.

③ $G_{\alpha o}$ - opioid / canabinoid receptors

④ $G_{\alpha q}$ - activates Phospholipase C → ↑ prod. of 2nd messs IP_3 + diacylglycerol → Ca^{2+} (α_1 receptors)

③ Receptor kinases:

↳ found in membranes

↳ effector = protein kinases

↳ direct coupling

↳ wide variety of protein mediators (incl. GF + cytokines) + hormones (insulin / ephrin)

↳ large proteins, single chain of upto 1000 residues; large extracellular ligand binding domain

↳ 4 main types:

① Receptor tyrosine kinases (RTKs): insulin receptor; GF - epidermal / nerve GF

② Serine / threonine kinases: phosphorylate serine / threonine instead of tyrosine

↳ Transforming GF (TGF)

③ Cytokine receptors: no intrinsic enzyme activity

↳ assoc. w/ & activate - cytosolic tyrosine kinase (Jak - Janus kinase)

↳ Interferons + colony stimulating factors - immunological responses

④ Guanylyl cyclase - linked receptors: similar structure to RTKs

↳ stimulate cGMP form.; receptor for ANF

④ Nuclear receptors:

↳ intracellular! e.g. steroid receptors

↳ effector = gene transcription; coupling via DNA

↳ monomeric structure w/ separate receptor- & DNA-binding domains

↳ 2 main categories: ① found in the cyto; migrate to the nl; endocrine

② found in the nl; usually lipid ligands (eg. FA)

⑨ Competitive dualism (partial agonism)

Intrinsic activity: ability of a drug once bound to activate the receptor

Partial agonists: can occupy receptors but cannot elicit a max. response

↳ intrinsic activity <1 ; e.g. buspirone, buprenorphine (good), pendaraxine (good)

↳ Clinically: ① activate receptors + give a submax. response when inadequate amounts of the endogenous ligands are present OR e.g. 5HT1A partial agonist (Buspirone) + Bromocriptine (Dopamine)

② ↓ overstimulation of receptors when xs amounts of the endogenous ligand are present

↳ ↓ rate & ↓ severity of dependence & withdrawal sy, e.g. Methadone

Full agonist: occupy receptors to cause max. activation

↳ intrinsic activity = 1

↳ e.g. isoproterenol - mimics the action of adrenaline at β-adrenoreceptors

Inverse agonist: an agent that binds to the same receptor binding-site as an agonist for that receptor & reverses activity of receptors. e.g. H_1 anti-histamine

↳ opp. pharmacological effect of a receptor agonist

Superagonist: compound capable of producing a greater max. response than the endogenous agonist for the target receptor, ∴ efficacy >100%.

↳ doesn't mean it is more potent, but it is a comparison of the max. poss. response that can be prod. inside the cell, after binding.

Full inverse agonist	Partial inverse agonist	Silent Antagonist	Partial Agonist	Full Agonist	Super Agonist
-100%		0%		100%	

Efficacy relative to endogenous agonist

(10) Dependence of drug effect on a route of administration

- **oral route**: most common, convenient + economical; generally safe.
  - ↳ Stomach: lipid-soluble + weak acids (un-ionised)
  - ↳ S. intestine: 1° site of absorp. for most drugs =>
    - ↳ Large SA - partially ionised weak acids + bases can diffuse

↳ **Bioavailability (F)**: fraction of a drug that reaches the bloodstream unaltered
  - ↳ IV => F = 1

↳ **Bioequivalence**: the condition in which the [plasma] vs time profiles of 2 drug formulations are identical.

↳ **First pass effect**: phenomenon of drug metabolism whereby the [drug] is greatly ↓ before it reaches the systemic circulation.
  - ↳ fraction of lost drug during the process of absorption => due to the liver + gut wall
    - ↳ usually after the oral route; other routes avoid this
    - ↳ 4 systems which affect first pass effect:
      1. enzymes of the Gastrointestinal lumen
      2. gut wall enzymes
      3. bac. enzymes
      4. hepatic "

↳ other factors, which may influence absorption:
1. Gastric contents + motility (intestinal)
2. GI B.F. => lipid soluble molecules = blood flow limited
   highly polar " => " " independent
3. Stomach A. inactivating enzymes => destroys some drugs.
4. Interactions => w/ food, other drugs ...
5. Inert ingredients => alter absorp.

Parenteral route: ind IM, IV, S.C.
- ↳ IV = 100% F; most rapid + good in emergencies + when u need absolute control
- ↳ IM / S.C = drugs enter capillaries thru endothelial pores.
  - ↳ for sustained release; can cause irritation + pain

Inhalation: rapid absorption ⇒ large SA + rich blood supply
↳ gaseous anaesthetics, epinephrine, glucocorticoids (asthma)

Sublingual: good for drugs w/ high first pass metabolism
↳ e.g. nitroglycerin

Intrathecal: for drugs that don't readily cross the BBB.

Rectal: ↓ first pass metab. by 50%; epileptic kids
avoid nausea/vomiting
↳ inconvenient / patient noncompliance

Topical: when local effect is needed
↓ systemic effects, esp in dermatology + ophthalmology
must be non-irritating.
can prod. systemic effects (sometimes).

(11) Development of a new drug 19781

Drug dev: a blanket term used to define the entire process of bringing a new drug/device to the market.

↳ ind. discovery/(1) prod. dev, pre-clinical (2) research (micro-orgs, animals) & clinical trials (3) (humans)

① Drug discovery phase: 2-5 years

↳ ~100 projects

↳ ① Target selection (usually func. prot) - find + decide on a target

② Lead finding - cloning of the target prot (human form)

main prob; Sometimes impossible → ③ " optimisation - ↑ potency of the compound on its target + optimise it

④ Pharmacological profiling

② Pre-clinical development: 1.5 years

↳ Aim: satisfy all the requirements that have to be met before a new compound is deemed ready to be tested for the first time in humans.

↳ 4 categories:

① Pharmacological testing: check for any hazardous acute effects, e.g. bronchocons, BP changes, dysarrhythmias, ataxia. = SAFETY PHARMACOLOGY

② Preliminary toxicological testing: to eliminate genotoxicity + to determine the max. non-toxic dose (daily for 28 days + 2 diff species)

↳ weight loss checks etc & post-mortem chks (histo/biochem. evidence)

③ Pharmacokinetic testing: studies on the absorp... ADME studies in lab animals.

④ Chemical + pharmaceutical dev: assess the feasibility of large scale synthesis/purification; stability of the compound + dev. a formulation suitable for clinical studies

All pre-clin. dev. is done under Good Laboratory Practice (GLP) → aim is to ↓ human error as much as poss. + ensure reliability

↳ record-keeping procedures, data analysis, instrument calibration + staff training.

③ Clinical development: 5-7years!

↳ 4 phases:

① Phase I: small group (20-80) healthy volunteers

↳ check for safety (dangerous AE - e.g. on CVS, resp, hepatic, renal func?)
tolerability (unpleasant symp-headaches, nausea...)
pharmacokinetic properties (well absorp? time course of (plasma))

② Phase II: groups of patients (100-300)

↳ test efficacy in the clinical situation

↳ covers various clinical disorders (eg depression, phobias...) to identify indications for the new compound + dose required

↳ LACK OF THE EXPECTED EFFICACY = common reason for FAILURE!

③ Phase III: definitive double-blind randomised trials

↳ multicentre trials, 1000-3000 patients => aimed at comparing the new drug w/ commonly used alternatives

↳ v. costly, diff to organise, years to complete

↳ drug can look less impressive in this phase!

↳ economic benefits should be assessed aswell.

↳ end of phase, drug is submitted to the authorities for licensing

↳ evaluation takes ~1yr or more.

④ Phase IV: obligatory postmarketing surveillance

↳ detect any rare/long-term AE

↳ may limit the usage of the drug OR withdraw it.

Commercial Aspects:

① high risk business - 1 in 50 successful drugs.

② takes a long time - avg = 12 yrs.

③ expensive - £500million - £1 billion!

(12) Drug addiction

pg 619 Addiction ⇒ physical + ψ dependence that dev. to drugs which cross the BBB

Dependence: compulsive craving that develops as a result of repeated administration of that drug.

↳ w/ a wide range of psychotropic drugs, acting by many diff mechanisms.

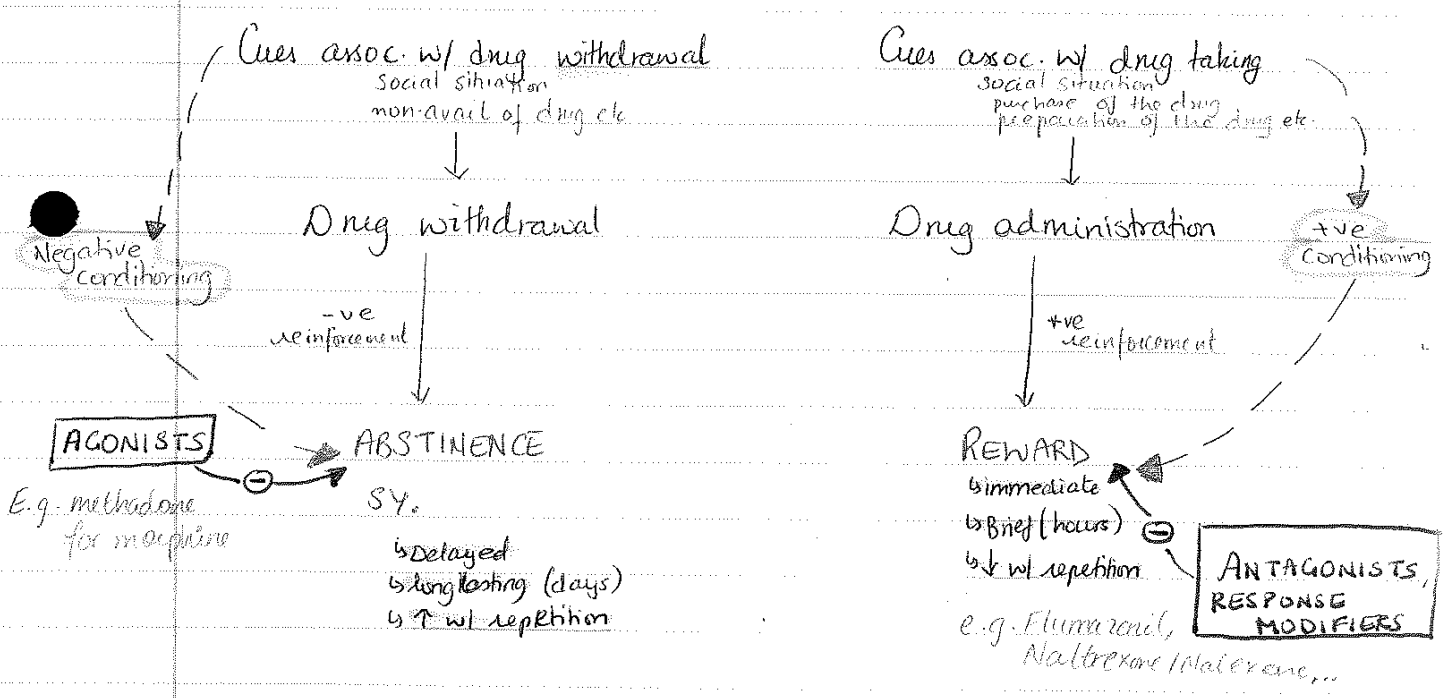
↳ psychological + physical dependence
(outlasts the phys. dependence)

Abuse: recurrent use of subs that are illegal / that cause harm to the individual.

Tolerance: ↓ pharmacological effect on repeated administration
↳ accomp. dependence

Withdrawal / Abstinence sy: describes the AE (ψ + phys.)
↳ lasting for a few days / weeks of stopping taking a drug

Psychological factors involved in drug dependence:



↳ Reward: working via activation of the mesolimbic dopaminergic pathway

↳ Chronic drugged state ⇒ Adaptive changes in receptors, transporters, 2nd mes. etc
↳ eg. ↑ adenylyl cyclase, Dopamine ↑ transporter

Treating drug dependence pharmacologically:

↳ Mechanisms:

① Substitution to alleviate withdrawal symp. => e.g. methadone is used short-term to blunt opiate withdrawal.

② Long-term substitution => nicotine patches/chewing gum; methadone.

③ Blocking response => Naltrexone to block opiate effects

④ Aversive therapies => Disulfiram to induce unpleasant response to ethanol

⑤ Modification of craving => Naltrexone; bupropion

(13) Drug allergy pg 761

↳ common form of Adverse reactions to drugs.

↳ most drugs = low molecular weight ∴ not immunogenic BUT the drug/its metabolites can act as haptens, by interacting w/ [host] to form a stable immunogenic conjugate. ↳ covalent bonds.

↳ main criteria that are suggestive of an immune response:

① Time course differs from the main action of the drug ⇒ delayed OR occurs only w/ repeated exposure

② Allergy may result fm doses that are too small for any effects

③ the reaction conforms to one of the types of hypersensitivity. + unrelated to the pharmacodynamic effect of the drug

↳ incidence = 2-25%.

↳ majority ⇒ minor skin eruptions.

↳ Serious reactions = FATAL + RARE! = anaphylaxis, haemolysis + b.marrow depression

↳ Penicillins - commonest cause of drug-induced anaphylaxis

↳ 1/50,000 patients

↳ Skin eruptions - severe + fatalities occur w/ Steven-Johnson sy w/ toxic epidermal necrolysis

↳ allergy more likely to occur w/ large doses + extended exposure

Antibiotics: Penicillin ; Sulfa drugs ; Tetracyclines POADs!

Analgesics: Codeine ; NSAIDs + Clozapine ⇒ agranulocytosis

Anti-seizure: Phenytoin ; carbamazepine

↳ Haematological reactions (type 2, 3 or 4): incl. haemolytic anaemia, agranulocytosis, thrombocytopenia ; aplastic anaemia

↳ other clinical manifestations: ↳ quinine, hepatin, thiazide diuretics

① hepatitis (types II, III) - eg halothane, phenytoin

② Rashes (types I + IV) - mild but can be life-threatening

③ Drug-induced systemic lupus erythematosus (type II) - ath to nuclear material are formed., e.g. procainamide (ester LA, anti-arrhy 1A)

(14) Drug delivery approaches

Drug delivery => method / process of administering a pharmaceutical compound to achieve a therapeutic effect in humans / animals.

↳ oral, IV, I.M, S.C, topical, rectal, transmucosal (nasal, bucal/ sublingual, vaginal, ocular) + inhalation

↳ Prot + peptides = INJECTION

↳ Suscep. to enzyme degradation

↳ cannot be absorbed into the systemic circ. efficiently dare to molecular size / charge

(15) Drug elimination half-life ; rate constant

↳ drugs are terminated by enzyme-catalysed conversions to an inactive / less active compound

Rate of elimination:

① First-order elimination: constant fraction of drug is eliminated per ~~time~~ unit of time (clearance)

* Rate of elim. fm body (mass/time) = Constant × $[Drug]_{plasma}$ (mass/vol)

↳ linear func. of the [plasma drug]

↳ occurs when elimination systems are not saturated by the drug

② Zero-order elimination: constant amount of drug is eliminated per unit time

↳ mechanisms by which elimination occurs are saturated / therapeutic doses of drugs exceed the capacity of elim. mech.

↳ rate of elim is constant + DOESN'T depend on [plasma].

Clearance (CL): measure of the capacity of the body to remove a drug. Units = volume / time

↳ drugs w/ HIGH CL ⇒ rapidly removed from the body

LOW CL ⇒ slowly " " " "

① Specific organ clearance: capacity of an individual organ to eliminate a drug., due to metabolism (hepatic clearance) or excretion (Renal Clearance)

$$CL_{organ} = \frac{\text{Rate of elim. by organ}}{[Drug]_{plasma\ perfusing\ organ}}$$

② Whole body clearance: capacity of the body to eliminate the drug by all mechanisms, ∴ sum of all specific organ CL:

$$CL_{whole\ body} = CL_{organ_1} + CL_{organ_2} + \dots$$

Clearance usually refers to the whole body :.

$$CL = \frac{\text{Rate of elim from body}}{[\text{Drug}]_{\text{plasma}}}$$

③ Plasma Clearance : Same as whole body CL BUT this terminology is used because CL maybe viewed as the vol. of plasma that contains the amount of drug removed per unit time

Half-life : ($t_{1/2}$)

time taken for [plasma drug] to be reduced by 50%

↳ only applies to drugs elim by 1st order kinetics!

↳ as long as the dose admin. doesn't exceed the capacity of the elimination systems, $t_{1/2}$ will remain the same.

↳ > 95% of the drug will be elim in a time interval = 5 $t_{1/2}$

↳ applies for therapeutic doses of most drugs.

↳ $t_{1/2}$ => related to elim rate constant(k) => $t_{1/2} = \frac{0.693}{k}$

vol of distribution (V_d) + CL => $t_{1/2} = \frac{0.693 \times V_d}{CL}$

Extraction ratio : ↓ in the [drug] in plasma from arterial to venous side of kidney

↑ $t_{1/2}$ => ↑ V_d of drug

↓ RBF

↓ extraction ratio (renal insuff)

↓ metab (liver insuff).

drug-drug interaction

(16) Drug excretion

Routes: urine, faeces (unabsorbed drugs / drugs secreted into bile), saliva, sweat, tears, milk, lungs (alcohols + anaesthetics)
↳ **KIDNEY** = major site of excretion

Net excretion of drugs:
↳ Result of 3 separate processes: (↓BF = ↓GFR)
① Filtration: at the glomerulus
↳ most drugs = low molecular weight ∴ filtered
↳ Serum prot⁻ binding ↓ filtration - plasma prot⁻ too big to pass.
↳ GFR = 30-40% ↓ in newborns (<1yr) than adults
② Secretion: active transport - prox tubules
↳ 2 transport systems that secrete drugs into the ultrafiltrate ≤ organic Acids / organic Bases
↳ site for drug-drug interactions - drugs compete w/ each other for binding to the transporters - digoxin, verapamil + amiloride
↳ affinity of transport sy ~~affinity for~~ for most drugs >>> affinity of plasma binding prot⁻
③ Reabsorption: throughout the tubule
↳ glc - actively reabsorbed.
↳ un-ionised forms (weak acids + bases) - simple + passive diffusion
↳ Rate depends on lipid solubility, pK of the drug, + conc grad.
↳ affected by changes in urinary pH - affect elim of weak acids + bases by affec. degree of ionisation

Renal clearance: vol of plasma that is cleared of drug per unit time

$$Cl\ (ml/min) = \frac{[U] \times V}{[P]}$$

[U] = conc of drug mlk of urine
V = vol of urine, excreted / min
[P] = plasma conc of drug (ml)

↳ a drug excreted only by filtration (eg. insulin) : CL = GFR (125-130 ml/min)

↳ " " " by filtration + complete secretion (eg PAH) => CL = Renal plasma CL (650 ml/min)

↳ CL values = 130-650 ml/min => drug is filtered, secreted + partially reabsorbed

↳ CL influenced by age, other drugs + disease

↳ Renal failure -> ↓ CL -> ↑ plasma levels

(17) Drug interactions w/ serum proteins pg102

↳ At [therapeutic] plasma - many drugs = bound ~99%
↳ Fraction of free drug = ≤ 1% => only this unbound amount is pharmacologically active
↳ Albumin => most imp plasma prot⁻
  ↳ many acidic drugs e.g. Warfarin, NSAIDs, Sulfonamides
  ↳ fewer basic drugs e.g. Tricyclic anti-depressants, Chlorpromazine
↳ Some other plasma prot⁻ => β-globulin } certain basic drugs, e.g. quinine
  Acid glycoprot⁻
↳ Amount of drug bound to prot⁻, depends on:
  ① Conc. of free drug
  ② its affinity for the binding site
  ③ Conc. of prot⁻

↳ usual [albumin plasma] = 0.6mmol/l
  ↳ 2 binding sites per molecules = 1.2mmol/l
↳ usual therapeutic doses : conc. bound [DS] is in direct proportion to the free conc. [D]

$$[D]_{\text{free drug}} + [S]_{\text{binding site}} \rightleftharpoons [DS]_{\text{complex}} \qquad [DS] \propto [D]$$

↳ Saturable binding sometimes leads to a non-linear relation between dose + free (active) drug conc.

↳ Few therapeutic drugs affect the binding of other drugs => they occupy only a tiny fraction of avail. sites (Sulfonamides & tolbutamide)
  EXCEPT: Sulfonamides => occupy ~50% of binding sites at [therapeutic] ∴ cause harmful effects by displacing other drugs, in premature babies

↳ Extensive prot⁻ binding, slows down drug elim (metab &/or GFR)

Dose capacity ratio => if high - lots of free drug conc nd enuf prot to bind
  low - ↓ of albumin, not enuf drug to fill them

(drug mainly in plasma)

low V_d => ① drug bound to prot

② drug interaction → then not bound anymore

③ ↑ [drug free]

if high V_d - not that much of an effect cos widely distributed

(18) Drug metabolism pg 147

↳ Biochemical modification of pharmaceutical subs. by living orgs, usually through systemic enzyme systems
↳ form of xenobiotic metabolism
↳ converts lipophilic chemical compounds → polar prods.
↳ mainly in the SER of the liver cells
  ↳ other sites: epi. cells of GIT, lungs, kidneys + skin ⇒ these sites – localized toxicity reactions
↳ Phase I + II

Phase I:

① Oxidation: CYP450 monooxygenase sys.
phenothiazines, paracetamol, steroids → " "
Flavin-containing "
Alcohol dehydrogenase + Aldehyde dehydrogenase
Monoamine oxidase
Co-oxidation by peroxidases

② Reduction: NADPH - CYP450 reductase
Reduced (ferous) CYP450

③ Hydrolysis: Esterases + Amidase
Epoxide hydrolase

↳ drug is still partly lipophilic; produces active metabolites

Phase II: Conjugation reactions

① Methyltransferase ← Methylation
② Sulphation: Glutathione S-transferases
Sulfotransferases
③ Acetylation: N-acetyltransferases
Bile A. Co-A: amino acid N-acyltransferases
④ Glucuronidation: UDP-glucuronosyltransferases

↳ detoxication reactions
↳ ⊕ interactions of the polar func. groups of phase I metabolites
↳ prods = ↑ molecular weight + inactive

Drugs can either inhibit or induce drug-metabolising enzymes.

Enzyme Induction: synthesis of an enzyme in response to an ↑ conc of its substrate in the cell

↳ >200 drugs cause enzyme induction ∴ ↓ pharmacological activity of other drugs.

↳ inducing agent = substrate for the induced enzymes, the process leads to slow dev tolerance

↳ enzyme induction can ↑ toxicity of a 2nd drug, if the toxic effects are mediated via an active metabolite

↳ variability in rates of drug metabolism between individuals -- environmental contaminants (eg alcohol)

↳ exploited therapeutically! ⇒ admin phenobarbital to premature babies → induce glucuronyltransferase → ↑ bili. conju. → ↓ risk of kernicterus!

CYP450 inducers ⇒ rifampicine, phenobarbital, phenytoin, dexamethasone

Enzyme Inhibition:

↳ mainly of CYP450 ⇒ slows down metabolism ∴ ↑ action of other drugs metab. by the enzyme

↳ several inhib of metab. influence the metab. of diff stereoisomers selectively

↳ therapeutic effect of some drugs = direct consequence of enzyme inhib, e.g. xanthine oxidase inhib ⇐ ALLOPURINOL - prevents gout.

↳ sometimes, inhib of drug metab. = less expected coz. enzyme inhib. is not the main mechanism of action, e.g. steroids + cimetidine - enhance the actions of a large of drugs, e.g. antidepressants, cytotoxic drugs.

CYP450 inhibitors ⇒ Antidepressants (fluoxetine, fluvoxamine, paroxetine), grapefruit juice, erythromycin, Chloramphenicol, Ketoconazole, itraconazole, ~~cimetidine~~ quinidine (optical isomer of quinine).

(19) Drug-receptor interactions

↳ Drugs bind to receptors (cell membrane OR cytoplasm)
↳ Ability to bind to a receptor is influenced by ext. factors + intracellular regulatory mechanisms
↳ Receptor density + efficiency of stimulus-response mechanisms - varies fm tissues-tissues
↳ Up/down regulation of the no. & binding affinity of receptors can occur => drugs, aging, genetic mutations + disorders.
  ↳ Affects adaptation to drugs.
↳ drug's ability to affect a receptor - related to its affinity (probability of the drug occupying a receptor at any given instant) & its intrinsic efficacy (degree to which a ligand activates receptors + leads to cellular response)
  ↳ Chemical structure determines affinity + intrinsic activity.

Down regulation => process by which a cell ↓ the no. of receptors.
Up " => " " " " " " ↑ " " " "

Down reg => cellular ↓ in no of receptors to neurotr/hormone, which ↓ the cell's sensitivity to the molecule
  ↳ e g of locally acting -ve feedback mechanism

Up-reg => ↑ no. of CYP450 enzymes in liver cells when digoxin is admin -> ↑ degradation of these molecules
  ↳ ↑ no. of NMDA glutamate receptors - in ppl who have consumed xs quantities of alcohol ∴ inhibiting those same receptors

(20) Effects of age on drug effects pg 740

↳ drug elim varies w/ age!
↳ newborns + old ppl have less efficient drug elim → ∴ drugs prod. greater & more prolonged effects
↳ Other factors:
  ↳ variations in pharmacodynamic sensitivity
  ↳ physiological factors (altered e.g. cardiovascular reflexes)
  ↳ pathological factors e.g. hypothermia
  ↳ changes in body composition w/ age → changes in vol. distribution
  ↳ elderly - consume more drugs than younger ppl ∴ ↑ drug-drug interactions.

① Age related variation in sensitivity to drugs:
  ↳ same [plasma] can cause diff effects, e.g. Benzodiazepines - more confusion + less sedation in elderly than young subjects.

② Effects of age on renal excretion:
  ↳ Newborn GFR = 20% of adult value + ↓ tubular func. => ∴ $t_{1/2}$ = longer
  ↳ improvement of renal func in premature babies occurs slowly; full term babies ⇒ ↑ to young adult value in 1 week & keeps on↑ to a max. of x2 adult value at 6 months.
  ↳ E.g. Adult $t_{1/2}$ plasma = 1-4 hours
  Babies born at term = 10 hours
  premature babies = ≥ 18 hours
  } Gentamicin
  ↳ ∴ need to ↓ and/or space out doses to avoid toxicity!
  ↳ GFR↓ fm the age of 20; falling by about 25% at 50yrs & 50% at 75yrs;
  ↳ chronic admin of the same daily dose (digoxin), over years, as they age → progressive ↑ in [plasma] → common cause of glycoside toxicity in old ppl!

③ Effects of age on drug metabolism:

↳ several imp. enzymes, incl hepatic microsomal oxidase, glucuronyl-transferase, acetyltransferase & plasma esterases, have ↓ low activity in neonates, esp. premature ones.

↳ ≥8 weeks to reach adult level.

↳ lack of conjugating activity → serious consequences → (kernicterus)

↳ e.g. "grey-baby" sy → due to chloramphenicol - FATAL!

↳ accum. of ↑ high tissue [chloramphenicol] due to slow hepatic conjugation.

↳ Reason why morphine is NOT used as an analgesic in labour.

↳ Goes to baby via placenta → long $t_{1/2}$ & can cause prolonged respiratory depression

↳ Activity of hepatic microsomal enzymes ↓ slowly w/ age + distribution vol of lipid-soluble drugs ↑ (fat ↑ w/ advancing age)

PREGNANCY

↳ Maternal plasma [albumin] ↓ → influences drug protein binding

↳ ↑ CO → ↑ RBF + GFR → ↑ renal elim. of drugs

↳ lipophilic molecules rapidly cross the placental barrier; hydrophilic drugs = slow - limiting fetal exposure following a single maternal dose

↳ slow elim does occur!

↳ placental barrier excludes some drugs → can admin them chronically w/ no effects in the fetus.

Fetal kidney (NOT EFFICIENT) → excreted drug → amniotic fluid → swallowed by the fetus.

(21) Enteral administration of drugs pg 104

Enteral admistration : thuagh the GIT - incl. oral + rectal
↳ drugs in form of tablets, capsules, drops - orally

ORAL ADMIN :

↳ most drugs - easiest, cheapest + commonest
↳ little absorption occurs until the s. intestine
↳ Factors affecting absorption :
① Gastrointestinal motility
② Splanchnic B.F.
③ Particle size + formulation
④ Physiochemical factors

* look at Q10 *

pH ⇒ uncharged pass thru membranes more readily
- conc grad ⇒ passive diffusion
- membrane permeability
- lipid solubility - ↑ ⇒ pass better
- SA - s. intestine = good
- contact time at absorption surface

Bioavail : influenced by ⇒ 1st pass metab
drug solubility
Chemical instability, eg PENG (unstable in gastric pH)
↳ insulin - destroyed by enzymes in GIT
Drug formulation + size

(22) Enzyme induction + inhibition

* look at Q 18 - Drug metabolism *

Induction: phenobarbital - prematures - ↑ glucuronyltransferase → prevent kernicterus.
↳ sup reg.
↳ phenytoin, phenobarbital (CYP450)

Inhibition: CYP450 ⇒ grapefruit juice, TCAs, rifampicine, erythro, chloramphenicol.
↳ slows metab of other drugs
↳ ↑ toxicity of 2nd drug.
↳ prevent gout ⇒ ALLOPURINOL - xanthine oxidase inhibition

(23) Excretion of drugs

* look at Q 16 - Drug Excretion *
mainly Renal.

3 phases: ① Filtration - glomerulus - ~130ml/min = GFR (CL)
② Secretion - prox tubule - ~650ml/min
③ Reabsorption - thru out the tubule

Clearance → $CL = \frac{[U] \times V}{[P]}$ ml/min

if all 3 then GFR (130-650ml/min)

Renal failure - ↓ GFR - ↓ CL - ↑ plasma levels
Age, disease, genetics, other drugs

*

(24) General principles of pharmacokinetics pg 120

Pharmacokinetics :
- What the body does to the drug
- Describes changes in [plasma drug] over time - related to amount in tissues
- ADME : Absorption, Distribution, Metabolism (↓ Q18) & Elimination (↓ Q16)

General rules for drug movement:
* physical-chemical charac of drug :
  - ↳ lipophilic vs hydrophilic
  - ↳ size, charge, pKa
  - ↳ ↑ acid (H^+) content = ↑ amount in unionised form

$$AH \rightleftharpoons A^- + H^+ \qquad B + H^+ \rightleftharpoons BH^+$$

* drug transport through biological barriers
  - ↳ lipophilic ⇒ passive diffusion
  - hydrophilic ⇒ pore transmission + active transport

Distribution: One or Two - compartment model

① One-compartment:
- ↳ drug distributes instantaneously after IV admin of a single dose
- ↳ if mechanism for drug elim + renal secretion - are not saturated then the semilog plot of [plasma] vs time = LINEAR
- ↳ 1st ORDER drug elim ⇒ constant fraction of drug is elim per unit time

* incomplete *

(23) Kinetics of drug oral administration

* look at Q21 * + Q31 *

↳ GIT motility, pH, drug binding, flora, malabsorption
↳ B.F
↳ Size + formulation
↳ Physicochemical factors - pka, charge, solubility (lipid), metal binding (tetracyclines + Ca^{2+})
↳ Interactions
↳ 1st pass effect : 4 systems — liver, gut wall, GIT lumen enzymes

L. intestine - large SA
↳ most absorp here

Bioavail (F).

C-max => max. conc after a single dose
T-max => Time, when it reaches c-max
F => if F < 0.02 (20%) - not worth admin this way.

(26) Non-specific mechanisms of drug effects

① Laxatives ② Antacids ③ Topical agents

↓ gastric pH - neutralise it

① Laxatives : act on large intestine ; to ↑ movement of food through GIT

↳ lead to electrolyte imbalances if used chronically

① Bulk ② Irritants + stimulants ③ Osmotic (salt / salt-free)

④ stool softeners ⑤ Lubricant

Bulk ⇒ hydrophilic colloids ; form gels in the large intestine → water retention + intestinal distention → ↑ peristaltic activity

↳ for chronic constipation

↳ methylcellulose, psyllium seeds, bran (fibre!)

Irritants + Stimulants ⇒ e.g. Senna, Bisacodyl, Castor oil

AE: ab cramps, long use - atonic colon.

↳ stim. smooth mus. contractions from their irritant action on the bowel mucosa

↳ local bowel inflam → accum. of water + electrolytes → stimulate reflex peristalsis

Bisacodyl ⇒ stimulant of the colon ; directly acts ons Nerve fibres in the mucosa of the colon

Castor oil ⇒ broken down in the s. intestine → Ricinoleic A → irritating to the gut → ↑ peristalsis

Osmotic ⇒ Saline laxatives vs Salt-free osmotic laxatives

Mg sulphate, Mg citrate, $Mg(OH)_2$, Na phosphates ⇒ non-absorbable ⇒ retain water by osmosis → distend the bowel → ↑ peristalsis

↳ Elim. of parasites / short term evacuation before surgery / other procedures.

Glycerin, Polyethylene glycol (PEG) ⇒ chronic lavage solutions

↳ Lactulose = cnt be hydrolysed by intestinal enzymes

↳ degraded in the colon by bac into lactic, formic + acetic A → ↑ osmotic press ⇒ fluid accum → colon distention

Stool softeners ⇒ docusate Na, docusate Ca / K

↳ surface active agents because emulsified w/ stool → soft stool

↳ short term, prevent constipation

Lubricant ⇒ mineral oil + glycerin suppositories

↳ coats faecal contents + inhibits absorption of water

↳ ↓ absorp of fat sol vit.

↳ taken orally + upright - prevent lipoid / lipid pneumonia

② Antacids : they are weak bases react w/ gastric H^+ → H_2O + salt ∴ ↓ gastric acidity

↳ pepsin = inactive at pH > 4 ∴ they also ↓ pepsin activity

↳ $Al(OH)_3$ (constipation), $Mg(OH)_2$ (diarrhoea)

↳ $CaCO_3 + HCl \rightarrow CaCl_2 + CO_2$ - commonly used

③ Topical agents : wiki - "topical"

ointment - drives the med into the skin more rapidly

topical solutions ⇒ low viscosity + water / alcohol in the base

lotions ⇒ thicker than sols, oil mixed w/ water

ointment ⇒ homogeneous, viscous, semi-solid, greasy, thick oil (80% oil, 20% water), high viscosity

↳ base ⇒ vehicle of an ointment ⇒ hydrocarbon, e.g. hard / soft paraffin

↳ dry skin - very moisturising

Absorption bases e.g. beeswax

Water sol bases e.g. macrogols 200, 300, 400

Emulsifying base e.g. emulsifying wax

Veg oil, e.g. peanut oil, olive, coconut, almond...

Gels ⇒ thicker than sol ⇒ semisolid emulsion in an alcohol base

↳ Scalp + body folds

Paste ⇒ oil, water + powder

+ (28) Paenteral routes of admin - Charac, demands on injec - sol

(27) Paenteral drug administration

(F)
Bioavail = 100%

Paenteral : involves piercing the skin/mucous mem.

Routes:

- IV - many drugs. total paenteral nutrition
- Intra-arterial - vasodil drugs in the treatment of vasospasm + thrombolytic drugs for emboli treatment
- Intraosseous infusion (into bone marrow) => indirect IV accen because b. marrow drains into the venous sys.
  - ↳ drugs/fluids in emergency med / paed. when IV is diff.
- IM

IV:

↳ fastest + most certain route of drug admin
↳ [v. high] of drug - Right heart -> lungs -> sys. circ.
↳ peak conc. reaching the tissues, depends on the rate of injec.
↳ several atb, anaesthetics (propofol) + diazepam for patients w/ status epilepticus

S.C + IM:

↳ faster effect than oral route but rate of absorp. depends on ① Injection site ② Local BF

↳ Rate limiting factors:

① Diffusion through the tissues
② Removal by local BF => ↑ BF = ↑ Absorption
Hyaluronidase => ↑ drug absorption

Methods for delaying absorption:

↳ Adding adrenaline to LA => ↓ systemic effects by ↓ absorp. into systemic circ. ∴ prolonging the anaesthetic effect

↳ Insulin + protamine/zinc ⇒ long acting form
↳ Procaine penicillin ⇒ poorly soluble salt ; injec. as aq. suspension
Slow absorption + prolonged action
↳ Esterification of steroid hormones (medroxyprogesterone acetate, testosterone propionate) + antipsychotic drugs (decanoate) ⇒
↑ sol. in oil → slows their rate of absorption
↳ S.C. implantation of solid steroid pellets ⇒ rate of absorp is proportional to the SA of the implant! Rate ∝ SA!

Intrathecal injection:
↳ into the subarachnoid space via lumbar puncture
↳ Methotrexate - certain childhood leukaemias - prevent relapse in the CNS
↳ Regional anaesthesia - bupivacaine, opoid analgesics
↳ Baclofen - treat disabling muscle spasms - intrathecal to ↓ AE
↳ Some Abs cross BBB v. slowly (aminoglycosides) & if needed - (↳ CNS infx w/ resistant bac)
① intrathecally OR
② Directly into the cerebral ventricles (via a reservoir)

Advantages:
① Fast: IV = 15-30s ; IM/S.C = 3-5min
② F = 100%
③ For irritant drugs / those not absorbed by gut
④ 1 injec can last for days/months
⑤ IV - continuous medication

Disadvantages:
① quick onset of action ∴ ↑ risk of addiction
② not usually self-administered
③ shared needles - HIV / fear of needles/injec = Belonephobia
④ Asepsis needed
⑤ Fatal air bubbles, if not done properly
⑥ Bypasses most of the body's defenses ∴ most dangerous route - abscesses, hepatitis, infec.

(29) Pharmacodynamic drug interactions

① Additive (aka synergistic) pharmacodynamic effects: When ≥2 drugs are given w/ similar pharmacodynamic effects, the additive effects may result in excessive response + toxicity
e.g. combinations of drugs that prolong the QT_c interval → ventricular arrythmias

② Antagonist pharmacodynamic effects: drugs w/ opposing pharmacodynamic effects may ↓ the response to 1 or both drugs. (on the same receptor)
e.g. drugs that ↑ BP (eg NSAIDs) may inhibit the antihypertensive effect of drugs such as ACE inhibitors. ; Salbutamol (β2 agonist) w/ metoprolol (β2 antagonist)

↳ Due to competition at receptor sites OR activity of the interacting drugs on the same physiological sys.
↳ NO change of [plasma] of interacting drugs.

③ Fluid/electrolyte imbalance
e.g. diuretics that cause hypokalaemia can ↑ toxicity of digoxin

④ Indirect interactions
E.g. NSAIDs can ↓ effectiveness of anti-hypertensives by causing Na^+ / H_2O retention

(30) Pharmacogenetics

"Study / clinical testing of genetic variation that gives rise to differing responses to drugs."

↳ differences in enzyme activity:
- acetylpolymorphism - fast / slow
- butylcholinesterase alteration
- CYP450 aberration

↳ differences can be qualitative OR quantitative
(qualitative ↓ action of drugs in diff ways; quantitative ↓ ↑ or ↓ effect)

↳ Considers 1 OR most few genes of interest
(pharmacogenomics = whole genome)

↳ underlying disease state may not be seen until an unexpected reaction to an anaesthetic agent occurs
e.g. atypical Achesterase enzyme suggested by prolonged Succinyl chloline (Anectine) OR mivacurium (Mivacron) induced neuromuscular blockade.

(31) Pharmacokinetic drug interactions

↳ When 1 drug affects the ADME of another drug.
↳ A change in [blood] causes a change in the drug's effect.

Absorption: route of admin
↳ penetration of dissolved drug from the site of admin. to the systemic circulation
↳ General + local effects, e.g. skin, ventricles, mucosa
↳ absorp. is undesirable - possible AE
↳ i.e. local corticoids, cocaine as LA

Speed + extent of absorption = P-kinetic parameters:
C-max = max. conc. of drug in plasma after single dose.
T-max = Time, when drug reaches C-max.
F = Bioavail (extent); how much from the admin dose gets to the circ.

IV = 100%
Extravascular = 0-100%.
Resp = 0-1%.

If F = <20% (0.02) - not worth admin drug this way!

↳ Depends on: route of admin
structure
drug dosage form.

↳ Most interactions => ↓ absorp. fm the gut
↳ Interactions affecting absorp. rate = insignificant unless therapeutic plasma levels are needed quickly, eg. analgesics.
↳ interactions affecting the extent of absorp = affect efficacy of a drug.

Factors affecting absorp:
① Change in GIT pH: ketoconazole (poorly soluble base) - needs to be in a more soluble form: hydrochloride salt via gastric A. H_2 antagonists (cimetidine) + antacids ↑ gastric pH → : ↓ absorp. of ketoconazole.

② Drug binding in GIT (adsorption, chelation, complex form):
Ca^{2+} binds to tetracyclines ⇒ ↓ absorp.

③ Change in GIT flora: short-term use of atb → alter gut flora → ↓ reabsorp. of oestrogens fm contraceptives. ↓ effectiveness

④ Change in GIT motility: Metoclopramide ↑ gut motility → prevents complete absorp. of slow dissolving digoxin preparations

⑤ Malabsorption caused by other drugs: Orlistat (Xenical) ↓ absorp. of fat-soluble vit ⇒ ↓ fat absorp. fm the gut

Distribution: penetration of drug from blood → tissues
↳ is a dynamic process
↳ depends on: lipid solubility, pH, binding w/ plasma prot + tissue prot, regional B.F., capillary permeability & CO.

Vol. of distribution: V_d: rate between amount of drug in organism + plasmatic conc
↳ quantifies the extent of distribution.

$$V_d = \frac{D \times F}{cpc}$$

D = Dose ; F = Bioavail
cpc = plasma conc.

↑ V_d ⇒ Renal failure (fluid retention); liver failure (altered body fluid & plasma prot-binding)
↓ V_d ⇒ Dehydration

Low V_d = all in blood ~5l (plasma prot bound)
Medium V_d = ~10l = ECF
High V_d = ~30l = ICF
100's V_d = ~100l = Muscles
1000's V_d = ~1000l = Fat / adipose tissue

Metabolism:

↳ most drugs undergo hepatic metabolism to more water-soluble compounds → urine excretion

↳ drug interactions affecting metabolism — induction (↑ metab) OR inhibition (↓ metab) of enzymes

↳ main enzyme = CYP450 enzymes in the liver

↳ oxidation, hydrolysis + reduction

↳ partly water-soluble, active metabolites

↳ various isoforms of CYP450 ⇒ most abundant = CYP3A4

↳ in the SER of liver hepatocytes; also in s.intestine, kidneys, lungs + brain

* look at Q18-drug metabolism *

Excretion:

↳ drugs + active metabolites ⇒ most common urinary excretion of water-soluble conjugates (e.g. glucuronides) ⇒ phase I liver metabolism.

↳ some drugs are partly metabolised + partly excreted unchanged ⇒ in urine

↳ Some not metabolised at all + excreted totally unchanged eg. Lithium, gentamicin, metformin

① Changes in active excretion in the kidney tubule:

↳ if drugs have the same active transport mechanism, they compete for excretion, e.g. Probenecid ⇒ ↓ penicillins excretion ∴ ↑ [blood]

② Changes in biliary excretion:

↳ Some drugs are excreted in bile as water-soluble conjugates

↳ broken down by gut bac. → liberate the free drug → Reabsorbed.

↳ between Atb + oral contracep. (OC)

③ Changes in renal BF (RBF):

↳ ↓ RBF = ↓ excretion of some drugs.

↳ vasodil. prostaglandins control RBF

↳ Indomethacin inhibits synthesis of renal prostaglandins → ↓ RBF → ↓ lithium excretion

④ Changes in urine pH:

- many drugs are reabsorbed
- only non-ionised, lipid soluble form can be reabsorbed
- change in pH = change of ionisation status of some drugs.
- not very clinically significant => most drugs = inactive metabolites
- e.g. weakly acidic drugs – ionised in highly alkaline urine + NO reabsorp

(32) Pharmacokinetic processes determining serum drug concentration

Kinetics of IV infusion:
↳ in continuous IV infusion, rate of drug entry = constant!
↳ drug elim = usually 1st order
∴ rate of drug exit fm body ↑ proportionately as plasma conc ↑

① Steady state drug levels in blood:
↳ after starting an IV infusion [plasma] will ↑ until rate of exit = entry
↳ ∴ steady state is achieved when [plasma] of drug is constant
↳ To achieve a steady state:
? ① Time needed to reach it
② Rate of drug infusion + [plasma] ⇒ plateau state.

Entry = Exit ⇒ Steady State

② Influence of rate of infusion on steady state:
↳ steady state ⇒ Rate of drug elim = rate of admin

$C_{ss} = \frac{R_0}{k_e V_d} = \frac{R_0}{Cl_t}$ → 1st order rate constant
(C_{ss} = steady state conc of drug; V_d = Vol. of dis; Cl_t → total body clearance)

$C_{ss} \propto R_0$

C_{ss} inversely proportional to Cl_t

③ Time required to reach steady state [drug]
① !! exponential approach to steady state !!
↳ $t_{1/2}$ = time taken for [drug] to half.
↳ Rate constant for attainment of steady state is rate constant for total body elim of drug, k_e
② Effect of the rate of drug infusion
↳ rate to achieve steady state is NOT affected by the rate of drug infusion; doesn't influence TIME required to reach the ultimate steady state conc.
↳ this is because the steady state conc of drug ↑ w/ infusion rate
③ Rate of drug decline when infusion is stopped: [plasma] ↓ w/ the same time course seen in approaching steady state.

④ loading-dose: can be injected as a single dose to achieve the desired plasma level Rapidly, followed by an infusion, to maintain a steady state

Kinetics of fixed-dose, fixed-time, interval regimens.

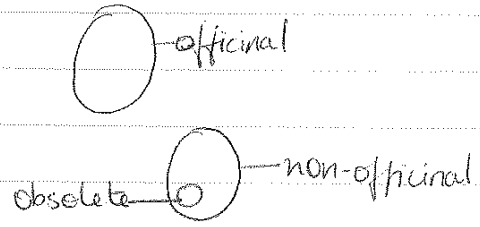
↳ more convient than continuous IV infusion

↳ fixed doses, given at fixed time intervals ⇒ time dependent fluctuations in the circulating level of the drug.

(34) Pharmacopoea

Publications containing aggregated data about medicinal substances, healing preparations & helping compounds, as well as info about their processing preparation, control, storage, prescription & distribution.

↳ Officinal drugs: subs presented in pharmacopoeia
↳ Non-officinal " : medicines which are not mentioned in the pharmacopoeia
↳ Obsolete medicinal preparations: already deleted fm the current "



Drug names:

① Chemical names = formula
↳ acc. to IUPAC

② Generic name ⇒ related to the chemical or official name.
↳ INN = International Non-Proprietary name
↳ not registered; supposed to be used internationally
↳ has to be printed on the drug packaging
↳ in lower case, e.g. amoxicillin

③ Trade name ⇒ catchy, easy (easier to remember)
↳ often relate to the drug's intended use
↳ it is the name given by the manufacturer
↳ First letter = CAPITAL! e.g. Amoxil, Trimox

Drug-family names:

- olol ⇒ β-receptor antagonist
- Caine ⇒ LA
- tidine ⇒ H_2-receptor antagonists
- dipine ⇒ Ca^{2+} channel blockers of dihydropyridine type
- Statin ⇒ inhib of HMG-CoA transferase

(36) Possible mechanisms of synergistic drug effects

Drug synergism: when drugs can interact in ways that enhance/magnify effects or side effects of those drugs.

↳ used in combination preparations, e.g. codeine mixed w/ acetaminophen or ibuprofen - to enhance func. of codeine as a pain killer

-ve effects of synergism => form of contraindication

↳ if >1 depressant drug is used that affects the CNS, e.g. alcohol + valium (diazepam) => produces a greater reaction than simply the sum of the individual effects of each drug, if used separately.

↳ Resp. depression!

(37) Principles of the "Good Clinical Practice"

GCP ⇒ international quality standard that is provided by International Conference on Harmonisation (ICH), which governments can transpose into regulations for clinical trials involving human subjects

Guidelines incl. protection of human rights as a subject in clinical trial

↳ Also ⇒ provides assurance of the safety + efficacy of newly dev. compounds

↳ standards on how clinical trials should be conducted

↳ Define the roles + responsibilities of clinical trial sponsors, clinical research investigators + monitors

Planning: protocol CRF → ethical, minimum risk to subjects

↓

Regulatory + ethical approval

↓

Trial documents - materials

↓

Select investigators → principal, co-invest, study co-ordinator

Conduct
- clinical trial
- ensure medical care of subjects
- monitor subjects' safety

↓

Site assessments → Patient recruitment

↓

Periodic monitoring → Study termination

Data Entry | Data Cleanup | Statistical Analysis | Final Report

Ethical medical research: human subject has the right to understand the nature, risks + benefits of research & to agree / disagree to participate

↳ Duty of physicians to observe + uphold rights of patients'

(38) Receptor-mediated drug effects

* look at Q 19 *

- Up/down reg
- Depends on age, genetics, drugs
- Affinity + Intrinsic activity

↳ ↑/↓ cAMP → G coupled ones ...

(39) Regulation of drug development

* look at Q11 *

(42) Synergism in drug effects <+ve -ve

* look at Q36 *

Additive pharmacodynamic effects
eg ∝ drugs that ↑ QTc ⇒ cardiac arythmias

(40) Sites of drug binding...

- Receptors
- Tissues
- Proteins
- Enzyme inhibition
- Ion channel blocking
- Transporters => Symport, Anti-port - Na^+/K^+ * $Na^+/K^+/Cl^-$ (Co-transport =>)
  - ↳ ATP dependent or independent

(44) Management of poisoning

Role of antidotes ⇒ restricted to a minority of drugs

Survival is crucial:

1. monitor airway
2. maintain normoxia
3. " body temp
4. correct hypo/hypertension
5. " electrolyte disbalance
6. Treat any fits
7. Monitor dysrhythmias
8. Beware of skin blistering + rhabdomyolysis
9. Take account of concurrent medical problems.

Manoeuvres to modify drug pharmacokinetics:

1. Prevention of gut absorption.
   - Gastric lavage (stomach pumping) superceded by activated charcoal in most situations
     - 50–100g; SA = 1000m²/g
     - w/ a large SA for binding poisons
   - intubation if un-cooperative

   prevents absorption of most drugs if given within 1hr of ingestion; effectiveness falls rapidly after that

   Prolong effectiveness, if gastric emptying is delayed:
   1. by drug ingested (eg opiates)
   2. by the formation of tablet bezoars (a mass found trapped in the GIT, usually stomach) (eg. salicylates)
   3. ingestion of sustained-release preparations (eg. theophylline)

2. Enhanced elimination:
   1. Forced diuresis: NO longer recom.! but ensure adequate rehydration + gentle alkalinisation for salicylates
   2. Dialysis: peritoneal or haemodialysis ⇒ ethylene glycol, ethanol, salicylate & Li.
   3. Haemoperfusion: severe theophylline / barbiturate intox.
   4. Repeated activated charcoal to interrupt enterohepatic circ, e.g. phenytoin, theophylline, quinine (Biliary A -fm liver → S.intestine → liver)

Specific poisoning:

① Amphetamine : Diazepam IV / Haloperidol (if psychotic)

② Benzodiazepines (BZD) : Flumazenil - IV bolus of 0.2mg then every 1-2min, bolus dose of 0.1mg, until patient is able to protect their airway

③ Carbon Monoxide : O_2 by mask ; control fits w/ IV diazepam

④ Cocaine : monitor ECG ; clear airway, intubate if necessary
- ↳ Seizures : IV diazepam (10-20mg stat ; IVI 200mg/24hrs-max)
- ↳ HBP : Labetalol IV
- ↳ Ventricular arrythmias : lignocaine (100mg stat ; IVI 4mg/min)

⑤ Digoxin : gastric lavage, if seen within 4hrs of ingestion then activated charcoal (100g stat). If >4hrs at presentation ⇒ cholestyramine
- ↳ Sinus bradycardia ⇒ Atropine
- ↳ Ventricular tachyarrythmia ⇒ phenytoin IV
- ↳ Haemodynamic instability, resistant VT / hyperkalaemia ⇒ Digoxin-binding antibody fragments (Fab, DIGIBIND)

⑥ Ethylene glycol : presentation within few hrs = gastric lavage
- ↳ Severe acidosis / oliguria = haemodialysis

⑦ Methanol : gastric lavage, if presents within 2 hours, NO activated charcoal
- ↳ Seizures - phenytoin
- ↳ Specific antidote ⇒ ETHANOL ⇒ IV 10% sol in 5% dextrose
  - ↳ check ethanol levels = 1-1.5g/l
- ↳ most effective clearance ⇒ peritoneal dialysis.

⑧ Opiates : NALTREXONE / NALOXONE - IV boluses of 0.4mg at 2-3 min. intervals

⑨ Paracetamol : gastric lavage within 4hrs of ingestion
- ↳ N-acetylcysteine IV (if above the treatment curve line)

Anti-acne!

(10) Salicylate: Therapeutic levels < 300 mg/l
- mild/moderate salicylism: oral/IV rehydration
- marked salicylism: ① oral activated charcoal (50g 4 hr)
  ② Haemodialysis: levels > 1000 mg/l

(11) Tricyclic Antidepressants: gastric lavage within 12 hours.
- Activated charcoal - oral 50-100g - single dose
- Seizures: IV diazepam 5-10 mg bolus.
- Acidosis: IV $NaHCO_3$

- LSD ⇒ Haloperidol
- Alcohol ⇒ BZD + Carbamazepine
- Aminoglycosides ⇒ Calcium gluconate + neostigmine
- Heparin ⇒ protamine sulphate
- MTX ⇒ Leucovorin

(45) Therapeutic ratio

↳ A.k.a therapeutic index : comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes death.

↳ Ratio given by the lethal dose of a drug for 50% of the pop / therapeutic dose (min effective) dose for 50% of the pop.

bigger the gap between LD_{50} & ED_{50} = the better it is

incl. inter-individual variability

doesn't incl that!

$$\text{Therapeutic ratio} = \frac{LD_{50}}{ED_{50}} \left(\Rightarrow \frac{\text{Max non-toxic dose}}{\text{Min. effective dose}}\right)$$

↳ Higher index is preferred to a lower one ⇒ a patient would have to take a much higher dose to reach the lethal threshold, than the dose taken to elicit the therapeutic effect.

↳ Indicates the margin of safety in use of a drug

↳ NOT a useful guide to the safety of a drug in clinical use

↳ Drugs w/ narrow therapeutic range, may have dosage adjusted acc. to measurements of actual blood levels by therapeutic drug monitoring (TDM) protocols.

↳ Main limitations:

① it is based on animal toxicity data, which may not reflect forms of toxicity/AE that are clinically imp.

② takes no account of idiosyncratic toxic reactions. (reactions which occur rarely + unpredictable; non immunological hypersensitivity to a subs, without connection to pharmacological toxicity)

(46) Type of drug effect changes after its repeated administration

Tachyphylaxis: a rapid ↓ in the response to a drug due to previous (long term) exposure to the drug
- ↳ ↑ dose will NOT ↑ pharmacological response
- ↳ e.g. amphetamine, ephedrine
- ↳ Metoclopramide, nicotine, dobutamine

Resistance: ① Prod of enzymes that inactivate drug
② ↓ intracellular availability
③ ↓ affinity of drug binding

Tolerance: a subject's reaction to a drug ↓, so larger doses are needed to achieve the same effect
- ↳ Characteristics: ① Reversible
  ② Rate depends on the drug, dosage + freq. of use
  ③ differential development occurs for different effects of the same drug.
- ↳ 2 major mechanisms:
  ① Dispositional tolerance: ↓ quantity of the subs, reaching the site it affects
  ② Reduced Responsiveness: response to the subs is ↓ by cellular mechanisms

Sensitisation: ↑ effect of drug, following repeated doses. Opp. to tolerance
- ↳ changes in brain mesolimbic dopamine transmission

Cumulation: action of ↑ intensity, as the sudden + markedly ↑ action of a drug after admin. of several doses, due to the accumulation of the drug in the body.
- ↳ Greater biological effect than the initial dose.
- ↳ E.g. digoxin toxicity in old ppl coz take it for many yrs

(47) Types of drug doses

Dosage form (DF): the physical form of a dose of a chemical compound used as a drug or medication intended for administration/consumption.

Common forms:
- pill - small, round
- tablet or capsule
- drink or syrup
- aerosol or inhaler
- liquid injection

- pure powder or solid crystal
- natural/herbal form → plant/food of sorts

Parenteral: IV, IM, ID, S.C., IR (intraosseous), IP (intraperitoneal)

Topical: cream, gel, liniment/balm, lotion/ointment etc
Ear drops (otic)
Eye drops (ophthalmic) Inhalers
Skin patch (transdermal)

Suppository: Rectal (e.g. enema)
Vaginal (e.g. douche, pessary etc)

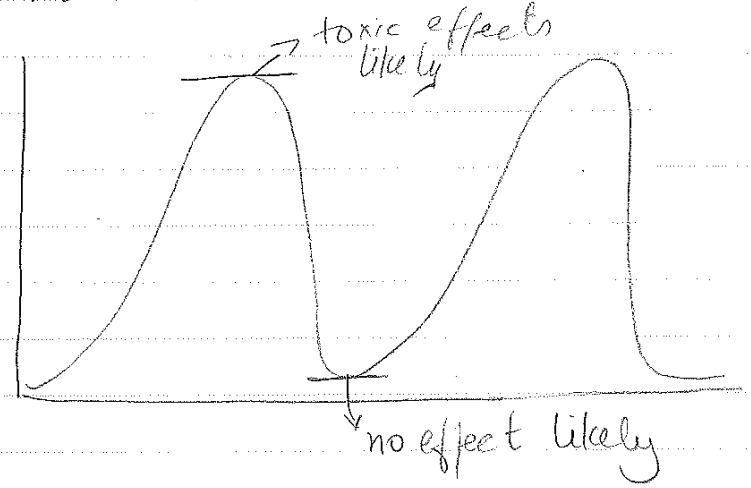
Influence of dosing regimen on plasma drug levels:
① Single dose: [plasma] ↑ as the drug distributes to the bloodstream, then falls as it is distributed to the tissues, metabolised + excreted

② Continuous IV infusion: steady state plasma drug conc is reached after continuous infusion for 4-5 half lives.
is ↑ rate of infusion: ⊙will NOT ↓ the time needed to reach steady state
② ↑ plasma [drug] at steady state.

③ Intermittent Dose: must be administered for 4-5 half-lives before steady state is reached. →

Peaks = high points of fluctuation. Toxic effects are most likely observed then

Troughs = low points of fluctuation. Lack of drug effect = most likely to occur here.



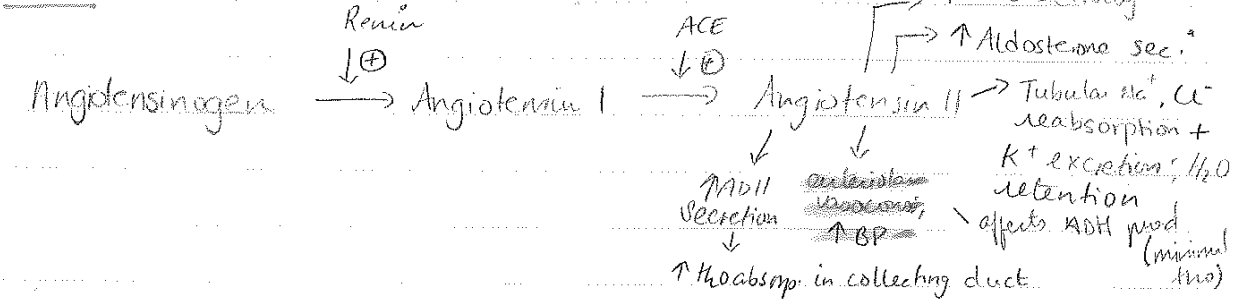
DRUG CLASSES (SECTION B)

DRUG CLASSES

① ACE-inhibitors

↳ Angiotensin-converting enzyme inhibitors
↳ Hypertension + congestive heart failure, ↓ risk of recurrent post-MI
↳ block the conversion of angiotensin I ⟶✗⟶ angiotensin II
↳ ∴ ↓ arteriolar resistance, ↑ venous capacity, ↑ CO, ↑ Stroke vol,
↑ natriuresis + venodil = ↓ preload ↳ via vasodil.
↳ good for long term therapy

RAAS:



↳ minimal electrolyte disturbances + fewer AE than other anti-hypertensives

↳ ACE inhibitors: Sulfhydryl, dicarboxylate or Phosphonate containing agents

→ Captopril ⇒ Sulfhydryl ✓s
Enalapril (P)
→ Fosinopril (P) ⇒ Phosphonate ✓
Lisinopril
Quinapril
Benazepril
Moexipril
Perindopril
→ Ramipril
→ Trandolapril

(P) ⇒ prodrug; active metabolite prod by de-esterification

largest group, all of the ones mentioned below apart from 2 ✓

AE: hypotension, fatigue
cough, renal impairment
hyperkalemia, nausea
headache
dizziness

- cough (dry) coz no degradation of sub P + bradykinins, which ACE usually degrades

Cl + precautions:

Cl in patients w/: preg!

- ↳ prev. angioedema assoc. w/ inhibitor therapy
- ↳ Renal A. stenosis
- ↳ Hypersensitivity to ACE Inh Lib.

Caution:

① impaired renal func
② Aortic valve stenosis
③ hypovolaemia / dehydration
④ haemodialysis

* Birth defects if taken during the 2nd + 3rd trimester
1st trimester ⇒ major risk of congenital malform. esp cardiovascular + CNS *

(2) Adrenomimetic agents

↳ adrenergic drugs affect receptors stimulated by NE OR E

Directly acting adrenomimetic agonists:

↳ directly bind to adrenergic receptors

↳ **Don't** interact w/ presynaptic neuron

Epinephrine / Adrenaline: natural catecholamine

↳ fm tyrosine in adrenal medulla

↳ interacts w/ α + β receptors

α → vasocons (high doses); β → vasodil (low doses)

↳ Cardiovascular (C.V) effects: +ve chronotropic + inotropic action, ↑CO, ↑BP, ↑ contractility, ↓ RBF

constricts arterioles in skin, mus., viscera.

Resp sys: bronchodil, ↑ tidal vol, relieves dyspnoea

hyperglycaemia: ↓ insulin, ↑ glycogenolysis + glucagon release

↳ metabolism: MAO + COMT (adrenergic synapses)

↳ renal - urine - excretion; $t_{1/2}$ = 2mins

↳ IM, IV, endotracheal, intracardiac inj^n (emergencies)

↳ **Therapeutic uses:** Cardiac arrest

Shock + anaphylaxis

in LA - as a vasocons to prolong the action of the LA

Autoinjectors

↳ **AE:** anxiety, fear, tension, headache, tremor

pul. oedema; haemorrhage.

cardiac arrhythmias

↳ **Interactions:** hyperthyroidism - ↑ C.V effects

cocaine - ↑ C.V. effects

Norepinephrine / Noradrenaline: α-adrenergic receptor - mostly affected

↳ C.V effects: vasocons, ↑B.P.

Baroreceptor reflex; reflex bradycardia

effect of atropine pretreatment → Tachycardia

↳ **Therapeutic uses:** shock (but ↓ BF to kidneys)

(Isoprenaline)
Isoproterenol: stimulates both β_1 + β_2, but non-selective agonist, Sympathomimetic

↳ C.V. effects: ↑ force + Rate of contraction → ↑CO ; ↑ HR
Cardiac arrest ; skeletal mus = vasodil
↓ BP (diastolic ⇐ vasodil effect) & ↑ SBP (inotropic + chronotropic effects)

Pul: Bronchodil

Other: ↑ blood sugar + ↑ lipolysis

↳ **Therapeutic uses**: stimulate heart in emergencies
Bradycardia / heart block
was used to treat asthma (NOW RARE)

↳ IV, oral, intranasal, S.C. I.M., inhaled aerosol

↳ $t_{1/2}$ = ~2hrs

↳ **AE**: similar to epinephrine ; ↑HR (tachy) → Cardiac arrhy.

↳ **CI**: patients w/ MI

Dopamine: natural catechol neuroT in CNS (→BG)

↳ prod in subs nigra + ventral tegmental area (VTA) + adrenal medulla

↳ can activate α + β adrenergic receptors

↳ D_1 + D_2 receptors → in periph mesenteric + renal vascular beds → vasodil
↓
also found on pre-synaptic adrenergic neurons → interfaces w/ NE

↳ C.V effects: +ve chronotropic + inotropic effect
↑ Blood flow to kidneys + viscera

↳ **Therapeutic uses**: shock
Levodopa - treat Parkinson's.

↳ **AE**: OD - same as symp. stim.
rapidly metabolised to homovanillic A ∴ nausea, ↑BP, arrhythmias

Dobutamine: synthetic β_1 receptor agonist

↳ ↑ HR + CO

↳ **Therapeutic uses**: ↑CO in congestive HF ; cardiogenic shock.
doesn't significantly ↑ O_2 demands of myocardium

↳ **AE**: caution in Afib
same as E
Tolerance may dev. after prolonged use

Other drugs:

Phenylephrine: α receptors (α_1 + α_2)
- ↳ nasal decongestant
- ↳ used to ↑ BP + episodes of SV tachy.
- ↳ vasocons + mydriasis

Methoxamine: α_1 receptors
- ↳ ↑BP
- ↳ relieves attacks of paroxysmal SV tachy
- ↳ hypotension

Clonidine: α_2 agonist → central ↑BP to ↓ BP

Metaproterenol: bronchodil.
- ↳ not catechol!
- ↳ oral, inhalation – β_2-receptors

Terbutaline: β_2 agonist
- ↳ oral, S.C → bronchodil

Albuterol: selective β_2 agonist → bronchospasm relief

Indirectly acting adrenomimetic agonists:
- ↳ cause NE release fm presynaptic terminals

Amphetamine: ↑BP by α- agonist action on vasculature + β-stim. effects on heart
- ↳ periph actions → cellular release of catechol.
- ↳ CNS stim – treat depression, narcolepsy etc.
- ↳ AE: fetal dev. → Avoid during preg.

Tyramine: not clinically useful – fermented foods
- ↳ displaces NE – acts on adrenoreceptors

Mixed Action adrenomimetic agonists
- ↳ release of NE fm presynap. terminals + activate adrenergic receptors on post-synaptic mem

Ephedrine: plant alkaloid; synthetic
- ↳ releases NE + directly stimulates α + β receptors
- ↳ excellent oral absorp.

↳ ↑ BP by vasocons.
↳ bronchodil → asthma
↳ enhances contractility + ↑ motor func in myasthenia gravis
↳ mild CNS stim ⇒ ↑ alertness, ↓ fatigue + prevents sleep

Metaraminol: parenteral admin
↳ similar to NE
↳ treatment of shock + acute hypotension
↳ prod. mild vasocons.

Adrenergic Receptors

α_1 => PLC activation → ↑ IP_3 + ↑ DAG → ↑ Ca^{2+} → SM contract + bronchial constriction; Sphincters constrict; ↑ motility of GIT; ↑ BP (↑ peripheral resistance (∵ in vessels))

Post-synaptic

NE ≥ E >> ISO

SELECTIVE AGONISTS => Phenylephrine (decongestant), methoxamine → vasocons + mydriasis, to ↑ BP + in episodes of SV tachy

SELECTIVE ANTAGONISTS => Prazosin, doxazocin (AE: dizziness, sexual dysfunc, headache)

Pre-synaptic α_2 => ↓ cAMP → ↓ Ca^{2+} + ↑ K^+ → ↓ motility of SM in GIT; constrict/dilate b. vessels (veins, arteries); platelet aggregation; inhibits SNS outflow fm B.S. => inhib Ach release

(-ve feedback (inhib adenylate cyclase) (Gi protein linked))

E > NE >> ISO

SELECTIVE AGONISTS => Clonidine (spasmolytics), Clenbuterol, Methyldopa

ANTAGONISTS => Yohimbine, Idazoxan

Agonists can be:
- direct acting => bind to receptors, e.g. phenylephrine, NE, E, ISO
- indirect acting => ↑ release of catechol fm vesicles/cyto if needed, e.g. amphetamine, tyramine
- Mixed acting => do both, e.g. ephedrine ↓ releases NE + directly stim. α + β

β_1 (G_s) => ↑ cAMP => PK A activated → ~~↑ Ca^{2+}~~ → ↑ HR + contractility, ↑ renin secretion

ISO > NE > E

SELECTIVE AGONISTS => Dobutamine, Xamoterol

ANTAGONISTS => Atenolol, Metoprolol

β_2 (G_s) => ↑ cAMP => PK A activated → ~~↑ Ca^{2+}~~ => b. vessels + bronchodil; relax uterine smooth mucs (non-preg uterus)

ISO > NE ≥ E

SELECTIVE AGONISTS: Salbutamol, tebutaline, Salmeterol

ANTAGONISTS => Butoxamine

③ α-Sympatolytics – bind to the receptors; inhibits post-gang. func of the SNS
(α₁ antagonists)

Non-selective – α_1 & α_2 both

Selective

Rev

Irre

Competitive, e.g. Phenotolamine (non-selec)

Non-competitive

Competitive Irrev. Non-selective => Phenoxybutamine for phaechromocytoma / ↑ of catechol

Reversible => Phenotolamine " " " / " " "

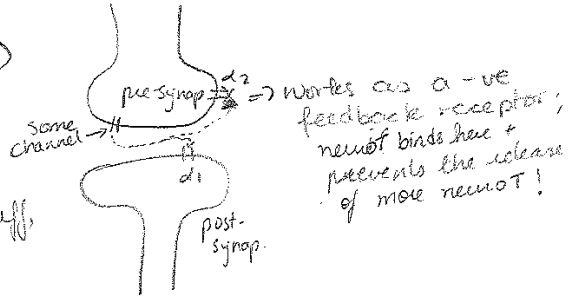
(CO2 vs catechol => it causes a ↓ in agonist)

Selective α_1 – Prazosine, doxazin → ↑BP treatment – ↓ periph resis, prevent GIT relax, ↓ arterial BP

Antagonist (AE – other side)

Selective α_2 – Yohimbin – pelvic vessel vasodil → aphrodisiac

α_2 agonists =>



=> worries as a -ve feedback receptor; neurot binds here + prevents the release of more neurot!

$\underline{\alpha_1}$ => $\underline{AE}$: 1st dose phenomenon – sudden ↓BP + syncope!

↓ inhibit. of vasocons => vasodil

↓ facilitation of micturation + good influence on lipid metab

$\underline{\alpha_2}$ => ↑ symp activity → AE

Indications: α_1-SL – ↑BP, Asthma, periph circ. insuff.

Non-selective ones => $\alpha_1 + \alpha_2$ block – reflex tachy + ↑ SNS activity

$\underline{AE}$: arry, cardiac insuff, fluid retention

Phenoxybutamine, Phenotolamine

③ Alpha-Sympathodytics

↳ inhibits the postganglionic func of the SNS

* Direct → Non-selective α (α blockers) ⇒ only affect α OR β, not both!
  → selective α1 (α blockers)
  → " α2 (yohimbin)
  → Non-selective β
  → selective β1 (β blockers)
  → " β2 (not used)

* Indirect

α1 → inhib. of vasocons. ⇒ vasodil; ↓ preload; ↓ diastolic BP
  → facilitation of micturation; good influence on lipid metab.
  → AE: 1st dose phenomenon ⇒ sudden strong ↓ of BP + syncope
α2 → ↑ Symp activity → unwanted effects

Selective α1-SL

Indications: Urapidil, indoramin (no ↑ in HR!)
* Prazosin, metazosin, terazosin *
① Hypertension (in DM); ⑤ asthma
② peripher. circ. Insuff ⑥ dyslipoproteinemia
③ benign prostate hyperplasia ← Tamsulosin
④ premed. to prevent ↑BP during surgery.

Non-selective α-SL:
↳ block α1 + α2 receptors → reflexive tachycardia + ↑ SNS activity.
↳ AE: stim. β1 in heart + kidney
arrythmias, cardiac insuff & fluid retention

Ergot alkaloids: derivative of lysergic A.
↳ block α receptors; uterotonic, 5HT & D receptors
Indications: migrane, periph + central vascular ischaemias, psychic disorders caused by insuff. perfusion of CNS
↳ Natural: dihydroergotamine, dihydroergotoxin & nicergoline
↳ Synthetic: Tolazolin ⇒ ENT, ophthal; newborn RDS

Phentolamine ⇒ ↑BP, pre med · in surgery of phaeochromocytoma

Phenoxybenzamine ⇒ irreversible antagonist ! also used as a pre-med.

Selective α2 sympathodytics:

Yohimbin: yohimbin bark

- ↑ NOR (noradrenaline) release from axon terminal
- tachycardia + ↑ in BP
- pelvic vessel vasodil ⇒ afrodisiac, weight loss prod.

SL clinical use:

- ↑BP
- Angina
- MI
- Congestive HF
- Cardiac arrythmia
- Hyperthyroidism
- Migrane prophylaxis
- Wide-angle glaucoma

↑Ca^{2+} + DAG ⇒ PK mac C

IP_3 + PLC ← G_q ← α_1 = vasocons, GI relax, mydriasis

(like H_2) α_2 = pre-junc · inhib of release of NE + other neuroT

↓ G_i inhib of insulin release

inhib · adenylyl cyclase " " lipolysis.

↓ cAMP → ↓ activity of cAMP dependent prot kinases

④ Aminoglycosides

↳ inhibit bac prot synthesis : interact w/ receptor proteins on the 30S ribosomal subunit.

↳ freezes initiation complex → build up of monosomes ; translational errors

↳ 30S initiation complex ⟶✗ 70S initiation complex

↳ BACTERIOCIDAL - most G- bac (aerobic) ; some G+

↳ Resistance occurs when the bac. enzymes can inactivate the drug

↳ DON'T cross BBB

Uses: parenterally in sepsis + enteric infec

↳ ↓ usage ⇒ narrow spectrum of activity + toxicity

Streptomycin ⇒ plague, brucellosis (severe cases),

Gentamicin + tobramycin ⇒ Enterobacter, Proteus, Pseudomonas, Klebsiella + Serratia

↳ often used w/ β-lactam atb for serious infec

Amikacin ⇒ severe G- infec, those resistant to Gentamicin / tobramycin

Neomycin + kanamycin ⇒ topically - minor soft tissue infec OR orally → hepatic encephalopathy

Spectinomycin ⇒ IM → alternative for treatment of acute gonorrhoea in penicillin resistant gonococci / patients hypersensitive to penicillin

AE:

↳ narrow therapeutic index → strep, gent + tobramycin

↳ ototoxic ⇒ vestibular + auditory func / cochlear → neo, kana, amikacin, gent a + tobramycin

↳ Nephrotoxic ⇒ Acute tubular necrosis → ↓ GFR → ↑ serum creatinine + blood urea nitrogen (BUN).

↳ Neurotoxicity ⇒ high doses, curare-like neuromuscular blockade w/ resp. paralysis. Calcium gluconate + neostigmine = Antidotes

(P.T.O →)

↓ interacts w/ AChE ⇒ ∴ ↑ ACh levels

Post-antibiotic effect (PAE):

persistent suppression of bac. growth after a brief exposure (1-2hr) of bac to an atb, even in the absence of host defence mechanism

⑤ Antacids

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↳ for upper GIT disorders - peptic ulcers, GERD - to ↓ gastric A prod. / neutralise gastric H^+ / protect the walls of the stomach fm the acid / pepsin released by the stomach
for all agents used for GIT disorders.

↳ weak bases / basic salts, which neutralise stomach acidity → ↑ gastric pH
↳ inhibit activity of peptic enzymes & stimulate prostaglandin production
↳ ↓ pepsin activity

↳ can heal duodenal ulcers but less effective for gastric ulcers ⇒ if given in sufficient quantity for long enough
↳ ↓ pain assoc. w/ ulcers
↳ most antacids have been replaced by other drugs, but are still used commonly by patients as non-prescription remedies for dyspepsia.
↳ taken orally
↳ usually a mixture of Mg (diarrhoea) & Al (constipation) salts, so these 2 together = good mix
↳ some preparations, have high Na^+ content ∴ not for patients on a sodium restricted diet. ← CAREFUL

① Magnesium hydroxide ($Mg(OH)_2$): insoluble powder $Mg(OH)_2 + 2HCl \rightarrow MgCl_2 + 2H_2O$
↳ forms $MgCl_2$ in the stomach
↳ no systemic effects / alkalosis - not well absorbed from the gut
↳ long term therapy
↳ Most freq. Al → diarrhoea

② Aluminium Hydroxide ($Al(OH)_3$):
↳ not well absorbed from GIT ∴ no systemic effects
↳ forms $AlCl_3$ in the stomach → Cl is released & reabsorbed in the intestine
↳ $Al(OH)_3$ ↑ pH of gastric juice to 4 + adsorbs pepsin
↳ gradual action + continues for several hours
↳ colloidal $Al(OH)_3$ combines w/ PO_4^{3-} in GIT → ↑ excretion of PO_4^{3-} in the

feces → ↓ excretion of PO_4^{3-} via the kidneys. ⇒ Good in treating ppl w/ chronic renal failure (CRF).
↳ AE ⇒ constipation

③ Sodium bicarbonate ($NaHCO_3$):
↳ absorbed systemically → NOT for long term treatment
↳ CI: in ↑BP, HF + RF ⇒ due to high Na^+ content

④ Calcium carbonate ($CaCO_3$):
↳ partially absorbed from GIT ∴ some systemic effects → NOT for long term.
↳ may stimulate gastrin release → rebound acid prod.
↳ CI: in patients w/ renal disease ⇒ nausea + belching.

Interactions: alter the bioavail. of many drugs:
① ↑ in gastric pH ⇒ ↓ absorption of acidic drugs + ↑ absorption of basic drug
② metal ion ⇒ can chelate other drugs (eg. tetracyclines & digoxin) + prevent their absorption
↳ $Al(OH)_3$ + tetracycline ⇒ nausea, vomiting + PO_4^{3-} excretion ⇒ PO_4^{3-} deficiency

⑥ Antianginal agents

Always: no smoking, ↓ weight, avoid stress + long term therapy

Actions of antianginal drugs:

① Improve blood delivery to the heart muscle by dil. blood vessels → ↑ O_2 supply
② " " " " " " " " ↓ work of the heart → ↓ O_2 demands

Classes of drugs used to treat AP:

① Vasodil (arteries + veins) ⇒ Ca^{2+} channel blockers
Nitrodilators
② Cardioinhibitory drugs (↓ HR + contractility) ⇒ β-blockers
Ca^{2+} channel blockers
③ Anti-thrombotic drugs (prevent thrombus form.) ⇒ anticoagulants
anti-platelet drugs

NITRODILATORS

NO (organic nitrates / nitroprusside) → passes through the endo cell → intercell diffusion → enters SMC → binds to soluble guanylylcyclase

↓

activated guanylylcyclase

↓

GTP → cGMP → Protein kinase (PK) → phosphorylated PK → ↑ Ca^{2+} avail. (??)

phosphorylated PK → dephos. of myosin light chains occurs → relaxation of contractile apparatus

large 1st pass effect ⇒ high capacity organic nitrate reductase in the LIVER! → inactivates drugs

↳ work directly on SMC → relaxation + depress muscle tone

↳ Types: ① Nitroglycerin ⇒ in acute anginal attack!

↳ IV, Sublingual, Translingual spray, Transmucosal tablet, ORal, topical ointment, Transdermal, SR tablet

↳ ORAL → liver metabolism ∴ ↓ efficacy (First pass effect) — passes the 1st pass effect

↳ Sublingual → effect onset in 1-3 mins, max after 15 mins; lasts upto 1hr.

↳ SR → onset after 30mins, upto 3-4hrs. — Severe, recurrent vasospastic angina

② Isosorbide dinitrate ; isosorbide mono-nitrate
↳ before chest pain begins
↳ dinitrate ⇒ long $t'_{1/2}$ ~ 3hrs, better oral bioavail + longer $t'_{1/2}$ than nitroglycerin
↳ mono-nitrate ⇒ even longer $t'_{1/2}$

Molsidomin ⇒ "pro-drug", metabolite stimulates guanylylcyclase, delayed onset of effect ; for attack prophylaxis

↳ Freq. attacks ⇒ Nitrates
↳ IHD w/ few attacks ⇒ β-blockers & Ca^{2+} antagonists
↳ Severe IHD ⇒ nitrates + β-blockers
↳ Vasospastic angina ⇒ nitrates + Ca^{2+} antagonists

Tolerance + AE :
↳ Tolerance: impaired biotransform. Develops when glutathione ↓
diminished response
↳ AE : headache, dizziness, fainting
orthostatic hypotension
cerebral ischaemia
weakness

β-ADRENERGIC RECEPTOR BLOCKERS / β-ADRENORECEPTOR ANTAGONISTS
↳ MoA : inhibit SNS :
↳ Block β_1 effects : ↓ HR + contractility → ↓ O_2 consump. → Antianginal effect
↳ Block β_2 effects : vasodil
↳ Membrane stabilising effects
↳ Uses : AP - in combination w/ nitrates
↳ AE : bronchospasm (dose dependent)
hypoglycaemia
myocardial depression
↳ -ve inotropic effect (affecting muscle contraction, esp. cardiac mus.) ↓ contractility ∴ ↓ cardiac workload → weaken the force of contrac.
↳ inconvenient in ↓pastic angina + HF

↳ CI: in bradycardia, AV block + asthma/COPD
↳ often combined w/ nitrates → ↓ AE of both agents

Propranolol, Esmolol, Atenolol

CALCIUM CHANNEL BLOCKERS (look at specific Q23 ques)
↳ Functions: ① block SMC contraction + ↓ workload
② Relax spasms in Prinzmetal's (vasospasmic) angina
③ Block prolif of damaged endothelium in coronary vessels
↳ MoA: Block voltage dependent Ca^{2+} channels => ↓ cytosolic $[Ca^{2+}]$
Relax arteries
Cardiac vs vascular effects
↳ orally & IV - effective within mins
↳ variant + chronic stable AP & when nitrates are ineffective OR when β-adrenoreceptor antagonists are CI!
↳ Uses: angina, ↑BP, cerebral haemorrhage, supraventricular arrhythmia
AE: Dizziness, nausea
headache, flushing, ↓BP, oedema
arrhythmias, reflex tachycardia
gingivitis
↳ Drugs: verapamil, nifedipine, isradipine, nisoldipine, nicardipine, amlodipine, diltiazem

! chew 500mg ASA after AP/MI!

ANTI-AGGREGANT DRUGS:
① Acetylsalicyclic A => blocks cyclooxygenase (COX 1+2 → ↓ PG synthesis + anti-aggregant action)
② >100mg => PGI_2 formation
③ 100mg => Thromboxane (TxA_2) form.

Other therapies => Aspirin
Heparin
ACE inhibitors
Lipid lowering agents

* slide 35 in anti-anginal lec! *

⑦ Anti-anxiety drugs aka anxiolytics

↳ treatment of symptoms of anxiety & anxiety disorders: generalised anxiety d. (GAD), panic disorder (PD), phobias, post-traumatic stress disorder (PTSD) & OCD.

↳ main medication → Benzodiazepines (BZD)

↳ long or short term therapy

Effects of BZD:

① Hypnosedative - Triazolam, nitrazepam
② Anxiolytic - Alprazolam, Oxazepam
③ Anti-epileptic
④ Myorelaxant - Klonazepam
⑤ Amnesia

another use: pre-medication for surgery

MoA: facilitate γ-aminobutyric A (GABA)-mediated inhib. of neuronal activity in the CNS

↳ facilitation of GABA binding on GABA A receptor (GABAergic subs) → the Cl^- ionophore opens → hyperpol. → inhibits signal transmission.

↳ BZD - allosterically ↑ GABA affinity + freq. of GABA-stimulated Cl^- channel opening (↳ binds elsewhere, rather than to the active site)

↳ NO action in the absence of GABA!

↳ orally, parenterally

↳ highly lipid soluble ones ⇒ more rapid onset of action

Drugs in use: Zolpidem

Diazepam, Chlordiazepoxid, Medazepam, Lorazepam, Flunitrazepam, Oxazepam (short t½), Bromazepam, Alprazolam, Nitrazepam, Klonazepam (anti-epi) & Tetrazepam (myorelax.)

ANTAGONIST → Flumazenil - used in intoxication

Barbiturates - phenobarbital

Other anxiolytics:

① small doses of anti-depressants : Fluvoxamine, Fluvoxetine
② Neuroleptics : Levopromazine
③ H1 - antihistaminics : Promethazine (1st gen) — for drug addicts
④ β-blockers : Metoprolol, pindolol, propranolol
⑤ Myorelaxants : Guaifenesin, meprobamat
⑥ Partial agonist 5-HT 1A receptor : Buspirone
↳ activates 5HT1A receptors → ↓cAMP → ↓ firing of serotonergic neurons
⑦ Zolpidem ⇒ non-BZD - same mechanism

AE:

↳ low activity, indifference, cognitive impairment, personality changes
↳ muscle relaxation + apnoea in newborns !
↳ synergism w/ alcohol + other drugs
↳ addiction
↳ Rush, constipation, depression, weight gain

CI:

↳ pregnancy + lactation
↳ Mysthenia gravis
↳ Alcohol abuse
↳ Sleep apnoe

⑧ Antibiotics against G- bac. — inhib cell wall syn => Bactericidal
— inhib prot syn => Bacteriostatic
— inhib NA syn => Bactericidal

★ Betalactam antibiotics:
↳ β-lactam ring - prevent formation
↳ inhibition of cell wall synthesis
↳ bactericidal - activation of autolytic enzymes in the cell wall
↳ low toxicity + good tolerance ; during inflam - PNC found in CSF + ocular fluid
↳ most numerous
↳ p.o , I.V.
↳ allergic cross-sensitivity
↳ PNC + CEF resistant to β-lactamase (penicillinases) prod. org.
↳ Penicillins, Cephalosporins, Monobactams, Carbapenems, PNC w/ β-lactamase inhibitors

① Penicillins: most G- are resistant ; GI absorp ↓ after eating
① Basic (narrow spectrum): benzylpenicillin (PEN G), phenoxymethylpenicillin (PEN V), penamecillin
↳ procainepenicillin, benzathinpenicillin
② β-lactamase resistant (S. aureus): methicillin, oxacillin, cloxacillin, flucloxacillin ; oral admin ; penicillinase-prod. Staphy infec
③ Broad spectrum penicillins: inactivated by β-lactamases
↳ G- coverage ; resistance more common.
↳ Aminopenicillins: Ampicillin => H.influenzae, S. pneumoniae, S. pyogenes, N. meningitides, Proteus mirabilis + Enterococcus faecalis + Gonococci
NOT for MRSA!
Amoxicillin => better oral absorp.
↳ endocarditis prophylaxis before major procedures
Acylureidopenicillins => Piperacillin => Pseudomonas spp + Enterobacter spp.
④ Extended spectrum (Ps. aeruginosa):
Carboxypenicillins => Ticarcillin
↳ irreversibly inhibits β-lactamase ; parenteral admin

AE: hypersensitivity (2mins → 3days after admin)
direct irritation / pain on injection
GI upset
Superinfection

② Cephalosporins:

↳ broad spectrum ; effect grows against G-, declines to G+

↳ P.O. ; I.V. ; I.M. ; parenterally

↳ AE: hypersensitivity
Alcohol intolerance
bleeding disorders (vit K admin = prevention)
Nephrotoxic (when given w/ diuretics)
Superinfec w/ G+ or fungi ⇒ Cephalosporins = no 1 cause of hosp acquired C. difficile colitis

↳ 4 generations:

① 1st Gen: some G+ orgs (Strep) + some G-

↳ Mainly for E. coli, Klebsiella infec, penicillin + sulfonamide resistant UTIs ; prophylactically - surgical procedures

↳ don't enter CSF

↳ Cefalotin, Cefazolin ⇒ parenteral ; Cefalexin, Cefaclor ⇒ p.o.

② 2nd Gen: broader spec ; strep infec + E. coli, klebsiella, Proteus spp + anaerobes

↳ UTI, Resp infec, bone + soft tissue infec + prophy - surgery.

↳ don't enter CSF EXCEPT Cefuroxime

↳ Cefuroxime (Cefoxitin) ⇒ paent ; Cefaclor ⇒ p.o.

③ 3rd Gen: against G- ⇒ high potency - H. influenzae, N. gonorrhoeae, N. meningitides, Enterobacter, Salmonella, indole-positive Proteus, E. coli

↳ enter CSF EXCEPT Cefoperazone

↳ Renal excretion EXCEPT Cefoperazone + Ceftriaxone ⇒ via biliary tree hence good for infec of the biliary tree

↳ Cefotaxime, Ceftazidime, Ceftriaxone ⇒ parenterally

→ Cefixime, Cefpodoxime ⇒ p.o.

④ 4th Gen: Pseudomonas + G- bac.

↳ Cefepime, Cefpirome ⇒ parenterally.

③ PNC w/ β-lactamase inhibitors:

↳ strengthen effect against G- (Sulbactam) : Klebsiella, Neisseria, Enterobacter, E. coli, Proteus, Salmonella, Haemophilus, M. catarrhalis, Bacteroides

↳ drug of choice in otitis media + sinusitis

Clavulanic Acid, Sulbactam, tazobactam

④ Monobactams

↳ Aztreonam: β-lactamase prod G- rods resistant to PNC
- ↳ no activity against G+ orgs + anaerobes
- ↳ no cross-reactivity w/ penicillins or cephalosporins
- ↳ parenterally
- ↳ H.influenzae, Pseudomonas, Neisseria, Klebsiella, Proteus, E.coli

⑤ Carbapenems: broad spec antibac. activity

↳ Meropenem

↳ Imipenem: aerobic + anaerobic, G+ + G-
- ↳ parenterally; resistant to β-lactamases
- ↳ Reserved therapy

↳ infec: penicillinase-prod S.aureus, E.coli, Klebsiella spp. Enterobacter spp, H.influenzae; Pseudomonas!

↳ AE: nausea, vomiting, diarrhoea, skin rashes
higher doses = seizures

✱ Tetracyclines: Rickettsia

↳ Bacteriostatic; broad spec ⇒ G-, G+, mycoplasm, Chlamydia, protozoa...

↳ Prot syn. inhibitors! - bind reversibly to the 30S subunit

↳ AE: photosensitivity, hepatotoxicity (esp preg. women)
stains teeth in children, bone deformities (binds to Ca^{2+} in bone)
GI upset - nausea, vomiting, diarrhoea ⇒ Superinfec!
↓ oral contraceptive effect
Absorption impaired by antacids, milk + Ca^{2+} rich foods.

↳ p.o; parenterally; IV - only Tigecycline

↳ all body fluids incl. CSF — binds to $Al(OH)_3$ ⇒ PO_4^{3-} def occurs!

↳ kidney elim.

↳ many undergo enterohepatic recirculation: Doxycycline - excreted into bile → faeces ∴ safest one to admin in impaired renal func!

Tetracycline (TCN), Doxycycline, Minocycline (acne)

Macrolides:

↳ inhibits prot synthesis (RNA dependent) by binding irreversibly to 50S ribosomal subunit
↳ inactivated by stomach acid ∴ enteric-coated TABLET
↳ all body fluids except brain + CSF
↳ G+ orgs ; good for penicillin-hypersensitive patients
↳ AE: IV - thrombophlebitis
GIT, Cardiac effects
orally
Superinfections

Erythromycin ⇒ CYP 3A4 inhibitor ← Bile
↳ Legionnaires disease, Syphilis, H. pneumoniae, whooping cough
Spiramycin ⇒ Toxoplasmosis
Azithromycin ← Bile
Clarithromycin ← urine
} ⇒ multidrug regimen of disseminated Mycobacterium-avian-intracellulare complex infec in AIDS

Chloramphenicol: Bacteriostatic!

↳ inhib. of prot syn - binds to 50S subunit
↳ broad spec - G+, G-, Rickettsiae, mycoplasma, chlamydia, Anaerobes, clostridia
↳ p.o.; parenterally ; found in CSF ; inhibits CYP 450
↳ 10% urine + 90% hepatic excretion
* NOT DRUG OF 1ST CHOICE *
↳ AE: idiosyncratic b.marrow suppression ⇒ irreversible aplastic anaemia / pancytopenia → high mortality rate
Grey baby sy - inadequacy of CYP450 + glucuronic A conjugation systems to detoxify the drug
↳ 40% fatality
Hypersensitivity, GIT intolerance

Glycopeptides: VANCOMYCIN

↳ binds to the terminal end of growing peptidoglycan to prevent further elongation + cross-linking => inhibits cell wall synthesis + RNA synthesis
↳ G+ life threatening infec, GIT infec, C. difficile (p.o.), MRSA (I.V)
↳ narrow therapeutic margin - monitor kidney func

↳ enters CSF during inflam.
↳ no cross-resistance
↳ admin via slow I.V. infusion, except in enterocolitis
↳ AE: ototoxicity, neurotoxicity, nephrotoxicity
fever, chills, infusion reactions
haematologic reactions
"Red neck" Sy ⇒ rapid infusion → anaphylactoid reactions (release of histamine)

SOS!

* Lincosamides: inhibit prot° syn. CLINDAMYCIN
↳ similar to erythromycin
↳ G+ cocci, anaerobic bac
↳ wide distribution in tissues (bone) + fluids, except CNS
↳ oral admin, bile + urine
↳ Topically - eye drops + Acne
↳ Alternative therapy for abscesses assoc. w/ infec by anaerobes, eg. B. fragilis.
↳ prophylactic - dental patients - endocarditis (valvular heart disease)
↳ AE: GIT upset - diarrhoea
Pseudomembranous colitis (superinfec by resistant clostridia)

NITROFURANS: Bacteriostatic ; ↑↑ conc = bactericidal

↳ G+ & G- (E.coli, Salmonella, Campylobacter, V. Cholerae)

↳ release superoxides + other O_2 reactants => don't affect human body coz quickly inactivated by liver =>

Selective toxicity for bac. cells

AE: allergy, megaloblastic anaemia, pneumonia, hepato/neurotoxicity

↳ w/ food => milder GIT AE

Nitrofurantoin, Nifurnatel => oral ; renal excretion

↳ UTI - better effect in acidic urine pH<5.5

Nifuroxazide => not absorbed frm GIT

↳ diarrhoeas of infectious origin, chronic diarrhoeas, accomp. colitis + enteral dysmicrobia

(NITRO)IMIDAZOLES: bactericidal effect – anaerobes + protozoas

↳ inhibit DNA replication

I: H. pylori !! Trichomonas vaginalis, Giardia lambia (intestinalis), Entamoeba histolytica

Septic conditions in surgery

↳ oral - nearly 100% absorption → all tissues, incl BBB + milk

CI: nursing mothers, preg.

AE: unpleasant after taste, nausea, vom, diarrhoea, CNS disorders (vertigo, insomnia, depress), dark red/brown urine

chronic treatment => neutropenia, leukopenia

Metronidazole: CI: alcohol (effect similar to disulfiram)

Ornidazole

Tinidazole

(8) ATB

Quinolones => Bactericidal drugs - inhib. of NA synthesis → Inhib bacterial DNA gyrase + topoisomerase IV => block DNA transcription

↳ p.o. ; 4 gens : 1st gen - not fluorinated + replaced by higher gens!

↳ quinolones → urine/bile ; Fluoroquinolones → Renal/hepatic

A.E: mild - nausea, vom, neurotox, cramps, vertigo, headache, nephrotoxicity / phototox.

Cl: epilepsy, 1st trimester of preg, children (inhib. of bone cartilage growth) ; nursing mothers

Gen

1 : Nalidixic A, Oxolinic A, pipemidic A

2 : Norfloxacine, Ciprofloxacine, levofloxacine => used most often; broad spec (G- (klebsiella, proteus, Hib), chlamydia, mycoplasma, TB); skin; gonorrhoea, resp + urogenital infec

(Sometimes classed as 1st gen - narrow spec.)

↳ Resistance

3 : Sparfloxacine, Gatifloxacine => Broad spec (G+ - shep. pneumoniae)

4 : Moxifloxacine, Gemifloxacine => for serious-life threatening infec - MRSA, Vancomycin resistant enterococcus (VRE) ; p.o.

① Anti-coagulants

↳ a subs that prevents coagulation - reduce blood clotting
↳ don't work against old thrombi
↳ influence Anti-thrombin III (ATIII) OR synthesis of coag factors
↳ need to monitor therapy via APTT or PT ⇒ Prothrombin Time
↳ A = Activated Partial Thromboplastin time

Indications: DVT
Lung embolism, arterial embolisation
Prevention of arterial emboli in patients w/ heart valve failure, ~~AF~~ & Acute MI

Direct Anticoagulants ⇒ heparin + its derivatives
Indirect " ⇒ p.o. anticoag.

DIRECT: ① Heparin → mol. weight = 15-20 kDa ⇒ IV, SC, also used in vitro to coat inside surface of test tubes, dialysis machines etc.
↳ very / highly -vely charged at physio. pH
↳ synthesised as a norm. prod. of many tissues ⇒ lung, liver + intestines
↳ released together w/ histamine ⇒ prevent form. of thrombi in dil. vessels
↳ prod. by mastocytes, basophils then released into
↳ Low molecular-weight heparins (LMWH) also avail.
↳ commercial preparations ⇒ bovine lung or pig intestines.
↳ doesn't cross placenta

partially degraded heparin - formed in urine

Actions: ① ↑ ×1000 fold activity of anti-thrombin (↑ the rate of this activity)
↳ Heparin binds to ATIII, blocks IIa, IXa, Xa
↳ anti-thrombin inhibits activated serine proteases, incl. IIa (thrombin), IXa & Xa.

↳ Heparin, antithrombin + clotting factors form a ternary complex. Clotting factor is inactivated, intact heparin is released + recycled in a catalytic manner
↳ LMWH act via antithrombin to inhibit factor Xa

② Direct anti-coagulant ∞ activity

↳ Give parenterally (slow infusion / deep S.C injec) ; not IM ⇒ haematoma.
↳ $t_{1/2}$ = dose dependent
↳ LMWH = advantage ⇒ greater pharmacokinetic predictability ∴ 1-2 times a day S.C. without monitoring
↳ hepatic metabolism via HEPARINASE → smaller molecules → urine!

Uses: pre-op prophylaxis against DVT
after AMI or PE
vascular + cardiac surgery
Arterial + venous catheters, pul. A. catheters
Diagnostic + therapeutic interventional radiologic procedures

CI: bleeding ; after major surgery
malignant ↑BP ; alcoholics
thrombocytopenia ; hypersensitivity
abortus imminens.

AE: bleeding - GIT, urinary sys + adrenals
thrombocytopenia
hypersensitivity

* Protamine Sulphate ⇒ specific antagonist *
↳ basic prot- w/ affinity to -vely charged heparin → Complex.
↳ Of treatment => 1mg /100u of heparin

② **Low-molecular weight heparins (LMWH):**
↳ heparin fragments
↳ Nadroparin, enoxaparin, daltepain
↳ mol. weight => 4-6 kDa
↳ ↑ ATIII activity against X_a
↳ S.C ; ↓ risk of AE + less freq. dosing ; done at home
↳ don't prolong APTT ∴ no monitoring needed.
↳ activated partial thromboplastin time

③ Heparinoids :
↳ polysulphuric esters of saccharides, e.g heparansulphate
↳ animal intestines mucous mem.
↳ substitue heparin when severe AE
↳ locally on skin

④ Sulphonated pentasaccharide:
↳ fondaparinux, indraparinux
↳ anti-Xa
↳ DVT, orthopaedics, PE

⑤ Thrombin Inhibitors:
① Hirudin: polypeptide found in leech saliva
↳ reacts directly w/ thrombin without ATIII
↳ parenteral ⇒ Lepirudin, desirudin
② Melagatran x Ximelagatran (prodrug)
↳ p.o., no need for monitoring
↳ direct thrombin inhibition
③ Anti-thrombin III ⇒ congenital deficiency

⑥ Xa inhibitors:
↳ Xabans: direct Xa inhibition
↳ orally
↳ no effect on platelets or thrombin / no need for monitoring
↳ CI: liver diseases!
Apixaban, Betrixaban, Rivaroxaban

INDIRECT: Coumarin derivatives (vit K antagonist)
↳ structurally similar to vit K ⇒ imp. for carboxylation in clotting factors II (prothrombin), VII, IX, X, prot C & prot S.
↳ inducing synthesis of structurally incomplete coag. fac.
↳ only in vivo + delayed effect
↳ 99% binding to plasma prot ⇒ can displace many other drugs

NSAIDs / Sulphonamides + Warfarin ⇒ post binding drug-drug interaction

↳ hepatic metab. CYP450 ; excretion ⇒ bile, urine
↳ monitoring by measuring INR (International normalised ratio)
↳ healthy person INR 0.8-1.2
w/ warfarin INR 2-3

AE: haemorrhage in skin, GIT, kidneys, brain
case ⇒ necrosis of s. intestine / skin / soft body parts

CI: GIT ulceration
thrombocytopenia
malignant ↑BP
pregnancy (teratogenic, bleeding) + breast-feeding

!! Acute Alcohol / disulphiram - potentiate anti-coag effects
- Chronic alcohol / Barbiturates / Rifampicine - attenuate effect

Uses: prevention of thrombembolic diseases
DVT, PE
↳ anticoag. effect can be supressed by admin. dose of vit K 20-40mg IV

goes into placenta

Warfarin: p.o. 100% bicavail
↳ t½ = 2.5 days
↳ Doses ⇒ starting doses 5-15mg
long term doses 5-7mg

Epoxide reductase - needed for vit K synthesis ← WARFARIN inhib
↳ ∴ inactive clotting fac. formed

Dicumarol: less well absorbed
↳ t½ = 2-10 days ; ↑ the potential for bleeding episodes.
Fenprokumon, Etylbiskumacetate

FIBRINOLYTICS!
↳ plasminogen activators (PA)
↳ ideal ones, should be admin I.V. + should cause selective thrombolysis in the thrombus, without converting plasminogen → plasmin
↳ 1st generation ⇒ Non-selective → together w/ the lysis of the thrombus system, fibrinolysis takes place
↳ Streptokinase, Urokinase

Streptokinase => non-enzymatic prot isolated fm β-haemolytic strep.
↳ indirect activation of plasminogen
↳ parenteral admin. → lysis of ACUTE thrombi
↳ cheap but ANTIGENOUS => dnt give within 1yr of prev. usage
Uses: recanalisation after acute MI - infusion 1.5 mil. u/h + AcSal
DVT, PE, acute arterial occlusion → low doses long-term
↳ therapy lasts 24-72hrs, max. 5 days.

Urokinase => from human urine, metabolic prod. of u-PA
↳ direct plasminogen activator
↳ NOT antigenous
↳ weaker than streptokinase & t-PA

↳ 2nd generation => Binding to fibrin → fibrinolysis targeted on the thrombus
↳ t-PA, anistreplase, saruplase

t-PA => high affinity to fibrin
↳ ↑ x1000 conc. used in therapy
↳ IV admin; short t½ ∴ risk of re-occlusion
↳ recombinant origin, single chain t-PA = alteplase
double chain t-PA = duteplase
↳ Reteplase => similar but longer t½ ∴ bolus admin. poss.
↳ Tenekteplase (TNK-t-PA) => better pharmacokinetic chance + better effects

Anistreplase => acetylated streptokinase - plasminogen activator complex
↳ inactive form => binding to fibrin → deacetylation ∴ activation
↳ activated form - quickly elim fm circ by α2 antiplasmin → t-PA
↳ v. good effect in AMI
↳ antigenous!

Saruplase => (rscu-PA); similar to urokinase, high affinity to fibrin
↳ Saruplase + t-PA for reperfusion of coronary A.

Uses: Severe PE, DVT, Arterial occlusion
Acute MI therapy

AE: Bleeding

CI: Absolute ⇒ Active bleeding fm intracranial/chest trauma
Bleeding fm tu. or fm vascular abnormality

Relative ⇒ ↑BP + other risks of bleeding

DEFIBRINANTS !

↳ snake toxins; degrade fibrinogen ⟶ fibrin → consumption.
↳ anti-coagulants

① Ankrod (ancrodum): purificated protease, fm
↳ fibrinogenolytic anticoag.

② Batroxobin: serine protease
↳ ↓ plasma levels of fibrinogen, plasminogen + α2 antiplasmin

ANTIFIBRINOLYTICS/

↳ inhibit plasmin from binding to fibrin

Uses: ↳ additive drugs used when substituting loss of coag. factors to stop bleeding during/after surgery (e.g. tonsilectomy, prostatectomy)
↳ menorrhagia
↳ dental surgery in haemophilic patients (extraction)

AE: nausea

CI: DIC

ε-aminocaproic acid (EACA) ⇒ p.o, iv; ↓ plasminogen activation
tranexamic A
p-aminomethylbenzoic A (PAMBA)
aprotinin ⇒ inhibits proteolytic enzymes
↳ for hyperplasminaemia, caused by fibrinolytic drugs OD
↳ pancreatitis, patient at loss during cardiac surgery.
major blood

Anti-platelet drugs / (Anti-aggregants)

↳ MoA: ① inhibition of thromboxane A2 synthase - inhibition of COX:
↳ ASA, indobufen, sulfinpyrazon

② inhibition of thromboxane A2 synthase via ↑cAMP levels in thrombocytes:
↳ inhibition of phosphodiesterase - dipyridamol, pentoxifylin
↳ stimulation of adenylatcyclase - prostacycline & analogs

③ inhibition of fibrinogen cross-binding among thrombocytes:
↳ inhib. of ADP receptor in thrombocyte membrane - tiklopidin, Klopidogrel
↳ inhib. of fibrinogen receptor in thrombocyte membrane (IIb/IIIa)
tirofiban, lamifiban, monoclonal atb - abciximab

Indications: Ischaemic cerebrovascular diseases
IHD
Periph. artery diseases
to ↓ thrombogenous effect of synthetic materials

① Aspirin (acetylsalicylic A) ⇒ it deacetylates + irreversibly ⁑ inhibits COX (type I)
↳ COX: in thrombocytes → TXA2 (aggregation)
in endothelial cells → PGI_2 (anti-agg + vasodil)
↳ thrombocytes can't synthesise COX ∴ selective inhib. of COX in thromb.
↳ effects depend on dose; high dose block endothelial cox.
↳ low doses ⇒ ↓ risk of AMI + sudden death in patients w/ AP (↓ 50%)
↳ AMI ⇒ immediately admin 500mg ASA!
↳ usually give 50-100mg/day
↳ NSAIDs same effect but not irreversible (∴ reversible)

② Sulfinpyrazon ⇒ NSAID; COX inhib.
↳ inhib. adhesion of thrombocytes + releasing of several subs.
↳ ↑ persistance of platelets in circ.

③ Pentoxifylin ⇒ improves deformability of ery.
↳ ↓ level of fibrinogen + blood viscosity ∴ improving microcirc + anti-inflam effect

④ Indobufen ⇒ Reversible inhib. of cox
↳ max effect = 12hrs + stops completely in 24h.

⑤ Dipyridamol ⇒ phosphodiesterase inhib.
↳ coronary vasodil
↳ ↓ adhesivity of platelets to damaged endo. ↑cAMP in platelets → ↓TXA_2
↳ combination w/ aspirin, warfarin
↳ D: 75mg 3x/day

Binds to $P2Y_{12}$ ADP receptors ∴ ADP is blocked → no activation of IIb/IIIa receptors →

⑥ Ticlopidine & Clopidogrel ⇒ blocks ADP via $P2Y_{12}$ (G_i prot⁻ receptor)
↳ ADP activates IIb/IIIa receptors on surface of thrombocytes where fibrinogen binds. (no fibrin formed → no 2° clot → no thrombi)
↳ slow onset (several days) & lasts for 7-10 days.
↳ AE! haemorrhage, diarrhoea + leucopenia
↳ Clopidogrel ⇒ better effect, less AE
↳ comb. w/ ASA after PCI (percutaneous coronary intervention) w/ stent implantation

TxA2 antagonists: sulotroban, ditazol, dextransulfate

GP IIb/IIIa Rc antagonists: block all ways since they all converge on activation of GP IIb/IIIa receptor
tirofiban, lamifiban, eptifibatide ⇒ similar struc. to ligands for GP IIb/IIIa recep
abciximab ⇒ monoclonal atb fragment, directed against the receptor
↳ high risk patients only! ; immunogenous

Haemostatics: to control/stop bleeding in injured patients/after surgery/in diseases causing xs bleeding.
↳ Systemic: frozen blood plasma, human fibrinogen thrombin, coag fac. (Novo VII)
↳ Local: w/ vasocons ⇒ etamsylate, ornipressin, terlipressin, desmopressin
without " ⇒ collagen, gelatine, gelatine sponge

Dextran → anti-platelet, ↓ blood viscosity + vol. expander in anaemia

Uses: microsurgery → ↓ vascular thrombosis
lubricant in eye drops
↑ blood sugar levels

DEXTRAN 40 = most common antiwag!

MoA: Reduce VW factor → ↓ platelet func
↑ electronegativity of RBCs, platelets + vascular endothelium → ↓ RBCs aggregation + platelet adhesiveness
inhibits α-2 antiplasmin ∴ plasminogen activator
↳ ∴ has thrombolytic features

→ Liver metab → Renal excretion (↑ molecular weight → ↓ excretion)

AE: few but serious - anaphylaxis
pul. oedema / cerebral oedema
platelet dysfunc
Acute renal failure (due to its osmotic effect)

CI: chronic renal insuff.
DM

(10) Anti-depressants

↳ Depression => severe + long-lasting feeling of sadness beyond what was the precipitating event

↳ Symptoms: autonomic NS disorders => sleeping probs, anorexia, sexual disorders
impulsivity control => suicides, murders
behavioural => tiredness, lack of interest
somatic => headaches, stomach-aches, muscle rigidity

4 groups: ① Tricyclic antidepressants (TCAs) - 1st gen
② Selective serotonin reuptake inhibitors (SSRIs)
③ Atypical (heterocyclic 2nd + 3rd gen.) antidepressants
④ Monoamine oxidase inhibitors (MAOIs) - 1st gen

Therapeutic efficacy => of all these drugs, occurs after several weeks of admin. + assoc. w/ adaptive changes over the same time period, incl. ↓ cAMP accum. & down-reg. of post junc. β-adrenoreceptors.

Adaptive desensitisation of prejunc. norepinephrine & serotonin autoreceptors may also be factors

Therapeutic uses:

① Major depressive disorder: they elevate mood, ↑ phys. activity & mental alertness, ↑ appetite & sexual drive, improve sleep patterns & ↓ preoccupation w/ morbid thoughts.
↳ effective in 70% of patients
↳ SSRIs preferred over TCAs - more limited toxicity

② Bipolar affective disorder: in the depressed phase of bipolar aff. dis.
↳ comb. w/ lithium /other drugs to control mania.

③ Anxiety disorders: SSRIs - need a few weeks to see full efficacy
↳ GAD + PD
↳ OCD (also treat w/ clomipramine)
↳ Social phobia, situational anxiety disorder + PTSD

④ Enuresis (inability to control urination): TCAs can be used, e.g. imipramine in children > 6yrs + adults

⑤ ADHD ⇒ TCAs (eg. imipramine, desipramine) - in patients unresponsive / intolerant to stimulants

↳ Atomoxetine - selective inhib. of norepinephrine reuptake

⑥ Chronic pain: TCAs + venlafaxine - pain of unknown origin

↳ Duloxetine ⇒ neuropathic pain assoc. w/ DM

⑦ Others: Bulemia

Premenstrual dysphoric disorder

TRI-CYCLIC ANTIDEPRESSANTS (TCAs): - prevent re-uptake of neurot ∴ longer action

↳ highly lipid soluble + long $t_{1/2}$

↳ potentiate the actions of norepinephrine, serotonin or both by blocking their uptake by transporters into pre-junc. nerve endings. → ↑ [extracellular] of NEUROT ∴ enhancement of neurotransmission

↳ metabolised by ring hydroxylation + glucuronide conjugation OR by demethylation.

AE: due to their antagonist activity at α_1-adrenoreceptors, muscarinic (M_1) cholinoceptors, H_1-receptors + Others

Sedation - H_1 receptors
Confusion, memory dysfunc.
Mania; tremor, seizures; movement disorders
Agitation, psychosis
Postural ↓BP - α_1 receptors
Tachycardia, conduction defects + arrhythmias → similar to atropine.
Dry mouth, blurred vision, urination probs + constipation + sleepiness - M_1 receptors
weight gain, sleepiness - H_1 receptors

OD + toxicity: OD → severe anticholinergic + antiadrenergic signs, resp. depress, arrhythmias, shock, seizures, coma + death!

↳ Treatment = supportive: Cardiac toxicity - Sodium Bicarbonate
Seizures - BZDs
Hypotension - IV fluids + norepinephrine

Interactions: ① potentiate CNS depressant effects of alcohol
② " pressor activity of norepi.
③ Additive anticholinergic effects w/ antiparkinsonian drugs, antipsychotic drugs + others
④ Block α-adrenoreceptors ∴ ↓ anti-hypertensive action of clonidine + α-methyldopa.
⑤ w/ MOAIs - excitment, hyperpyrexia + hypertensive episode.

Atypical →
- Amoxapine - also blocks dopamine receptors
- Trazodone + nefazodone - antagonists at post-junc 5HT$_2$ recep. + also block presynaptic serotonin 5HT$_1$ recep.
- Bupropion
- Mirtazapine

Imipramine, doxepin, Clomipramine, amitriptyline, butriptyline!!

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs):

AE: fewer than TCAs, little sedation, postural ↓BP, anticholinergic activity & cardiovascular toxicity → 5HT$_2$ receptors
5HT$_3$ receptors ↓ Headache, sexual dysfunc, gastric irritation → 5-HT$_3$ receptors, weight loss, apathy
↓ Rebound/discontinuation effects - most likely to occur w/ Paroxetine

OD + toxicity: safer than others
↳ ↑ suicidal ideation for children, adolescents + young adults ∴ "Blackbox" warning

Interactions: ① Fluoxetine & paroxetine - inhibit liver microsomal enzymes - CYP2D6 - ∴ rarely potentiate actions of other drugs
② Rare + fatal interaction w/ MAOIs ⇒ Serotonin Syndrome - tremors, hyperthermia, muscle rigidity, ataxia, diarrhoea, profuse sweating, ↑BP & cardiovascular collapse.

Fluoxetine, Sertraline, paroxetine, fluvoxamine + citalopram

ATYPICAL ANTIDEPRESSANT AGENTS :

↳ Similar MoA like TCAs

Trazodone, Nefazodone & Mirtazapine

↳ highly sedating ⇒ drowsiness + dizziness

↳ insomnia + nausea

↳ Trazodone → postural ↓BP in elderly + rare priapism in men

↳ safer than TCAs in OD

↳ Mirtazapine → weight gain

Bupropion : no significant anti-cholinergic activity or hypotensive activity

↳ more likely to cause seizures than TCAs

↳ insomnia, weight loss + stimulation (dysphoria, agitation, anxiety ; ↑ motor activity, tremor, excitment).

↳ sustained release aid for stopping smoking

Maprotiline: highly sedating

↳ OD - ↑ cardiotoxicity

Amoxapine : movement disorders, incl. tardive dyskinesia → due to dopamine receptors antagonist activity

↳ OD → seizures

SNRI ↳

Venlafaxine - nausea, dizziness, sexual disturb, anxiety + insomnia

Duloxetine - GI disturbances (nausea, consp., diarrhea, ↑ vomitting), sexual dysfunc, insomnia + sedation

MONOAMINE OXIDASE INHIBITORS (MAOIs)

↳ rapid, non-selectivity + irreversibly inhibit the activity of enzymes MAO-A & MAO-B (→ dopamine degradation)

↳ MAO-A ⇒ degrades norepi + serotonin → therapeutic efficacy of MAOIs as anti-depres.

↳ "suicide" enzyme inhib, wl inhib continuing for upto 2-3 weeks after elim from the body

↳ AE: postural ↓BP, headache, dry mouth, sexual dysfunc, weight gain + sleep disturbances.

OD toxicity ⇒ agitation, hyperthermia, seizures, TBP or ↓ BP

Interactions ⇒ ① presence of indirectly acting (organophosphates, neostigmine) sympathomimetics → headache, nausea, cardiac arrhythmias, hypertensive crisis & rarely- subarachnoid bleeding + stroke

↳ due to ↑ release of catechol. stores ⇐ Inhib. of MAO

② pressor effect of high dose of directly acting sympathetic amines

③ Serotonin Sy - in the presence of SSRIs, some TCAs + opioids (meperidine)

④ Additive sedation + CNS depression in the presence of barbiturates, alcohol + opioids.

Phenelzine, Tranylcypromine ⇒ used infreq. → serious interactions

Phenylcidine ⇒ inactivated by acetylation

↳ genetically slow acetylators → exaggerated effects

(10) Anti-depressants => depression due to lack of NE, dopamine + 5HT.

↳ MAO - break them down → recycled or restored in the neuron

↳ rapid fire → depletion

↳ no./sensitivity of post-synap. recep. ↑ → ↓ neuroT levels.

3 actions: ① Inhib MAO → ↑ NE / 5HT / Dopamine

② Block re-uptake → ↑ neuroT levels in cleft

③ Reg. receptor sites + breakdown of neuroT => accum. of neuroT in cleft

MAOIs: 1st gen => nonselective + irreversible Iproniazide, phenelzine, tranylcypromine

1st gen!

2nd " => selective + reversible

↳ RIMA => Reversible inhib of MAO_A moclobemide

↳ Selective inhib of MAO_B ⟵ Reversible Caroxazone / Irreversible Selegiline

MAO_A (GIT) → NE, 5HT

MAO_B (Brain) → Dopamine

TCAs: Selective inhib of NE uptake inhib => Maprotiline + desipramine

1st gen!

Non selective => Imipramine, amitriptyline

Noradrenergic + specific Serotonergic antidepres. => α_1 + α_2 (NaSSAs) + $5HT_{2A/2C/3}$ => Mianserin, Mirtazapine

SSRIs: inhib. reuptake of 5HT3 into pre-synap. cleft => Fluoxetine, Fluvoxamine

AE: atropine like
Sedation
Orthostatic ↓BP
GI disturbances
Sexual dysfunction
headache

Atypical: 2nd / 3rd gen!!

Block reuptake: Trazodone ↓ $5HT_2$, Bupropion

↳ Dopamine NE Re-uptake Inhibitors

(10) Anti-depress.

NE, 5HT & Dopamine!

1st gen — TCA — Amitriptyline, butriptyline
MAOI — (Phencyclidine) Phenelzine

↳ XS-Serotonin → -ve feedback
↳ downreg. of 5HT receptors → effect after time

2nd gen — SSRI — fluoxetine, fluvoxamine → drowsiness + insomnia
↳ CYP450 inhib!
↳ CI: MAOIs

- SNRI — Serotonin NE Reuptake Inhib.
  ↳ if SSRIs don't work
  ↳ fewer AE — nausea, constip, sedation, dizziness, insomnia
  * ~~Ven~~ Venlafaxine — lower doses 5HT reuptake inhib only
    higher D + NE + 5HT " "
  * Duloxetine — NE, 5HT at all doses — reuptake inhib. of them.

- Atypical : Diff AE than TCA
  ↳ Trazodone, Nefazodone, Mirtazapine (NaSSAs), bupropion (NDRI).
  ↳ 5HT$_2$ receptor block.
  Mirtazapine → 5HT$_2$ + α_2
  bupropion → NE/Dopamine Re-uptake Inhibitors

Trazodone, Nefazodone = Serotonin$_2$ Antagonist + Re-uptake Inhibitors

⑪ Anti-diabetics

Insulin OR Peroral antidiabetic drugs (POAD)

Insulin:

- low molecular prot, 2 chains, 2 S-S bonds
- Synthesis: preproinsulin (107 AA) → proinsulin (82 AA, A, B + C peptide) → insulin (marker of endogenous secretion of insulin)
- endogenous secretion ~ 40 units/day (28 U = 1 mg)
- Therapeutical uses:
  1. admin. in DM I. type (ketosis, ketonuria or ketoacidosis)
  2. patients w/ serious infec/gangrene
  3. DM II, where blood glc. is not normalised w/ POAD, diet etc
  4. DM II patients, use corticosteroids, liver/kidney impairment
- Principles of insulin therapy:
  1. prevent fluctation of glc levels in plasma
  2. tight glycaemic control
  3. control of glycated-Hb (HbA1c) ⇒ indicator of long + short term compensation
- Human proinsulin - Recombinant!
  - 8-12% activity of H ins.
  - 6x longer $t_{1/2}$

Insulin preparations:

1. solutions/suspensions of insulin
2. suspensions of "zinc-insulin"
3. " " "protamine-zinc-insulin"

Σ insulin ⇒ as a mixture of mono/di/tetra/hexamers + pH, stability, isotonicity adjusted.

① **Short-acting preparations ⇒ "Rapid"**

- Insulin lispro - B29. Lys ↔ 28. Pro
  - quick dissociation to monomers (peak activity = 1hr)
- Insulin aspart - Asp → B28. Pro
  - self-aggregation

↳ Insulin glulisin ⇒ 3B-Asp → 3B-Lys & 29B-Lys → 29B-Glu.
↳ Regular insulin ⇒ "Crystalline"

② Intermediate-acting insulins ⇒ "Dep" (D) ; "Semilente"
" " w/ prolonged duration action ⇒ "Interdep" (ID) ; "lente"
↳ amorphous, dimmed sol. of Zn Ins in acetate buffer (semilente) ⇒ rapid onset, relat. sustained action
↳ S.C. & I.M only.
① Semilente, lente ⇒
Lente : 30% semilente + 70% ultralente
② Isophan (NPH) insulin ⇒ protamine-zinc-Ins.
↳ intermediate activity w/ delayed onset

③ Long-acting insulins ⇒ "ultralente" / "Superdep" (SD)
↳ ultralente ⇒ slow onset + prolonged duration, poorly soluble crystalline Ins. - delayed onset
↳ slowly dissoc. complexes of Zn-Ins. in suspension
↳ S.C. admin
↳ Glargin, Determin

* 40/100 IU/ml *
* Syringes/solutions *

Delivery systems :
① Ins. injec. - syringes calibrated by IU (40/100 IU/ml)
② Ins. pens. - pen sized injec. + blood glc. detectors
③ Ins. pumps - automated admin of Ins. (S.C / I.V) acc. to glycaemia
④ Ins. inhalations.

Pharmacokinetic parameters : S.C / I.M
↳ Inter- & Intra-individual variability in absorp. (25-50% after
↳ application site ⇒ vascularity, temp, massage, sunbathing, vasodil
↳ t'1/2 = 7-10 mins

POAD - more efficient if DMII < 5 yrs, > 40 yrs

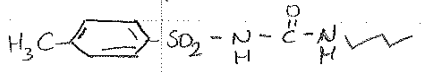
↳ Sulfonylurea derivatives (SU) - MoA = like meglitinides
Biguanides
Thiazolidinediones
α-glucosidase inhib.
meglitinides
GLP1 analogues

① Sulfonylurea derivatives (SU): 1st choice in DMII - combined w/ biguanides OR α-glucosidase inhib

MoA: extrapancreatic: ↓ hepatal glc prod + ins. degrad.; ↓ serum [glucagon]

pancreatic: block ATP-sensitive K^+ channels in β-cell membrane
↓
depol. of mem
↓
activation of voltage gated Ca^{2+} channel
↓
influx of Ca^{2+}
↓
insulin release

Tolbutamide



↳ 3 Generations:
① Gen I: Chlorpropamide, tolbutamide
② Gen II: Glibenclamide, glipizide, gliclazide, gliquidone
③ Gen III: Glimepiride

↳ Don't affect insulin synthesis
↳ ↑ insulin release
↳ ↑ no. of insulin receptors on ERYs, adipocytes + monocytes
↳ well absorbed after p.o.
↳ 99% prot binding ⇒ competition w/ other drugs (Sulfonamides)
↳ metabolic inactivation - hepatic P450
↳ excreted in urine, bile (gliquidone), faeces
↳ $t_{1/2}$ ⇒ 5 - 48 hrs.

AE: ↑ appetite; metal taste in mouth; hypoglycaemia; headaches; nausea (5%), fluid retention; allerg + photosensitivity

CI: hypoglycaemia, ketoacidosis, renal/hepatic impairment, preg, age & hypersensitivity

② Biguanides: 1st choice in DM II patients w/ BMI >25

Uses: 2nd choice in DM II type
hyperinsulinaemia
combination w/ SU in resistant patients

MoA: ↑ sensitivity of periph. tissues to insulin
↑ insulin binding to its receptor
↓ hepatic gluconeogenesis
↓ glc. absorption fm GIT

* Don't affect insulin secretion + func of β-cells → no hypoglycaemia
↳ "EUGLYCAEMIC AGENTS"

↓ LDL, VLDL, FFA + TAG
↑ fibrinolytic activity (inhib. of PAI-1)

Metformin ⇒ only one in use
Glibomet (Metformin + Glibenclamide)
Avandamet (Metformin + Rosiglitazon)

↳ 50-60% bioavail
↳ insignificant prot binding
↳ not metabolised
↳ renal excretion, as the active compound (AE: Lactic acidosis in renal insuf)
↳ t½ = 3-6hrs

CI: ketoacidosis
renal diseases (creatinine >1.5mg/l)
liver disease / alcoholism
predisposition to tissue hypoxia
hypersensitivity

③ Thiazolidinediones:

MoA: ↑ sensitivity of periph. tissues to insulin
↓ glycaemia - +ve effect on insulin resistance
better glc. utilisation in mus.
↓ prod. of FFA, TNFα, resistin - causes insulin resistance in periph. tiss.
Affect lipid metab - hypoglycaemic effects ↓ TAG + FFA ; ↑ HDL ; unchanged chol. Level & inhib. peroxidation LDL

↳ bioavail ~50% - 99% ; meals ↓ (slows) absorp.
↳ ≈99% prot binding
↳ hepatic cytochrome P450 metab.
↳ renal excretion → urine as conjugates
↳ $t_{1/2}$ = 3-7hrs
Rosiglitazone (F=99%)
Pioglitazone (F=50%)

AE: effects on vascular endothelium, immune sys, ovaries, fx. cells.
free radical scavengers
fluid retention + heart failure, ↑ CV risk
↑ subcutaneous fat + LDL chol.
↓ hepatal, ab. fat
AST / ALT

CI: hypersensitivity
heart failure risk
liver insufficiency
pregnancy, lactation

Uses euglycaemic drugs
↳ NOT the drugs of 1st choice
↳ if patient compensated well w/ SU - no need to change drugs.
(AE, price, few experiences, ↑ CV risk)
↳ combined w/ biguanides !

(4) α-glucosidase inhibitors (gut-glucosidase) intestinal brush border
MoA: ↓ saccharide absorp. fm GIT
↳ competitive inhib of α-glucosidases (inhibit cleavage of polysac fm food)
↳ ↓ postprandial glycaemia
↳ don't affect monosaccharide absorption
↳ acarbosis doesn't reach systemic blood ; miglitol does!

↳ "Educative drugs" - Consequences in bad compliance
* In hypoglycaemia + treatment w/ POADs, SUCROSE cannot be administered => monosacc. necessary (Glu, Fru) / Glucagon *
Acarbosis
Miglitol

⑤ Meglitinides:
MoA similar to SU derivatives
block ATP-sensitive K^+ channels in β-cell mem. → depol. of mem → activation of voltage-gated Ca^{2+} channels → Ca^{2+} influx → Insulin release
↳ through diff receptor at K^+ channel
Pharmacokinetics: good bioavail
↳ 98 % post binding
↳ metabolised to inactive compounds
↳ excreted in faeces!
Repaglinicle
Nateglinicle

Cl: hypersensitivity
DM I type
Diabetic ketoacidosis
Pregnancy, lactation
Uses combined w/ metformin - esp. if patient not sufficiently compensed.
alternative of SU medication in patients w/ Renal impairment
(↓bile excretion)

⑥ GLP 1 (→ Glucagon like peptide 1) + analogues "Gliptins"
↳ physiologically secreted postprandially, in DM II - not sufficient
↳ stimulate insulin secretion (dependent on glycaemia)
inhibit glucagon secretion
prolong stomach content evacuation

Advantages: no hypoglycaemia
Stops progression of illness

↳ Nowadays: in combination w/ other POADs
↳ better glycaemic control than conventional drugs.

Sitagliphne
Vildagliphne

(12) Antidysrhythmic drugs I.

Causes of arrhythmias: ① electrolyte disturbances that alter the AP
② ↓ O_2 delivery to cells
③ Structural damage, changing conduction pathways
④ Acidosis/accum. of waste prod. - alter AP
⑤ Drugs that alter AP / cardiac conduction

↳ Improper impulse generation & impulse conduction → Conduction block
↳ 1st, 2nd or 3rd Degree block

- Automatic rhythms: ① enhanced norm. plasticity ② Abnorm. plasticity
- Triggered rhythms: ① early after depol ② delayed " "
- Re-entry, circus movement, Reflection.

Class I Anti-arrhythmics: block the fast Na^+ channels in the cell. mem. during an AP → ↓ rate of phase 0 depol, prolong the effective refractory period → ↑↓ threshold of excitability + ↓ phase 4 depol.

↳ Also have LA properties

↳ IA: prolong the refractory period & ↓ conduction — Quinidine, procainamide, phenytoin

IB: shorten the duration of the refractory period — Lidocaine, Trimecaine, Mexiletine

IC: slow conduction — Flecainide, propafenon

Class IA: (↑ AP duration)

Quinidine: orally, rapid GIT absorp. CYP450 inhib!
↳ liver hydroxylation - t ½ ~ 5-12hrs (↑ in hepatic/renal failure)
↳ Supraventricular + ventricular arrhythmias
↳ To maintain a sinus rhythm after conversion of AF/flutter by digoxin, propanolol or verapamil.
↳ Prevent freq. premature ventricular complexes + VT
↳ Anti-malarial, antipyretic + oxytocic actions (← isomer of quinine)

AE: muscle depression → skeletal muscle weakness
hypotension (severe) + shock after rapid infusion
cinchonism (ringing in the ears + dizziness) + diarrhoea
thrombocytopenia

can cause ventricular arrhythmias / quinidine syncope, due to VT
GI disturbances - ab pain, diarrhoea, nausea + oesophagitis

Interactions: ↑ digoxin plasma levels ∴ risk of digoxin toxicity
↳ ↓ quinidine $t_{1/2}$ by agents that induce drug-metab. enzymes (phenytoin, phenobarbital)
↳ enhance activity of coumarin anticoag. - quinidine inhibits synthesis of vit K-dependent clotting factors!

Procainamide: similar actions to quinidine but safer IV use + ↓ GIT AE
↳ liver acetylation, renal elim, $t_{1/2}$ ~ 3-4 hrs
↳ ↑ incidence of AE w/ long term use; more likely to prod. severe / irreversible heart failure than quinidine; hallucinations
↳ Can cause drug induced lupus like sy.

Disopyramide: longest $t_{1/2}$; similar to quinidine
↳ V Arrhythmias - cases refractory / intolerant to the other 2.
↳ AE: anti-cholinergic effects - dry mouth, blurred vision, constipation, urine retention + (Rarely) acute angle-closure glaucoma.

MAIN FOCUS →

Class 1B: (↓ duration of AP + refractory period)
Lidocaine: acts on Na^+ channels (activated & inactivated ones) + very selective for damaged tissues -ve ionotropic effect + periph vasodil
↳ ↓ depol, ↓ automaticity of the ventricular cells; ↑ ventricular fibrillation threshold
↳ 2nd choice (1st = Amiodarone) for treatment of VArrhythmias during MI or cardiac surgery
↳ ∴ ineffective in the prevention of arrhythmias
↳ Doesn't slow conduction ∴ little effect on atrial func.
↳ large 1st pass effect; IV / IM ; $t_{1/2}$ = 1.5-2 hrs. ; renal excretion
IV → immediate onset 10-20 mins
IM → 5-10 min onset
↳ admin in a loading dose followed by infusion ⇒ dose must be adjusted in CHF / Recent hepatic disease

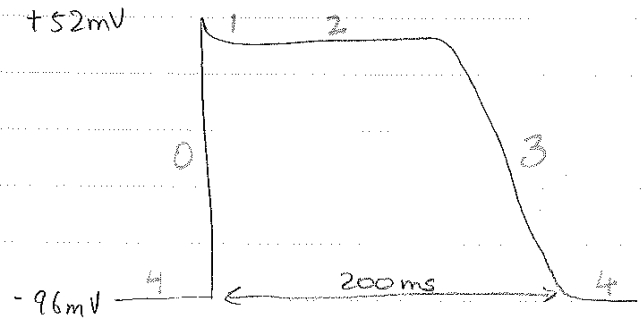
↳ low level of cardiotoxicity
↳ most common AE => neurologic + little affect on ANS.

Mexiletine: orally; similar to Lidocaine
↳ long term treatment of ventricular arrhythmias assoc. w/ prev MI.

Class Ic:

Flecainide: orally active
↳ ventricular tachyarrhythmias + maintainence of sinus rhythm in patients w/ paroxysmal AF/flutter.
↳ limited use - proarrhythmic actions
↳ caution in patients w/ sinus node dysfunc, post MI & CHF

Propafenone: similar to quinidine
↳ β-adenoreceptor antagonist activity
↳ Supraventricular arrhythmias + suppression of life-threatening ventricular arrhythmias
↳ may cause bradycardia, CHF or new arrhythmias



Phase 0 = Rapid depol phase => fast Na^+ channels open (Na^+ influx)
1 = Inactivation of fast Na^+ channels
2 = "Plateau" phase => Balance of Ca^{2+} in & k^+ out
3 = "Rapid repol" phase => Ca^{2+} (L-type) channels close; k^+ still open
4 = Resting mem. potential

ISA - Intrinsic Sympathomimetic Activity

(13) Anti-dysrhythmics II, III & IV

Class II: Block β-receptors → depression of phase 4 of the action P.
↳ ↓ symp. stimulation → depress automaticity, prolong AV conduction & ↓ HR + contractility

Propranolol: non-selective β-adrenoreceptor antagonist
↳ Anti-hypertensive, anti-anginal, anti-migrane headache drug + anti-arrhythmic (Supraventricular tachycardias)

Acebutolol: selective β_1-adrenoreceptor antagonist; w/ ISA ∴ better in asthmatics + COPD patients.
↳ effective in the treatment of PVCs (premature ventricular complexes)

Esmolol: selective β_1-adrenoreceptor antagonist
↳ ultrashort acting, infusion admin, used to titrate block during surgery
↳ short-term management of supraventricular tachycardia + tachycardia that isn't responding to other measures.

Metoprolol: without ISA
↳ CI: asthma bronchiale, Acute Heart failure

AE (of all): arteriolar vasoconstriction
(Atropine OR Isoproterenol ⟶) bronchospasm, bradycardia, heart block, myocardial depression

Class III: Block K^+ channels → prolong AP duration (phase 3) + effective refractory period.
Amiodarone: structurally related to thyroxine ORAL
↳ ↑ refractoriness & depresses sinus node automaticity + slows conduction.
↳ long $t_{1/2}$ = 14-100 days ! ↑ risk of toxicity
↳ anti-arrhythmic effects may last weeks-months after discontinuation
↳ only for treatment of life-threatening arrhythmias (2nd choice = lidocaine ↳ prev. Q!)
↳ 1st line agent for patients unresponsive to CPR!
↳ dose-related + cumulative AE (esp. GIT related ones) ~ 70% patients

AE Serious toxic reactions
pul. fibrosis + interstitial pneumonitis
photosensitivity
"grey man sy."
corneal microdeposits
thyroid disorders (Iodine in the drug preparation)

Tremors, Ataxia, dizziness, muscle weakness, GI disturbances

Ibutilide: IV to rapidly convert AF/flutter → norm. sinus rhythm.
↳ blocks slow inward Na^+ currents + prolongs the AP duration → slowing of the sinus rate + AV conduc. velocity

Sotalol: prolongs cardiac AP → ↑ duration of the refractory period
↳ non-selective β-adrenoreceptor antagonist
↳ life-threatening arrhythmias => atrial arry. OR Vent. arry. & ~~sustained~~ treatment of sustained VT

Dofetilide: AF/flutter → norm. sinus rhythm + maintain it
↳ potent inhibitor of K^+ channels & no effect on conduction velocity

Bretylium: inhibits neuronal release of catecholamines
↳ prolongs ventricular AP.
↳ IV for short-term treatment of VFib or vent. arry. that don't respond to other drugs.

Class IV: selectively block L-type Ca^{2+} channels in the cell mem.
↳ prolong nodal conduction & effective refractory period
Diltiazem: IV to treat paroxysmal supravent. tachy.

Verapamil: phenylalkylamine, blocks both active + inactive slow Ca^{2+} channels
↳ oral admin bioavail = 20%; lower doses when IV
↳ Renal excretion; dose reduc in presence of hepatic disease & elderly
↳ Supravent. tachy; ↓ ventricular rate in AF/flutter

↳ has -ve inotropic effects - limits its use in damaged hearts
↳ Can lead to AV block when given in large doses OR in patients w/ partial blockage.

AE: Sinus bradycardia, transient asystole + other arry.
↳ worse in ppl taking β-adrenoreceptor antag.

CI: in patients w/ abnorm. conduc. circuits, e.g. Wolff-Parkinson-White Sy.

Class V: Others!

Adenosine: via specific purinergic (P_1) receptors
↳ ↑ K^+ efflux & ↓ Ca^{2+} influx → hyperpol. cardiac cells → ↓ Ca^{2+} dependent portion of AP
↳ convert supravent. tachy → sinus rhythm, when vagal maneuvers = ineffec.
↳ treatment of paroxysmal supravent. tachy.

Digoxin: slows Ca^{2+} fm leaving the cell → ↑ AP duration → ↓ HR + cond.
↳ control ventricular response in AF/flutter

Mg^{2+}, K^+: in tachy. after digitalis + other inotropics

* All anti-arrhythmics ⇒ Pro-arrhythmic influence! *
* Class IA, IC & Ca^{2+} antagonists, β-blockers = -ve inotropic effect
* Others ⇒ toxic hepatic effects

Bradycardia:

Atropine: blocks effects of Ach ⇒ ↑ sinus rate & AV nodal + sA conduc. velocity + ↓ refrac. period.
↳ bradyarry. that accompany MI.

Isoproterenol: stim. β-adrenoceptors → ↑ HR + contrac.
↳ maintain adequate HR + CO in patients w/ AV block

(14) Anti-emetics

Useful in the treatment of vomiting assoc w/ motion sickness
chemotherapy-induced emesis (CIE)
radiation - " " (RIE)
post-op nausea + vomiting (PONV)
other causes

Drugs: Anti-cholinergic drugs
Anti-histaminics (H1) BZD - diazepam, lorazepam...
Neuroleptics
$5HT_3$ antagonists
Cannabinoids
Prokinetics

① Anti-cholinergic drugs (cholinoceptor antagonists):
↳ ↓ excitability of labyrinthine receptors & ↓ conduction fm the vestibular apparatus → vomiting centre
↳ Motion sickness, pre-op situations
↳ AE drowsiness, dry mouth + blurred vision (atropine like AE)
↳ NOT useful in treating chemo induced nausea
Scopolamine (TTS): acts centrally + periph.
↳ preferred over atropine - longer duration of action + a more pronounced CNS action.
↳ transdermal delivery ⇒ ↑ incidence of AE + relief for 72hrs.
↳ Motion sickness dose = 0.5 mg

② Anti-histaminics (H_1-receptor antagonists):
↳ act by inhibiting histamine pathways & cholinergic pathways (Receptor "crossover") of the vestibular apparatus.
↳ H_1 anti-histaminics of the 1st gen - anticholin action & BBB passage
↳ Motion sickness (sedative action) & true vertigo
↳ NOT useful in treating chemo induced nausea
↳ AE: sedation, photosensitivity, allergy, dry mouth, urine retention
↳ Caution pass BBB + placenta; prevent combination w/ other sedative drugs. (opioids, hypnosedatives, neuroleptics)

↳ Meclizine, Cyclizine, Dimenhydrinate, promethazine ← Nausea + vomiting assoc w/ preg! Hydroxyzine

↳ Theoclates: salts of H_1 antagonists + 8-chlortheophylline

↳ weak sedation, low occurence of AE

↳ prolonged $t_{1/2}$

↳ anti-vertiginous effect

③ Neuroleptics:

↳ inhib. vomiting centre in reticular formation (FR)

↳ strong anhemetic effect, except thietylperazine - ineffective in motion sickness

↳ lower doses than in psychosis

↳ Phenothiazines: Prochlorperazine, perphenazine, thietylperazine → blocks muscarinic cholinoceptors

AE: Sedation, tiredness, dry mouth, ↓BP, constipation, photosensitivity & extrapyramidal symp. (CI in Parkinson's)

↓ can be given in 1st trimester of preg.

Indications: CIE, RIE & PONV

↳ Butyrophenones: Haloperidol, droperidol

↳ block dopamine receptors in the chemoreceptor trigger zone (CTZ)

↳ CIE, RIE & PONV

↳ AE: same as above

↳ Droperidol: prior to GA; severe vomiting in cytostatic treatment

↳ AE: Rare - neuroleptic sy. (10% mortality)

↳ its use is assoc. w/ QT prolongation & torsade de pointes

↳ BLACK BOX WARNING

↳ Haloperidol: AE: somnolence, tiredness, hypoglycaemia, constipation

④ Serotonin $5HT_3$ antagonists:

↳ in peripheral tissues - block vagus N. stimulation; blocks $5HT_3$ receptors in CTZ → prevent emesis

↳ in FR

↳ No sedative effect

↳ more effective in cytostatic treatment than prokinetics + glucocorticoids

↳ AE: constipation, headaches, vertigo, ↑ALT/AST

Ondansetron (→ prolongs QT interval), Dolasetron, Granisetron, palonosetron, Tropisetron
↓ dose reduc in patients w/ hepatic insuff. $t_{1/2}$ = 40hrs

↳ often combined w/ corticosteroids (dexamethasone + methylprednisolone) ⇒ enhanced antiemetic effect → due to corticosteroid inhib of prostaglandin synthesis

↳ oral + parenteral admin, except palonosetron.

↳ Good for CIE + RIE & 2nd in line for PONV.

⑤ Cannabinoids: Dronabinol, Nabilon

↳ Dronabinol: oral preparation of Δ-9-tetrahydrocannabinol.

↳ inhib. the vomiting centre thru stimulation of CB_1-subtype of cannabinoid receptors; acts centrally + periph.

↳ control CIE

↳ AE: sedation, tachycardia, hypotension, behavioral alterations

⑥ Prokinetics: type of drug which enhances gastrointestinal motility, by ↑ freq. of contractions in the s.intestine OR by making them stronger

↳ stim. peristalsis in prox. part of GIT

↳ partial antagonists of D_2 & 5HT receptors

↳ Indications: nausea, vomiting, reflux oesophagitis, prevention of bile reflux, improvement of gastric emptying

↳ Metoclopramide, cisapride, domperidone, alizapride

↳ blocks dopamine D_2-receptors within the Chemoreceptor trigger zone (CTZ) + vomiting centre

↳ enhances GI motility + gastric emptying by ↑ GIT sensitivity to Ach action.

↳ treat nausea due to chemo & narcotic induced vomiting

↳ AE: sedation, diarrhoea, extrapyramidal effects + ↑ prolactin secretion.

CI: Parkinson's + seizure disorders

Blocks pre-synap. D_2 recep + ↑ Ach release + stim. of SM muscle

(15) Anti-epileptic drugs

↓ neuronal firing of small groups of neurons

Epilepsy => chronic disease, in ~1% of the pop.
- ↳ anti-epileptic drugs (AEDs) are effective for ~80% of patients.
- ↳ takes weeks to have adequate plasma levels
- ↳ Monotherapy - most effective & least AE
- ↳ Some have teratogenic potential.

Partial seizures => Simple/Complex : Phenytoin, Carbamazepine, Lamotrigine, Valproic A, phenobarbital

Gen. seizures => Tonic clonic : Phenytoin, Carbamazepine, Topiramate
Absence : Ethosuximide, valproic A, clonazepam
Myoclonic : Valproic A, Lamotrigine

Status epilepticus => IV diazepam/lorazepam then IV fosphenytoin (phenytoin) or phenobarbital

MoA:

Phenytoin, carbamazepine, valproic A + lamotrigine : block Na^+ channels + inhibit the generation of AP
- ↳ "use dependent" effect : related to their selective binding & prolongation of the inactivated state of the Na^+ channel.
- ↳ ↓ neurotransmission by actions on pre-junc. neurons

Ethosuximide : ↓ the low-threshold T-type Ca^{2+} current, that provides the pacemaker activity in the thalamus

barbiturates (eg phenobarbital) & benzodiazepines (e.g. diazepam) : facilitate GABA mediated inhibition of neuronal activity

Phenytoin, fosphenytoin:
- ↳ phenytoin : well absorb. after oral admin, but rate + extent of absorp. altered by its formulation
  - ↳ metabolised by microsomal enzymes + excreted as glucuronide
  - ↳ $t_{1/2}$ => ~ 24hrs ; IM => it precipitates ∴ NOT poss.
  - ↳ plasma conc that varies disproportionately w/ dose.
- ↳ Fosphenytoin : parenteral admin, more rapid loading, IM admin, IV w/ minimal vascular erosion.

AE: Nystagmus, diplopia, ataxia (most common), blurred vision, slurred speech, hirsutism, gingival hyperplasia

↳ Rare: w/ long term use - coarsening of facial features, w/ mild periph neuropathy, Osteomalacia; idiosyncratic reac.

↳ Fetal malform ⇒ "fetal hydantoin sy" - growth retard., micro encephaly & cranio-facial abnorm.

Interactions: stimulates hepatic metabolism (microsomal enzyme induction) ⇒ ↓ [plasma] of carbamazepine, valproic A, atb, oral anticoag + oral contracep.

↳ $[\text{phenytoin}]_{\text{plasma}}$ - ↑ by drugs that inhibit metabolism (hepatic) ⇒ cimetidine, isoniazid

↳ ↓ $[\text{phenytoin}]_{\text{plasma}}$ - drugs that stimulate hepatic metab ⇒ Carbamazepine

Carbamazepine, Oxcarbazepine

↳ Carbamazepine ⇒ good oral absorp.

↳ induces microsomal enzymes + ↑ its own hepatic clearance (autometabolism) ∴ ↓ it's own $t_{1/2}$ (~20hrs)

↳ drug of choice: Trigeminal neuralgia + other pain sy.; bipolar disorder

↳ Oxcarbazepine ⇒ pro-drug; similar actions to carbamazepine

↳ $t_{1/2}$ = 1-2hrs; better AE profile + less potent inducer of hepatic microsomal enzymes.

AE: diplopia, ataxia, GI disturbances; sedation at high doses.

water retention & hyponatraemia, rash, agitation in children

Idiosyncratic blood dyscrasias + severe rashes

Interactions: induces microsomal enzymes + ↑ hepatic clearance - phenytoin + valproic A

↳ ↑ $[\text{Carbamazepine}]_{\text{plasma}}$ by drugs which inhib. hepatic metab.

Valproic A:

migraine prophylaxis & bipolar disorder treatment

↳ inhibits metab. of phenytoin + carbamazepine

AE: GI disturbances + hair loss

Weight gain, sedation, ataxia

Idiosyncratic hepatotoxicity - fatal in infants + in patients using multiple anticonvulsants

Fetal malform ⇒ spina bifida

Ethosuximide: Effective in fewer patients w/ absence seizures, but preferred ⇒ Safer!

AE: GI disturbances, fatigue, dizziness

Idiosyncratic rashes + blood dyscrasias

Phenobarbital: neonatal seizures + control of status epilepticus.

↳ at less than hypnotic doses

↳ Sometimes, treatment of complex partial seizures

Benzodiazepines, diazepam, lorazepam, clonazepam + clorazepate:

↳ Diazepam + lorazepam ⇒ Status epilepticus (short-term treatment)

↳ Clonazepam ⇒ Absence seizures

↳ Clorazepate ⇒ complex partial seizures

↳ AE: Sedation!

⑯ Anti-fungal drugs

Mycoses - systemic or superf.
↳ more common in immunosuppressed + diabetics (chronic hyperglycaemia + insuff non-specific immunity)
↳ most common agents: Candida Albicans
Dermatophytes

Antifungal atbs: bind to ergosterol in the cell membrane → create pores → alter membrane stability + allow leakage of cellular contents
↳ Toxic ⇒ kidney, CNS, fever, inflam in place of application
↳ Superficial = Nystatin, natamycin, pimaricin
Systemic = amphotericin B, ambisom, azoles
↳ Azoles: synthetic; inhibit CYP450 mediated sterol demethylation of lanosterol → ergosterol in fungal mem.

Superficial:
Nystatin: polyene atb; similar structure + MoA to amphotericin B.
↳ too toxic for systemic use
↳ NOT absorbed from GIT: oral prep = infec of the mouth
↳ Aspergillus, Trichosporon BUT mainly - Candida infec of the skin, mucous mem + intestinal tract
Natamycin: Trichomonas vaginalis, Candida
Econazole: Dermatophytes, Candida, mixed bac + fungal infec.
Clotrimazole: dermatologic + gynaecological indications
↳ Dermatophytes, Candida, interdigital mycoses, vulvitis & balanitis
↳ Clotrimazole - betamethasone: topical antifungal corticosteroid combination
Tioconazole, oxiconazole: Only for Candidal vaginitis
Echinokandines: newer drugs; also damage fungal cell wall
Miconazole: tinea pedis, ringworm, cutaneous + vulvovaginal candidiasis is CI.
↳ avail. for IV admin - but lots of AE + high incidence; only when amphotericin B ✗
↳ broad spectrum, oldest, easy penetration

Systemic:
Amphotericin B: macrolide atb
↳ poorly absorbed from GIT - this route only effective in GI fungal infec.
↳ large distribution vol & ~90% plasma prot binding

↳ usual - IV admin as a lipid formulation ; endobronchial , p.o., topical
↳ intrathecally poss ; poor BBB penetration
↳ 1st choice in aspergillus infec (transplantations)
↳ Actinomycetes = RESISTANT!
↳ most severe fungal infec (broad spectrum) ⇒ Candidas, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis , Blastomyces dermatitidis , Aspergillus spp & Sporothrix schenckii
↳ Combined treatment :
  ↳ + flucytosine : improves BBB penetration :: Candida infec, cryptococcal meningitis + systemic candidiasis
  ↳ + Rifampicine + tetracyclines

AE: Acute (during admin) : prostaglandin synthesis
  ↳ fever, vomiting, allergy, pain, chills
Chronic : nephrotoxic (80% of ppl) ⇒ irritation of small vessels, vasoconst+, anaemia
  ↳ thrombocytopaenia , severe pain + seizures

Indications: Above + prophylactic treatment in immunosuppressed patients - transplantation, cancer chemo & granulocytopenia

Azoles: fewer AE ; CI = hypersensitivity
  ↳ resistance = problem!
  ↳ broad-spectrum antifungals
  ↳ inhibit some G+ bac & some protozoa
  ↳ Candida spp, Blastomyces spp, Dermatophytes, P. falciparum, Leishmania ...
  ↳ Imidazole derivates: Miconazole (p. T.O), ketoconazole (replaced by Itraconazole except when expensive)
  ↳ Triazoles: Fluconazole , Itraconazole

↓ inhibits gonadal + adrenal steroid synthesis

Itraconazole , ketoconazole :
  ↳ orally / topically ; systemically (IV) - certain mycoses
  ↳ doesn't penetrate CSF
  ↳ disseminated blastomycosis, histoplasmosis , paracoccidioidomycosis
  ↳ ketoconazole: topically - dermatophyte infec , mucocutaneous candidiasis & shampoo for seborrheic dermatitis (skin + adnex. infec.)
  ↳ AE: gastric upset , itching, rashes, headaches ; RARE ⇒ hepatic failure

Fluconazole: systemic ; only oral that is also hydrophilic!
- ↳ IV, oral, parenteral - good absorp + penetration (CSF)
- ↳ inhibits CYP3A4 & CYP2C9 - ↑ plasma levels of other numerous drugs.
- ↳ oropharyngeal, isophayngeal + systemic candidiasis
- ↳ shortterm + maintainence therapy of cryptococcal meningitis
- ↳ treatment of disseminated histoplasmosis + coccidioidomycoses
- ↳ AE: mild: nausea, vomiting, diarrhoea, reversible alopecia
  in patients w/ AIDS - exfoliative sy.

Other antifungals:

Terbinafine: fungal infec of the nails

Griseofulvine: binds to microtubules + prevents spindle form. & mitosis in fungi.
- ↳ accum. in skin, hair, nails (binds to filamentous prot⁻ => keratin)
- ↳ orally - dermatophyte infec
- ↳ narrow spectrum ATB
- ↳ longterm therapy of hair + nail infec.
- ↳ Cross-sensitivity w/ PENICILLIN!
- ↳ CI: pregnancy, lactation, SLE, hepatic diseases
- ↳ AE: GI distress, rash
  Rare CNS effects & hepatotoxicity
- ↳ induces CYP450
- ↳ hepatic metab + renal excretion

⑰ Anti-hypertensive drugs

↑BP = 160/95 mmHg
↳ 90% = essential ↑BP ; 10% = 2° ↑BP (renal disease or endocrine dx.)
BP = CO x periph. vascular resistance (lower one of these 2!)
↳ Carotid baroreceptors respond to stretch
Goal of therapy: ↓ elevated BP + ↓ cardiovascular morbidity + mortality
↳ combination of agents
↳ most ppl: life-long treatment of an asymp- disease

Agents: ① Diuretics
② Ca^{2+} channel blockers
③ ACE Inhibitors
④ Angiotensin Receptor (ARB) Antagonists
⑤ Periph. vasodil.
⑥ α_1 blockers
⑦ β-blockers
⑧ α_2 - agonists
⑨ Ganglionic inhib
⑩ Adrenergic neural terminal inhib.

(0.27!)

① Diuretics: ↑ Na^+ excretion & ↓ blood vol. (↓ CO, ↓ preload) - distal convoluted tubules - block Na^+-Cl^- symporter

① Thiazide diuretics: (+w/ K^+ sparing)
↳ effective in lowering BP - 10-15 mmHg
↳ if admin alone - good for mild/moderate ↑BP
↳ comb. w/ sympatholytic agents & vasodil for severe ↑BP
↳ comb. w/ ACEIs & β-blockers
↳ once a day - elderly / obese

pwb ⇒ some Na^+ is reabsorbed in collecting ducts, but more is still excreted in distal tubules

* In collecting ducts ⇒ Na^+ is reabsorbed ∴ K^+ is excreted

↳ Initial effects: natriuresis, diuresis, ↓ extracellular + circ. vol.
↳ Chronic effect: ↓ periph. vascular resistance
↳ AE: hypokalaemia, hyperglycaemia, hypersensitivity reaction, hyperuricaemia

Na^+ ↓ hypokalaemia ↓ K^+

Thiazides: Hydrochlorothiazide, Chlorothiazide, benzothiazide
Thiazide-like: Sulfonamide related compounds ⇒ Chlorthalidone, Indapamide
↳ CI: hyperlipidaemia, gout, sexually active MALES, CrCl ≤ 30 ml/min

② Potassium sparing diuretics: competitive antagonists - compete w/ aldosterone for intracellular cytoplasmic receptor sites or directly block Na^+ channels
↳ avoid K^+ depletion, esp when admin w/ cardiac glycosides
↳ 2nd line of anti-hypertensives
↳ work on collecting ducts

↳ used in comb. (→ thiazide/loop diuretic) or for correction of hypokalemia
Amiloride, Triamterene, spironolactone (in severe HF)

③ Loop diuretics: ascend. loop of Henle – Na^+-K^+-$2Cl^-$ symporter – inhibit $Na^+ + Cl^-$ reabsorp. ⇒ compete for the Cl^- binding site
↳ 2nd line anti-hypertensives
↳ comb w/ sympatholytic agents + vasodil
↳ in patients w/ chronic renal disease for vol/salt control
↳ in the presence of azotemia
↳ AE: hypokalemia, ↓BP, vol depletion, ↓$[Mg^{2+}]$, ↓$[Ca^{2+}]$, hyperglycaemia & hyperuricemia ↓$[Na^+]$, dehydration
Furosemide, bumetanide, ethacrynic A.

② Ca^{2+} channel blockers: (Q23)
↳ inhib the entry of Ca^{2+} into cardiac + smooth mus cells by blocking L-type Ca^{2+} channels → inhib. excitation-contraction → ∴ ↓ periph resistance
↳ mild/moderate ↑BP
↳ ↓ BP even more when comb. w/ a β-adrenoreceptor antagonist
↳ Dihydropyridines: amlodipine, isradipine, nimodipine
felodipine, nicardipine, NIFEDIPINE
↓
long acting/slow release formulations used.

↳ Phenylalkylamine: Verapamil
↳ Benzothiazepine: Diltiazem

AE: facial flushing, headaches, constipation + non-pitting ankle oedema
CI: HF, heart block, receiving β-blockers
short acting dihydropyridines (unstable angina, recent MI)

③ ACEIs: (Q1 for complete details)
↳ ↓ vascular resistance + blood vol → ∴ ↓ BP by ↓ resistance
↳ mild-severe ↑BP
↳ less effective in African-Americans than Caucasians

↳ elicits the baroreceptor reflex ∴ co-admin w/ diuretics → for $Na^+ + H_2O$ retention
β-blocker → prevent tachy.

↳ in slow acetylators ⇒ lupus like sy.

Minoxidil: ↑ K^+ efflux → hyperpolarises cells → ↓ activity of (voltage dependent) L-type Ca^{2+} channels.
↳ mainly vasodil → arteriolar vessels
↳ elicits baroreflex ∴ β-adrenoceptor antagonist + diuretics needed
↳ long term therapy of refractory ↑BP
↳ prod. hirsutism! headaches, sweating
↳ "Last choice" for treatment of ↑BP.

Sodium nitroprusside: dilates resistance + capacitance vessels
↳ ↑ HR NOT CO!
↳ hypertensive emergencies (← rapid action); continuous infusion to maintain effects
↳ usually admin w/ Furosemide
↳ initial infusion ⇒ xs vasodil + ↓BP
↳ converted to cyanide + thiocyanate ⇒ Risk of toxicity
↳ admin. of Sodium thiosulphate / hydroxocobalamin (↓ risk of toxicity)

Diazoxide: IV - rapidly ↓ BP - emergencies
↳ w/ furosemide - prevent fluid overload
↳ ↓ use of drug!

⑥ α_1-blockers: ↓ total periph resistance by preventing stimulation of α_1 receptors (resistance vessels of the skin, mucosa, intestine + kidney)
↳ ↓ preload ; NOT to be used as first line agents
↳ effectiveness ↓ in some patients due to tolerance
↳ ↑BP in presence of CHF
↳ admin w/ diuretic & a β-adrenoreceptor antagonist
↳ AE: first dose hypotension, dizziness, lethargy, fatigue, periph oedema, syncope, incontinence

AE: Cough, hypotension, hyperkalemia, angioedema, Renal insuff
Fetal injury (2nd/3rd trimester)
"High-dose captopril" AE - neutropenia, proteinuria & impaired taste

CI: Renal A stenosis, pregnancy,
fluid-depleted patients & premenopausal women, who may become preg.

Classification:

Chemical classi.
① Sulfhydryl group:
Captopril
② Carboxyl-group:
Benazepril, enalapril, lisinopril, quinapril, ramipril, spirapril
③ Phosphoryl-group:
Fosinopril

Pharmacokinetic classi.
① Class I: Captopril-like
Captopril
② Class II: Pro-drug
Fosinopril
③ Class III: Not metabolised
lisinopril

④ Angiotensin Receptor Antagonists/Blockers (ARBs): "...SARTANS"
↳ selective + competitive antagonists of angiotensin II type 1 (AT_1) receptors & DON'T inhibit them.
↳ block receptors → ↑ plasma levels of angiotensin I, angiotensin II + periph. vascular resistance ↓
↳ effective monotherapy.
↳ AE: dizziness, angioedema, fetal injury/death (2nd/3rd trimester),
hyperkalaemia (← due to angiotensin II)
Losartan, valsartan, Irbesartan, Candesartan, Eprosartan

⑤ Peripheral vasodilators: 2nd/3rd line of drugs for ↑BP
↳ relax smooth mus + ↓ total periph resistance ∴ ↓ BP
↳ ↓ in their use - newer drugs => fewer AE + moe effective
Hydralazine: relaxes arteriolar muscle - ↑ K^+ efflux & ↓ Ca^{2+} influx & ↑ NO prod.
↳ chronic ↑BP & in hypertensive crises accomp. acute glomerular nephritis/eclampsia

Prazosin, terazosin, doxazosin
↳ older drugs: phentolamine (parenteral), phenoxybenzamine (P.O)
↳ antagonise α_1 + α_2 - adrenoceptors
↳ ↑BP in the presence of pheochromocytoma

⑦ β-blockers: (Q22 for more details)
↳ Cardioselectivity (β_1, β_2); gradual ↓ when stopping! Sudden = ↑risk of MI + worsen AP
↳ Intrinsic Sympathomimetic Activity (ISA; partial agonistic activity)
↳ affinity for α_1 - adrenergic receptors (labetalol); inhib of renin release
↳ AE: Bronchospasm, bradycardia/heart block
Cold extremities, Raynaud's phe., ↓ exercise tolerance
CNS: sleep disturbances, nightmares
↳ Indications: Younger patients + anxious ones
AP, post-MI
↳ CI: asthma, depression, periph. vascular disease, AV block, CHF, Raynaud's phe.

β-1, 2 - Non-selective:
propranolol, carteolol*, pindolol*, penbutolol* (* w/ ISA → bradycardia, HF, post-MI)
nadolol, timolol, sotalol

β-1-Selective (cardioselective): Pregnancy + DM!
acebutolol*, atenolol, betaxolol, bisoprolol, esmolol, metoprolol

β-1, 2/α_1 selective: labetalol

⑧ Central α_2 - agonists:
↳ ↓ periph resistance, inhibit cardiac func + ↑ pooling in capacitance venules
Methyldopa: its active metabolite = α-methylnorepinephrine = false neurotransmitter (potent)
↳ activates presynaptic inhib α-adrenoceptors + post synap. α_2 adrenocep. in CNS + ↓ symp. outflow; ↓ total periph resistance
↳ ↓ pres. in standing + supine positions
↳ mild - moderate HBP; can be added when diuretic not successful
↳ AE: drowsiness, dry mouth, GI upset, sexual dysfunc.

Clonidine: stimulates post-synaptic α_2-adrenoreceptors in CNS → ↓ peripheral resis.
↳ comb. w/ diuretic
↳ AE: drowsiness, lethargy, dry mouth + constipation
↳ transdermal patch - weekly dosing

⑨ Ganglion inhibitors: (PNS + SNS)
↳ inhibit neurotransmission in autonomic ganglia by competing w/ Ach for ganglionic cholinergic receptor sites – Nicotinic
↳ ↓ periph resistance & venous return
Mecamylamine, Trimethaphan

("ANTIs")

⑩ Adrenergic neuronal terminal inhibitors: (comb. w/ diuretics)
Reserpine: binds to catecholamine storage vesicles in periph + central neurons → making them unable to store/release NE + E → Depression
↳ mild-moderate ↑BP
↳ GI disturbances; CI: in patients w/ a history of depression
Guanethidine + guanadrel: stored in periph neurosecretory granules + released as "inactive" neuroT in place of NE + E
Metyrosine: ↓ Catechol. biosyn. in periph NTs + adrenals by inhibiting rate-limiting enzyme, tyrosine hydroxylase

Interactions: + TCA ⇒ ↓ anti-hypertensive effects
+ MAO ⇒ ↑ ↑BP
+ digoxin, quinidine + β-blockers ⇒ bradycardia, AV block
CI: pheochromocytoma (severe ↑BP)

- NSAIDs
- COX2 - inhib
- non-opoid analgesic
- DMARDS
- Anti-gout

(18) Anti-inflammatory drugs

↳ Reduce inflammation ; make up 1/2 of analgesics, remedying pain by ↓ inflam

Types: ①Steroids - glucocoeticoids - ↓ inflam/swelling by binding to glucocorticoid receptors ; known as corticoids

② NSAIDs (look at Q40)

③ Immune selective anti-inflam derivatives (ImSAIDs)

Prostaglandins:

↳ Synthesis - fm Arachidonic A (20-CFA)

↳ 2 major pathways for synthesis of eicosanoids fm arach. A:

① Cyclooxygenase pathway (eico's w/ ring struc.)

↳ Prostaglandins, thromboxanes + prostacyclines

NSAIDs ⟹ work here + inhibit it ↳ So pathway goes to COX2

↳ COX-1 (ubiquitous + constitutive) + COX-2 (sites of disease + inflam) (Brain, kidney, bone)

COX-2 induced in response to inflam stimuli → leukotrienes are produced ∴ NSAIDs can cause asthma

② Lipooxygenase pathway:

↳ several lipooxygenases act on arach. A to form → 5-HPETE, 12-HPETE + 15-HPETE

↳ convert to corresponding hydroxylated derivatives (HTETE's) OR to leukotrienes / lipoxins

↳ Prostaglandins ⇒ activate / inhibit adenylate cyclase OR stimulate PL-C ↑ DAG + IP_3

↳ func depends on tissue, e.g. ↑ release of TxA_2 fm platelets → recruitment of new platelets for aggregation

↳ other tissues: ↑ TxA_2 ⇒ contraction of smooth mus.

COX 2 inhibitors: Celecoxib, Valdecoxib

↳ lower risk of dev of GIT bleeding no affect on platelet aggregation

↳ AE ↑ risk of ↑BP, renal insuff

Celecoxib → Reversible inhibition + time-dependent

↳ Rheumatoid + osteoarthritis

↳ orally ; CYP450 metab ; urine + faeces ! t½ = 11 hrs !

AE: ab pain, diarrhoea, dyspepsia, renal toxicity

↳ less prone to dev^n of peptic ulcers (compared to diclofenac + ibuprofen)

CI: severe HTN, Chronic Renal insuff, hepatic failure

↳ may have same effects, like aspirin + asthma thingy!

Interactions: inhib CYP2D6 ∴ ↑ levels of β-blockers, anti-depress + anti-psycho

(18) Anti-inflam

Gout

Indomethacin
↳ non-sel COX inhib

↳ acute inflam. arthritis - xs uric A deposition in joints, kidneys (stones), tendons.

↳ Kidneys can't remove uric A from the body

1° gout - genetics 2° gout - medication / bad diet

Acute gout attack

1st line
- NSAIDs - diclofenac, indomethacin (Acetic A derivatives)
- colchicine - mitotic poison
↓
AE: GI upset & neutropenia
high doses ⇒ b. marrow damage → anaemia

CYP3A4 inhib → ↑ risk of colchicine toxicity

MoA: inhibits deposition of uric A crystals
neutrophil mobility & activity → ↓ inflam!

Colchicine + Probenecid ⇒ Gout treatment!

Chronic →

Uricosurics

① Probenecid ⇒ - w/ ATB - last longer
↳ uricosuric - ↑ uric A excretion
↳ binds to organic anion transporter (OAT) → prevent re-absorp of uric A.

can give w/ Paracetamol ⇒ NSAIDs - compete for excretion ⇒ don't mix!

inhibits renal tubular secretion of penicillins - ↑ their t½

② Anti-urates ⇒

Purine analogues

Allopurinol
Enzyme = Xanthine - oxidase
↳ competitive inhib of these

Hypoxanthine → (enzyme) Xanthine → (enzyme) Uric Acid

Oxipurinol

6-mercaptopurine - inhibits xanthine oxidase ⇒ ↑ effect of allopurinol

(19) Anti-psychotics (neuroleptics)

- they are tranquilising psychiatric medication, I' used to manage psychosis (incl. delusions, hallucinations) esp in schizophrenia + bipolar disorder
  - ↳ Hallucinations: auditory, visual, olfactory, gustatory, tactile - Sensory perception in the absence of external stimuli
  - Delusions: misinterpretations of perceptions or experiences

Indications: psychoses, Schizophrenia, Acute mania in bipolar disorder
prochlorperazine → Severe nausea, vomiting, sleeping disorders, anxiety
Huntington's, Tourett's sy, anaesthesiology/neuroleptanalgesia

Main symptoms of schizophrenia:

Positive Symptoms: delusions, hallucinations, disorganised speech + behaviour, catatonic behaviour

Negative Symptoms: affective flattening (restriction of emotional expression)
alogia (general lack of additional, unprompted content in norm-speech)
anhedonia (lack of pleasure)
attention impairment
avolition (general lack of desire, motivation, difficulty or inability to initiate + persist in goal-directed behaviour)

Classification: Conventional or atypical

① Conventional: acc. to oral milligram potency
- doses in mg or tens of mg → ↳ High-potency (Incisive) drugs: piperazine, phenothiazines (e.g. fluphenazine), haloperidol ⇒ more likely to produce extrapyramidal reactions
- doses in hundreds of mg → ↳ Low-potency (Basic/Sedative) drugs: aliphatic phenothiazines (e.g. triflupromazine), piperidine phenothiazines, e.g. thioridazine ⇒ more likely to produce sedation + postural hypotension → blockade of α-adrenoreceptors
  - ↳ central histamine H_1 - blockade.

② Atypical: replaced conventional drugs for initial treatment of first-episode patients, Risperidone, olanzapine
- ↳ Clozapine ⇒ treatment resistant patients

③ Other conventional heterocyclic antipsychotic drugs - loxapine + molindone is intermediate potency; no clear advantage over other conventional drugs

MoA:

↳ Antagonist activity at post-junc. dopamine D_2-receptors, where dopamine norm. inhibits adenylyl cyclase activity
  ↳ Suppression of +ve symp.

Receptor subtypes:

① DA r. - partly sensitive to Adrenaline + noradrenaline
② Family D1 : $D_{1 \& 5}$ ⇒ Coupled to adenylyl cyclase → ↑cAMP → excitatory influence
③ Family D2 : $D_{2,3,4}$ ⇒ coupled to phosphodiesterase (cAMP degradation)
  G_i → ↓cAMP → inhibitory influence

Therapeutic action ⇒ antagonist activity at $5HT_2$-receptors + dopamine D_2 or D_4 receptors
  ↳ best actions ⇒ mesolimbic area (midbrain VTA - nl. accumbens)
    ↳ +ve symp., euphoria
    mesocortical area (midbrain - limbic cortex)
    ↳ −ve symp, cognitive side effects

↳ highly lipophilic + long $t_{1/2}$ (10-20hrs)
↳ hepatic metabolism (microsomal oxidation + conjugation)
  Thioridazine → mesoridazine ⇒ accounts for most of the effects

Conventional drugs:

↳ Aliphatic phenothiazines: Chlorpromazine, Trifluopromazine
↳ Piperidine phenothiazines: Thioridazine, Mesoridazine
↳ Piperazine " : Trifluoperazine, Fluphenazine
  ↳ esterification → depot form
↳ Butyrophenones: Haloperidol
↳ Other related drugs: Loxapine, molindone

Atypical drugs:

Aripiprazole, Clozapine → NO tardive dyskinesia, Olanzapine, Quetiapine, Risperidone, Ziprasidone

AE: CNS - extrapyramidal (EPS) sy ⇒ Acute dystonia
  Akathisia
  Parkinsonian-like sy

CNS (contd) - Tardive dyskinesia - often irreversible (10-20% incidence)
↳ doesn't occur w/ clozapine
Neuroleptic malignant sy - 20% mortality rate
↳ hyperthermia, myoglobinemia, muscle rigidity, diaphoresis
Sedation
Confusional state + memory impairment
Seizures

ANS - orthostatic hypotension + syncope } block of α-adrenoreceptors
impotence + inhib. of ejaculation
dry mouth, constipation, tachycardia } block of muscarinic receptors ∴ atropine-like effect
blurred vision, diff. in urination

Endocrine + metabolic disturbances - gynaecomastia + impotence (men)
galactorrhea, loss of libido (women)
weight gain (H1 receptor antagonist)

OD: rarely fatal, except when caused by thioridazine / mesoridazine
↳ drowsiness, agitation, coma, vent. arrhy., heart block or sudden death

Atypical (2nd gen): without EPS, tardive dyskinesia, prolactinemia, neuroleptic malig. sy.

① MARTA: Multi-Acting Receptor Targeted Agents
Clozapine, olanzapine, quetiapine

② SDA: Serotonin-Dopamine Antagonist
Risperidone, ziprasidone, sertindole

③ D_2/D_3 antagonists:
Sulpiride, amisulpride

④ DSSS: Dopamine-Serotonin System Stabilizers
Aripiprazole

Interactions: Sedative effect in the presence of CNS depressants
↳ some pred. additive anticholinergic effects w/ TCAs, anti-parkinsonian drugs + other drugs w/ anticholinergic activity

(20) Anti-rheumatic drugs

↳ To treat rheumatoid authritis (AI disease)
↳ In the early stages - DMARDs are used = Disease Modifying Anti-Rheumatic Drugs
↳ Strategy of treatment: ① NSAIDs (look at Q40)
② DMARDs
③ 3rd range of anti-rheumatics
↳ Steroid anti-inflam. drugs (glucocorticoids)
↳ Cytostatics + anti-metabolites
↳ Immunosuppresives
↳ Proteolytic enzymes

DMARDs: influence the disease process itself, not only treat symp.
↳ have anti-inflam effects
↳ were borrowed fm the treatment of other diseases, eg. Cancer / Malaria

① Anti-malarial drugs:
Chloroquine
Hydroxychloroquine ⇒ SAARDs - slow acting ARDs
↳ effect is slow acting & not as apparent as that of NSAIDs
↳ inhib of leukocyte chemotaxis

② Thio-compounds of gold: (powerful DMARDs)
Auranorphine ⇒ p.o.
Aurothiomalate ⇒ I.M.
↳ inhib. phagocytosis ∴ the immune response

③ Penicillamin: lessen collagen synthesis
↳ Powerful DMARD

④ Sulphasalazine: Powerful DMARD
↳ E. coli metabolises it, in the colon → Aminosalicyclic A ⇒ inhibits COX

NSAIDS:

↳ Symptomatic relief of both inflam + pain
↳ limited effect on the progressive bone + cartilage loss.
↳ slow the body's prod of prostaglandins
↳ Ibuprofen, naproxen & indomethacin

3rd range Anti-rheumatics:

① Steroid anti-inflam drugs:

↳ Synthetic analogs of cortisone
↳ ↓ inflam + suppress immune sys (I.S.) activity
↳ Glucocorticoids / corticosteroids: Prednisone + dexamethasone

② Cytostatics + anti-metabolites:

↳ if treatment w/ NSAIDs + SAARDs have no effect
↳ Methotrexate, azathioprine, cyclophosphamide

③ Immunosuppressives:

↳ stabilising effect on the I.S.
↳ Since inflam assoc. w/ chronic arthritis is due to malfunc of the I.S. - these drugs are beneficial.
↳ Cyclosporin A

④ Proteolytic enzymes

↳ Bromelaine, papaine, trypsine

↳ DMARDs - usually used in combination - & smaller doses when combined ∴ ↓ risk of AE
↳ NSAID + DMARD (+ sometimes glucocorticoid)
↳ discontinuing DMARD - may reactivate disease OR cause "rebound flare"

(20) Anti-rheumatic

- Rebound flare => when u stop taking DMARDS, disease reactivates!

(1) NSAIDS - ↓ inflam + pain
↳ inhib PG synth
e.g. ibuprofen, indomethacin

(2) DMARDS → slow progression of disease
Used in combo. => ↓ risk of AE

(1) Anti-malarial - Chloroquine / hydroxy => inhib leukocyte chemotaxis
CI: porphyria, psoriasis
↑ for ppl unresponsive to NSAIDS
orally ; urine excretion
AE: GIT disturbances, headache, skin rash

(2) Thio comps of gold ⇒ Auranofin, Aurothiomalate ⇒ inhib phago -> slows disease + prevents further damage
IM, orally
* Macros take up gold →
+ lysosomal enzyme activity
urine, faeces
AE: proteinuria, aplastic anaemia, nephrosis
CI: preg, hepatic/Renal disease

(3) Sulfasalazine - inhibs Cox
(Sulfonamide) ↳ E. coli metabolises this drug → 5-aminosalicylic A.

(4) Penicillamine - ↓ collagen synthesis
↳ After failure of gold salts + before glucocort.

(3) Others - (1) Glucocort - Prednisone
(2) Cytostatics +
Anti-metab - Methotrexate
↓
if NSAIDS + anti-malarials have NO effect

(3) Immunosup - cyclosporin A => stabilise l.s

(4) Proteolytic enz - trypsine, papaine, bromelaine

(21) Anti-viral drugs

MoA: ① Inhib. of penetration or/& uncoating ⇒ Amantadin
② Selective inhib. of enzymes specific for viral genome replication ⇒ Virostatic anti-metabolites - Acyclovir, Ganciclovir, Zidovudin
③ Inhib. of translation of viral mRNA ⇒ Interferons

Groups: ① Anti herpes
② Anti-influenza
③ Anti-retroviral
④ Others

① Anti-herpetic agents:

① Virostatic antimetabolites: false nucleoside = synthetic nucleoside analogs
↳ drug is activated by 3 phosphorylation steps (needs viral enzymes)
↳ Acyclovir, Valacidovir, famciclovir, gancidovir, idoxuridin, trifluridin, dihydroxypropyladenin

① Acyclovir: Guanosine analog
↳ selective for infected cells
↳ HSV, VZV ; crosses BBB
↳ topical, p.o., i.v. ; partially metabolised → urine
local irritation

② Gancielovir: Guanine analog + less specific → eye, lung infec
↳ Indications: severe infec. caused by CMV in immunocomp. ppl
↳ inhibits replication of CMV
↳ AE: blood disorders, upto 40% - anaemia, neutropenia, thrombocytopenia
GIT, psychosis, cramps, coma
teratogenous

③ Valaciclovir: Aciclovir pro-drug ; ↑ bioavail by 50%

④ Famciclovir: prodrug → penciclovir
↳ VZV, genital herpes

⑤ Idoxuridin: toxic! - also affects host cells.
↳ Supery. therapy in ophthalmology

⑥ Trifluridin: topical treatment of eye infec + chronic skin lesions

⑦ Cidofovir: HSV-1+2, EBV, ~~VZV~~ VZV, CMV retinitis in patients w/ AIDS + HSV resistant to aciclovir
↳ AE - nephrotoxicity

⑧ Dihydroxypropyladenin:
↳ oral HSV

② Enzyme inhibitors:
↳ inhibits viral DNA polymerase directly by reversibly but non-competitively binding to the pyrophosphate binding site

① Foscarnet: CMV retinitis + acyclovir resistant HSV infec. - IV
↳ acts synergistically w/ ganciclovir
↳ immunodef. patients
↳ give freq. to prevent relapse when plasma levels fall
↳ urine: not metabolised
↳ limited due to nephrotoxicity + hypocalcaemia related symp - arrhythmias, paresthesia + seizures ↓[K^+], ↓[PO_4^{3-}], ↓[Mg^{2+}], anaemia, nausea, fever

② Anti-influenza drugs:

① Inhibition of uncoating: inhibition of membrane H^+ channel → prevents entering of virus NA into the cell + lining up of new virions near the mem.
↳ prophylaxis of influenza A ; orally ; urine
↳ upto 30% of patients rapidly develop resistance.
↳ treatment of influenza A when admin. within 48 hours of symp.
↳ mild CNS effects - nervousness, insomnia & GI dysfunc. (seizures, dizziness, ataxia)

Amantadine → methylderivate rimantadine → partially metabolised
crosses BBB ← / not metabolised
↳ don't admin in preg + lactation

② Anti-metabolites: Ribavirin - partially metabolised → urine
↳ Synthetic analog of guanosine
↳ MoA not clear but inhibits inosine monophosphate dehydrogenase & viral DNA + RNA polymerases
↳ in form of an aerosol to treat RSV (Severe) ; oral, IV
↳ AE: bronchial irritation, anaemia, ↑ bilirubin

③ Inhibition of neuraminidase: inhibits releasing of new virions fm host cell
↳ Zanamivir & Oseltamivir (Tamiflu) : acute uncomplicated influenza infec
↳ influenza A + B
↳ start treatment in first 48hrs, prophylactic treatment

③ Anti-retroviral drugs:

↳ HIV → AIDS ⇒ ↓ CD4+ T-lymphs ⇒ immunodef.

↳ Therapy of AIDS: ① anti-retroviral therapy
② Therapy of accomp. opportunistic infec / tu.

↳ can't completely treat HIV infec but minimalise / postpone symp.

↳ combined therapy is used = HAART - highly active anti-retroviral therapy

↳ dev. of resistance ↙

↳ Combination: 2 nucleoside analogs + 1 protease inhib
Zidovudin + lamivudin + indinavir

↳ Classical group of drugs:

↳ RT inhibitors - ① Nucleoside anti-retrovirotics: Zidovudine, Stavudine, Zalcitabine, lamivudine, didanosine

Nucleotide anti-retrovirotics: Tenofovir

② Non-nucleoside anti-retrovirotics: Nevirapine, Delavirdine, Efavirenz
↳ ↓ vertical transmission

② ↳ Protease inhibitors: Indinavir, saquinavir, ritonavir, nelfinavir

① Nucleoside reverse transcriptase inhibitors (NRTIs):

↳ oldest group ; need to be phosphorylated to be active

↳ competitive inhib. of viral RT - blocks replication ⇒ prevent infec. but don't clear already infected cells.

↳ AE: GIT intolerance + myelosuppression

Zidovudine: first drug postponing manifestation of AIDS

↳ ↓ risk of opp infe + infec of fetus in preg women (vertical trans) (↓ by 25%)

↳ dose limiting toxicities ⇒ anaemia + granulocytopenia

Nucleotide RTI: Tenofovir

↳ prodrug - metabolised into nucleoside analog

↳ in patients resistant to NRTI

② Non-nucleoside RTIs (NNRTIs):

↳ inhib of RT is by changing its conformation

↳ don't need phosphorylation for their activity

↳ if not used in comb, resistance devs.

③ Protease Inhibitors:

↳ bind to active site of HIV protease + inhibit its func → blockage of completing the capsid + release of virions (inactive ones formed)

↳ affects assembly of new virions

↳ very effective + well tolerated

↳ used in comb. w/ nucleoside analogues to delay + possibly reverse the clinical progression of AIDS.

↳ po admin.

↳ AE: GIT intolerance

New groups of drugs: Fusion inhibitors (FI): Enfuvirtide

↳ blocks entry of virus into the cell by binding to viral gp41

↳ subcutaneously - injec. site reactions.

↳ used in multiresistant patients

↳ very exp. (US$ 25,000 a yr)

Integrase inhibitors: Raltegravir

Entry " : Maraviroc

Maturation " : block the conversion of the polyprotein into the mature capsid prot⁻

↳ virions released are non-infectious particles

↳ under investigation - Bevirimat

④ Others: Interferons

↳ cytokines / messengers - affect infected cells

↳ made by recombination

↳ 1hr after penetration of viral NA → infected cell prod. INF → receptors of nearby cells → translation of inhibitory prot⁻ = VIROSTATIC, ANTIPROLIFERATIVE, IMMUNOMODULANT EFFECT

Similar antiviral effects:

- ∝ - prod. by leukocytes; stim by viruses, bac or mitogens
- β - prod by fibroblasts after stim by viruses + inhib. of NA + prot⁻ synthesis

immunomodulant:

- γ - prod by NK cells + T cells after stim by antigens, mitogens & cytokines

Indications: Chronic hep B/C
severe infec - encephalitis, generalised herpes zoster
treatment + prevention of viral infec in immunodef. patients (Kaposi's Sarcom leukaemia
tumours + AI diseases

AE flu-like symp, leukopenia, GIT, skin

Gammaglobulin: fraction of plasma of healthy ppl, rich wl Ig - IgG - imp. against viral infec
↳ inhibition of penetration
↳ prophylaxis - I.M. in early stages of infec to modify progress of diseases (hepatitis, polio, rabies)
Indications: prevention / treatment of CMV, HBV, RSV, VZV, rabies
AE: Ig= prot → allergy + anaphylaxis

* non-selective SL don't affect α & β receptors; ONLY α OR β *
(unlike non-selective SM)

(22) β-blockers pg 180

↳ aka β-adrenergic blocking agents, β-adrenergic antagonists or β-antagonists
↳ Cardiac arrhythmias, cardioprotection after MI & ↑BP
↳ sympathomimetic drugs => subs. that mimic the effects of the catecholamines (adrenaline, noradrenaline &/or dopamine)

↳ Act at the post-ganglionic sympathetic terminal by:
① directly activating post-synaptic receptor
② blocking breakdown & re-uptake
③ stimulating synd + release of catecholamines

β_1 receptors => heart + kidneys
β_2 " => lungs, GIT, uterus, liver, vascular SM cells & skeletal mus
β_3 => fat cells.

↳ Direct: β => isoprenaline
→ selective β_1 - dobutamine
→ selective β_2 - anti-asthmatic, tocolytic
↳ Indirect:

DIRECT:

Isoprenaline
β => ↑ systolic BP; vasodil + ↓ diastolic BP
↳ Indications: cardio-stimulant, broncho-obstructive disorders
↳ AE: high doses = myocardial necrosis, tachycardia + dysrhythmias

Selective direct β_1 SM:
① Dobutamine: dopamine derivative
↳ main effects on β_1; doesn't affect D!
↳ +ve ionotropic effect
↳ Doesn't affect periph resistance
↳ ↑CO without ↑ of HR!!
Indications: cardiogenic shock
dobutamine stress test - mimicking exercise

Selective direct β_2 SM:

↳ treatment of asthma, bronchial obs + tocolytic drugs

↳ not absolute selectivity !, AE in heart => tachyarrhythmias, ischaemia, ↑ of glycaemia

↳ risk of AE in patients w/ CVS diseases, treated by tricyclic anti-depressants, diabetics

↳ in ASTHMA => combined w/ anti-asthmatic glucocorticoids (← prevents β_2-down regulation)

Anti-asthmatics:

① Short-acting: p.o., inhalation, injections
↓ effects in few mins, lasts 3-6 hrs

↳ acute asthma

↳ Salbutamol (albuterol), terbutalin, hexoprenaline, phenoterol

② Long-acting: p.o., inhalation, retarded form

↳ chronic / night asthma

↳ Reproterol, salbutamol retard

↳ Salmeterol, formoterol, clenbuterol → affects skeletal mus.: can be used as an anabolic steroid

↳ longer $t_{1/2}$ => 12-30 hrs!

Tocolytics:

↳ possible adverse cardiovascular effects

↳ phenoterol, ritodrine, hexoprenaline

START here!

SYMPATHOLYTICS: - inhibit post-gang. func. of the SNS

↳ Direct: nonselective β

↳ selective β_1 (β-blockers)

↳ " β_2 (not used!)

Clinical use ↑BP, angina (typical), MI, CHF, cardiac arrhythmias (supraventricular tachycardia), hyperthyroidism, migrane prophylaxis & wide angle glaucoma

Diuretics

-ve ionotropic!

Effects: most imp ⇒ HEART!
- ↓ HR, conduction (↑ AV conduction time), contractility, excitability
- ↓ O_2 requirements of myocardium
- ↓ release of renin in kidney
- ↓ BP in ↑BP but not norm BP! (no postural ↑BP)
- inhib. of SL effect in patients w/ COPD / Asthma.
- Metabolism ⇒ AE - inhib. of glycogenolysis & lipolysis ⇒ ∴ ↑ VLDL, TAG & K^+ ⇒ hypoglycaemia

AE: cardiac insufficiency
AV blocks, arrhythmias + asystole
hypotension
bronchoconstriction
insuff. periph. perfusion
hyperkalaemia, hypoglycaemia
↑ allergic reactions
rebound phenomenon
insomnia, depression

Non-selective β SL: ∴ at β_1 & β_2!

① **without ISA** = competitive antagonists
- Sotalol, metipranolol, Propranolol:
  - long term therapy of ↑BP; supraventricular & ventricular arrhythmias - IV emergency of arrhythmias
  - 90% bound to plasma prot
  - hepatic metabolism ∴ prolonged action in liver disease.

② **with ISA** = (Intrinsic) Inner Sympathotropic Activity ⇒ show both antagonism + agonism at a receptor, depend on the conc of the agent & conc of the antagonised agent
- less AE (↓ bradycardia, -ve inotropic effect + metabolic effects)
- non-selective antagonists w/ partial β_2-receptor agonist activity
- Pindolol, bopindolol, oxprenolol, alprenolol, cloranolol, penbutolol

Selective β_1 SL : Cardioselective

↳ some advan. over non-selective β-adrenoreceptor antagonists to treat CVS diseases in asthmatics

Without ISA

↳ Atenolol => kidney elim ; little hepatic metabolism
↳ little LA activity ; poorly enters the CNS.
↳ Betaxolol => topical ; chronic open angle glaucoma
↳ Esmolol => ultrashort acting ($t_{1/2}$ = 10mins) ← extensive plasma hydrolysis by esterases ; IV infusion
↳ Metoprolol => also avail. in sustained release preparation
↳ Bisoprolol, nebivolol, talinolol

With ISA

↳ Acebutolol => partial agonist activity
↳ Celiprolol => ISA on β_2 → vasodil.

Eye = glaucoma — ↓ intraocular press.
↳ Topical application of => timolol, betaxolol, levobunolol + carteolol
sufficient can be absorbed after topical app to ↑ airway resistance & ↓HR+ contractility

Other uses:

Propranolol => control clinical symp. of sympathetic overactivity in hyperthyroidism
↳ prophylaxis of migraines
↳ relieves acute anxiety + panic symp by inhib overactivity of the SNS.

CI: chronic HF
Asthmatics
AV block
Raynaud's phenomenon

(23) Calcium channel blockers

↳ MoA: block L-type (slow) Ca^{2+} channels → ↓ contractile force + O_2 requirement
↳ Block voltage dependent Ca^{2+} channels
↳ ↓ cytosolic Ca^{2+} → heart = ↓ contractility; vessels = ↓ contraction of vascular smooth muscle
↓ periph. resistance ← ↳ Relax arteries / vasodil + relief of spasm (Prinzmetal's angina)
↳ dilate periph. vessels + ↓ cardiac afterload

Properties: orally ', IV - within mins!
↳ variant + chronic stable angina - where nitrates are ineffective or when β-adrenoreceptor agtagonists are C!!
↳ no ↑ in serum lipids.
↳ cause hypotension + oedema — -ve ionotropic effect

Uses: Angina
Hypertension
Supraventricular arrhythmias
Cerebral haemorrhage

AE: Dizziness, nausea
Headache, flushing, hypotension, oedema
Arrhythmias, reflex tachycardia
Gingival inflam.

Classes:

① Dihydropyridine: often used to ↓ systemic vascular resistance + arterial press.
↳ NOT (except amlodipine, nicardipine + nifedipine) for angina ⇒ because vasodil + hypotension → reflex tachycardia
↳ can worsen proteinuria in patients w/ nephropathy.
↳ Suffix "-dipine"
* Amlodipine, nicardipine, nifedipine,

② Non-dihydropyridine:

① Phenylalkylamine: selective for myocardium, ↓ myocardial O_2 demand + reverse coronary vasospasm

↳ Angina treatment!

↳ minimal vasodil. effects compared w/ dihydropyridines

↳ mechanism: causing -ve inotropy

↳ Verapamil: slowed conduction through the AV node (unwanted in HBP treatment)

↳ may prod. AV block when used in comb. w/ β-adrenoceptor antagonists

↳ Toxic effects: myocardial depression, HF + oedema.

↗ IV, oral

② Benzothiazepine: intermediate class between phenyl. & dihydro. in their selectivity for vascular Ca^{2+} channels.

↳ Cardiac depressant + vasodil actions => ↓ arterial pres WITHOUT prod. the same degree of reflex cardiac stimulation.

↳ Diltiazem: variant (Prinzmetal's) angina, either naturally occurring or drug-induced & stable angina.

(IV)

③ Non-selective: incl. mibefradil
bepridil
fluspirilene
fendiline

㉔ Cancer chemotherapeutics

Anticancer drugs = chemotherapeutics = cytostatic / cytotoxic drugs
↳ drugs used in therapy of all types of cancer disease

Chemoprotective subs => protect somatic cells against the toxic effect of chemotherapeutics = mesna, AcCys, dexrazoxane

Sites of action:
① interference w/ DNA/RNA: alkylating + intercalating agents, inhibitors of topoisomerase, radiomimetics
② Antimetabolites: pyrimidine + purine analogues, folate antagonists
③ Interference w/ microtubules
④ hormones
⑤ others

Classification:
↳ w/ regard to:
① cell cycle: cell cycle specific (CCS) → phase specific
" " non- " (CCNS) → phase non-specific
② chemical structure
③ principle of action: alkylating agents + related compounds
intercalating agents
antimetabolites
inhibitors of topoisomerases I & II
hormones
miscellaneous agents

AE:

EARLY
nausea, vomiting
fever
sweating
allergic reaction

RETARDED
myelotoxicity
GIT toxicity
alopecia
local toxicity / reproductive toxicity
dev. of resistance
2° malignity

① Alkylating agents + related compounds: ↳ cell cycle non-specific ⇒ more toxic in cells that are rapidly dividing

↳ MoA: forms covalent bonds to cell structures (DNA)

↳ AE: myelotoxicity, vomiting, 2° malignity ⇒ mutagenic + carcinogenic ⇒ also for AI diseases - lupus nephritis + arteritis

↳ Members: Nitrogen mustards: Cyclophosphamide, ifosfamide (crosses BBB), chlorambucil, melphalan Hodgkins + other lymphomas; orally ⇒ liver metab (almost fully) → bile + urine; (IV) possible

(IV) preferred { Nitrosoureas: Carmustine (BCNU), lomustine (CCNU), streptozocine
Platin complexes: Cisplatin, Carboplatin, oxaliplatin
Procarbazine, dacarbazine
Busulphan

Mesna = adjuvant, given w/ cyclophos + ifosfamide ⇒ ↓ incidence of haemorrhagic cystitis & haematuria

↳ Cyclophos + ifosfamide ⇒ converted to urotoxic metabolites

② Intercalating agents: (Antibiotics) bind to the phosphate backbone & to the bases - prevent winding of DNA

↳ MoA: non-covalent bonds; intercalates between adjacent guanosine-cytosine base pairs of DNA; cell cycle specific; (IV); bile + urine; Dactinomycin partially metabolised; poorly crosses BBB

↳ AE: prev-side

↳ Members: Anthracyclines: doxorubicin: most used anticancer agent comb w/ other drugs

↳ myelosuppressive; blocks DNA + RNA synthesis by causing uncoiling

↳ Hodgkins + non-Hodgkins, Breast ca, bladder ca + multiple myeloma

Daunorubicin + idarubicin: Acute lymphocytic + myelogenous leukaemias

Epirubicin: early stage + metastatic breast ca.

Valrubicin: u. bladder ca.

Mitoxantrone: prostate cancer + non-Hodgkin lymphoma.

Actinomycin D: phase non-specific

↳ impairs RNA synthesis, lesser extent - DNA synthesis

↳ IV infusion ↳ Dactinomycin + Vincristine

↳ rhabdomyosarcoma, Wilms' tu, gestational trophoblastic tu, metastatic testicular ca + Ewing sa. ↳ Dactinomycin + MTX

Doxorubicin & Daunorubicin ⇒ non base pair specific

③ Inhibitors of topoisomerases:

Topoisomerase I: enzyme that allows relaxation + replication of specific regions of supercoiled DNA

Topoisomerase II: cut both strands of the DNA helix simultaneously, to unwind it

→ DNA damage results.

↳ Members: Topoisomerase I: Topotecan ⇒ ovarian cancer + small cell lung ca.
Irinotecan ⇒ metastatic colorectal ca.

Topoisomerase II: Etoposide ⇒ testicular tu
↳ in comb. w/ Cisplatin ⇒ AML + small cell lung ca.
Teniposide ⇒ ALL (Acute lymphocytic leukaemia)

double stranded DNA breaks

↳ block cells at the entry of the S phase + prevent entry into the G_2 phase
↳ IV route ; dose limiting toxicity = leukopenia

④ Anti-metabolites:

↳ S-phase specific drugs + structural analogues of essential metabolites → interfere w/ DNA synthesis ; myelosuppression = dose-limiting toxicity

① Folate antagonists: Methotrexate (MTX), Trimetrexate

↳ inhibit dihydrofolate reductase (DHFR) → indirect inhib. of DNA synthesis
↳ MTX - also inhib. RNA + prot synthesis
↳ orally, IV, IM or intrathecally
↳ enters cells via folate carriers OR if in high conc - diffusion
↳ Childhood Acute lymphoblastic leukaemia, choriocarcinoma + trophoblastic tu. in women
↳ useful in comb. (5-FU) for Burkitt's lymphoma, non-Hodgkin lymphomas, osteogenic sarcoma, lung ca, head + neck ca.
↳ AE: nephrotoxicity + hepatotoxicity

Folic A —DHFR→ Tetrahydrofolic A

Antagonist ⇒ Leucovorin (in MTX OD/ Acute)

② Purine analogues: 6-mercaptopurine, 6-thioguanine, fludarabine, azathioprine (immunosuppressant), cladribine, pentostatin

↳ MoA: antagonism of purine bases + enzymes = defect of transcription + replication of NA + dysfunctional prot

↳ 6-mercaptopurine: orally ; incorporated into DNA + causes base mispairing
↳ ALL + AML ; Crohn's disease AE: Nephrotoxicity + myelotoxicity
↳ 6-thioguanine: orally ; incomplete absorption
↳ remission reduction + maintenance of AML
↳ Cladribine: adenosine analogue ; DNA strand breaks + loss of NAD
↳ hairy cell leukaemia + non-Hodgkin lymphoma
↳ ↓ CD4 + CD8 counts - transient effect ; IV admin

Adenine, Guanine

↑effect by inactivating xanthine oxidase (allopurinol)

=> Thymine & Cytosine & uracil

③ Pyrimidine analogues: leucovorin - "rescue" b. marrow + GIT mucosa

↳ MoA: incorporation to DNA or inhibition of replication enzymes

↳ AE: myelosuppression, myelotoxicity, GI disturbances

↳ 5-fluorouracil (5-FU): (non comp) inhibits thymidylate synthase → No thymidine → no DNA synthesis

Synergises w/ MTX

↳ parenterally, topically - skin cancers; Admin w/ leucovorin (IV)

↳ solid ca. - breast, + GI ca., metastatic colon ca

↳ Topically - pre-malig. keratoses + superf. basal cell ca.

↳ Cytarabine: accum. of one of its metabolites → inhibits the activity of DNA polymerases

↳ most active in the S phase

↳ IV continuous infusion OR intrathecally (poor / unpredictable oral absorp)

↳ remission in acute leukaemia, esp AML, non-Hodgkins lym.

↳ Gemcitabine: inhibits DNA synthesis via chain termination

↳ IV agent; pancreatic cancer, small cell lung ca + bladder cancer

③ Inhibitors of mitosis:

↳ MoA: interact w/ mitotic spindle

Vinca alkaloids: AE: neurotoxicity, myelotoxicity

↳ fm periwinkle plants; bind to β-tubulin

↳ most active during metaphase - M-phase specific

↳ Vinblastine: IV admin

↳ Vincristine: IV " + less toxic

↳ dose limiting toxicity - periph. neuropathies

↳ Vindesine, Vinorelbine: orally

Taxanes: AE: neurotoxicity, bradycardia, granulocytopenia

↳ fm pacific yew

↳ Paclitaxel + docetaxel.

④ Inhibitors of protein synthesis: Asparaginase, crisantaspase (IM, IV)

↳ MoA: Asn ⇸ Asp + NH_3 (Asparagine → Aspartate + NH_3)

↳ AE: allergic reaction, neurotoxicity, hepatotoxicity, pancreatitis

NOT myelosuppressive OR GIT toxic

(5) Hormones + hormone antagonists:

(1) Androgens: antagonism of oestrogens
- AE: Na^+ retention, hepatotoxicity, virilisation
- comb. w/ anti-oestrogens
- Testosterone, fluoxymesterone

(2) Anti-oestrogens:
- AE: flush sy, nausea
- Tamoxifen

(3) Anti-androgens: antagonism of androgens
- AE: gynaecomastia
- Cyproterone, flutamid, nilutamid, bikalutamid

(4) Oestrogens:
- AE: moobs, thromembolia, Na^+ retention
- Ethinylestradiol

(5) Inhibitors of gonadoliberin (Gonadotropin releasing hormone):
- MoA: ↓ release of sex hormones
- AE: flush sy, myalgia, osteoporosis
- Leuprolid acetate, goserelin, buserelin

(6) Inhibitors of aromatases:
- AE: swelling, myalgia, arthralgia
- Aminoglutethimide, anastrozole

(7) Glucocorticoids: inhibition of lymphocyte prolif.
- Prednisone, dexametazone.

(6) Biological therapy: uses natural protection of I.S.
- more specific to tu. cells = low AE + diff AE to cytostatic drugs
- Effects: Slower tu. prolif., ↓ invasivity of ca. cells, higher resolution of cancer cells for I.S.

① Anti-angiogenic therapy:
↳ tu. prod VEGF + new vessels ∴ block sufficient tu. perfusion
↳ influences vessels in the whole body
↳ Sorafenib, Sunitinib, Temsirolimus, Bevacizumab

② Differential therapy:
↳ induces cell differentiation + ↓ speed of proliferation
↳ Bexaroten: retinoid - analogue of vit A
↳ capsules
↳ Treti'noin: all-trans retinoic A.
↳ induces diff. of malignant promyelocytes = remission of acute promyelocytic leukaemia

③ Inhibitors of proteasome:
↳ intracellular signal chaos = cell death Bortezomib

④ Inhibitors of tyrosine kinases:
↳ inhib. of intracellular signal transduction
↳ block growth stimulus + cell death
↳ selectivity to diff. types of tyrosine kinases = selectivity to diff receptors
↳ Erlotinib, Lapatinib

⑤ Monoclonal Atbs: usually humanised
↳ focused against specific antigen
↳ Alemtuzumab = CD52
Bevaci'zumab = EGFR = Cetuximab
IBRITUMOMAB tiuxetan = CD20 = Rituximab
Trastuzumab = HER receptor

⑥ Immunomodulating cytokines: Changes activity of diff tissues or immune cells
↳ suppress tu. growth OR stimulation of I.S. activity
↳ INF-α, Imiquimod, aldeseleukin - interleukin 2

⑦ Vaccines: causes prod. of specific atb against target structures (receptor on oncoviruses)
↳ against HPV

(25) CNS stimulants

Stimulants ⇒ psychoactive drugs, which induce temporary improvements in either mental or physical func. or both.

↳ Common effects ⇒ alertness, awareness, wakefulness, endurance, productivity & motivation, ↑ arousal, locomotion, HR & BP

↳ perception of ↓ requirement for food + sleep

Indications ⇒ counteract ↑ lethargy + fatigue throughout the day - work, other ach.
↳ sleepiness + keep the person awake when necessary + treat narcolepsy
↓ appetite + promote weight loss (treat obesity)
improve concentration + focus.
occasionally ⇒ treat clinical depression

Psychomotor stimulants ⇒ all mentioned below.

(Theobromide) → Methylxanthines ① **Caffeine**: mild stimulant compound - tea, coffee, cocoa, chocolate, soft drinks — stimulates the cortex + other areas
Contained in Coffee
↳ most widely used drug. MoA: inhibit phosphodiesterase ⇒ no degradation of cAMP + cGMP → ↑ cAMP + cGMP → PK activation → phosphorylate Lipase → LIPOLYSIS
↳ part of some medications - to enhance the 1° ingredient OR ↓ its AE (esp. drowsiness)

② **Nicotine**: part of tobacco + various gases (e.g. CO, Hydrogen cyanide, nitrosamines)
↳ MoA: mimics the action of Ach at cholinergic nicotinic receptors of ganglia, skeletal mus + CNS. low doses - ggl stimulation; high " - ggl inhibition
↳ volatile liquid alkaloid - well absorbed fm the lung + rapidly distributed
↳ hepatic metabolism - rapid! $t_{1/2}$ = ~1hr
↳ early stages: nausea, vomiting
↳ ↑ psychomotor activity + cognitive func; ↑ release of adrenal catecholamines + ADH; ↑ HR + BP; ↑ tone + secretions of GIT
↳ AE: lung cancer, Cancer of oral cavity, bladder, pancreas
obstructive lung disease, coronary artery disease + peiph. vascular dis.
↳ Tolerance: devs. rapidly
↳ 1° cellular; some metabolic tolerance
↳ Dependence: strong psychologic dependence - activates the "brain reward sys" ⇒ ↑ activity of dopamine in the nl. accumbens
↳ withdrawal like symp, occurs within 24hrs & persists for weeks → months

↳ dizziness, tremor, ↑BP, drug craving, irritability, anxiety, restlessness, diff in conc, drowsiness, headache, sleep disturbances, ↑ appetite, GI complaints, nausea + vomiting

↳ Medications + replacement therapies: Nicotine polacrilex - nicotine resin in gum.

↳ Transdermal patch: local skin irritation = prob.

↳ Nasal spray: local irritation of the mouth + throat

B2D + Neurdep in withdrawal symp.

↑ physical + emotional dependence.

③ Cocaine: forms a complex w/ the transporter ∴ accumulates in synaptic cleft ↑

↳ MoA: blocks the dopamine (+NE + 5HT3) transporter in CNS → inhibits reuptake of dopamine into nerve terminals in the mesolimbic pathway, that incl. the "brain reward" centre

↳ inhaled (snorted), smoked (crack cocaine); produces a "rush"

↳ t½ = ~ 1hr

↳ plasma + liver cholinesterase metabolism

↳ LA for ENT surgery (+ ophthalmology) - only one w/ inherent vasoconstrictor activity

↳ OD: hypertensive crisis w/ cerebrovascular haemorrhage + MI

Short term + AE + Tolerance + dependence (Cocaine + amphetamine)

↳ euphoria, ↑ wakefulness, alertness, self-confidence + ability to concentrate

↳ ↑ motor activity + sexual urge + ↓ appetite

↳ AE: anxiety, inability to sleep, hyperactivity, sexual dysfunc, dangerous behaviour followed by exhaustion ("crash")

↳ Toxic psychosis: paranoia + tactile + auditory hallucinations

↳ Reversible or permanent

↳ Necrotising arteritis: due to amphetamine

↳ brain haemorrhage + renal failure

↳ Perforation of nasal septum (- snorting coke)

↳ Cardiac toxicity - cocaine + ethanol ⇒ cocaethylene

↳ Fetal abnorm + early childhood disabilities - "cocaine babies"

↳ OD: tachy, ↑BP, hyperthermia + tremor

seizures, coronary vasospasm, arrhythmias, shock + death

↳ Tolerance + Dependence: Strong ↑ dependence devs

↳ tolerance devs.; withdrawal like symp - long periods of sleep, ↑ appetite, anergia, depression + drug craving

④ Amphetamines: — indirectly acting adrenergic agonist

NE, E + dopamine

↳ MoA: blocks the uptake of biogenic amines

↳ Major effect: ↑ the release of pre-junc neuronal catechol. incl. dopamine + NE.

↳ weakly inhibits MAO_{A+B} → ↓ dopamine, NE + 5HT degradation

↳ Taken in the form of methamphetamine - orally, IV, smoked ⇒ "ice"

↳ Therapeutic uses: Methylphenidate (Ritalin)

↳ ① ADHD: ↓ behavioral probs, aggression, noncompliance + negativity assoc. w/ ADHD

↳ ② Narcolepsy ⇒ methyl Amphetamine - ↑ in wakefulness + sleep latency.

Acts as a ligand for DAT (dopamine transporter) + slows reuptake by a 2° mechanism via phosphorylation of DAT

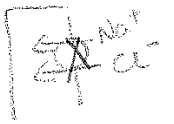
Hallucinogens: ① LSD - Lysergic A diethylamide - 5HT$_{1,2}$ receptor agonists, activate SNS (↗ Haloperidol = antagonist)

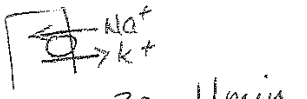
② Cannabis (Tetrahydrocannabinol) - CB_1 recep → G prot

③ PcP - Phencyclidine

(27) Diuretics : Indications : Congestive HF, oedema, ↑BP

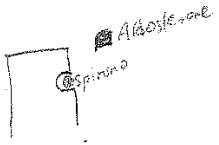
① Thiazide diuretics: Chlorothiazide, hydrochlorothiazide – 1st line of choice
- ↳ distal tubules ⇒ block Na^+/Cl^- symporter → ∴ ↓ Na^+ reabsorp + H_2O + Cl^-
- ↳ ↓ vol → ↓ CO + preload / Chronic use – ↓ periph vascular resistance
- ↳ orally ; combined w/ ACE, K^+-sparing OR β-blockers
- ↳ AE: hypokalaemia, ↓S hypovolaemia, hyperglycaemia, hypersensitivity, hyperuricaemia, hypercholesteroamia
  - ↳ collecting ducts ⇒ Na^+ reabsorbed, K^+ excreted





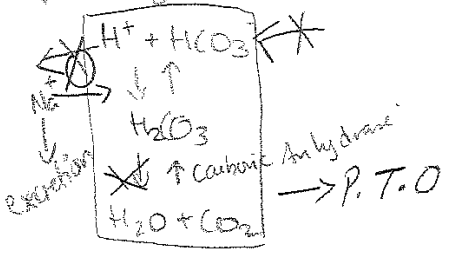
CI: hyperlipidemia, gout, sexually active males, GFR < 30ml/min

② K^+ sparing diuretics: Spironolactone (renew HF), Amiloride
- ↳ comb. w/ thiazide/loop diuretics ; 2nd line hypertensives
- ↳ MoA: Block Na^+ channels ∴ less Na^+/K^+ exchange (in the collecting ducts)
  (Spironolactone) Competitive antagonist w/ Aldosterone for cytoplasmic receptor sites → ∴ ↓ Na^+/H_2O reabsorption + ↓ K^+ secretion in collecting ducts
- ↳ use in CIRRHOSIS



③ Loop diuretics: Furosemide
- ↳ Loop of Henle ⇒ inhibits $Na^+/K^+/2Cl^-$ symporter
- ↳ ppl w/ chronic renal disease + when thiazides don't work
- ↳ orally ; 2nd line
  AE: hypo K^+, hypo Mg^{2+}, ↓$[Ca^{2+}]$, ↓$[Na^+]$, ↓$[Cl^-]$, hyperglycaemia, hyperuricaemia, dehydration

④ Carbonic Anhydrase Inhibitors: Acetazolamide, Methazolamide Rarely used! mainly → ↓prod. of aq. humour ↳ ∴ ↓ intra-ocular pressure



→ P.T.O

- ↳ prox. tubule ⇒ ↓ HCO_3^- (bicarbonate) reabsorption + ↓ Na^+ uptake ∴ no H^+ excretion
- ↳ CI: CIRRHOSIS
  AE: metabolic acidosis, ↓$[K^+]$, renal stone (urine alkalinity ↓ Ca^{2+} salts)

(5) Osmotic agents : Mannitol, urea, glycerin, hypertonic saline

- easily filtered, poorly reabsorbable ∴ they filter out + H_2O follows
- removes less Na^+ than others ∴ not good in Na^+ retention diseases

(33) Hypno-sedatives : mix of anxiolytic + hypnotic drugs

① BZD : Clonazepam, Diazepam, Flurazepam

↳ oral → liver → urine ; NO ANALGESIA!
↳ Alcohol interaction! => -ve synergism (+ other CNS depressants)
↳ AE: confusion, drowsiness
↳ CI: liver disease

② BZD Antagonists : Flumazenil – (IV) ONLY!

↳ $GABA_A$ receptor antagonist
↳ quick action + short duration ; freq admin for long acting BZD
↳ AE: nausea, vomiting, dizziness, agitation

③ Barbiturates : Thiopental, Pentobarbital, phenobarbital

↳ replaced by BZD => coz they cause tolerance, induce enzymes, physical dependence & severe withdrawal symptoms
↳ CYP450 inducers
↳ acts within secs + lasts for 30 mins
↳ phenobarbital => lasts for a day! Pentobarbital => short acting; hypno-sedative

④ Others : Zolpidem, Buspirone, Hydroxyzine → dental patients + ppl w/ history of drug abuse

Zolpidem: ↓
Works on BZD_1 receptors; no withdrawal, no anti-convulsive or muscle relax, min. rebound insomnia, little/no tolerance w/ prolonged use
↳ oral; short $t_{1/2}$; liver metab; drug-drug interaction (Rifampicine)

Buspirone:
↳ prolactin + Growth hormone ↑ in plasma
↳ hypothermia occurs
AE: headache, dizziness, nightmares, GI dysfunc, agitation

⑤ Non-Barbiturate sedatives:

Chloral hydrate: sleep in 30 (min) + lasts for 6 hrs
AE: GI irritation, epigastric distress, unusual taste sensation
↳ synergy w/ ethanol

Anti-histamines: Diphenhydramine + Doxylamine
↳ mild insomnia
↳ AE: many (less useful than BZD)

Ethanol : CNS depres w/ sedation + hypnosis
↳ orally; High Vd ; liver metab → urine + little via lungs
↳ CNS depres w/ Barbiturates / Anti-histamines
↳ For withdrawal => BZD + Carbamazepine

Disulfiram : blocks oxidation of acetaldehyde → Acetic A.
↓
inhibits aldehyde dehydrogenase
↳ flushing, tachy, hyperventilation, nausea
↳ Given in ppl who want to stop drinking

PARASYMPATHOMIMETICS All of these are (PM)!

(42) (34) **Direct Cholinergic Agonists** – Atropine – counteracts these – Antagonist – both Muscarinic + Nicotinic receptors

eye surgery – miosis

① Carbachol – PM (Muscarinic + nicotinic) – Glaucoma

② ~~Sechol~~ Bethanechol – Same as Ach (Muscarinic) – Stimulation (non-obs. urinary retention)

③ Pilocarpine – PM (Muscarinic) – Glaucoma (NATURAL)

} opp effects to * Bind to receptors * Atropine

Vasodil

AE: ↓BP, ↓HR, nausea, GIT disturbances, vasodil

NOT used clinically (apart from localised eye use) => coz they are non-specific ∴ too many other AE

* 1 has more affinity for * muscarinic

-Longer duration than Ach! ↳ Given (IV)

Effects: ↓HR, ↓CO, ↓BP, vasodil, ↑salivary, gastric + bronchial secretions, MIOSIS (constriction of pupil), ↑tone of urinary detrusor muscle (u piss)

Indirect Cholinergic Agonists – block Achesterase ∴ ↑ effect.

enzyme needed for Ach breakdown

Salivation, Lacrimation, Urination, Diaphoresis (xs sweating), Gastrointestinal motility, Emesis } Atropine for treatment

Reversible

Neostigmine – PM – Symptomatic treatment of Myasthenia gravis; poorly absorbed

Physostigmine – crosses BBB, lasts longer, nicotinic + muscarinic receptors in ANS & nicotinic receptor in NMJunc.

↳ ↑GIT + bladder motility

↳ Atropine + Scopolamine poisoning => central & some periph. competitive muscarinic antagonists

Irreversible – Organophosphates (Isoflurophate) – Nerve gas – Echothiophate

* permanent inactivation of enzyme

& open angle glaucoma (chronic)

} Antagonist = Pralidoxime (PAM) ↓ – within 30mins – IV => only at NMJ; ineffective in CNS

form covalent bonds

Give atropine (parenterally) * first then PAM

Cholinergic Antagonists – (PL)

↳ just block agonists from binding!

Effects: Mydriasis, blurred vision, dry mouth, ↓ parasymp. activity of muscles + glands

① **Anti-muscarinics**: block M_1 receptors of PNS → Atropine, Scopolamine

↳ used in agonist poisoning

↳ Motion-sickness
blocks short-term memory
Sedation but high doses ⇒ excitement
antiemetic

② **Ggl blockers**: Nicotine, Trimethaphan, Mecamylamine → emergency HBP – (IV)

(look at Q).

- Nicotinic receptors mainly in SNS → ↓BP
- sexual dysfunc

③ **Neuromuscular Blockers**: (Antagonists) Non-depolarising (Competitive) OR (Agonists) Depolarising type

Also Q38

(facial mus → intercostal → diaphragm)

↳ complete muscle relax ⇒ Surgery!

(Combine w/ anaesthesia, so u give lower doses of anaesthesia) called adjuvants!

Tubocurarine, Mivacurium, CisAtracurium, Vecuronium

↳ histamine release

For Reversal: AchE inhibitors, e.g. Neostigmine

① Non-depol: competitive Nicotinic receptor binding

Low doses [↳ can overcome them if ↑[Ach] ⇒ Low doses
↳ prevent depol + inhibit muscular contrac

high doses [↳ block ion channels → weaken NM transmission →
∴ harder to overcome them

↳ IV; hepatic metab → bile + urine (only some)

↓

Vecuronium

AE: hypotension (histamine release), tachycardia, bronchospasm

CI: asthma OR anaphylaxis ppt

Interactions: ① GA (inhaled): Isoflurane ⇒ ↑ NMJ block (∴ ↓ dose)
② Aminoglycosides ⇒ inhib. presynaptic Ach release
③ Ca^{2+} blockers ⇒ ↑ NM block
④ Dantrolene: ↑ NM block

Succinylcholine

↳ Nicotinic receptor agonist ⇒ persistant stimulation + depol. of the muscle

↳ Succinylcholine-metab slower than Ach ∴ muscle cells remain depol + unresponsive to further stimulation (phase I block – 5–10 mins)

↳ Long term exposure (45–60 mins) – cells repolarise BUT can't depol. again while succinyl. is there ∴ remain unresponsive. (phase II block)

↳ AChE inhib – enhances phase I block
reverses " II block

↳ plasma/liver cholinesterase

↳ AE: ↑[K+], Malignant hyperthermia, post-op muscle pain, bradycardia, ↑ Intraocular press,

Uses: brief paralysis in short surgical procedures e.g. tracheal intubation

(35) Ionotropic drugs: affect cardiac muscle contractility => affect cytoplasmic $[Ca^{2+}]$

(+ve) – ↑ contractility by ↑$[Ca^{2+}]$

I: Congestive HF, MI, shock, cardiomyopathy

① Cardiac glycosides: Digitalis < Digoxin / Digitoxin

MoA: inhibits Na^+/K^+-ATPase → ↑intracellular $[Na^+]$ + ↓$[K^+]$ → too much $[Na^+]$ inside → Na^+/Ca^{2+} pump stops working → no $[Ca^{2+}]$ going out & Na^+ coming in → ∴ ↑cyto $[Ca^{2+}]$

↳ orally, IV; liver → urine

↳ Interaction: quinidine displaces digoxin fm tissues → ↑[plasma] → ∴ less effective! Verapamil + Amiodarone ⇒ fight for renal excretion

↳ AE: hypokalaemia, any arrhythmia, GI disturbances

② Catecholamines: Dobutamine (β_1-agonist!)

↳ mainly β_1 → ↑cAMP mediated phosphorylation → ↑activity of Ca^{2+} channels

↳ needs high doses; (IV)

↳ short term therapy - severe chronic HF & after cardiac surgery

↳ comb. w/ vasodil (nitroprusside / nitroglycerin) ⇒ improve cardiac performance - ppl w/ advanced HF

↳ AE: ↑BP, ↑HR

Dopamine – ↑ contractility

③ Phosphodiesterase Inhibitors: Inamrinone Lactate & Milrinone

↳ ↑cAMP → ↑$[Ca^{2+}]$ intracellular (same as dobutamine)

↳ when digitalis is ineffective

↳ AE: hypotension, transient thrombocytopenia, GI dysfunc, fever

(IV) short term

④ Ca^{2+} sensitisers: ↑sensitivity of the heart to $[Ca^{2+}]$ BUT NO ↑ in $[Ca^{2+}]$ LEVOSIMENDAN

(-ve) – ↓ force of contractility by ↓$[Ca^{2+}]$

I: angina, arrhythmias, ↑BP

① β-blockers: Prop ones w/ ISA: Bopindolol, Pindolol (non-selec.); Acetobutolol (selective β_1)

② Ca^{2+} channel blockers: Amlodipine (not really (more peripH)), Nifedipine, Verapamil, Diltiazem

③ Class IA + IC anti-arrhythmics: Quinidine + Flecainide → they slow conduction

Calcium Sensitisers ⇒ ↑ sensitivity of the heart to Ca^{2+} ⇒ ↑ contractility w/ NO ↑ in intracell $[Ca^{2+}]$

(35)

↳ +ve inotropic effect by ↑ Ca^{2+} sensitivity → binds to troponin C in myocytes ⇒ ↑ force of contraction ↓ preload & ↓ afterload

↳ vasodil. effect ⇒ opening ATP-sensitive K^+ channels in vascular smooth mus

↳ opening of these = cardioprotective effect

LEVOSIMENDAN

↳ management of acutely decompensated Congestive HF

↳ IV infusion - dil. w/ glucose

C I: moderate-severe renal impairment
severe hepatic impairment
" ventricular filling/outflow obs.
" hypotension + tachy.
history of torsades de pointes

AE: headache
hypotension
Arrhythmias (AF, VT, Atrial tachy, extrasystole)
Myocardial ischaemia
hypokalaemia + nausea

↳ hepatic metab + renal excretion

(36) Lipid & drugs : target the mob of ↑serum lipids

3 MoA: ① ↓ prod of lipoprotein carriers of Chol + TAG
② ↑ lipoprot⁻ degradation
③ ↑ Chol. removal

① Niacin - B3 vit: inhib lipolysis in adip. tiss.
↓
↓ Liver TAG synthesis
↓ VLDL + LDL ← used in hypertriglyceridaemia
↳ ↓ plasma levels of Chol + TAG + ↑ [HDL]
↳ ↓ urine excretion; incorporated in cofactor NADPH + NAD+
orally
AE: nausea, ab pain, hyperuricaemia, pruritus
NOT really used!

③ HMG-CoA Reductase Inhib: Lovastatin, Pravastatin, Simvastatin, Fluvastatin
↳ comp. inhib for HMG-CoA reductase enzyme → ↓ I.C. Chol. supply → ↑ no. of cell surface LDL recep → more LDL internalised → ↓ [Chol] plasma.
↳ all types of hyperlipidemias
↳ bile + faecal excretion; oral; liver metab
↳ AE: myopathy + rhabdomyolysis (detected by ↑ [CK] levels)
Cl: preg + nursing

HMG-CoA ⇒ 3-hydroxy-3-methyl glutaryl

VLDL / LDL = bad ones
HDL = good one

② Fibrates → ★ Clofibrate + Gemfibrozil
↳ stim. LPL ∴ ↓ TAG + VLDL ; ↑ HDL ; ↓ fibrogen levels
→ Hypertriglyceridaemias, Type 3 hyperlipidemia
AE: GI dysfunc, lithiasis
→ urine excretion; prot⁻ binding;
→ oral → liver metab; Interaction ⇒ compete w/ WARFARIN for p.prot
Cl: hepatic / renal dysfunc + gall bladder probs

★ Cholestyramine + Colestipol
↳ anion exchange resins - bind -vely charged bile acids / bile salts → faecal excretion ∴ less returning to liver (enterohepatic circ) ∴ More produced.
↳ Type 2a + 2b hyperlipidaemia
↳ cholestyramine - relieves itching due to bile acid accum. w/ Biliary obs.
↳ Total unchanged faecal excretion
↳ cause hepatocytes to ↑ Chol → Bile Acids!
↳ ∴ ↓ [Chol] plasma
↳ orally!; can be combined w/ Niacin
AE: GI dysfunc, impaired absorp of fat sol vit + folic Acid + Vit C
Cl: hypertriglyceridemia
Interaction: interfere w/ intestinal absorption of many drugs ⇒ Tetracyclines, phenobarbital, Digoxin, Warfarin, Aspirin, "statins", thiazide diuretics ⇒ take them before/after

(37) # Local Anaesthesics : Block N conduction of sensory impulses fm periph → CNS

↳ inhib. Na^+ channels → No Na^+ influx → No AP! ⇒ Block inactive + active Na^+ channels

No K^+ outflux → no depol ↑

Amides Lidocaine, Bupivacaine, Mepivicaine, Prilocaine

↳ liver metab → inactive agents

↳ True allergic reactions = RARE!

↑ no. of connecting groups (ester/amide) → ↑ potency + toxicity

Add epinephrine ⇒ vasocons! ⇒ ↓ systemic absorption & ↑ duration of action

Esters Cocaine, procaine, tetracaine, Chloroprocaine, Novocaine

↳ plasma pseudocholinesterase hydrolysis

↳ By products = Para-aminobenzoic A (PABA) ⇒ cause of allergy!

AE (of both):

CNS toxicity < low dose - excitment ⇒ tremors, shivering
high " - depression ⇒ resp. depres.

CVS toxicity - ↓BP + AV block (depression)

V.V. high conc ⇒ seizures, coma, death

Factors affecting LA action:

① pH ⇒ uncharged penetrate better

② Lipid solubility ⇒ ↑ solubility = ↑ potency (coz u need less of it)

③ Prot- binding ⇒ ↑ binding = ↑ duration of action

④ Diffusibility ⇒ ↑ diffusibility = ↓ time of onset

⑤ vasocons ⇒ ↑ duration + ↓ absorp.

⑥ Nerve fibre ⇒ gen. small fibres more susceptible BUT:

↳ type of fibre ("B" more easily than "C")

↳ degree of myelination

↳ fibre length

↳ frequency-dependence i..

Types: Topical
Infiltrative
Plexus block
Epidural
Spinal